Children selected for adenotonsillectomy

Experimental and non-experimental studies

Birgitta K van Staaij

Children selected for adenotonsillectomy; experimental and non-experimental studies

Thesis, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht with a summary in Dutch

ISBN: 90-393-3821-3
Author: BK van Staaij
Cover: Studio Vrijdag, Utrecht
Print: Febodruk BV, Enschede

Utrecht 2004

Children selected for adenotonsillectomy

Experimental and non-experimental studies

Kinderen met een indicatie voor adenotonsillectomie

Experimenteel en niet-experimenteel onderzoek

(met een samenvatting in het Nederlands)

Proefschrift

Ter verkrijging van de graad van doctor aan de Universiteit Utrecht,
op gezag van de Rector Magnificus, Prof. Dr. WH Gispen,
ingevolge het besluit van het College voor Promoties
in het openbaar te verdedigen op

dinsdag 26 oktober 2004 des middags te 12.45 uur

door

Birgitta Katarina van Staaij

Geboren 23 juli 1965 te Den Haag

Julius Center for Health Sciences and Primary Care
University Medical Center Utrecht, the Netherlands

Promotor
Prof. Dr. AW Hoes
Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, the Netherlands

Co-promotor
Dr. AGM Schilder
Wilhelmina Children's Hospital, University Medical Center Utrecht, Department of Otorhinolaryngology, Utrecht, the Netherlands

The studies presented in this thesis were supported by grants from the Dutch Health Care Insurance Board (OG-99-060) and GlaxoSmithKline, the Netherlands.

The author gratefully acknowledges financial support for printing of this thesis by the Julius Center for Health Sciences and Primary Care.

Voor Stef

Matthijs, Boele en Karlijn

Thesis committee

Prof. Dr. MJM Bonten
Prof. Dr. J Kimpen
Prof. Dr. WJJ Assendelft
Prof. Dr. M Offringa
Prof. Dr. PB Van Cauwenberge

Contents

Chapter 1

Introduction

In part published as:
Adenotonsillectomie bij kinderen: nog onvoldoende wetenschappelijk onderbouwd. [Adenotonsillectomy in children: not yet scientifically validated].
van Staaij BK, van den Akker EH, Poels PJ, Hoes AW, Schilder AGM.
Ned Tijdschr Geneeskd 2002;146:8-12.

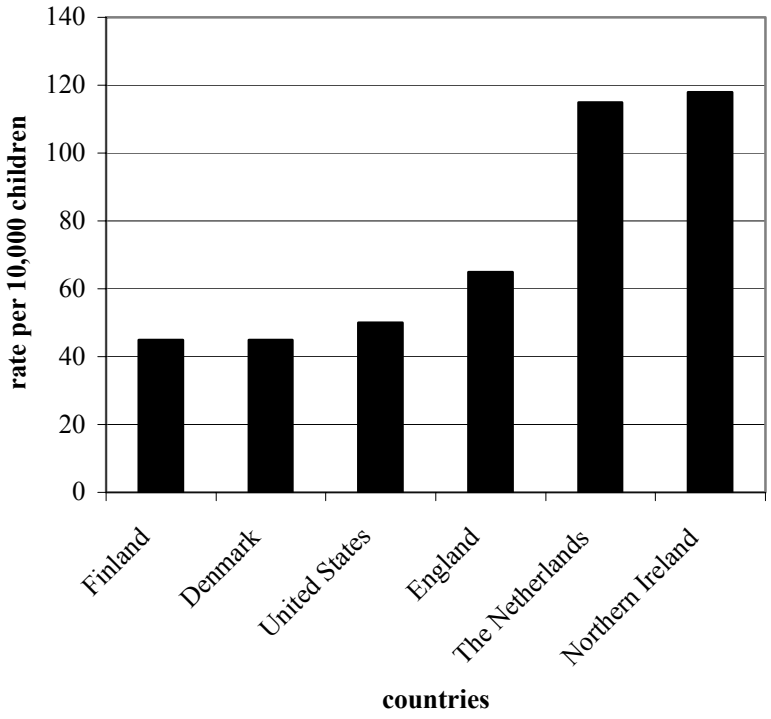
General introduction

Tonsillectomy with or without adenoidectomy is one of the most commonly performed surgical procedures in children in western countries.[1] Until the 1960s (adeno)tonsillectomy was almost routinely performed in children as a measure to prevent complications from acute tonsillitis caused by *Group A beta-haemolytic streptococci* i.e. acute rheumatic fever and acute poststreptococcal glomerulonephritis. A study from 1934, performed in England, showed that 58% of the boys entering boarding school had undergone tonsillectomy.[2] Due to improved living conditions, better hygiene, less crowding, improved nutrition and the introduction of penicillin in the 1940s, the incidence of these complications decreased dramatically. In the Netherlands, acute rheumatic fever now has a reported annual incidence of approximately 0.4/100,000[3] while the annual incidence of acute poststreptococcal glomerulonephritis is 1/100,000.[3] As the fear for these complications decreased, the number of adenotonsillectomies also decreased in the 1960s and 1970s (figure 1). Since 1985 this number has remained more or less constant, at 115 per 10,000 children per year in the Netherlands.[1]

Figure 1. Paediatric (0-14 years) (adeno)tonsillectomy rates in the Netherlands between 1974 and 1998. For the years 1986-1990 (adeno)tonsillectomy rates are not known. (adapted from van den Akker EH, et al. *Clin Otolaryngol* 2004;**29**:161-4).

Surgical rates of adenotonsillectomy do not only vary in time, but also across and even within countries (figure 2). A survey in 1998 showed that 17.3% of all children in the Netherlands aged 15 years had undergone (adeno)tonsillectomy. Corresponding figures for England and the United States were 9.8% and 7.5%, respectively.[1] Cultural differences, such as a preference for antibiotic (United States) or surgical management (the Netherlands) of upper respiratory infections partly explain this variation,[4] but lack of (inter)nationally accepted guidelines on indications for (adeno)tonsillectomy also plays an important role. The main reason for the absence of generally accepted clinical guidelines is the poor quality of the scientific evidence for the effects of (adeno)tonsillectomy in children.[5]

Figure 2. 1998 paediatric (adeno)tonsillectomy rates in different countries (adapted from van den Akker EH, et al. *Clin Otolaryngol* 2004;**29**:161-4).



Most doctors agree that (adeno)tonsillectomy is beneficial for children with very frequent throat infections (i.e. 7 or more per year) and in children with obstructive sleep apnoea (OSA) due to adenotonsillar hypertrophy.[6,7] The effectiveness of (adeno)tonsillectomy for very frequent throat infections was studied in the United States by the group of Paradise et al. in a randomised trial among a selective population of children with very frequent throat infections.[8,9] The effectiveness of adenotonsillectomy for obstructive sleep apnoea has not been studied in randomised

studies, but several uncontrolled studies have shown considerable postoperative improvement of objective sleep parameters and obstructive complaints. Randomisation of these children to either surgery or watchful waiting is therefore considered unethical and unnecessary.[10-12]

There is no evidence for the benefits of adenotonsillectomy in a large proportion of children currently undergoing this procedure for less frequent throat infections and milder symptoms of adenotonsillar hypertrophy, or for other indications such as upper respiratory infections.[13-16] For these children the medical literature offers the physician little support in deciding which child might benefit from the operation. Publications show that ENT-surgeons and general practitioners regard moderate frequent throat infections, upper respiratory infections and complaints such as restless sleep and poor appetite important indications for (adeno)tonsillectomy.[13-16] Children with very frequent throat infections or a high suspicion of OSA constitute approximately 35% of the children currently undergoing adenotonsillectomy in The Netherlands, whereas 65% are operated for non-evidence based indications like less frequent throat infections and milder symptoms of adenotonsillar hypertrophy.[13]

Trials on adenotonsillectomy published so far have focused on the reduction of throat infections and upper respiratory infections.[8,9,17-19] However, a reduction of the number of these infections is not the only desired effect of adenotonsillectomy. Improvement of health-related quality of life and sleeping and eating pattern is important as well to the patient. So far, health related quality of life has only been measured in non-controlled studies.[12]

Not only is our knowledge of the effects of the operation limited, the complaints of children undergoing adenotonsillectomy are also poorly studied. As De Melker stated in 1995 “Diseases: the more common the less studied.”[20] Due to large gaps in our knowledge of so-called common diseases, a scientific basis for their management is lacking. For example, we know little of the incidence of upper respiratory infections and associated fever episodes in “healthy” children and children undergoing (adeno)tonsillectomy, which symptoms they report during fever episodes and which children consult a physician and receive antibiotics.

In addition, the pathogenesis of upper respiratory infections has not been fully elucidated and it is not known why some children are more susceptible to infections of Waldeyer’s ring than others. Exposure to respiratory tract pathogens influenced by environmental factors such as day care attendance and the number of siblings, and the response of the innate and adaptive immune system all play a role in the occurrence and duration of upper respiratory infections. However, none of these factors is

pathognomic and there is an urgent need to study the aetiology of the respiratory illness in greater detail. If the aetiology is better understood, preventive and therapeutic approaches can be improved.
Recurrent throat infections and other upper respiratory infections have a serious impact on the child and its family resulting in, for example, school absence, loss of working hours of parents and disruption of family activities.[21,22] Therefore, these children require our attention. Most of these children will recover spontaneously from their upper respiratory infections and will not need surgical interventions such as adenotonsillectomy, while others will develop chronic recurrent upper respiratory infections. If it were possible to identify children at high-risk of developing frequent infections or complications, we could target our interventions at these children. So far, however, physicians do not have adequate tools to identify children at high risk of chronic recurrent upper respiratory infections and this may result in unnecessary interventions in children that would have recovered spontaneously and relatively fast.
To provide further evidence on these issues we designed a randomised trial on the effectiveness of adenotonsillectomy in children selected according to current medical practice in the Netherlands and we initiated several additional studies, addressing the following research questions:

Research question 1: *What is the incidence of fever in children?*
In *Chapter 2* we will describe the age and sex-specific incidence and duration of fever episodes in children with relatively mild symptoms of throat infections or adenotonsillar hypertrophy, the main symptoms experienced by these children during fever episodes, and the consequences in terms of physician consultation rates and antibiotic prescription rates.

Research question 2: *Is it possible to predict the occurrence of chronic recurrent upper respiratory infections in children?*
In *Chapter 3* we will attempt to define a prediction rule that is easily applicable and can be used by general practitioners as a screening tool to identify children at risk for developing chronic recurrent upper respiratory infections.

Research question 3: *Does variation in the tonsillar surface flora predispose children to recurrent upper respiratory infections?*
Variation in the microbial flora in the tonsillar and adenoidal tissue may predispose children to upper respiratory infections and/or adenotonsillar hypertrophy. In *Chapter*

4 we will investigate whether the tonsillar flora of children with adenotonsillar disease differs from that in children without adenotonsillar disease.

Research question 4: *What is the current evidence for the effectiveness of adenotonsillectomy in children?*
In *Chapter 5* a systematic review based on all available evidence from randomised trials and non-randomised controlled studies on adenotonsillectomy in children will be presented. This review will provide a quantitative estimate of the effects of (adeno)tonsillectomy on sore throat episodes, upper respiratory infections and sore throat associated school loss.

Research question 5: *Is an infrared tympanic membrane thermometer an adequate tool to measure body temperature and is it feasible to measure body temperature daily?*
Since we decided to use the occurrence of fever as the primary objective outcome of our trial, we instructed parents to measure their child's temperature daily with an infrared tympanic membrane thermometer. To ensure objectivity and avoid information bias we incorporated an electronic device in the thermometer that stored temperature measurements automatically on a daily basis. In *Chapter 6* accuracy and feasibility of such daily temperature measurements at home are reported.

Research question 6: *Is adenotonsillectomy an effective procedure in children with relatively mild symptoms of throat infections or adenotonsillar hypertrophy?*
In *Chapter 7* we present the results of our randomised trial on the effects of adenotonsillectomy in children with relatively mild symptoms of throat infections or adenotonsillar hypertrophy. Outcome measures are fever episodes, throat infections, upper respiratory infections and health-related quality of life.

Research question 7: *Is adenotonsillectomy in children with relatively mild symptoms of throat infections or adenotonsillar hypertrophy a cost-effective procedure?*
The cost-effectiveness of adenotonsillectomy as compared to watchful waiting is presented in *Chapter 8*. Main outcome measures are incremental cost-effectiveness in terms of costs per fever episode avoided, per throat infection avoided and per upper respiratory infection avoided.

Challenges for the future

In the Netherlands, the general practitioner has an important role in the management of children with throat infections and other upper respiratory infections. Prior belief of parents and doctors in the beneficial effect of adenotonsillectomy is usually strong. The results of trials, including ours, may not be in accordance with these beliefs and this may hamper successful implementation of the results. In the *General discussion* factors are explored that influence patients help-seeking behaviour and the tools that general practitioners have to implement the results of our randomised trial. Finally, the challenges for future research will be discussed.

References

1. van den Akker EH, Hoes AW, Burton MJ, Schilder AG. Large international differences in (adeno)tonsillectomy rates. *Clin Otolaryngol* 2004;**29**:161-4.
2. Medical research council. Epidemics in schools. X tonsillectomy. *Spec Rept Ser* 1938;118-25.
3. Hoogendoorn D. Acuut reuma en acute glomerulonefritis: huidige klinische incidentie en de sterfte in Nederland. *Ned Tijdschr Geneeskd* 1989;**133**:2334-8.
4. Schilder AG, Lok W, Rovers MM. International perspectives on management of acute otitis media: a qualitative review. *Int J Pediatr Otorhinolaryngol* 2004;**68**:29-36.
5. Burton MJ, Towler B, Glasziou P. Tonsillectomy versus non-surgical treatment for chronic / recurrent acute tonsillitis. *Cochrane Database Syst Rev* 2000;CD001802.
6. Scottish Intercollegiate Guidelines Network. Available from http://www.sign.ac.uk/guidelines (cited 20-05-04).
7. American Academy of Otolaryngology-Head and Neck Surgery. Clinical Indicators for Otolaryngology-Head and Neck Surgery. Available from: http://www.entlink.net/practice/products/indicators/tonsillectomy.html (accessed 17-06-2004)
8. Paradise JL, Bluestone CD, Bachman RZ, Colborn DK, Bernard BS, Taylor FH, et al. Efficacy of tonsillectomy for recurrent throat infection in severely affected children. Results of parallel randomized and nonrandomized clinical trials. *N Engl J Med* 1984;**310**:674-83.
9. Paradise JL, Bluestone CD, Colborn DK, Bernard BS, Rockette HE, Kurs-Lasky M. Tonsillectomy and adenotonsillectomy for recurrent throat infection in moderately affected children. *Pediatrics* 2002;**110**:7-15.
10. Nieminen P, Tolonen U, Lopponen H. Snoring and obstructive sleep apnea in children: a 6-month follow-up study. *Arch Otolaryngol Head Neck Surg* 2000;**126**:481-6.
11. de Serres LM, Derkay C, Astley S, Deyo RA, Rosenfeld RM, Gates GA. Measuring quality of life in children with obstructive sleep disorders. *Arch Otolaryngol Head Neck Surg* 2000;**126**:1423-9.
12. Flanary VA. Long-term effect of adenotonsillectomy on quality of life in pediatric patients. *Laryngoscope* 2003;**113**:1639-44.
13. van den Akker EH, Schilder AG, Kemps YJ, van Balen FA, Hordijk GJ, Hoes AW. Current indications for (adeno)tonsillectomy in children: a survey in The Netherlands. *Int J Pediatr Otorhinolaryngol* 2003;**67**:603-7.
14. Blair RL, McKerrow WS, Carter NW, Fenton A. The Scottish tonsillectomy audit. Audit Sub-Committee of the Scottish Otolaryngological Society. *J Laryngol Otol* 1996;**110 Suppl 20**:1-25.
15. Donnelly MJ, Quraishi MS, McShane DP. Indications for paediatric tonsillectomy GP versus consultant perspective. *J Laryngol Otol* 1994;**108**:131-4.
16. Capper R, Canter RJ. Is there agreement among general practitioners, paediatricians and otolaryngologists about the management of children with recurrent tonsillitis? *Clin Otolaryngol* 2001;**26**:371-8.
17. Mc Kee WJE. A controlled study of the effects of tonsillectomy and adenoidectomy in children. *Br J Prev Soc Med* 1963;**17**:49-69.
18. Mc Kee WJE. The part played by adenoidectomy in the combined operation of tonsillectomy with adenoidectomy. Second part of a controlled study in children. *Br J Prev Soc Med* 1963;**17**:133-40.
19. Mawson SR, Adlington P, Evans M. A controlled study evaluation of adeno-tonsillectomy in children. *J Laryngol Otol* 1967;**81**:777-90.
20. de Melker RA. Diseases: the more common the less studied. *Fam Pract* 1995;12:84-7.
21. Howel D, Webster S, Hayes J, Barton A, Donaldson L. The impact of recurrent throat infection on children and their families. *Fam Pract* 2002;**19**:242-6.

22. Stewart MG, Friedman EM, Sulek M, Hulka GF, Kuppersmith RB, Harrill WC, et al. Quality of life and health status in pediatric tonsil and adenoid disease. *Arch Otolaryngol Head Neck Surg* 2000;**126**:45-8.

Chapter 2

Fever in children with recurrent upper respiratory infections: incidence and associated medical consumption

van Staaij BK, Schilder AGM, van den Akker EH, Hoes AW.
Submitted.

Summary

Background. Fever is an important physical sign in children. Notwithstanding its importance, studies quantifying the occurrence of fever, its possible causes and associated medical consumption are scarce.
Objective. To determine the age and sex-specific incidence and duration of fever episodes in children, the main symptoms experienced by children during these fever episodes, and the consequences in terms of physician consultation rates and antibiotic prescription rates.
Methods. This study was undertaken in a cohort of 321 children aged 2 to 8 years selected for adenotonsillectomy for relatively mild symptoms of throat infections or adenotonsillar hypertrophy. During follow up the child's temperature was measured daily with a validated infrared tympanic membrane thermometer. Parents kept a standardised diary if their child had fever or symptoms of an upper respiratory infection; consultation of a physician and prescribed medication were noted.
Results. The incidence rate of fever episodes per child year was 3.0. With advancing age the incidence of fever episodes did not materially change. The incidence rate of fever episodes was significantly higher in girls than in boys: 3.3 versus 2.8 fever episodes per child year (incidence rate difference 0.5; 95% CI 0.2 to 0.9). A physician was contacted in 12.7% and antibiotics were prescribed in 7% of all fever episodes.
Conclusion. The incidence of fever episodes in children aged 2 to 8 years selected for adenotonsillectomy for relatively mild symptoms of throat infections or adenotonsillar hypertrophy is high and remains so with advancing age. As much as 87.3% of these fever episodes never reach medical attention.

Introduction

Fever is an important physical sign in children and in most cases caused by a self-limiting viral illness. With 52.4 per 1000 consultations fever is the second most frequent reason for children to consult a general practitioner, after coughing with 84.1 per 1000 consultations.[1]

Notwithstanding its importance, studies quantifying the occurrence of fever, its possible causes and associated medical consumption are scarce. Only two studies measuring the occurrence of fever in children on a daily basis are available.[2,3] McCarthy et al.[2] reported an incidence rate of 1.2 acute infectious episodes with fever per child year in a cohort of children recruited at a well child care center, while Koch et al.[3] found an incidence rate of 17.9 fever days per child year in their very selective population of Inuit children.

The present prospective study was undertaken in a cohort of children aged 2 to 8 years selected for adenotonsillectomy (T&Ads) for relatively mild symptoms of throat infections or adenotonsillar hypertrophy.[4] The goals of our study were to describe 1) the age and sex-specific incidence and duration of fever episodes in these children, 2) the main symptoms experienced by children during these fever episodes, 3) and the consequences in terms of physician consultation rates and antibiotic prescription rates.

Methods

Patients

A cohort of children (n=321) provided data for the present study. Inclusion criteria were an indication for adenotonsillectomy according to the local ENT-surgeon and age between 2 and 8 years. Three hundred children participated in a randomised trial on the effectiveness of T&Ads and were assigned randomly to either T&Ads or non-surgical treatment[4]; 21 underwent T&Ads because of their parents' preference. Children with very frequent throat infections (7 or more in the previous year)[5] or a high suspicion of obstructive sleep apnoea[6] were excluded.

Follow-up

During the median follow-up of 1.54 (range 0.03 to 2.26) years, the child's temperature was measured daily with a validated infrared tympanic membrane thermometer. Parents were instructed by the study physician to take the tympanic membrane temperature according to the instructions of the manufacturer. To minimise

information bias, we had an electronic device built in the thermometer to store the date of the first temperature measurement of that day. In a previous study we have shown that this infrared tympanic thermometer as used in our study is an adequate tool to assess fever in a research seting.[7]
During follow up parents filled out a diary if their child experienced fever or symptoms of an upper respiratory infection; i.e. sore throat, pain and/or difficulty at swallowing, cough, rhinorrhea, earache, otorrhea. Other symptoms during fever episodes were also noted. Consultation of a physician and prescribed medication were recorded. To optimise patient compliance, a standardised telephone inquiry was performed each month by one of the research nurses. 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.

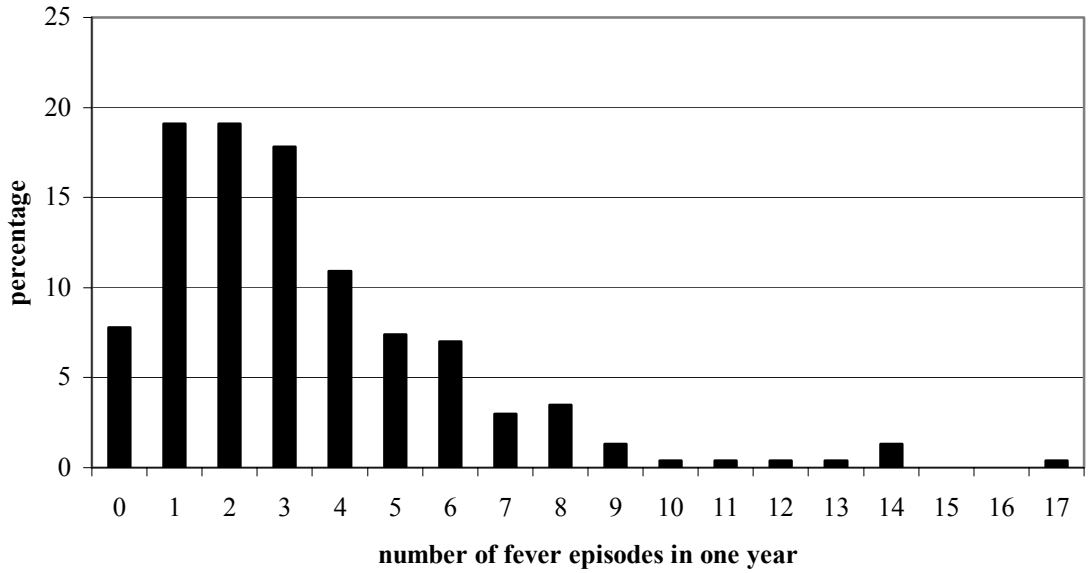
Data analysis
Fever was defined as a body-temperature of 38.0 °C or higher as measured by the infrared tympanic thermometer for at least one day. Fever was measured in fever days and episodes. An episode ended when a child was free from fever (< 38.0 °C) for at least one day. A new episode of fever was recorded after a fever free interval of at least 7 days.
The incidence rate per person year of all fever episodes and fever episodes lasting 2 days or longer were calculated, as well as the total number of fever days. To show the distribution of fever episodes per child during one year, only data from children participating for more than one year were included (n=230). The fever episodes experienced by these children in their first study year were calculated. This approach was chosen because season is known to influence the incidence of fever episodes. Therefore, extrapolation of the number of fever episodes experienced during a shorter period to one year would critically influence the estimates of the total number of fever episodes per child during one year. The median duration of fever episodes was determined with corresponding inter quartile ranges (25-75 percentiles).
Symptoms associated with fever were considered present if they were recorded for at least one day in the diary during a fever episode. Fever episodes were divided into 4 categories according to their associated symptoms as noted in the diary: 1) only upper respiratory infection symptoms, 2) upper respiratory infection and other localising symptoms, 3) only other localising symptoms, and 4) no localising symptoms.
Physician consultation rates and antibiotic prescription rates related to fever episodes were determined on the basis of diary data.

Incidence rates of fever episodes per sex were calculated. In addition, the incidence rates of fever episodes per season (spring, summer, autumn, and winter) were calculated by dividing the number of fever episodes per season by the total number of person years during that particular season (n=321).
The incidence rate of fever episodes per year per age category was calculated by dividing the number of fever episodes per age category (2 to 3, 4 to 5, and 6 to 9 years) by the total number of years that the children were in that age group.
Chi-square tests were used to test the differences between proportions. A p-value of <0.05 was considered statistically significant. Where appropriate, incidence rate differences (IRD) with 95% confidence intervals were calculated.

Results

The mean age of the participants at inclusion (n=321) was 4.6 (SD 1.4) years and 50.2% was male. Body temperature was measured on 67.3% of all study days (67.1% in boys versus 67.4% in girls), accounting for 112,750 documented temperature measurements.

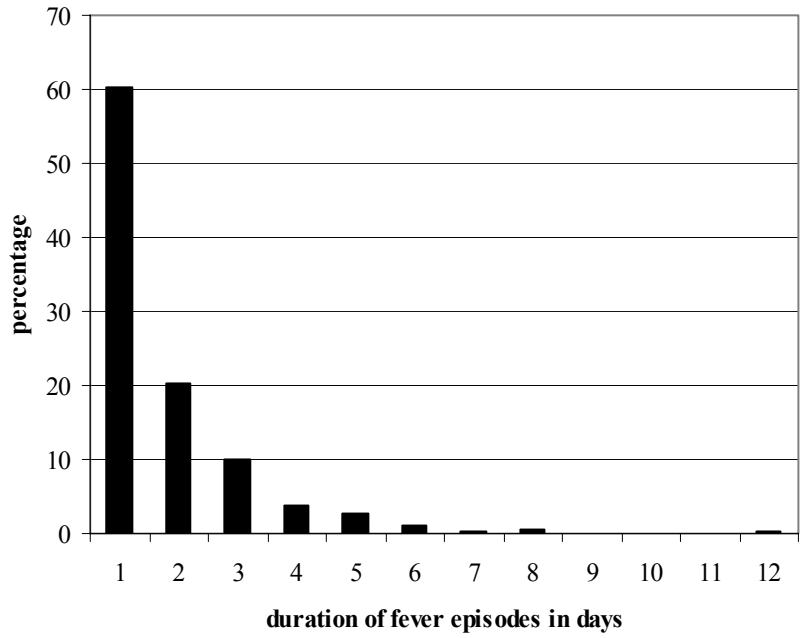
Figure 1. Distribution of the number of fever episodes experienced by the children (230 children) in one year.



In total 2543 fever days were measured, i.e. an incidence rate of 5.5 fever days per child year (n=321). The number of fever episodes was 1397, i.e. an incidence rate of

3.0 fever episodes per child year. Fifty-four percent of the children experienced at least 3 fever episodes per year (figure 1; n=230).
The median duration of a fever episode was one day (inter quartile range 1-2); 60.4% of all fever episodes lasted only one day (figure 2).

Figure 2. Distribution of the duration of fever episodes (321 children).



The total number of fever episodes lasting 2 days or longer was 553, i.e. an incidence rate of 1.2 fever episodes per child year with a median duration of 2 days (inter quartile range 2-3) per child year.
During fever episodes, symptoms of upper respiratory infections (notably rhinorrhea in 38.9% of fever episodes, sore throat in 20.5% and cough in 35.4%) and gastro-intestinal symptoms were most often reported (table 1).
One or more URI symptoms were present in 55.9% of the fever episodes and in 40.3% there were no localising symptoms (table 2). In fever episodes lasting 2 days or more, URI symptoms were recorded in 69.9% and no localising symptoms were present in 26.0%. A physician was consulted in 12.7% of all fever episodes (table 2). In 24.2% of the fever episodes lasting 2 days or longer a physician was consulted. Antibiotics were prescribed in 7.0% of fever episodes, and in 12.7% of fever episodes lasting 2 days or longer.

Table 1. Symptoms during fever episodes in children as reported by the parents (321 children).

Symptoms	**All fever episodes** (n=1397) n (%)	**Fever episodes lasting 2 days or longer** (n=553) n (%)
Sore throat	286 (20.5)	167 (30.2)
Pain and/or difficulty at swallowing	156 (11.2)	79 (14.3)
Rhinorrhea	544 (38.9)	303 (54.8)
Cough	495 (35.4)	272 (49.2)
Earache	168 (12.0)	102 (18.4)
Otorrhea	43 (3.1)	24 (4.3)
Gastro-intestinal (i.e. stomach ache, nausea, vomiting, diarrhoea)	156 (11.1)	95 (17.2)
Varicella	11 (0.8)	9 (1.6)
Influenza	3 (0.2)	2 (0.4)
Cystitis	4 (0.3)	2 (0.4)
Pneumonia	2 (0.1)	1 (0.2)
Difficulty breathing	5 (0.4)	4 (0.7)
Skin rash	1 (0.07)	1 (0.2)
Dog bite	1 (0.07)	
Tooth-ache	1 (0.07)	
	1846*	1028*

* number of symptoms exceeds number of fever episodes as parents were able to report more than one symptom

Table 2. URI and other symptoms experienced by children during fever episodes, and the consequences in terms of physician consultation rates and antibiotic prescription rates (321 children).

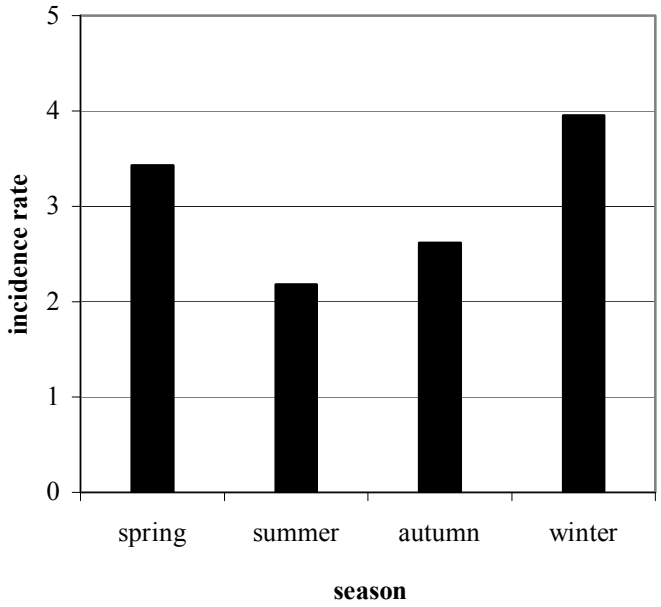
	All fever episodes (n=1397) n (%)	**Fever episodes lasting 2 day or longer** (n=553) n (%)
Symptoms in diary (%)		
• Only URI symptoms*	650 (46.5)	295 (53.3)
• URI and other localising symptoms	131 (9.4)	92 (16.6)
• Only other localising symptoms	53 (3.8)	22 (4.0)
• No localising symptoms	563 (40.3)	144 (26.0)
Total number of physician contacts (% of fever episodes in which at least one physician was contacted)**	248 (12.7)	199 (24.2)
Antibiotics prescribed	98 (7.0)	70 (12.7)

* URI=upper respiratory infection

** in some fever episodes a physician was contacted more than once

The incidence rate of fever episodes was significantly higher in girls than in boys: for all fever episodes 3.3 versus 2.8 fever episodes per child year (incidence rate difference 0.5; 95% CI 0.2 to 0.9), and for fever episodes lasting 2 days or longer 1.4 versus 1.1 fever episodes per child year (IRD 0.3; 95% CI 0.1 to 0.5). As expected, the number of fever episodes per person year was significantly higher during the winter season than during the summer season (incidence rate difference 1.8; 95% CI 1.3 to 2.2); figure 3.

Figure 3. Incidence of fever episodes per season (321 children).



With growing age the incidence of fever episodes did not materially change (table 3). The symptoms experienced during fever episodes changed with increasing age: in children aged 2 to 4 years upper respiratory infection (URI) symptoms were present in 69.0% of the fever episodes, in children aged 4 to 6 this proportion was 57.1%, and in children aged 6 to 9 years 45.0%, whereas no symptoms were present in 29.2%, 38.9% and 50.3%, respectively. With growing age, physicians were less often consulted for fever: in children aged 2 to 4 years in 17.6%; in children aged 4 to 6 years in 13.4%; and in children aged 6 to 9 years in 8.0% (table 3). No statistically significant difference in the proportion of physician's contacts for fever between boys and girls was found (p=0.40). With growing age antibiotics were less frequently prescribed (in children aged 2 to 4 years in 8.6%; in children aged 4 to 6 years in 7.1%; and in children aged 6 to 9 years in 5.8%). No difference in the proportion of antibiotic prescriptions per fever episodes between boys and girls was observed.

Table 3. The number of fever episodes and the consequences in terms of physician consultation rates and antibiotic prescription rates by age (321 children).

	Age in years		
	2 to 3	4 to 5	6 to 9
	n (%)	n (%)	n (%)
Total number of child years per age group	84.5	230.8	144.9
Total number of fever episodes	267	730	400
Incidence rate of fever episodes per child year	3.16	3.16	2.76
Incidence rate of fever episodes lasting 2 days or longer per child year	1.25	1.33	0.97
Incidence rate of fever days per child year	5.94	5.68	5.04
Total number of physician contacts (% of fever episodes in which at least one physician was contacted)*	66 (17.6)	140 (13.4)	42 (8.0)
Antibiotics for all fever episodes	23 (8.6)	52 (7.1)	23 (5.8)

* in some fever episodes a physician was contacted more than once

Discussion

Children aged 2 to 8 years, selected for adenotonsillectomy for relatively mild symptoms of throat infections or adenotonsillar hypertrophy, experienced 3.0 fever episodes per person year and 1.2 fever episodes lasting 2 days or longer per person year. With growing age the number of fever episodes did not materially change. Girls experienced more fever episodes than boys. In 12.7% of fever episodes a physician was contacted and in 7.0% antibiotics were prescribed.

To our knowledge, this is the first report on the incidence of fever measured objectively on a daily basis for a relatively long period. In only two earlier studies, including children younger than 2[3] and 2.6[2] years, respectively, the incidence of fever episodes in children in the population at large has been reported. Since in neither of these studies fever was measured daily, their results are likely to represent underestimations of in particular the shorter fever episodes.[2,3] Indeed, McCarthy et al.[2] found a lower incidence rate of fever episodes per child year compared to our study, i.e. 1.2 versus 3.0 episodes. Koch et al.,[3] on the other hand, found a much higher incidence rate of fever days: 17.9 versus 5.5 fever days per child year. His selective population of very young Inuit children is known to be prone to frequent upper respiratory infections, which might explain the high incidence rate of fever days in his study.

Patients' compliance during our study was good as parents took their child's temperature on 67.3% of all study days accounting for 112,760 stored temperature measurements. The missings (for 32.7% of the study days no temperature measurements were available) were partly random because of technical problems of the thermometers, and partly non-random as missings are more likely to occur on days without fever or other symptoms. Therefore, we have probably overestimated the incidence of in particular the one-day fever episodes. If all missings were not random, the maximum incidence of fever episodes would be 2.0 (3.0 x 67.3/100). Since most missings were probably not random, the true incidence lies somewhere between 2.0 and 3.0 fever episodes per person year.

To appreciate the results of this study, we should emphasise that the children were participating in a randomised trial on the effects of adenotonsillectomy and were selected for this operation for relatively mild symptoms of throat infections or adenotonsillar hypertrophy.[4] Children in our study are therefore more prone to upper respiratory infections with and without fever than the population at large and the incidence rate of fever episodes is therefore likely to be higher than in children without such symptoms.

Although fever is in children the second most frequent reason for consulting a general practitioner in the Netherlands,[3] our study shows that 87.3% of fever episodes in children never reach medical attention, indicating a true iceberg phenomenon. This study emphasizes the fact that most fever episodes are dealt with by the parents. Studies performed in general practice or in children presenting at emergency departments of hospitals have shown a reduction in the number of physician consultations for fever with growing age.[1,8,9] Interestingly, we found that the true incidence rate of fever episodes per child year did not depend on age (table 3), but with growing age a physician was less often consulted during fever episodes. Apparently, parents are less worried about fever episodes in older children or fever episodes are less severe, and this influences their decision to contact a physician.

In our study, girls experienced more fever episodes than boys. Koch et al.,[3] who studied the incidence of fever episodes in children under 2 years, did not find such sex-specific differences. The proportion of missing temperature measurements in boys and girls was the same (32.9% in boys versus 32.6% in girls), thus this cannot explain the difference in the number of fever episodes. A higher baseline body temperature in girls compared to boys (36.7 °C versus 36.5 °C; $p<0.05$) might explain the difference. When fever was present, however, both groups had the same mean temperature of 38.5 °C. Therefore, there is no obvious explanation for this difference and further studies are needed to confirm this finding.

In conclusion, fever episodes are common in children aged 2 to 8 years selected for adenotonsillectomy for relatively mild symptoms of throat infections or adenotonsillar hypertrophy. As much as 87.3% of these fever episodes never reach medical attention. With advancing age the number of fever episodes per year does not change, but the physician consultation rate and antibiotic prescription rate decreases.

References

1. Bruijnzeels MA, Suijlekom-Smit LWA, van der Velden J, van der Wouden JC. The child in general practice. Erasmus University Rotterdam; 1993.
2. McCarthy PL, Sznajderman SD, Lustman-Findling K, Baron MA, Fink HD, Czarkowski N, et al. Mothers clinical judgment - A randomized trial of the acute illness observation scales. *J Pediatr* 1990;**116**:200-6.
3. Koch A, Sorensen P, Homoe P, Molbak K, Pedersen FK, Mortensen T, et al. Population-based study of acute respiratory infections in children, Greenland. *Emerg Infect Dis* 2002;**8**:586-93.
4. van Staaij BK, van den Akker EH, Rovers MM, Hordijk GJ, Hoes AW, Schilder AGM. Adenotonsillectomy in children: a randomised trial. *BMJ* 2004. In press.
5. Paradise JL, Bluestone CD, Bachman RZ, Colborn DK, Bernard BS, Taylor FH, et al. Efficacy of tonsillectomy for recurrent throat infection in severely affected children. Results of parallel randomized and nonrandomized clinical trials. *N Engl J Med* 1984;**310**:674-83.
6. Brouillette R, Hanson D, David R, Klemka L, Szatkowski A, Fernbach S, et al. A diagnostic approach to suspected obstructive sleep apnea in children. *J Pediatr* 1984;**105**:10-4.
7. van Staaij BK, Rovers MM, Schilder AG, Hoes AW. Accuracy and feasibility of daily infrared tympanic membrane temperature measurements in the identification of fever in children. *Int J Pediatr Otorhinolaryngol* 2003;**67**:1091-7.
8. Bruijnzeels MA, Foets M, van der Wouden JC, van den Heuvel WJ, Prins A. Everyday symptoms in childhood: occurrence and general practitioner consultation rates. *Br J Gen Pract* 1998;**48**:880-4.
9. Finkelstein JA, Christiansen CL, Platt R. Fever in pediatric primary care: Occurrence, management, and outcomes. *Pediatrics* 2000;**105**:260-6.

Chapter 3

Is it possible to predict chronic recurrent upper respiratory infections in children?

van Staaij BK, Rovers MM, van den Akker EH, Schilder AGM, Hoes AW.
Submitted.

Summary

Background. Upper respiratory infection (URI) is the most frequently diagnosed condition in children in general practice. In most children URIs are self-limiting, but in some they persist or recur frequently.
Aim. To develop and validate an easily applicable prediction rule that can be used by general practitioners as a tool to identify children at risk from developing chronic recurrent URI.
Design of study. Prospective cohort study.
Setting. Primary care.
Methods. Two hundred and thirty children aged 2 to 8 years consulting the general practitioner with recurrent symptoms of URI were studied. They were part of a cohort participating in a randomised trial on the effects of adenotonsillectomy. Univariate and multivariate logistic regression modelling was used to evaluate which information - obtained from medical history, physical examination, and laboratory tests - independently contributed to the prediction of chronic recurrent URI. Chronic recurrent URI was defined as more than 84 days with upper respiratory symptoms per year, assuming an average incidence of 6 upper respiratory infections per year with a mean duration of 14 days. The area under the receiver-operating characteristic (ROC) was used to estimate the predictive ability of the prognostic models.
Results. During a 12-month-follow-up period, 111 out of 230 children experienced chronic recurrent URI. Independent predictors for the development of chronic recurrent URI were age, the number of URIs in the previous year, the number of throat infections in the previous year and parental smoking. The area under the ROC curve of this prediction rule was 0.68 (95% CI 0.61-0.75), which did not improve by adding other characteristics.
Conclusion. In children consulting the general practitioner with recurrent symptoms of URIs, the development of chronic recurrent URI cannot be predicted satisfactorily by a set of variables that can be easily obtained in general practice.

Introduction

Upper respiratory infection (URI) is the most frequently diagnosed condition in children in general practitice.[1] Children experience, on average, 6 upper respiratory infections per year.[2,3] In general, these episodes are self-limiting and most of them will never reach medical attention.[4] In a subgroup of children, however, URIs will persist or recur more frequently. These children often present themselves to primary care and the GP has to decide whether or not to intervene by means of e.g drug therapy or referral for surgical procedures. This decision depends on the GP's ability to predict that the child's symptoms will either persist or improve spontaneously without medical intervention.

In several studies, independent risk factors for upper respiratory infections in children have been identified such as age, attending day-care and parental smoking.[3,5-9] The focus of such studies was to find causal factors that might be used as targets for prevention. In clinical practice, it is also important to classify children according to their absolute risk of developing chronic recurrent URI, preferably by using easily obtainable information. An established approach for estimation of individual risk is the use of prediction rules, estimating the probability of occurrence of a relevant outcome as a combined function of the levels of various predictors. A general practitioner could use such clinical prediction rule as a tool to distinguish children with a high risk of developing chronic recurrent URI from those with a lower risk. To our knowledge, however, such a prediction rule is not yet available.

Methods

Patients

We studied children aged 2 to 8 years who consulted their general practitioner with upper respiratory complaints. A cohort of 321 children provided data for the present study: 300 children were assigned randomly to either adenotonsillectomy (T&Ads) or non-surgical treatment,[10] and 21 underwent T&Ads because of their parents' preference. Children with very frequent throat infections (> 6 in the previous year)[11] or a high suspicion of obstructive sleep apnoea[12] were excluded from the trial and, thus, from the present study. Children with such a short follow-up period that precluded assessment of the outcome (n= 91) were excluded from the present study, leaving 230 children in the present analysis.

Outcome: chronic recurrent URI

During the follow-up period of one year, parents were requested to record in a diary symptoms of upper respiratory infection in their child. These diary data were collected by the study physician at the scheduled follow-up visits at 3, 6 and 12 months. URI days were defined as days with one or more of the following symptoms: sore throat, pain/difficulty at swallowing, rhinorrhea, cough, earache, otorrhea. The total number of URI days was calculated for each patient. Outcome was assessed at one year follow-up.

Assuming an average incidence in children of 6 upper respiratory infections per year with a mean duration of 14 days,[13-15] the outcome chronic recurrent URI was defined as more than 84 URI days during follow-up; absence of the condition was defined as 84 or fewer URI days during follow-up.

Potential predictor variables

Based on a literature search and information available from routine clinical practice, the following candidate predictors for chronic recurrent URI were selected: age (<4 versus $\geq$ 4 years); gender (boys/girls); the number of throat infections in the previous year (0-2 versus $\geq$ 3-6); the number of URIs, excluding throat infections, in the previous year (0-6 versus > 6); snoring (yes/no); difficulty breathing at night (yes/no); previous ENT surgery (yes/no); atopic condition (yes/no); being breastfed for more than one month (yes/no); in day care or attending school for more that one day per week (yes/no); $\geq$ 1 older siblings (yes/no); parental smoking (yes/no); low education level of the mother (yes/no); enlarged tonsils (defined as protruding beyond the pillars but not meeting the uvula, or meeting the uvula and "kissing") (yes/no). In addition, haemoglobulin level $\leq$ 7.0 mmol/L (yes/no), immunoglobulin IgA level < 0.55 g/L (yes/no), and a positive throat swab for one or more potential respiratory pathogens[16] (yes/no) were included as potential predictors.[17]

Data analysis

The association between each prognostic factor and the presence or absence of chronic recurrent URI was examined by univariate logistic regression analyses. Predictors that were univariately associated with the outcome (p-value $\leq$ 0.15) were included in multivariate logistic regression analyses. The model was reduced by excluding predictors from the model with a p-value of > 0.10. Models were constructed in an order determined by the availability of predictors in clinical practice. Hence, we first included all variables from patient history and physical examination into an overall clinical model. This clinical model was subsequently extended by the addition of one

of the laboratory test (i.e. clinical model + haemoglobin level; clinical model + IgA level; and clinical model + throat culture). The predictive accuracy of the models was estimated by using Hosmer & Lemeshow tests.[18] The models ability to discriminate between children with and without chronic recurrent URI was estimated by the area under the receiver-operating curve (ROC) of the model.[19] The ROC area is a suitable parameter to summarise the discriminative or predictive value and can range from 0.5 (no discrimination, like a coin flip) to 1.0 (perfect discrimination). To obtain an easily applicable prediction rule, the adjusted regression coefficients of the model were multiplied by a factor 10 and rounded to the nearest integer. Scores for each individual patient were obtained by assigning points for each variable and adding the results. Patients were classified according to their risk score. To simplify the interpretation of the model, various cut-off points were chosen to show the number of children developing or not developing chronic recurrent URI in different risk score categories.

Missing values

Information concerning the children's medical history and physical examination was available for 99.3% of the variables (range 95.2 to 100%); Hb level, IgA-level and throat culture for 170 (74%), 168 (73%) and 197 (86%) children, respectively.

Data are seldom missing at random. It has been shown that removing subjects with a missing value for one of the predictors included in a multivariable model (so-called complete case analyses) commonly leads to biased results and surely to loss of power.[20,21] To decrease bias and to increase statistical efficiency, it is better to impute missing data rather than perform a complete case analysis. Accordingly, we imputed our missing data using the linear regression method (MVA analyses) available in SPSS (SPSS for Windows, version 11.0, SPSS INC.) software. Such imputation is based on the correlation between each variable with missing values and all other variables as estimated from the set of complete subjects.

Results

The mean age of the participating children (n=230) was 53.8 months (SD 15.7), 53.9% was male, and the median number of URI episodes experienced by the children in the year before inclusion in the trial was 12.0 (range 0 to 24) (table 1). During the follow-up year, chronic recurrent URI was present in 111 children (48%) (table 2). In the univariate analyses, age, the number of throat infections and the number of upper respiratory infections in the previous year, older siblings and parental smoking were

associated with the development of chronic recurrent URI (table 2). In the multivariate analysis, age, the number of throat infections and the number of upper respiratory infections in the previous year and parental smoking were independent predictors ($p<0.05$) for the development of chronic recurrent URI (table 3).

Table 1. Baseline demographic and physical characteristics of the 230 children included in the prognostic study.

Characteristic	
Male sex (%)	124 (53.9%)
Mean age (SD) in months	53.8 (15.7)
Median number (range) of throat infections episodes in the previous year	2 (0-6)
Median number (range) of URIs in the previous year	12 (0 to 24)
Median number (range) of otitis media episodes in the previous year	0 (0 to 12)
Tobacco smoke exposure indoors (%)	75 (32.6%)
Attending day-care or school (%)	219 (95.2%)
Number of siblings (%)	
0	44 (19.1%)
1	113 (49.1%)
>1	73 (31.7%)
Hemoglobulin $\leq$ 7.0 mmol/l (%)	23 (10%)
IgA < 0.55 g/l (%)	22 (9.6%)
Positive throat culture (%)	121 (52.6%)

The clinical model had an area under the curve (AUC) of 0.68 (95% confidence interval 0.61-0.75), indicating a moderate discriminability of the model (table 3). The AUC did not improve by inclusion of haemoglobulin level (AUC 0.69; 95% CI 0.62-0.75), throat culture (AUC 0.69; 95% CI 0.63-0.76) or IgA level (AUC 0.70; 95% CI 0.63-0.76) in the model. The fit of the models was good: p-values of the Hosmer & Lemeshow statistic ranged from 0.33 to 0.86.

Using the regression coefficients of the final predictive model, the risk score of developing chronic recurrent URI can be estimated for each child: score = 4 + (–8 x age $\geq$ 4 years) + (–6 x $\geq$ 3 throat infections in previous year) + (7 x > 6 URIs in previous year) + (–8 x parental smoking). For example, a 3-year-old child (0 points), with a history of 2 throat infections in the previous year (0 points), 8 URIs in the previous year (7 points), and no smoking parents (0 points), has a total score of 4 + (0) + (0) + (7) + (0) = 11 points. The probability of developing chronic recurrent URI can be calculated as: $P= 1 / 1 + e^{-(\alpha + \beta_1 \text{ x age} \geq 4 \text{ years} + \beta_2 \text{ x} \geq 3 \text{ throat infections in previous year} + \beta_3 \text{ x} > 6 \text{ URIs in previous year} + \beta_4 \text{ x parental smoking})} = 1 / 1 + e^{-(0{,}426 + -0.762 \text{ x age} \geq 4 \text{ years} + -0.616 \text{ x} \geq 3 \text{ throat infections in previous year} + 0.745 \text{ x} > 6 \text{ URIs in previous year} + -0.812 \text{ x parental smoking})} = 1 / 1 + e^{-(0{,}426 + -0.762 \text{ x } 0 + -0.616 \text{ x} \geq}$

$^{0 + 0.745 \times 1 + -0.812 \times 0)}$ = 76%. Table 4 shows the number of children in the cohort that did or did not develop chronic recurrent URI across different categories of the risk score. No threshold could be established satisfactorily classifying the children at high or low risk of chronic recurrent URI. For each arbitrary threshold too many children were misclassified to be of any clinical use (table 5). For example, by using a threshold of 4, 38% of the children would be misclassified (78 false negative and 10 false positive). Using a threshold of –3 would misclassify 40% of the children (47 false negative and 46 false positive).

Table 2. Crude association of potential prognostic determinants with the incidence of chronic recurrent URI* (i.e. more than 84 days with URI symptoms per year).

Determinant	≤ 84 URI-days n=119		> 84 URI-days n=111		OR (95% CI)	p-value
	N	%	N	%		
Medical history						
Age ≥ 4 years	84	70.6	57	51.4	0.44 (0.26-0.76)	0.003
Male	67	56.3	57	51.4	0.82 (0.49-1.38)	0.45
3 or more throat infections in the previous year	51	42.9	36	32.4	0.64 (0.37-1.10)	0.10
> 6 URIs in the previous year	63	52.9	78	70.3	2.10 (1.22-3.62)	0.007
Snoring and/or apnoea during sleep	76	63.9	77	69.4	1.28 (0.74-2.22)	0.38
Previous ENT-surgery (adenoidectomy or tympanostomy tubes)	31	26.1	26	23.4	0.87 (0.48-1.58)	0.65
Atopic condition (asthma or hay fever)	48	40.3	39	35.1	0.80 (0.47-1.37)	0.42
Breast feeding (> 1 month)	70	58.8	71	64.0	1.24 (0.73-2.12)	0.42
Day-care or school attendance	114	95.8	105	94.6	0.77 (0.23-2.59)	0.67
2 or more older siblings	57	47.9	64	57.7	1.48 (0.88-2.49)	0.14
Parental smoking	48	40.3	27	24.3	0.48 (0.27-0.84)	0.01
Low education level of mother	31	26.1	33	29.7	1.20 (0.67-2.14)	0.53
Physical examination						
Enlarged tonsils	94	79.0	86	77.5	0.92 (0.49-1.71)	0.78
Laboratory data						
Hemoglobulin ≤ 7.0 mmol/l	14	11.9	9	8.3	0.66 (0.27-1.60)	0.38
IgA < 0.55 g/l	9	7.6	13	11.7	1.62 (0.66-3.96)	0.29
Positive throat swab	58	48.7	63	56.8	1.38 (0.82-2.32)	0.22

* upper respiratory infection

Table 3. Independent predictors for chronic recurrent URI in children.

Variable	Odds ratio (95% CI)	Regression coefficient	Contribution to score
Age ≥ 4 years	0.47 (0.27-0.82)	–0.76	–8
≥ 3 throat infections episodes in previous year	0.54 (0.30-0.96)	–0.62	–6
> 6 URIs in previous year	2.11 (1.19-3.72)	0.74	+7
Parental smoking	0.44 (0.24-0.81)	–0.81	–8

Score = 4 + (–8 x age ≥ 4 years) + (–6 x ≥ 3 throat infections in previous year) + (7 x > 6 URIs in previous year) + (–8 x parental smoking)

Table 4. Number of children in the cohort with and without chronic recurrent URI during follow up across categories of the risk score.

Risk score	Number of children per score category	Children with > 84 URI days n (%)	Children with ≤ 84 URI days n (%)
≤ –10	50	11 (22)	39 (78)
–10 < risk score ≤ –3	70	36 (51)	34 (49)
–3 < risk score ≤ 4	67	31 (46)	36 (54)
> 4	43	33 (77)	10 (23)
Total	230	111 (48)	119 (52)

Discussion

To our knowledge, this is the first attempt to define a practical scoring rule to predict the absolute risk of chronic recurrent URI in children consulting the general practitioner with recurrent symptoms of URIs. To appreciate the results of our study, certain aspects need to be discussed in more detail.

First, we selected a group of children with recurrent symptoms of URI because it is such children who are most likely to consult their general practitioner for these symptoms and for whom the GP has to decide on medical and/or surgical interventions. Our results are therefore not applicable to children consulting the general practitioner with a first or infrequent upper respiratory infection.

Second, we decided not to include the randomly allocated treatment (adenotonsillectomy versus watchful waiting) in our model as a potential prognostic predictor in our model. We developed the prediction rule for the general practitioner as a screening tool to identify children at high risk of chronic recurrent URI. Obviously,

at the time the prognostic rule would be applied in every-day general practice, such presenting children would not have undergone adenotonsillectomy. Since adenotonsillectomy might influence the occurrence of the outcome parameter and may act as an effect modifier, we also studied the children in the watchful waiting group (n=107) separately. The prediction rule that could be derived for this group did not perform any better than the rule derived for the total cohort.

Table 5. Sensitivity, specificity, positive and negative predictive value for various thresholds of the risk score developed to identify children at risk for chronic recurrent URI.

Threshold	Children with score equal or lower than threshold. (Number of children with/ without chronic recurrent URI during follow up)	Number of children with score higher than threshold. (Number of children with/ without chronic recurrent URI during follow up)	Sensitivity	Specificity	Positive predictive value	Negative predictive value
–10	50 (11/39)	180 (100/80)	90%	33%	56%	78%
–3	120 (47/73)	110 (64/46)	58%	61%	42%	61%
+4	187 (78/109)	43 (33/10)	30%	92%	77%	58%

Third, some predictors in our study had an odds ratio (see table 1) that might not seem plausible a priori, i.e. parental smoking and 3 or more throat infections in the past year were associated with a low risk for chronic recurrent URI. From an etiological point of view passive smoking[22] and a history of recurrent throat infections would be expected to increase the risk of chronic recurrent URI. It may be that in our study smoking parents were less attentive regarding URI symptoms in their child and therefore less likely to note them in the diary. The choice of our outcome, i.e. more than 84 days with upper respiratory infection symptoms, might explain why a history of recurrent throat infections had an "opposite effect" in the model compared to a history of recurrent URI. It is simply more likely for the second group to be at risk for our outcome (chronic recurrent URI) than for the group with recurrent throat infections, that being another type of infection of the upper respiratory tract and affecting other children.[3,23]

Fourth, URIs are known to have a complex, multifactorial etiology involving demographic, environmental, immunological and genetic factors. Some of these factors, for example genetic factors, might be better prognostic predictors than those

we studied. The feasibility of using these predictors in general practice is, however, doubtful.
Fifth, in prognostic research, validation of the model is generally recommended.[24] We did not carry out an external validation study, as the performance of our prediction rule was poor. For the same reason random bootstrapping techniques to adjust for overfitting (i.e. over-optimistic estimates of the regression coefficients of the prediction model) were not performed.

We conclude that in children, consulting the general practitioner with recurrent symptoms of URI, the development of chronic recurrent URI cannot be predicted satisfactorily, either by a set of variables that can be easily obtained in general practice or by laboratory measurements such as haemoglobulin level, throat culture or IgA level.

Acknowledgments: Frank Leus for data management.

Funding: This study was funded by a grant from the Dutch Health Care Insurance Board (OG-99-060).

References

1. Suijlekom-Smit LW, Bruijnzeels MA, van der Wouden JC, van der Velden J, Visser HK, Dokter HJ. [For which health problems in children is the family physician consulted and how often?]. *Ned Tijdschr Geneeskd* 1995;**139**:1684-9.
2. Monto AS, Ullman BM. Acute respiratory illness in an American community. The Tecumseh study. *JAMA* 1974;**227**:164-9.
3. Kvaerner KJ, Nafstad P, Jaakkola JJ. Upper respiratory morbidity in preschool children: a cross-sectional study. *Arch Otolaryngol Head Neck Surg* 2000;**126**:1201-6.
4. Bruijnzeels MA, Foets M, Wouden van der JC, Heuvel van den WJ, Prins A. Everyday symptoms in childhood: occurrence and general practitioner consultation rates. *Br J Gen Pract* 1998;**48**:880-4.
5. Benediktsdottir B. Upper airway infections in preschool children - frequency and risk factors. *Scand J Prim Health Care* 1993;**11**:197-201.
6. Forssell G, Hakansson A, Mansson NO. Risk factors for respiratory tract infections in children aged 2-5 years. *Scand J Prim Health Care* 2001;**19**:122-5.
7. Harsten G, Prellner K, Heldrup J, Kalm O, Kornfalt R. Acute respiratory-tract infections in children - A 3-Year Follow-Up from Birth. *Acta Paediatr Scand* 1990;**79**:402-9.
8. Koch A, Molbak K, Homoe P, Sorensen P, Hjuler T, Olesen ME, et al. Risk factors for acute respiratory tract infections in young Greenlandic children. *Am J Epidemiol* 2003;**158**:374-84.
9. Selwyn BJ. The epidemiology of acute respiratory-tract infection in young-children - Comparison of Findings from Several Developing-Countries. *Rev Infect Dis* 1990;**12**:S870-S88.
10. van Staaij BK, van den Akker EH, Rovers MM, Hordijk GJ, Hoes AW, Schilder AGM. Adenotonsillectomy in children: a randomised trial. *BMJ* 2004. In press.
11. Paradise JL, Bluestone CD, Bachman RZ, Colborn DK, Bernard BS, Taylor FH, et al. Efficacy of tonsillectomy for recurrent throat infection in severely affected children. Results of parallel randomized and nonrandomized clinical trials. *N Engl J Med* 1984;**310**:674-83.
12. Brouillette R, Hanson D, David R, Klemka L, Szatkowski A, Fernbach S, et al. A diagnostic approach to suspected obstructive sleep apnea in children. *J Pediatr* 1984;**105**:10-4.
13. Steinweg KK. Natural history and prognostic significance of purulent rhinitis. *J Fam Pract* 1983:**17**;61-4.
14. Gulbrandsen P, Fugelli P, Kvarstein P, and Moland L. The duration of acute respiratory tract infections in children. *Scand J Prim Health Care* 1989;**7**:219-32.
15. Hay AD, Wilson AD. The natural history of acute cough in children aged 0 to 4 years in primary care: a systematic review. *Br J Gen Pract* 2002;**52**:401-9.
16. Staaij van BK, Akker van den EH, Dorsser van EHMD, Fleer A, Hoes AW, Schilder AGM. Does the tonsillar surface flora differ in children with and without tonsillar disease? *Acta Otolaryngol* 2003;**123**:873-8.
17. Yokoyama Y, Harabuchi Y. Decreased serum and pharyngeal antibody levels specific to streptococcal lipoteichoic acid in children with recurrent tonsillitis. *Int J Pediatr Otorhinolaryngol* 2002;**63**:199-207.
18. Hosmer DW, Lemeshow S. Applied logistic regression.New York: John Wiley & Sons, Inc 1989. p 140-5 .
19. Hanley JA and McNeil BJ. The meaning and use of the area under a receiver operating characteristics (ROC) curve. *Radiology* 1982;**143**:29-36.
20. Harrell FE, Lee KL, and Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med* 1996;**15**:361-387.
21. Greenland S, Finkle WD. A critical look at methods for handling missing covariates in epidemiologic regression analyses. *Am J Epidemiol* 1995;**142**:1255-64.

22 Cook DG, Strachan DP. Summary of effects of parental smoking on the respiratory health of children and implications for research. *Thorax* 1999;**54**:357-65.
23. Schilder AG, Zielhuis GA, Straatman HS, van den Broek P. An epidemiological approach to the etiology of middle ear disease in The Netherlands. *Eur Arch Otorhinolaryngol* 1992;**249**:370-3.
24. Altman DG, Royston P. What do we mean by validating a prognostic model? *Stat Med* 2000;**19**:453-73.

Chapter 4

Does the tonsillar surface flora differ in children with and without tonsillar disease?

van Staaij BK, van den Akker EH, de Haas van Dorsser EHM, Fleer A, Hoes AW, Schilder AGM.
Acta Otolaryngol 2003;**123**:873-8.

Summary

Objective. To investigate whether the tonsillar flora differs in children with and without adenotonsillar disease.
Material and Methods. Tonsil surface swabs were taken from 218 children selected for adenotonsillectomy for relatively mild symptoms of throat infections or adenotonsillar hypertrophy (T&Ads group). Control swabs were taken from 100 children without symptoms of adenotonsillar disease who visited the ophthalmology clinic. Potential respiratory pathogens were identified.
Results. Potential respiratory pathogens were found in 54% of the T&Ads group, compared to 41% of the control group (p=0.04). *Haemophilus influenzae* was the most common pathogen in both groups, being found in 41% of the T&Ads group and 34% of the control group. *Moraxella catarrhalis* was found more often in the T&Ads group compared to the control group: 7% vs 0% (p=0.004). *Haemophilus influenzae* was found in 32% of the children with recurrent throat infections, compared to 48% of the children with symptoms of tonsillar hypertrophy (p=0.03).
Conclusions. The prevalence of potential respiratory pathogens on the tonsillar surface of children with relatively mild symptoms of throat infections or adenotonsillar hypertrophy differs only slightly from that in children without symptoms of adenotonsillar disease. Variations in the microbial flora do not seem to play an essential role in the predisposition of these children to tonsillar disease.

Introduction

Adenotonsillar pathology is an important source of morbidity in children. During a 1-month period 7.5% of all 4-5 year olds experiences an episode of acute tonsillopharyngitis[1] and in the US 10% of all antibiotic prescriptions in children are prescribed for tonsillopharyngitis, accounting for 5.4 million prescriptions in 1992.[2] Adenoidectomy and tonsillectomy, selected for children with recurrent or persistent symptoms of infection or hypertrophy, are among the most frequent operations performed in children.

It has not been fully elucidated why some children are more susceptible to infections of Waldeyer's ring than others. Exposure to respiratory tract pathogens, influenced by environmental factors such as day-care attendance and the number of siblings, and the response of the innate and adaptive immune systems all play a role. Also, variations in the microbial flora in the tonsillar and adenoidal tissue may predispose children to upper respiratory infection (URI) and/or adenotonsillar hypertrophy.

Only a few studies[3-5] have compared the microbial flora on the tonsillar surface of children with recurrent throat infections or obstructive tonsillar hypertrophy with the flora of children without symptoms of tonsillar disease. These showed no[3,4] or small[5] differences between the two groups. These studies were limited by a small sample size,[3,4] i.e. < 65 children, or poorly documented medical histories.[5]

The aim of this study was to investigate whether the tonsillar flora differs in children with and without adenotonsillar disease. We compared the microbial flora on the tonsillar surface of a large group of children selected for adenotonsillectomy (T&Ads) with a well-documented history of throat infections and/or symptoms of adenotonsillar hypertrophy with that of a control group of children without such symptoms.

Material and methods

Study population

- Children selected for T&Ads.

Tonsil swabs were taken from 218 children participating in a Dutch randomised controlled trial on the effectiveness of T&Ads in children.[6] Inclusion criteria for the trial were: 1) selected for adenotonsillectomy according to current medical practice and 2) age 2 to 8 years.

Not included in the trial, because for these indications T&Ads is generally considered beneficial, were children with: 1) a history of seven or more throat infections in the

previous year, or five or more in each of the two preceding years or three or more in each of the three preceding years (Paradise criteria)[7]; and 2) a high suspicion of obstructive sleep apnoea (OSA; Brouillette's OSA score $\geq$ 3.5).[8] Other exclusion criteria for the trial were: 3) Down's syndrome; 4) craniofacial malformations; and 5) documented immune deficiency. Additional exclusion criteria for the present study were: 6) use of antibiotics during the 2 weeks preceding the study,[9] and (7) current symptoms of acute URI with fever.

- *Control children.*

A total of 100 consecutive children aged 2-7 years who visited the ophthalmology clinic of the University Medical Center Utrecht served as a control group; tonsil swabs were taken in 50 children in October 2001 and in another 50 in March 2002. Exclusion criteria for this group were: 1) on the waiting list for T&Ads; 2) a history of T&Ads; and 3) exclusion criteria 1-7 of the T&Ads trial population.

Measurements

Baseline measurements included administration of illness-specific questionnaires including questions concerning the number of throat infections in the year preceding the trial and the presence of obstructive symptoms during the night according to Brouillette's OSA score[8] (this score combines the degree of snoring, difficulty breathing during sleep and apnoea as observed by the parents).

Tonsil swabs of the T&Ads trial population were taken during the inclusion visit by one of three research physicians, who were trained to follow a standardized procedure. Culture results from these research physicians were compared at regular intervals and found to be similar. The tonsil cultures were taken using one cotton swab to streak the mucosa of the left and right tonsils. Contamination by oral flora was avoided. The material collected by the swab was stabbed into a modified Stuart medium and transported to the clinical microbiology laboratory of the University Medical Center Utrecht within 24 h. The samples were inoculated onto 5% sheep blood agar plates and chocolate agar plates. The plates were incubated both aerobically and under 5% carbon dioxide at 37ºC and examined at 24 and 48 h. Isolates were identified using conventional methods.[10]

Statistical analysis

The microbiological results were compared using a two-sided χ^2 test and Fisher's exact two-sided test. $P<0.05$ was considered statistically significant. To investigate the relationship between clinical history and tonsillar flora, the children were divided in two groups as follows: 1) 0-2 episodes of throat infections in previous year, i.e.

selected for T&Ads for (adeno)tonsillar hypertrophy, or for other indications such as upper respiratory infections; and 2) children with 3-6 throat infections in previous year, i.e. selected for T&Ads because of recurrent throat infections.
The Medical Ethics Committee of the University Medical Center Utrecht approved the study. Informed consent was obtained from the caregivers/parents of all children before participation in the study.

Results

The mean ages of the group with 0-2 episodes of tonsillitis (n=130), the group with 3-6 episodes of tonsillitis (n=88) and the control group (n=100) were 4.0 (SD 1.27), 4.0 (SD 1.43) and 4.6 (SD 1.44) years, respectively. In the group with 0-2 throat infections, 49% of the children were male, compared to 55% in the group with 3-6 throat infections and 54% in the control group.

Table 1. Potential respiratory pathogens isolated from the tonsillar surface in children selected for T&Ads and in control children without tonsillar disease.

	T&Ads selected (n=218)		Control group (n=100)		
Potential respiratory pathogen	n	%[a]	n	%	p
Group A β-haemolytic streptococci	19	8.7	5	5.0	0.27
Group C β-haemolytic streptococci	2	0.9	0	0.0	1.00
Group G β-haemolytic streptococci	2	0.9	3	3.0	0.18
Haemophilus influenzae (non-typable)	90	41.3	34	34.0	0.27
Moraxella catarrhalis	15	6.9	0	0.0	0.004
Staphylococcus aureus	13	6.0	6	6.0	1.00
Streptococcus pneumoniae	5	2.3	0	0.0	0.33
Neisseria meningitidis	0	0.0	0	0.0	1.00
No potential respiratory pathogens isolated[b]	101	46.3	59	59.0	0.04

[a] because more than one type of potential respiratory pathogen was isolated in some children, the totals are > 100%.

[b] no potential respiratory pathogens were isolated from these samples, but normal throat flora was found (such as Neisseria species, Streptococci viridans or Haemophilus species).

In the T&Ads group, potential respiratory pathogens were found in 54%, compared to 41% in the control group (p=0.04) (table 1). *Haemophilus influenzae* was the most common isolate in both groups, being found in 41% of the samples in the T&Ads group and in 34% of those in the control group (p=0.27). For only one species was the

difference between the two groups statistically significant, *Moraxella catarrhalis* being found more often in the T&Ads group compared to the control group: 7% vs 0% (p=0.004).

Table 2. Potential respiratory pathogens isolated from the tonsillar surface in children selected for adenotonsillectomy for relatively mild symptoms of throat infections or for adenotonsillar hypertrophy or other indications, such as upper respiratory infections.

	0-2 throat infections* (n=130)		3-6 throat infections† (n=88)		
	n	%‡	n	%‡	p-value
Group A β-haemolytic streptococci	10	7.7	9	10.2	0.63
Group C β-haemolytic streptococci	2	1.5	0	0.0	0.52
Group G β-haemolytic streptococci	2	1.5	0	0.0	0.52
Haemophilus influenzae (non-typable)	62	47.7	28	31.8	0.03
Moraxella catarrhalis	10	7.7	5	5.7	0.60
Staphylococcus aureus	10	7.7	3	3.4	0.25
Streptococcus pneumoniae	4	3.1	1	1.1	0.65
Neisseria meningitidis	0	0.0	0	0.0	1.00
No potential respiratory pathogens isolated**	52	40.0	49	55.7	0.03

* 0-2 throat infections in previous year, i.e. selected for T&Ads for (adeno)tonsillar hypertrophy, or for other indications such as upper respiratory infections

† 3-6 throat infections in previous year, i.e. selected for T&Ads because of recurrent throat infections.

‡ because in some children more than one type of potential respiratory pathogen was isolated, the total of percentages is more than 100%

** no potential respiratory pathogens were isolated from these samples, but normal throat flora was found (such as Neisseria species, Streptococci viridans or Haemophilus species)

In the group with 0-2 throat infections in the previous year, potential respiratory pathogens were found in 60% of the samples, compared to 44.3% in the group with 3-6 throat infections in the previous year (p=0.03) (table 2). *Haemophilus influenzae* was the commonest pathogen on the tonsillar surface in both groups, but was more prevalent in the group with 0-2 throat infections in previous year compared to the group with 3-6 throat infections in the previous year: 47.7% vs 31.8% (p=0.03).

Discussion

In the present population, differences between the tonsillar flora of children with and without symptoms of adenotonsillar disease are small. *Haemophilus influenzae* was

the commonest isolate in both groups. Potential respiratory pathogens were found in 54% of the adenotonsillar disease group (60% in the group with 0-2 throat infections in the previous year vs 44% in the group with 3-6 throat infections in the previous year) vs 41% of the controls.

We included children selected for T&Ads and indicative of those with adenotonsillar disease. The medical history of these children and of the control group was well documented: 60% of the children had 0-2 throat infections in the year preceding the study (i.e. selected for T&Ads for (adeno)tonsillar hypertrophy, or for other indications such as upper respiratory infections) and 40% had 3-6 throat infections in the year preceding the study (selected for surgery because of recurrent throat infections). The 100 control children had no history of tonsil disease. In previous studies, which included totals of 38,[4] 62,[3] and 228[5] children, only Toner et al.[4] described the medical history of their study and control populations carefully (all children of the surgical group were aged < 4 years and had had ≥ 6 episodes of acute throat infections per year for more than 1 year with evidence of chronic infection on repeated examination; the children in the control group had no past history of throat infections). Endo et al.[5] and Reilly et al.[3] did not give details of the age and medical history of their T&Ads and control groups, which precludes comparison with these results.

In our study, surface swabs were obtained by swabbing the left and right tonsillar surfaces firmly with one cotton swab, as recommended by Brook and Leyva.[11] The question is whether a tonsillar surface swab reliably predicts the presence of potential respiratory pathogens in the tonsil core. Various studies[12-17] have compared the microbial flora isolated from the tonsillar surface and tonsillar core in children with tonsillar disease. Their results were inconsistent: some authors[12-14] recovered more pathogenic microorganism from the tonsillar core than from the tonsillar surface, while others[15-17] found almost no difference. In two small studies[18,19] the recovery of pathogenic microorganism from the tonsillar core in children with recurrent throat infections and tonsillar hypertrophy and children without symptoms of tonsillar disease was compared. Brook and Foote[18](n=8) found similar polymicrobial aerobic and anaerobic flora from the cores of recurrently inflamed and normal tonsils. However, the concentration of most anaerobic bacteria, as well as Streptococci and Staphylococci, was higher in the recurrently inflamed tonsils. Brodsky et al.[19] (n=64) found significantly more isolates from the tonsillar cores of children with recurrent throat infections and tonsillar hypertrophy compared to those of control children. Our study did not allow us to assess which method of sampling, core or surface swabs, is

best for addressing the question of whether differences in the tonsillar flora predispose children to adenotonsillar disease.

Table 3. Studies comparing the microbial flora on the tonsillar surface of children with recurrent throat infections or obstructive tonsillar hypertrophy with that in control children.

	Percentages of isolates (%)							
	Van Staaij et al. (2002)		Endo et al. (1996)		Toner et al. (1986)		Reilly et al. (1981)	
	Study (n=218)	Control (n=100)	Study (n=96)	Control (n=132)	Study (n=20)	Control (n=18)	Study (n=37)	Control (n=25)
Mean age (years)	4.0	4.6	5.9	5.9	<4*	<4*	3-12*	2-17*
BHS group A, C and G	10	8	19	12	20	17	16	8
Haemophilus influenzae	41	34	33	24	10	6	8	8
Moraxella catarrhalis	7	0	2	0				
Staphylococcus aureus	6	6	27	28			0	4
Streptococcus pneumoniae	2	0	0	2	20	6	3	0
Anaerobes	not cultured		not cultured		85	28	95	92
No potential respiratory pathogens found	46	59						

* mean age not reported

Our results are consistent with those of previous studies[3-5] that compared the tonsillar surface flora of children with symptoms of tonsillar disease with that of children without such symptoms (table 3). In two small studies[3,4] no statistically significant differences in aerobic flora were found between the two groups. Toner et al.[4] did find anaerobic microorganisms more often in children with symptoms of tonsillar disease. Endo et al.[5] did not find statistically significant differences between the two groups overall. *Haemophilus influenzae* was the most prevalent pathogen both in the population studied by Endo et al.[5] and in our population: 33% in the T&Ads group vs 24% in the control group and 41% vs 34%, respectively. Differences between the two studies were found for *Staphylococcus aureus* (27% in the T&Ads group vs 28% in the control group and 6% in both groups, respectively) and *Moraxella catarrhalis* (2% in the T&Ads group vs 0% in the control group and 7% vs 0% respectively).

Several studies have compared the microbial flora on the tonsillar surface in children undergoing T&Ads for either recurrent acute throat infections or adenotonsillar hypertrophy.[12,16,20] The results were inconsistent. Surow et al.[12] found no differences in tonsil surface culture between the two groups. Similarly, Kielmovitch et al.[16] found *Haemophilus influenzae* to be the most common pathogen in both groups. *Group A ß-*

haemolytic Streptococci (GABHS) were found more often in the group with hypertrophy and *Staphylococcus aureus* more often in the group with recurrent throat infections. In the study of Francois et al.,[20] *Haemophilus influenzae* was isolated more frequently in the group with recurrent throat infections than in the group with hypertrophy. This is in contrast with our study. Our findings are in accordance with the results of the study of Brodsky and co-workers.[19,21] They observed more aerobic bacteria in children with hypertrophic tonsils than those with recurrent throat infections. For *Haemophilus influenzae* the mean bacterial load showed a significant positive correlation with tonsil weight, and they therefore suggested an aetiological role for *Haemophilus influenzae* in the pathogenesis of tonsillar hypertrophy in children. Our present study supports this hypothesis.

The results of our study may have been affected by the exclusion of children with very frequent (seven or more per year) throat infections and those with severe adenotonsillar hypertrophy causing OSA. Our study was, however, performed in children eligible for inclusion in a randomised trial of the effectiveness of T&Ads. In this trial children were excluded because for these indications the effectiveness of T&Ads has previously been studied by Paradise et al.[7] Although it seems plausible that the inclusion of these children may have resulted in a greater difference in the tonsillar flora of children with and without symptoms of adenotonsillar disease, the impact of this exclusion is probably not very great. For example, Toner et al.,[4] who included only children with six or more throat infections in the previous year, found no significant differences in bacterial flora between children with recurrent throat infections and healthy controls. In the study of Francois et al.,[20] who included children with five or more throat infections in the past year only, small differences were found between the group with recurrent throat infections and that with tonsillar hypertrophy: *Haemophilus influenzae* was found more often in the group with recurrent throat infections and *Streptococcus pyogenes* was found more often in the group with tonsillar hypertrophy.

Differences between culture results in various studies might be explained by (inter)national differences in indications for T&Ads. The different indications are due to different opinions regarding the use of antibiotics for URI and the absence of (inter)nationally accepted guidelines on indications for T&Ads. However, the aim of the present study was to answer the question whether the tonsillar surface flora of children with and without adenotonsillar disease differs. Although different indications exist between different countries, and also between studies, we do not feel that the symptoms of children suffering from adenotonsillar disease differ between countries. In the present study we investigated the tonsillar surface flora of children selected for

T&Ads for relatively mild symptoms of throat infections or adenotonsillar hypertrophy or for other indications such as upper respiratory infections. Our findings, therefore, seem generalisable to children with relatively mild symptoms of throat infections or adenotonsillar hypertrophy in other countries.

Season-dependent differences in tonsillar microbial flora were found by Endo et al..[5] They divided tonsillar surface samples into those taken in summer and those taken in winter. In summer, GABHS and *Haemophilus influenzae* were more prevalent in samples from children with symptoms of tonsillar disease than in samples from the control group: 16.7% vs 6.5% and 33.3% vs 16.4%, respectively. In winter no significant differences were observed. We also compared the culture results of the tonsillar surface samples taken from children in the T&Ads group in spring, summer, autumn and winter and found no differences. Neither did the culture results for the 50 samples taken in October 2001 in the control group differ from those for the 50 samples taken in the control group in March and April 2002.

Several studies[22-24] have focused on the carrier rate of *Group A ß-haemolytic Streptococci* in children. GABHS are the most notorious pathogens causing throat infections and feared for their complications, namely acute rheumatic fever and acute glomerulonephritis. The ability of the bacteria to colonize the respiratory tract depends on the properties of the respiratory tract epithelium and the characteristics of the specific bacterial species. In most normal subjects carriage is completely asymptomatic, representing a symbiosis between host and commensal bacteria.[25] The reported throat GABHS carrier rate in healthy children varies from 6% to 21%.[22-24] Remarkably, in our population the carrier rate of the children selected for T&Ads (8.7%) is within the range reported for healthy children. In our control group a carrier rate of 5.0% was found, suggesting that the carrier rate in The Netherlands is lower than that in other countries.

We conclude that the prevalence of potential respiratory pathogens on the tonsillar surface of children with relatively mild symptoms of throat infections or adenotonsillar hypertrophy differs only slightly from that in children without symptoms of adenotonsillar disease. Variation of the microbial flora does not seem to play an essential role in the predisposition of these children to tonsillar disease.

Acknowledgements: We thank Peter Zuithof for advice and assistance with the statistical analyses and Nelly van Eden for conscientious secretarial support.

Funding: The study was funded by grants from the Dutch Health Care Insurance Board and GlaxoSmithKline, The Netherlands.

References

1. Kvaerner KJ, Nafstad P, Jaakkola JJ. Upper respiratory morbidity in preschool children: a cross-sectional study. *Arch Otolaryngol Head Neck Surg* 2000;**126**:1201-6.
2. Nyquist AC, Gonzales R, Steiner JF, Sande MA. Antibiotic prescribing for children with colds, upper respiratory tract infections, and bronchitis. *JAMA* 1998;**279**:875-7.
3. Reilly S, Timmis P, Beeden AG, Willis AT. Possible role of the anaerobe in tonsillitis. *J Clin Pathol* 1981;**34**:542-7.
4. Toner JG, Stewart TJ, Campbell JB, Hunter J. Tonsil flora in the very young tonsillectomy patient. *Clin Otolaryngol* 1986;**11**:171-4.
5. Endo LH, Sakano E, Carvalho DS, Bilecki M, Oliveira UM. Comparative bacteriology of the surface of normal and pathological palatine tonsils in children. *Acta Otolaryngol Suppl* (Stockh) 1996;**523**:130-2.
6. van Staaij BK, van den Akker EH, Poels PJ, Hoes AW, Schilder AG. Adenotonsillectomie bij kinderen: nog onvoldoende wetenschapelijk onderbouwd. [Adenotonsillectomy in children: not yet scientifically validated]. *Ned Tijdschr Geneeskd* 2002;**146**:8-12 (in Dutch).
7. Paradise JL, Bluestone CD, Bachman RZ, Colborn DK, Bernard BS, Taylor FH, et al. Efficacy of tonsillectomy for recurrent throat infection in severely affected children. Results of parallel randomized and nonrandomized clinical trials. *N Engl J Med* 1984;**310**:674-83.
8. Brouilette R, Hanson D, David R, Klemka L, Szatkowski A, Fernbach S, et al. A diagnostic approach to suspected obstructive sleep apnea in children. *J Pediatr* 1984;**105**:10-4.
9. Woolford TJ, Hanif J, Washband S, Hari CK, Ganguli LA. The effect of previous antibiotic therapy on the bacteriology of the tonsils in children. *Int J Clin Pract* 1999;**53**:96-8.
10. Balows AA, Hausler JWJ, Hermann KL, et al. Manual of clinical microbiology, 5th edn. Washington D.C.: American Society for Microbiology, 1991.
11. Brook I, Leyva F. Discrepancies in the recovery of group A beta-hemolytic streptococci from both tonsillar surfaces. *Laryngoscope* 1991;**101**:795-6.
12. Surow JB, Handler SD, Telian SA, Fleisher GR, Baranak CC. Bacteriology of tonsil surface and core in children. *Laryngoscope* 1989;**99**:261-6.
13. Gaffney RJ, Freeman DJ, Walsh MA, Cafferkey MT. Differences in tonsil core bacteriology in adults and children: a prospective study of 262 patients. *Respir Med* 1991;**85**:383-8.
14. Brook I, Yocum P, Shah K. Surface vs core-tonsillar aerobic and anaerobic flora in recurrent tonsillitis. *JAMA* 1980;**244**:1696-8.
15. Almadori G, Bastianini L, Bistoni F, Paludetti G, Rosignoli M. Microbial flora of surface versus core tonsillar cultures in recurrent tonsillitis in children. *Int J Pediatr Otorhinolaryngol* 1988;**15**:157-62.
16. Kielmovitch IH, Keleti G, Bluestone CD, Wald ER, Gonzalez C. Microbiology of obstructive tonsillar hypertrophy and recurrent tonsillitis. *Arch Otolaryngol Head Neck Surg* 1989;**115**:721-4.
17. Brodsky L, Nagy M, Volk M, Stanievich J, Moore L. The relationship of tonsil bacterial concentration to surface and core cultures in chronic tonsillar disease in children. *Int J Pediatr Otorhinolaryngol* 1991;**21**:33-9.
18. Brook I, Foote PA Jr. Microbiology of ‘‘normal’’ tonsils. *Ann Otol Rhinol Laryngol* 1990;**99**:980-3.
19. Brodsky L, Moore L, Stanievich JF, Ogra PL. The immunology of tonsils in children: the effect of bacterial load on the presence of B- and T-cell subsets. *Laryngoscope* 1988;**98**:93-8.
20. Francois M, Bingen E, Soussi T, Narcy P. Bacteriology of tonsils in children: comparison between recurrent acute tonsillitis and tonsillar hypertrophy. *Adv Otorhinolaryngol* 1992;**47**:146-50.
21. Brodsky L, Moore L, Stanievich J. The role of Haemophilus influenzae in the pathogenesis of tonsillar hypertrophy in children. *Laryngoscope* 1988;**98**:1055-60.

22. Hoffmann S. The throat carrier rate of group A and other beta hemolytic streptococci among patients in general practice. *Acta Pathol Microbiol Immunol Scand* [B] 1985;**93**:347-51.
23. Gunnarsson RK, Holm SE, Soderstrom M. The prevalence of beta-haemolytic streptococci in throat specimens from healthy children and adults. Implications for the clinical value of throat cultures. *Scand J Prim Health Care* 1997;**15**:149-55.
24. Stromberg A, Schwan A, Cars O. Throat carrier rates of beta-hemolytic streptococci among healthy adults and children. *Scand J Infect Dis* 1988;**20**:411-7.
25. Mandell GL, Bennett JE, Dowlin R. Principles and practice of infectious diseases, 4th edn. New York: Churchill Livingstone, 1995.

Chapter 5

Adenotonsillectomy for upper respiratory infections: evidence based?

van Staaij BK, van den Akker EH, van de Heijden GJMG, Schilder AGM, Hoes AW. *Arch Dis Child* 2005 Jan;90(1):19-25.

http://adc.bmjjournals.com/cgi/content/full/90/1/19

Summary

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 days 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, $p<0.0001$). For sore throat associated days 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, sore throat associated days 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. Obstructive sleep apnoea due to adenotonsillar hypertrophy is generally considered an adequate indicaton for adenotonsillectomy in children.[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.

Eligibilily
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, sore throat associated days 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 days school absence and upper respiratory infections, 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 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. generalisibility) 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.

Table 1. Methodological assessment of randomised trials.

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

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 II 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 to 0.75)
Paradise II 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 I & II (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 I (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 days school absence	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 author	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 (percentage 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 are comparable	TE : 736 No surgery: 741	TE and no surgery: 4 to 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 no surgery: 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)	Retro-spective 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	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 years	- Sore throat episodes - Sore throat associated days school absence (both definitions 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% confidence interval could not be calculated

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 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 days school absence, 1669 person years were available (56% in intervention groups). The pooled risk difference was -2.8 days per person year (95% confidence interval -3.9 to -1.6) and the risk ratio for sore throat associated days 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 (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 $\geq$ 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 $\leq$ 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 days 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%. 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. 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 sore throat episodes 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 days 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 days 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 episodes 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.

Acknowledgments: We thank ART Donders, PhD, for advice and assistance with the statistical analyses.

Funding: Dutch Health Care Insurance Board (OG-99-060).

References

1. van den Akker EH, Hoes AW, Burton MJ, Schilder AGM. Large international differences in (adeno)tonsillectomy rates. *Clin Otolaryngol* 2004;**29**:161-4.
2. Shintani T, Asakura K, Kataura A. The effect of adenotonsillectomy in children with OSA. *Int J Pediatr Otorhinolaryngol* 1998;**44**:51-8.
3. Nieminen P, Tolonen U, Lopponen H. Snoring and obstructive sleep apnea in children: a 6-month follow-up study. *Arch Otolaryngol Head Neck Surg* 2000;**126**:481-6.
4. de Serres LM, Derkay C, Astley S, Deyo RA, Rosenfeld RM, Gates GA. Measuring quality of life in children with obstructive sleep disorders. *Arch Otolaryngol Head Neck Surg* 2000;**126**:1423-9.
5. American Academy of Otolaryngology-Head and Neck Surgery. Clinical Indicators for Otolaryngology--Head and Neck Surgery. Available from http://www.entlink.net/practice/products/indicators/tonsillectomy.html (accessed 17-06-2004).
6. Scottish Intercollegiate Guidelines Network Scottish Intercollegiate Guidelines Network. Available from http://www.sign.ac.uk/guidelines (accessed 20-05-04).
7. Burton MJ, Towler B, Glasziou P. Tonsillectomy versus non-surgical treatment for chronic / recurrent acute tonsillitis. *Cochrane Database Syst Rev* 2000;CD001802.
8. Marshall T. A review of tonsillectomy for recurrent throat infection. *Br J Gen Pract* 1998;**48**:1331-5.
9. Blair RL, McKerrow WS, Carter NW, Fenton A. The Scottish tonsillectomy audit. Audit Sub-Committee of the Scottish Otolaryngological Society. *J Laryngol Otol* 1996;**110 (Suppl 20)**:1-25.
10. Donnelly MJ, Quraishi MS, McShane DP. Indications for paediatric tonsillectomy GP versus Consultant perspective. *J Laryngol Otol* 1994;**108**:131-4.
11. Capper R, Canter RJ. Is there agreement among general practitioners, paediatricians and otolaryngologists about the management of children with recurrent tonsillitis? *Clin Otolaryngol* 2001;**26**:371-8.
12. van den Akker EH, Schilder AG, Kemps YJ, van Balen FA, Hordijk GJ, Hoes AW. Current indications for (adeno)tonsillectomy in children: a survey in The Netherlands. *Int J Pediatr Otorhinolaryngol* 2003;**67**:603-7.
13. Paradise JL, Bluestone CD, Colborn DK, Bernard BS, Rockette HE, Kurs-Lasky M. Tonsillectomy and adenotonsillectomy for recurrent throat infection in moderately affected children. *Pediatrics* 2002;**110**:7-15.
14. van Tulder MW, Assendelft WJ, Koes BW, Bouter LM. Method guidelines for systematic reviews in the Cochrane Collaboration Back Review Group for Spinal Disorders. *Spine* 1997;**22**:2323-30.
15. Mc Kee WJE. A controlled study of the effects of tonsillectomy and adenoidectomy in children. *Br J Prev Soc Med* 1963;**17**:49-69.
16. Mc Kee WJE. The part played by adenoidectomy in the combined operation of tonsillectomy with adenoidectomy. Second part of a controleed study in children. *Br J Prev Soc Med* 1963;**17**:133-40.
17. Mawson SR, Adlington P, Evans M. A controlled study evaluation of adeno-tonsillectomy in children. *J Laryngol Otol* 1967;**81**:777-90.
18. Paradise JL, Bluestone CD, Bachman RZ, Colborn DK, Bernard BS, Taylor FH, et al. Efficacy of tonsillectomy for recurrent throat infection in severely affected children. Results of parallel randomized and nonrandomized clinical trials. *N Engl J Med* 1984;**310**:674-83.
19. Paradise JL, Bluestone CD, Rogers KD, Taylor FH, Colborn DK, Bernard BS, et al. Comparative efficacy of tonsillectomy for recurrent throat infection in more vs. less severely affected children. *Pediatr Res* 1991;**31**:126A.
20. Mawson SR, Adlington P, Evans M. A controlled study evaluation of adeno-tonsillectomy in children. Part II. *J Laryngol Otol* 1968;**82**:963-79.

21. Kaiser AD. Effect of tonsillectomy on the general health of twelve hundred children. *JAMA* 1924;**83**:33-7.
22. Kaiser AD. The relation of tonsils and adenoids to infections in children. *Am J Dis Child* 1931;**41**:568-81.
23. Kaiser AD. Significance of the tonsils in the development of the child. *JAMA* 1940;**115**:1151-6.
24. Roos LL Jr. Alternative designs to study outcomes: the tonsillectomy case. *Med Care* 1979;**17**:1069-87.
25. Kaiser AD. Tonsillectomy in children. *JAMA* 1926;**87**:1012-5.
26. Kaiser AD. Results of tonsillectomy. *JAMA* 1930;**95**:837-42.
27. Monroe JD, Volk VK. Study of he effects of 736 tonsillectomies and of 741 controls. *Am J Public Health* 1930;495-502.
28. Roydhouse N. A controlled study of adenotonsillectomy. *Arch Otolaryngol* 1970;**92**:611-6.
29. Roos LL Jr., Roos NP, Henteleff PD. Assessing the impact of tonsillectomies. *Med Care* 1978;**16**:502-18.
30. Henteleff PD, Roos LL, Jr., Roos NP. Indications for tonsillectomy: a 4-yr follow-up evaluation. *Clin Invest Med* 1981;**4**:123-8.
31. van der Graaf Y. Clinical trials: study design and analysis. *Eur J Radiol* 1998;**27**:108-15.
32. McLeod RS. Issues in surgical randomized controlled trials. *World J Surg* 1999;**23**:1210-4.
33. van Staaij BK, Rovers MM, Schilder AG, Hoes AW. Accuracy and feasibility of daily infrared tympanic membrane temperature measurements in the identification of fever in children. *Int J Pediatr Otorhinolaryngol* 2003;**67**:1091-7.
34. Grobbee DE, Hoes AW. Confounding and indication for treatment in evaluation of drug treatment for hypertension. *BMJ* 1997;**315**:1151-4.
35. Selkirk TK, Mitchell AG. Evaluation of the results of tonsillectomy and adenoidotomy. *Am J Dis Child* 1931;9-41.

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 the assessment of 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, tympanostomy 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 $\leq$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 6

Accuracy and feasibility of daily infrared tympanic membrane measurements in children

van Staaij BK, Rovers MM, Schilder AGM, Hoes AW.
Int J Pediatr Otorhinolaryngol 2003;**67**:1091-7.

Summary

Background. Fever is an important physical sign in infectious diseases in childhood. Daily assessment of fever may be used to monitor the occurrence of infections for research purposes. The infrared tympanic membrane thermometer (ITT) seems ideal for measuring central body temperature. Its accuracy, however, is still debated, and the feasibility of daily temperature measurements with an ITT has not been described.
Objective. To determine the accuracy of infrared tympanic membrane temperature measurements and the feasibility of daily infrared tympanic membrane temperature measurements at home.
Methods. Tympanic membrane temperature was measured by the Braun Pro 3000, rectal temperature by the Omron MC 63. To establish the accuracy of the ITT, rectal and tympanic membrane temperature measurements were performed in 41 children, aged 2 to 10 years. To establish the feasibility of daily infrared tympanic temperature measurements at home, parents of 21 children performed daily measurements for 2 weeks.
Results. With fever defined as a body temperature of ≥ 38.0 ºC, sensitivity was 93.3%, specificity 92.0%, positive predictive value 87.5%, negative predictive value 95.8%, and the concordance rate 92.5%. Most of the parents found the instructions for the use of the ITT clear (93%) and the ITT easy to use (86%). During the test period of 2 weeks the technique of the tympanic membrane temperature measurements remained adequate in 93% of the parents.
Conclusion. The tympanic membrane temperature measured by the Braun Pro 3000 accurately reflects rectal temperature, validly assesses the presence of fever in children, and is easy to use. The Braun ITT therefore is an adequate tool to assess fever and may be used both in a clinical setting and for research purposes.

Introduction

Fever is an important physical sign in many childhood diseases. Daily assessment of fever may be used to monitor the occurrence of infectious diseases for research purposes. Various methods to detect fever are available: digital or glass mercury temperature measurements at the rectum, mouth or axilla, core temperature measurements with a sensor in the pulmonary artery or distal oesophagus, and infrared measurements of the tympanic membrane. Which of these methods is best, remains unclear.

The ideal thermometer should accurately and rapidly reflect central body temperature, be noninvasive, non-traumatic, user-friendly and hygienic.[1] In most Western-European countries the rectal temperature is considered the 'gold standard' for daily practice. However, rectal measurements are relatively time-consuming, invasive, uncomfortable and not hygienic, especially with respect to daily temperature measurements taken at home for research purposes. The infrared tympanic membrane thermometer (ITT) may come close to the ideal temperature measurement, both in a hospital setting and at home.[2]

The ITT measures the infrared heat generated from tissue within view of the probe and aims to measure the temperature from the eardrum and surrounding tissues. The eardrum lies very near to the temperature regulation centers in the hypothalamus and shares the same artery. Ever since the introduction of the ITT in 1986, however, its accuracy and reliability have been debated.[3-13] A recent systematic review of Craig et al.[12] comparing ITT with rectal thermometry in children concluded that measurements taken with ITT cannot be used as an approximation of rectal temperature, i.e. the presence of fever might not be detected. Another recently published study, however, showed utility, accuracy and reliability of ITT, and a high concordance rate between tympanic membrane and rectal temperatures.[13] It is therefore not yet clear whether tympanic thermometry is sufficiently accurate to measure the temperature.

In March 2000, we initiated a randomised clinical trial assessing the effectiveness of adenotonsillectomy in children in The Netherlands.[14] The incidence of fever is the main outcome measure in this trial; and the majority of fever episodes in children under the age of 8 years are caused by upper respiratory infections.[15] To record fever objectively, parents of participating children had to take their child's temperature every day with an ITT, i.e. the Braun Pro 3000. To ensure objectivity and avoid information bias an electronic device was incorporated in the ITT enabling the thermometer to store 1000 daily temperature measurements automatically.

The present study was undertaken to establish: (1) the accuracy of the Braun Pro 3000, i.e. its ability to detect fever in children; and (2) the feasibility of performing daily infrared tympanic temperature measurements at home.

Methods

Description of the thermometers

The Braun Pro 3000 measures the tympanic membrane temperature and can, according to the product description, display temperature measurements between 20.0 and 42.2 °C with an accuracy of ± 0.2 °C. The thermometer performs eight temperature measurements in 1 second and displays the highest recorded temperature. This temperature reflects the actual measured temperature plus a mathematical adjustment to make the measurement comparable with the actual oral temperature.

To record the temperature objectively in our trial, an electronic device was incorporated enabling the thermometer to automatically store up to 1000 measurements. The first temperature, measured every day between 05:00 and 11:00 h, was stored in the ITT. A time restriction for the measurements was introduced because the mean temperature varies diurnally, with a 6:00 h nadir and a 16:00-18:00 h zenith.[16] At follow-up visits the data were transferred to a computer and could be read with a specially developed programme. Every ITT was calibrated by the study personnel. If the measured temperature was outside the calibration temperature range, i.e. 39.6-40.1 °C, the ITT was rejected for the study.

A validated digital thermometer, i.e. the Omron MC 63 (Omron Medizintechnik, Mannheim) was used to determine the rectal temperature. The Omron MC 63 can measure temperatures between 32.0 and 43.0 °C with an accuracy of ± 0.1 °C (Omron Healthcare Europe, test report NO 1767048-9A).

Temperature measurements

The tympanic membrane temperature was taken according to the instructions of the producer of the Braun Pro 3000. For each measurement a new probe cover was attached. In accordance with daily practice, no attempt was made to remove the cerumen from the ear canal. While pulling the examined ear up and backwards, the probe was fit snugly into the ear as far as possible and the activation button was pressed. The activation button was released when an acoustic signal was heard. For the rectal temperature measurement a disposable sleeve was fitted over the tip of the thermometer before inserting the Omron thermometer probe at least 3 cm into the

rectum. The measurement was complete when the acoustic signal sounded. The recorded temperature was read from the liquid crystal display.

Validation study

The aim of the cross-sectional validation study was to establish the accuracy of the Braun Pro 3000, i.e. its ability to detect fever in children, with rectal temperature as the gold standard.

Temperature measurements were performed in two populations in total of 41 children, aged 2 to 10 years. Informed consent was obtained for all participating children. First, during a period of 2 weeks, parents of every child admitted to the general paediatric ward of the Wilhelmina Children's Hospital, University Medical Center Utrecht were asked permission for participation of their child in the study. Parents of 26 children agreed. Main reasons for non-participation were: (1) the measurements could not be fitted in the child's hospital programme; and (2) the child fulfilled one of the exclusion criteria. Exclusion criteria were: external otitis, otorrhea, recovery phase from an ear operation, craniofacial malformations, Down's syndrome, coagulation disorders, rectal disorders and severe diarrhea. Second, during a period of 4 weeks, 15 consecutive children presenting with fever to one of three participating general practices were included in the study. In both groups of participants, otoscopy was performed and the presence of cerumen occluding the ear canal was recorded. Tympanic membrane temperature measurements with the Braun Pro 3000 were performed in both ears immediately followed by a rectal temperature measurement with the Omron MC 63. All measurements were performed by one of three observers who were trained to follow a standardised procedure.

Feasibility study

The aims of the feasibility study were to determine whether: (1) the instructions for the use of the ITT were clear; (2) the parents were able to use the ITT at home according to our instructions during a longer period of time; and (3) the technique of the thermometer, especially the incorporated electronic device, was functioning well. During a period of 2 weeks, parents of all consecutive children aged 2 to 10 years, who visited the ENT outpatient clinic at the Wilhelmina Children's Hospital, University Medical Center Utrecht, were asked to participate in the study. The ENT surgeon performed otoscopy and checked the exclusion criteria that were identical to those of the validation study. Written informed consent was obtained for 21 children. Their parents were instructed by the study personnel to take the tympanic membrane temperature. Written instructions were also supplied. Measurements were performed

in the right ear. Only when this was contraindicated for medical reasons, the measurements were performed in the left ear. Parents were asked to take the temperature once a day for 2 weeks, preferably between 05:00 and 11:00 h.[16] After 2 weeks, a member of the study team visited the parents and the child at home. Parents were asked to take their child's tympanic membrane temperature in the presence of a member of the study team. He scored the temperature technique as good, quite good, moderate or bad. A standardised questionnaire was filled out on the quality of the oral and written instructions, the user friendliness of the ITT and the feasibility of the time restrictions for the measurement.
The ethics committee of the UMC Utrecht approved the protocol of both studies.

Data analysis
The accuracy of the ITT was assessed considering the rectal temperature as the reference standard. Mean values of the tympanic membrane (left and right) and rectal temperature measurements were compared using oneway ANOVA. The correlation between rectal and tympanic membrane temperature measurements (left and right) was determined using Pearson's rho.
By subtracting left and right tympanic membrane temperature measurements and rectal and right tympanic membrane temperature measurements the disparity between the measurements in individual patients were calculated.
Reproducibility of the measurements of the ITT over time, was determined by comparing measurements from the left and right ear of each subject, using the paired t-test. Sensitivity, specificity, positive and negative predictive values of the ITT, and corresponding 95% confidence intervals were calculated with different temperature thresholds, i.e. 38.0 ºC and 38.5 ºC to define fever. The concordance rate was calculated to determine the agreement of the ITT with rectal temperature measurements for different temperature thresholds, i.e. 38.0 ºC and 38.5 ºC.
Descriptive analyses were performed to describe the results of the feasibility study. The total number of temperature measurements stored in the ITTs from the children who participated for the full 14 days (n=19) were compared with the expected number of temperature measurements. Potential training effects were evaluated by comparing the mean temperature results of the first week with those of the second week.

Results

Validation study

The mean age of the children participating in the validation study was 5.9 years (SD 2.5), and 51.2% of the children was male. Four percent of the ITTs did not pass the calibration standards and were rejected.

The mean rectal temperature (n=40) was 38.0 ºC (SD 1.2) and that of the right (n= 41) and left (n=41) tympanic membrane were also 38.0 ºC (SD 1.3) and 38.0 ºC (SD 1.3), respectively (ANOVA P=0.98). Rectal measurements showed good correlation with both right and left tympanic measurements (Spearman's rho 0.89 and 0.93, respectively). Left and right tympanic measurements were also highly correlated (Spearman's rho 0.93).

The disparity between right and left tympanic membrane temperature was greater than ±0.5 ºC in three children (maximum disparity –0.70 to +0.60 ºC). The disparity between right tympanic membrane and rectal temperature was greater than ± 0.5 ºC in 10 children (maximum disparity –1.22 to +1.78 ºC). Paired t-test showed no differences between the left and right tympanic measurements in the same child (P=0.66).

When fever was defined as a temperature of ≥ 38.0 °C, sensitivity was 93.3% (95% CI 85-100%), specificity 92.0% (95% CI 84-100%), positive predictive value 87.5% (95% CI 78-98%), and negative predictive value 95.8% (95% CI 90-100%). When fever was defined as a temperature of ≥ 38.5 ºC all were 100%. With fever defined as a temperature of ≥ 38.0 ºC or ≥ 38.5 ºC the concordance rate were 92.5 and 100%, respectively. With fever defined as a temperature of ≥ 38.0 ºC only one child with fever would have been missed with the ITT, whereas with fever defined as a temperature of ≥ 38.5 ºC no child with fever would have been missed.

Feasibility study

The mean age of the 21 children participating in the feasibility study was 5.4 years (SD 2.0), and 47.8% of the children was male. Nineteen children participated for the full 14 days, two children did not complete the study: one child refused further measurements after 3 days and one mother, who found the study too time-consuming, withdraw after 2 days. In total 197 temperature measurements of the expected 266 were stored in the thermometers (74%).

The questionnaire presented at the end of the study was answered by 20 parents (response rate of 95%). The majority of parents found the provided instructions for the use of the ITT clear (96%), and the ITT easy to use (86%) (see also Table 1). For 64%

of the parents it was convenient to take the temperature between 05:00 and 11:00 h, whereas 36% preferred to take the temperature in the evening. Observation of the parents after 2 weeks (n=14) while taking their child's tympanic membrane temperature during the home visit showed that the technique of the tympanic membrane measurement was 'good' in 93% and 'quite good' in 7%. Mean temperature results of the first week were comparable to the mean temperature results of the second week, indicating that there is no learning effect.

Table 1. Parental evaluation of the feasibility of taking daily temperature measurements.

	Percentage
Instructions:	
Clear	96%
Quite clear	4%
Use of the ITT:	
Easy to use	86%
Quite easy to use	14%
Use after 2 weeks:	
According to our instructions	93%
More or less according to our instructions	7%
Taking temperature between 05.00-11.00 hours:	
Convenient	64%
Not convenient	26%

Discussion

The tympanic membrane temperature measured by the Braun Pro 3000 accurately reflects rectal temperature, validly assesses the presence of fever in children, and is easy to use.

The main advantage of the thermometer used in our study is that the data are stored automatically in the ITT, so that the presence of fever could be assessed objectively without the risk of information bias, one of the main problems of research.
Various studies have compared oral and rectal temperatures as measured by a digital thermometer with tympanic membrane temperatures obtained by an ITT in children.[3-13] Its results have not been consistent: in most studies rectal temperatures correlated strongly with tympanic membrane temperatures (Pearson r=0.80), but differences were found for the ability of the ITT to detect fever. For example, Stewart et al. found a very good sensitivity (97%), specificity (100%), positive (100%) and negative

predictive values (90%) for the detection of fever (defined as ≥ 38.0 8C, rectal temperature as the reference standard).[4] Lanham et al., however, found lower values (sensitivity, 80%; specificity, 85%; positive predictive value, 87%; negative predictive value, 85%), and concluded that the proportion of children with fever that would be missed by screening with an ITT is unacceptably high.[8] The reasons underlying these contradictory results are not clear. No important differences in design can be found and in most studies fever was defined as temperature ≥ 38.0 ºC. The most plausible explanation is the differences in the ITTs and digital thermometers used in these studies. Also, interobserver variability might play a role, although the impact of operator technique is questioned.[17-19] Finally, the age of the participating children may explain some of the observed differences, i.e. younger children have a smaller external auditory canal and eardrum and therefore less accurate temperature recordings.

A systematic review of studies comparing ITT with rectal thermometry in children also demonstrated that the mean differences between rectal and ear temperature measurements were small.[12] However, in contrast to our findings they found wide limits of agreement between both measurements. The poor degree of agreement in the review may be methodological, i.e. it might have been difficult to control for quality of instrumentation and technique.[20]

The disparity between right tympanic membrane and rectal temperature was greater than ± 0.5 ºC in 10 children (maximum disparity -1.22 to + 1.78 ºC). The disparity was mainly present in the lower temperature measurements (< 38.0 ºC). If fever was defined as a temperature of ≥ 38.0 ºC, only one episode of fever was missed (rectal 38.1 ºC, right tympanal 37.6 ºC). If fever was defined as a temperature of ≥ 38.5 ºC no incorrect assessment was made. In clinical practice, where accurate temperature measurements are important for medical decisions and treatment, an infrared tympanic membrane temperature measurement of 38.5 ºC or greater appears to be reliable. In case of a ITT measurement lower than 38.5 ºC and a warranted accurate temperature, control with the classical method may be necessary.

In 11 children (25%) cerumen was found to occlude the ear canal unilaterally. No differences in mean tympanic temperature were found between the ear with and without occluding cerumen of the same child. These results are in accordance with some studies, but in contrast with others.[10,19,21]

Although some parents reported that their technique to measure the temperature improved during the study, we did not found this to influence the temperature results. Theoretically, an improved technique may result in a better positioning of the probe in the direction of the tympanic membrane. As the temperature of the tympanic membrane is higher than the temperature of the external auditory wall, one would

expect the mean temperature to be higher in the second week compared to the first week. This was not the case in our study, which is in agreement with the study of Petersen and Hauge.[17]
Seventy-four percent of the expected temperature measurements were stored in the ITT. The missing 26% can be explained by the time restriction of the measurements and technical problems with the storage of the data. Time-restrictions led to a lower level of patient compliance: 46% of the parents reported that one or more measurements had been missed due to the time restriction given by us, especially during the weekends. Consequently, we removed the time limit in the trial that we are currently undertaking.[14] The technical problems with the storage of the data were proved to be easily avoidable by simple instructions to the parents. To evaluate these improvements we have also analysed the temperature data from the first 14 days of 20 randomised children participating in the trial: in these children 89% of the expected temperature measurements were stored.
Several limitations of this study deserve consideration. First, all measurements of the validation study were performed by experienced observers whose results might be better than those of the parents at home. We do, however, not believe this to be an important factor, because the observed temperature technique of most parents (93%) after 2 weeks of temperature measurements was found to be good. Second, in total 76 thermometers were calibrated: three had to be rejected as they measured outside the calibration temperature range of 39.6-40.1 ºC. Eliminating these from the study might bias the results of our study in favour of the ITT. In normal practice, calibration is not performed which means that the actual differences between rectal and tympanic membrane measurements will be greater. Calibration of the ITT therefore appears to be very essential. Third, in our country, like in most Western-European countries, the rectal temperature is considered the 'golden standard'. But in fact central body temperature as measured, for example, in the pulmonary artery should be considered the 'gold standard'. It has been shown that rectal temperature can differ from central body temperature because the rectal temperature changes slowly during rapid central body temperature changes.[22] Besides, the rectal temperature may be influenced by heat producing microorganism in the stool. Our study did not allow us to compare the tympanic membrane temperature with the central body temperature. Finally, the results of the study are only applicable to children in the studied age group, i.e. 2 to 10 years.

We conclude that the tympanic membrane temperature measured by means of the Braun Pro 3000 accurately reflects rectal temperature and validly assesses the presence of fever in children. With clear instructions parents find the ITT easy to use and are

able to take their child's temperature according to the instructions, even on a daily basis for longer time periods. The Braun ITT therefore is an adequate tool to assess fever, which can be used for daily temperature measurements taken at home for research purposes.

Acknowledgements: The study was funded by grant OG-99-060 from the Dutch Health Care Insurance Board, The Netherlands.

References

1. Brooks S, Khan A, Stoica D, Griffith J, Friedeman L, Mukherji R, et al. Reduction in vancomycin-resistant Enterococcus and Clostridium difficile infections following change to tympanic thermometers. *Infect Control Hosp Epidemiol* 1998;**19**:333-6.
2. Brinnel H CM. Tympanic temperature is a core temperature in humans. *J Therm Biol* 1989;**14**:47-53.
3. Harms HA, Stoffers, HEJH. Temperatuurmeting bij kinderen met een oorthermometer. *Huisarts Wet* 2000;**43**:69-73.
4. Stewart JV, Webster D. Re-evaluation of the tympanic thermometer in the emergency department. *Ann Emerg Med* 1992;**21**:158-61.
5. Chamberlain JM, Grandner J, Rubinoff JL, Klein BL, Waisman Y, Huey M. Comparison of a tympanic thermometer to rectal and oral thermometers in a pediatric emergency department. *Clin Pediatr (Phila)* 1991;**30**:24-9.
6. Kenney RD, Fortenberry JD, Surratt SS, Ribbeck BM, Thomas WJ. Evaluation of an infrared tympanic membrane thermometer in pediatric patients. *Pediatrics* 1990;**85**:854-8.
7. Childs C, Harrison R, Hodkinson C. Tympanic membrane temperature as a measure of core temperature. *Arch Dis Child* 1999;**80**:262-6.
8. Lanham DM, Walker B, Klocke E, Jennings M. Accuracy of tympanic temperature readings in children under 6 years of age. *Pediatr Nurs* 1999;**25**:39-42.
9. Latman NS, Hans P, Nicholson L, DeLee ZS, Lewis K, Shirey A. Evaluation of clinical thermometers for accuracy and reliability. *Biomed Instrum Technol.* 2001;**35**:259-65.
10. Brennan DF, Falk JL, Rothrock SG, Kerr RB. Reliability of infrared tympanic thermometry in the detection of rectal fever in children. *Ann Emerg Med* 1995;**25**:21-30.
11. Hooker EA. Use of tympanic thermometers to screen for fever in patients in a pediatric emergency department. *South Med J* 1993;**86**:855-8.
12. Craig JV, Lancaster GA, Taylor S, Williamson PR, Smyth RL. Infrared ear thermometry compared with rectal thermometry in children: a systematic review. *Lancet* 2002;**360**:603-9.
13. Akinyinka OO, Omokhodion SI, Olawuyi JF, Olumese PE, Brown BJ. Tympanic thermometry in Nigerian children. *Ann Trop Paediatr* 2001;**21**:169-74.
14. van Staaij BK, van den Akker EH, Poels PJ, Hoes AW, Schilder AG. Adenotonsillectomie bij kinderen: nog onvoldoende wetenschapelijk onderbouwd. [Adenotonsillectomy in children: not yet scientifically validated]. *Ned Tijdschr Geneeskd* 2002;**146**:8-12.
15. Bruijnzeels MA, Foets M, van der Wouden JC, van den Heuvel WJ, Prins A. Everyday symptoms in childhood: occurrence and general practitioner consultation rates. *Br J Gen Pract* 1998;**48**:880-4.
16. Mackowiak PA, Wasserman SS, Levine MM. A critical appraisal of 98.6 degrees F, the upper limit of the normal body temperature, and other legacies of Carl Reinhold August Wunderlich. *JAMA* 1992;**268**:1578-80.
17. Petersen MH, Hauge HN. Can training improve the results with infrared tympanic thermometers? *Acta Anaesthesiol Scand* 1997;**41**:1066-70.
18. Terndrup TE, Rajk J. Impact of operator technique and device on infrared emission detection tympanic thermometry. *J Emerg Med.* 1992;**10**:683-7.
19. Pransky SM. The impact of technique and conditions of the tympanic membrane upon infrared tympanic thermometry. *Clin Pediatr (Phila)* 1991;**30**:50-2.
20. Akinyinka OO. Infrared thermometry versus rectal thermometry in children. *Lancet* 2002;**360**:584.
21. Doezema D, Lunt M, Tandberg D. Cerumen occlusion lowers infrared tympanic membrane temperature measurement. *Acad Emerg Med* 1995;**2**:17-9.
22. Robinson J, Charlton J, Seal R, Spady D, Joffres MR. Oesophageal, rectal, axillary, tympanic and pulmonary artery temperatures during cardiac surgery. *Can J Anaesth* 1998;**45**:317-23.

Chapter 7

Effectiveness of adenotonsillectomy in children with mild symptoms of throat infections or adenotonsillar hypertrophy: open, randomised controlled trial**.**

van Staaij BK, van den Akker EH, Rovers MM, Hordijk GJ, Hoes AW, Schilder AGM. *BMJ* 2004 Sep 18;329(7467):651. Epub 2004 Sep 10.

http://bmj.bmjjournals.com/cgi/content/full/329/7467/651

Summary

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 centers in The Netherlands
Participants. 300 children, aged 2 to 8 years, indicated for adenotonsillectomy according to their local otorhinolaryngologist. Excluded were children with very frequent throat infections (7 or more in the 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

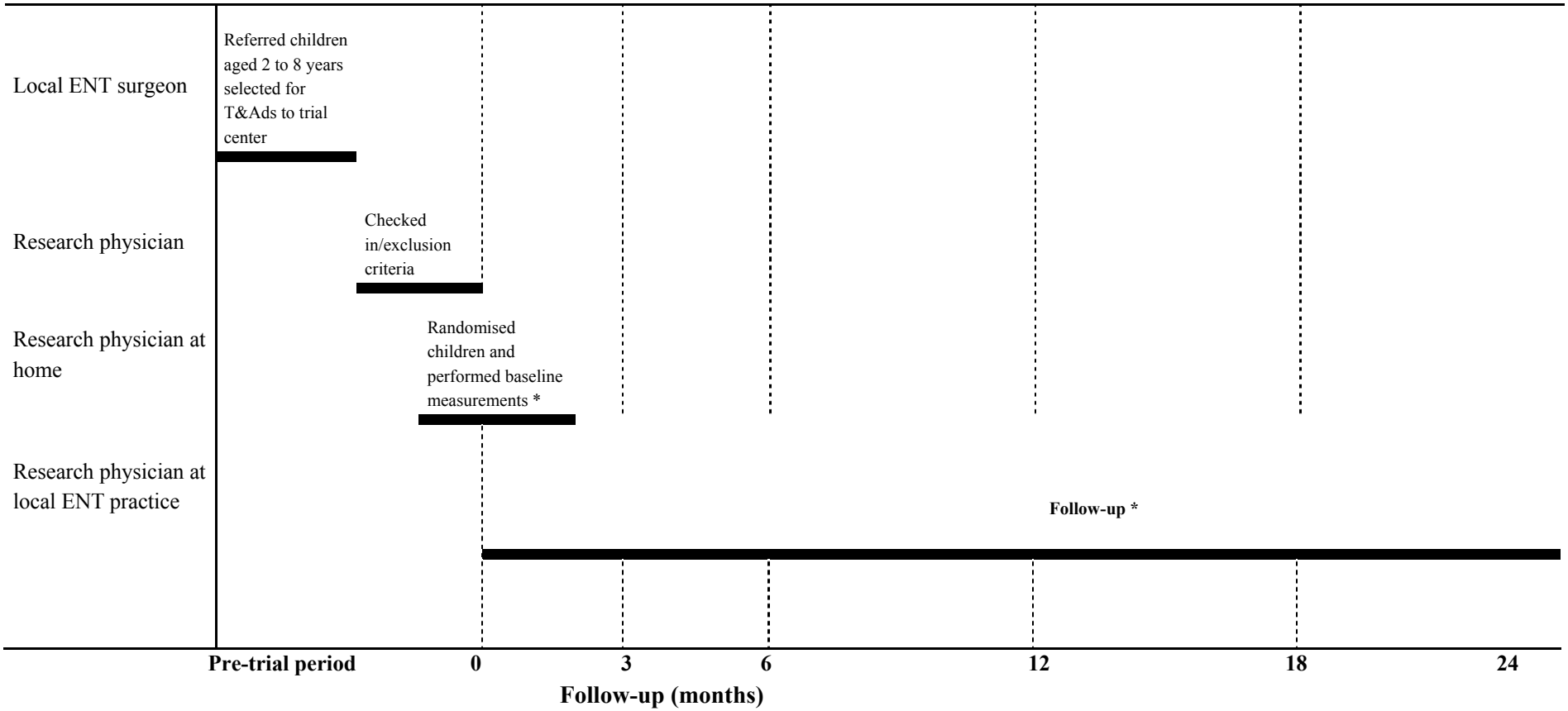
Tonsillectomy with or without adenoidectomy is one of the most commonly performed surgical procedures in children in western countries. Its indications, however, remain uncertain as reflected by the large variation in surgical rates across countries. In 1998, for example, 115/10,000 children underwent (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-center randomised controlled trial between March 2000 and February 2003. Otorhinolaryngologists in 21 general hospitals and 3 academic centers in The Netherlands (figure 1) were asked to provide our trial center 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.

Figure 1: Scheme of trial measurements.



* Baseline and follow-up measurements include:

- illness specific questionnaires
- health-related quality of life questionnaires
- ENT examination
- length and weight

Other exclusion criteria were: Down's syndrome, craniofacial malformation, such as cleft palate, and documented immunodeficiency, other than IgA or 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 the date of the 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 otorhinolaryngologists were encouraged to manage sore throats and upper respiratory infections during follow-up according to their regular practice.

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 episodes, throat infections and upper respiratory infections were calculated as incidence rate differences and incidence rate ratios per person year with

95% confidence intervals. Scores of health-related quality of life instruments were linearly transformed into 0-100 scales and presented per subscale. For the mean number of fever episodes, we calculated a short and 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 was 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.

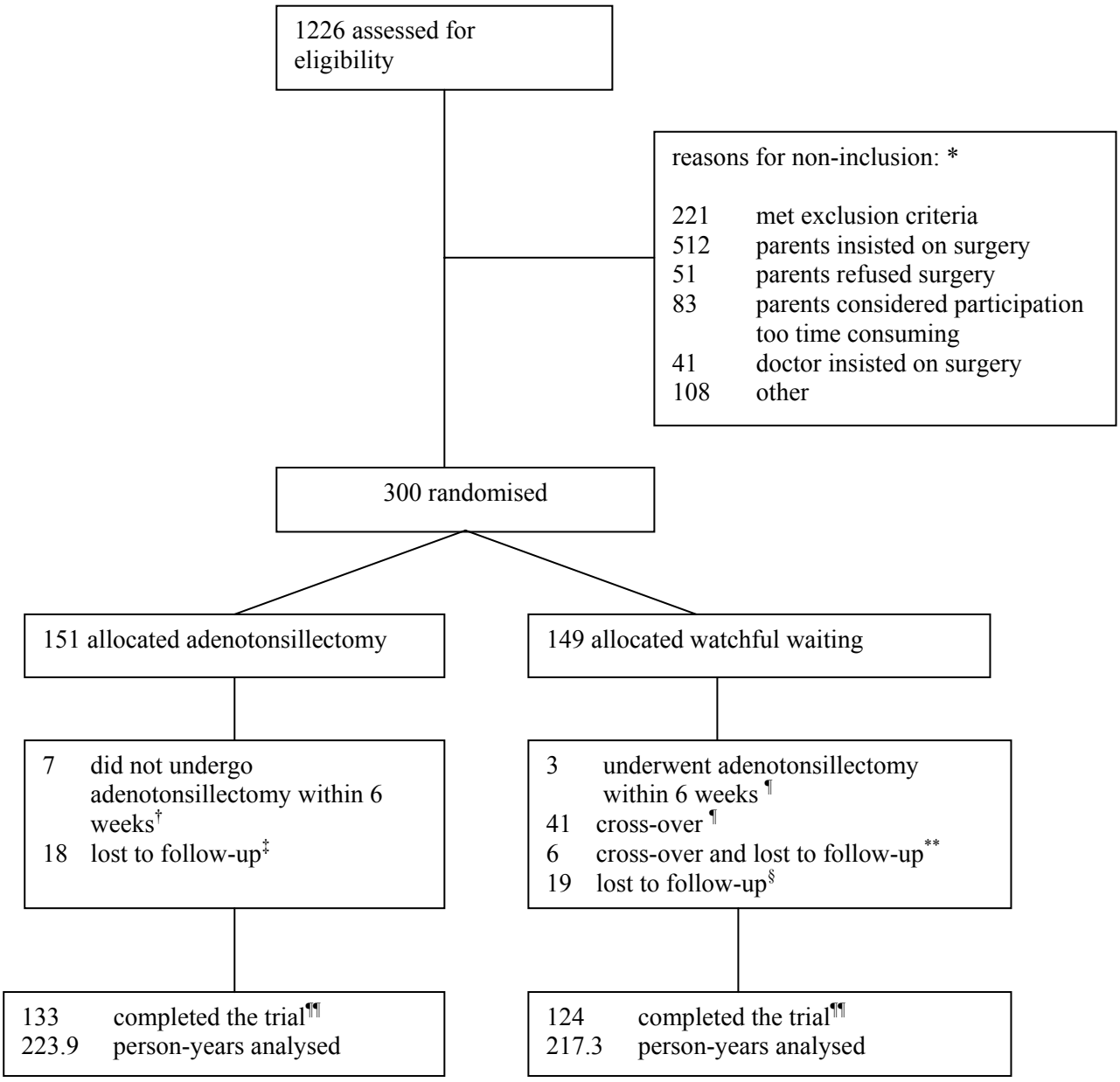
All analyses were performed on an intention-to-treat basis.

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 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.

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 children 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	**Adenotonsillectomy 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 otorhinolaryngologist		
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 previous year (only for children selected for recurrent throat infections; N=143)	3 (0 to 6)	3.0 (0 to 6)
Median duration of throat infections (range) in months (only for children selected 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 previous year	12 (0 to 24)	10 (0 to 24)
Median number of otitis media episodes (range) in the previous year	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 ear, nose and throat-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)
Day-care attendance (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 father		
Low	34 (22.5)	32 (22.5)
Middle	73 (48.3)	71 (50.0)
High	44 (29.1)	39 (27.5)
Educational level mother		
Low	22 (14.8)	27 (18.6)
Middle	95 (63.8)	81 (55.9)
High	32 (21.5)	37 (25.5)

* 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

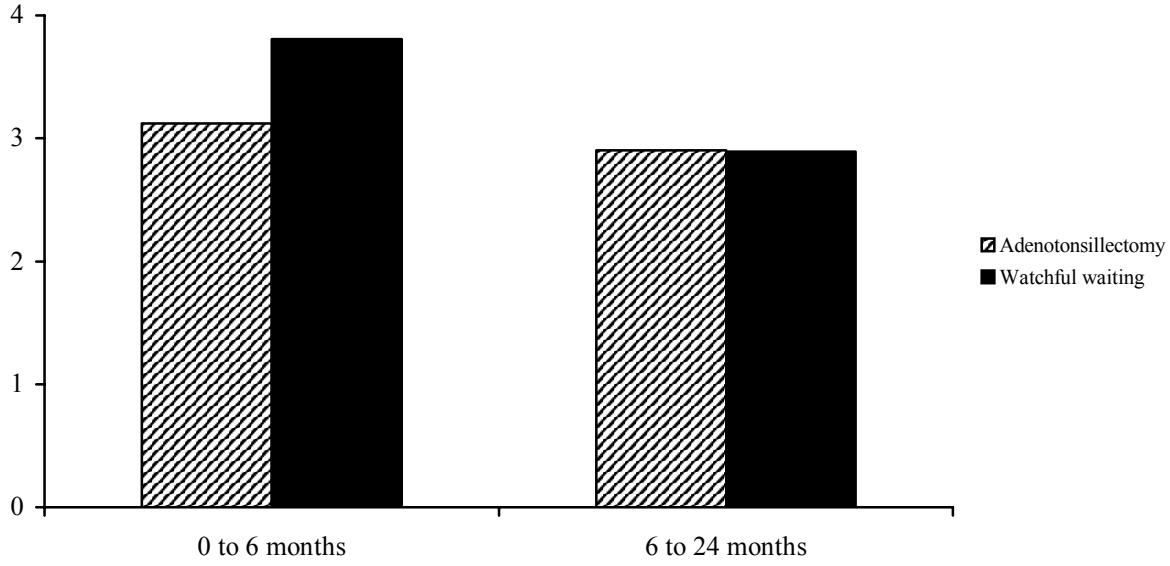
Primary outcome

Children in the adenotonsillectomy compared to the 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.

Table 2. Incidence of fever, throat infections, sore throats and upper respiratory infections per person year for adenotonsillectomy and watchful waiting group, incidence rate ratio (CI 95%) and incidence rate difference (CI 95%).

	Adeno-tonsillectomy Rate per person year	**Watchful waiting** Rate per person year	Incidence rate ratio (95% CI)	Incidence rate difference (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.



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 URI 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).

Figure 4a. Health related quality of life (TAPQoL) for the adenotonsillectomy and watchful waiting group at 6 months follow-up.

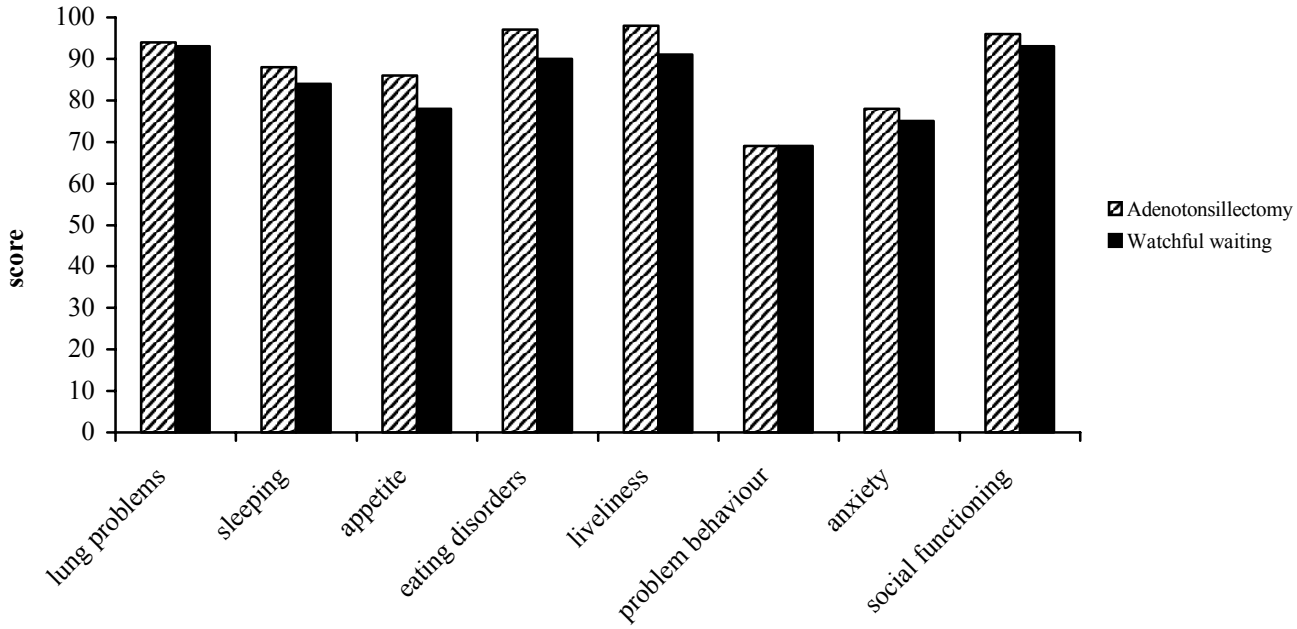


Figure 4b. Health related quality of life (TAPQoL) for the adenotonsillectomy and watchful waiting group at 24 months follow-up.

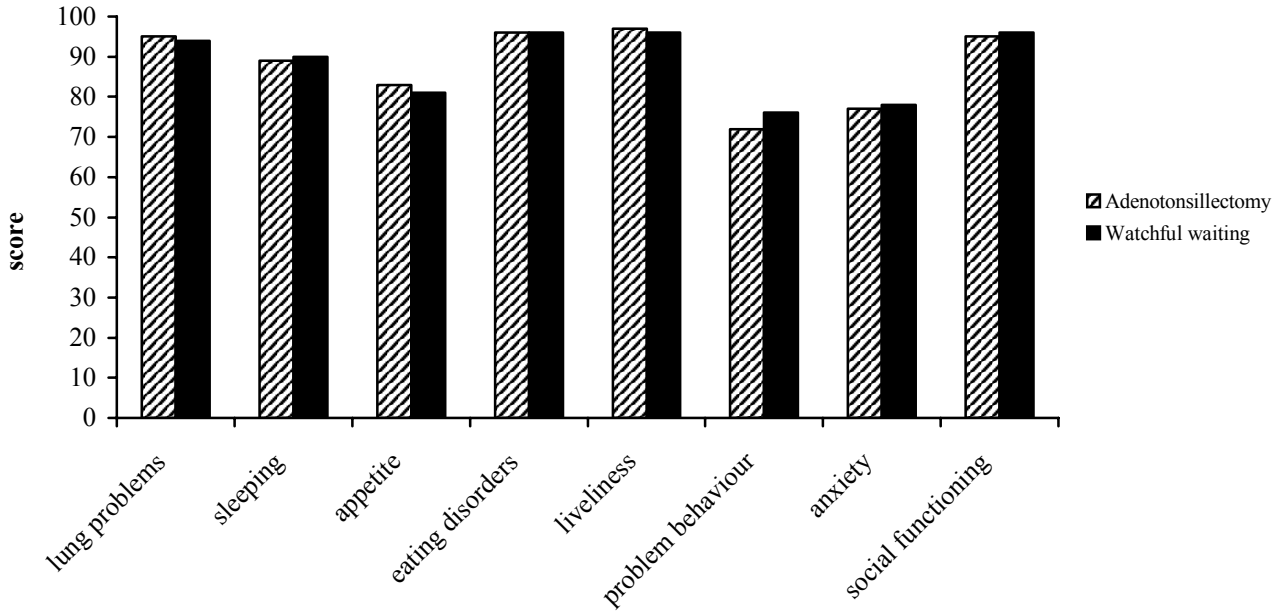


Figure 4c. Health related quality of life (CHQ) for the adenotonsillectomy and watchful waiting group at 6 months follow-up.

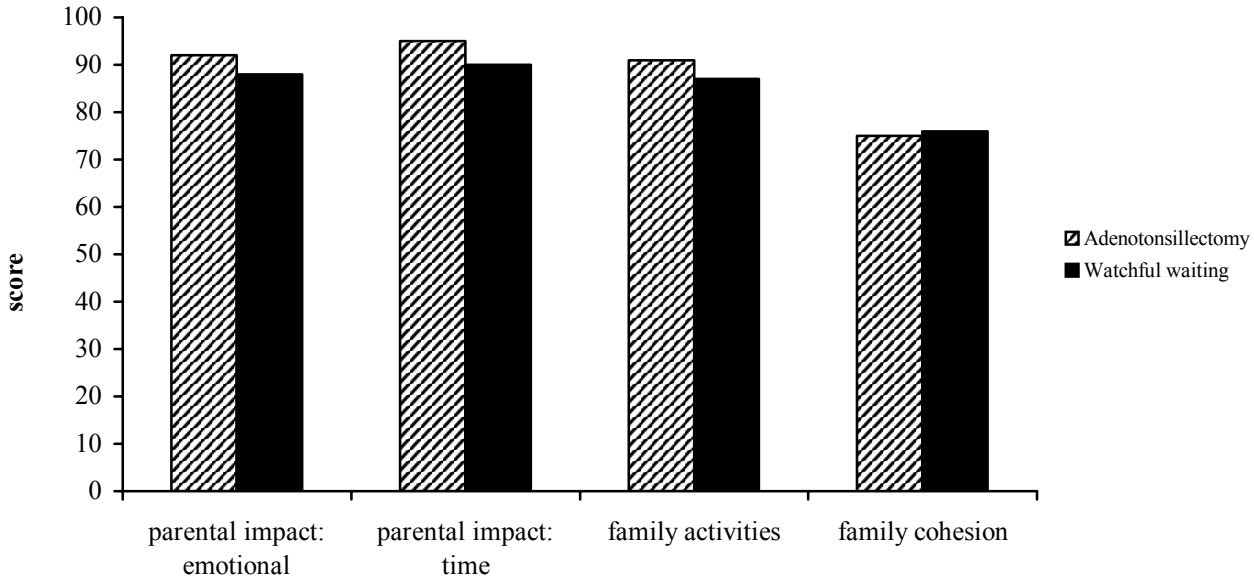


Figure 4d. Health related quality of life (CHQ) for the adenotonsillectomy and watchful waiting group at 24 months follow-up.

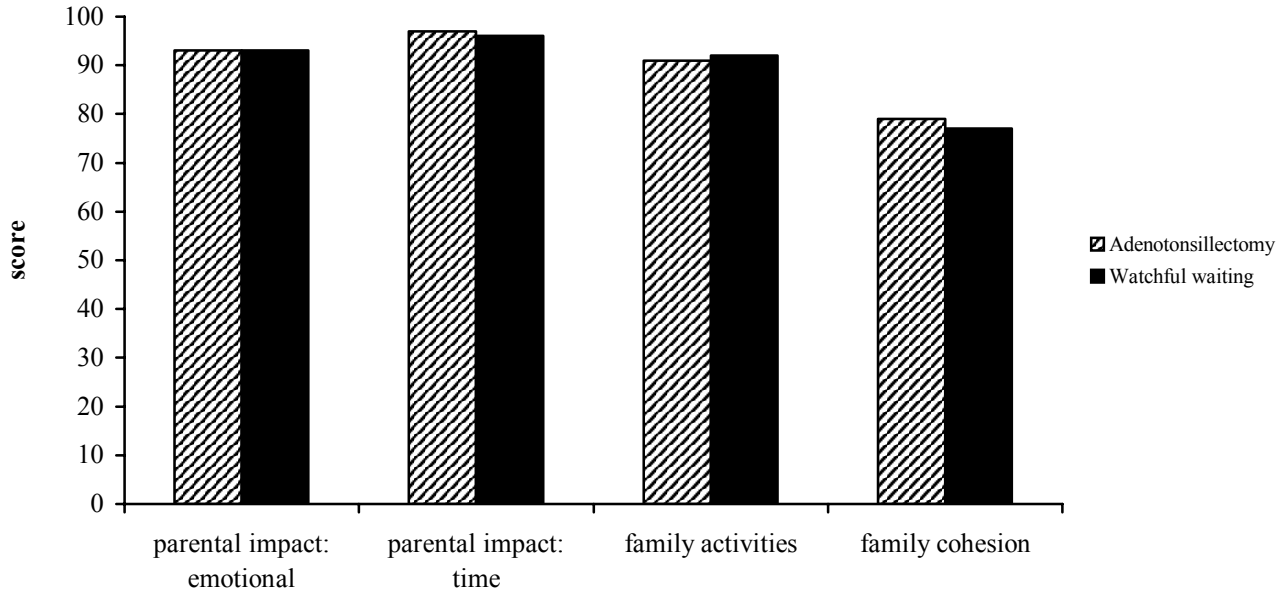
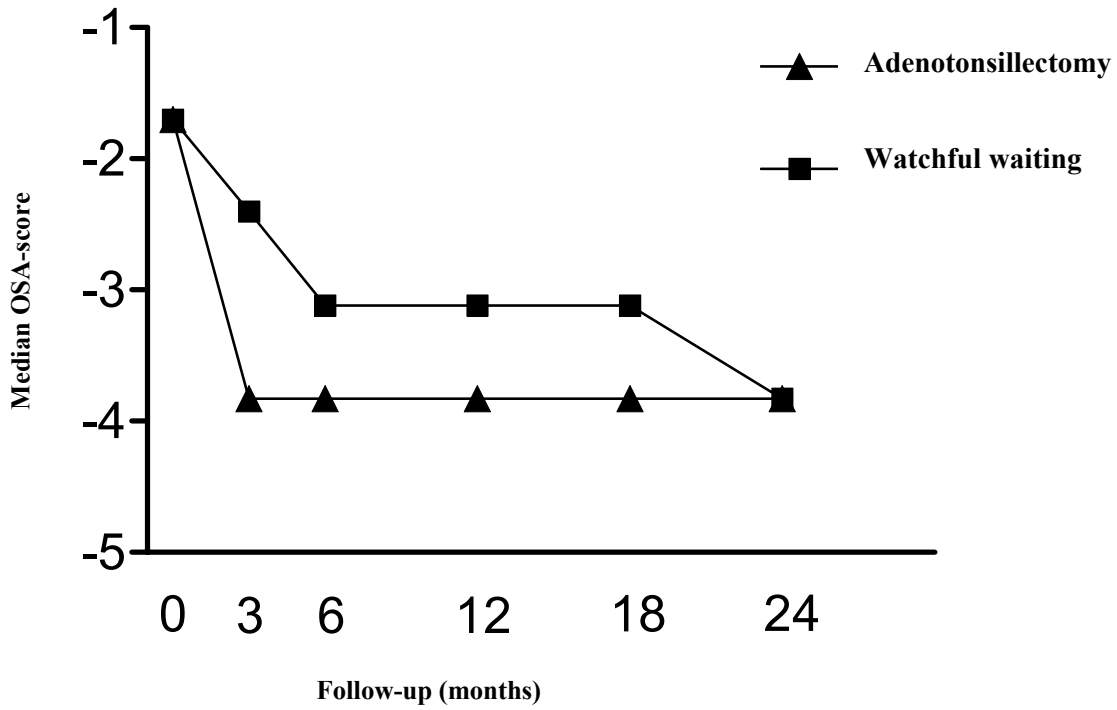


Figure 5. Median Brouillette OSA-score for the adenotonsillectomy and watchful waiting group during follow-up.



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 the 195 children (145 in the adenotonsillectomy group and 50 in the watchful waiting group) who underwent adenotonsillectomy, 12 (6%) 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 episodes, throat infections, sore throat days and upper respiratory infections in subgroups.

	Fever episodes	Throat infections	Sore throat days	Upper respiratory infections
	–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)	–0.08 (–0.28 to 0.11)	–3.19 (–4.04 to –2.35)	–0.63 (–1.24 to –0.02)
Number of throat infections in previous year				
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)	–0.49 (–0.75 to –0.22)	–11.33 (–12.48 to –10.17)	–0.92 (–1.61 to –0.23)

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 than in the watchful waiting group. From 6 to 24 months, however, the incidence rate 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 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 selected 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 adeno-tonsillectomy 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.[14] 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 and eligible but non-included 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.

Funding: Dutch Health Care Insurance Board (OG-99-060).

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.

Acknowledgements: We thank all participating children and their parents; our colleagues and nurses in the participating hospitals without whom this study could not have been carried out; Nelly van Eden for indispensable secretarial support; Patrick Poels, Ward Videler, Charlotte van Krevel and Wytske Richard who helped with the conduct of the trial and recruitment of the patients; Frank Leus for data management.

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, location Alexander and Carolus; 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; Prof. Dr. GJ Hordijk, MD PhD; JLL Kimpen, MD PhD; EAM Sanders, MD PhD; ThJM Verheij, MD PhD.

References

1. van den Akker EH, Hoes AW, Burton MJ, Schilder AGM. Large international differences in (adeno)tonsillectomy rates. *Clin Otolaryngol* 2004;**29**:161-4.
2. van den Akker EH, Schilder AG, Kemps YJ, van Balen FA, Hordijk GJ, Hoes AW. Current indications for (adeno)tonsillectomy in children: a survey in The Netherlands. *Int J Pediatr Otorhinolaryngol* 2003;**67**:603-7.
3. Paradise JL, Bluestone CD, Bachman RZ, Colborn DK, Bernard BS, Taylor FH, et al. Efficacy of tonsillectomy for recurrent throat infection in severely affected children. Results of parallel randomized and nonrandomized clinical trials. *N Engl J Med* 1984;**310**:674-83.
4. Nieminen P, Tolonen U, Lopponen H. Snoring and obstructive sleep apnea in children: a 6-month follow-up study. *Arch Otolaryngol Head Neck Surg* 2000;**126**:481-6.
5. de Serres LM, Derkay C, Astley S, Deyo RA, Rosenfeld RM, Gates GA. Measuring quality of life in children with obstructive sleep disorders. *Arch Otolaryngol Head Neck Surg* 2000;**126**:1423-9.
6. Flanary VA. Long-term effect of adenotonsillectomy on quality of life in pediatric patients. *Laryngoscope* 2003;**113**:1639-44.
7. Scottish Intercollegiate Guidelines Network. Available from http://www.sign.ac.uk/guidelines. (accessed 20-05-04)
8. American Academy of Otolaryngology-Head and Neck Surgery. Clinical Indicators for Otolaryngology--Head and Neck Surgery. Available from http://www.entlink.net/practice/products/indicators/tonsillectomy.html (accessed 17-06-2004)
9. Blair RL, McKerrow WS, Carter NW, Fenton A. The Scottish tonsillectomy audit. Audit Sub-Committee of the Scottish Otolaryngological Society. *J Laryngol Otol* 1996;**110** (Suppl 20):1-25.
10. Donnelly MJ, Quraishi MS, McShane DP. Indications for paediatric tonsillectomy GP versus consultant perspective. *J Laryngol Otol* 1994;**108**:131-4.
11. Capper R, Canter RJ. Is there agreement among general practitioners, paediatricians and otolaryngologists about the management of children with recurrent tonsillitis? *Clin Otolaryngol* 2001;**26**:371-8.
12. Faulconbridge RV, Fowler S, Horrocks J, Topham JH. Comparative audit of tonsillectomy. *Clin Otolaryngol* 2000;**25**:110-7.
13. Brouillette R, Hanson D, David R, Klemka L, Szatkowski A, Fernbach S et al. A diagnostic approach to suspected obstructive sleep apnea in children. *J Pediatr* 1984;**105**:10-4.
14 Fekkes M, Theunissen NC, Brugman E, Veen S, Verrips EG, Koopman HM, et al. Development and psychometric evaluation of the TAPQoL: a health-related quality of life instrument for 1-5-year-old children. *Qual Life Res* 2000;**9**:961-72.
15. Raat H, Bonsel GJ, Essink-Bot ML, Landgraf JM, Gemke RJ. Reliability and validity of comprehensive health status measures in children: The Child Health Questionnaire in relation to the Health Utilities Index. *J Clin Epidemiol* 2002;**55**:67-76.
16. Van Staaij BK, Rovers MM, Schilder AG, Hoes AW. Accuracy and feasibility of daily infrared tympanic membrane temperature measurements in the identification of fever in children. *Int J Pediatr Otorhinolaryngol* 2003;**67**:1091-7.
17. Wolfensberger M, Haury JA, Linder T. Parent satisfaction 1 year after adenotonsillectomy of their children. *Int J Pediatr Otorhinolaryngol* 2000;**56**:199-205.
18. Conlon BJ, Donnelly MJ, McShane DP. Improvements in health and behaviour following childhood tonsillectomy: a parental perspective at 1 year. *Int J Pediatr Otorhinolaryngol* 1997;**41**:155-61.
19. Mc Kee WJE. A controlled study of the effects of tonsillectomy and adenoidectomy in children. *Br J Prev Soc Med* 1963;**17**:49-69.
20. Mawson SR, Adlington P, Evans M. A controlled study evaluation of adeno-tonsillectomy in children. *J Laryngol Otol* 1967;**81**:777-90.

21. Mawson SR, Adlington P, Evans M. A controlled study evaluation of adeno-tonsillectomy in children. Part II. *J Laryngol Otol* 1968;**82**:963-79.
22. Paradise JL, Bluestone CD, Colborn DK, Bernard BS, Rockette HE, Kurs-Lasky M. Tonsillectomy and adenotonsillectomy for recurrent throat infection in moderately affected children. *Pediatrics* 2003;**110**:7-15.
23. Stewart MG, Friedman EM, Sulek M, deJong A, Hulka GF, Bautista MH, et al. Validation of an outcomes instrument for tonsil and adenoid disease. *Arch Otolaryngol Head Neck Surg* 2001;**127**:29-35.
24. van den Akker EH, Rovers MM, van Staaij BK, Hoes AW, Schilder AG. Representativeness of trial populations: an example from a trial of adenotonsillectomy in children. *Acta Otolaryngol* 2003;**123**:297-301.
25. Mc Kee WJE. The part played by adenoidectomy in the combined operation of tonsillectomy with adenoidectomy. Second part of a controlled study in children. *Br J Prev Soc Med* 1963;**17**:133-40.
26. van der Graaf Y. Clinical trials: study design and analysis. *Eur J Radiol* 1998;**27**:108-15.
27. McLeod RS. Issues in surgical randomized controlled trials. *World J Surg* 1999;**23**:1210-4.
28. Eskerud JR, Laerum E, Fagerthun H, Lunde PKM, Naess A. Fever in General-Practice .1. Frequency and Diagnoses. *Fam Pract* 1992;**9**:263-9.
29. Soman M. Characteristics and management of febrile young children seen in a university family practice. *J Fam Pract* 1985;**21**:117-22.
30. World Medical Association declaration of Helsinki. Available from www.wma.net/e/policy/b3.htm. (accessed 20-05-04)

Chapter 8

Cost-effectiveness of childhood adenotonsillectomy; a randomised comparison with watchful waiting

Buskens E, van Staaij BK, van den Akker EH, Hoes AW, Schilder AGM.

Summary

Objective. Evidence regarding the cost-effectiveness of adenotonsillectomy for a large proportion of children currently undergoing this intervention in the Netherlands is lacking. The objective of this study was to assess the balance between costs and effects of adenotonsillectomy as compared to watchful waiting in children with relatively mild symptoms of throat infections or adenotonsillar hypertrophy.
Design. Economic evaluation alongside an open randomised controlled trial.
Setting. Multi-center: 21 general and 3 university hospitals in the Netherlands.
Participants. 300 children, aged 2 to 8 years selected for adenotonsillectomy according to current medical practice. Excluded were children with very frequent throat infections (7 or more in previous year) and those with a high suspicion of obstructive sleep apnoea.
Intervention. Adenotonsillectomy versus watchful waiting.
Main outcome measures. Incremental cost-effectiveness in terms of costs per fever episode avoided, per throat infection avoided and per upper respiratory infection avoided.
Results. Costs incurred in the adenotonsillectomy group were € 1,196 as opposed to €804 in the watchful waiting group (49% increase; 100% certain). During a median follow-up period of 22 months, surgery as compared to watchful waiting reduced the number of fever episodes by 0.21 (95% confidence interval -0.12 to 0.54), throat infections by 0.21 (95% confidence interval 0.06 to 0.36), and upper respiratory infections by 0.53 (95% confidence interval 0.08 to 0.97) episodes per person year. The incremental cost per episode avoided were €2,333, €1,444 and €788, respectively.
Conclusion. For the majority of Dutch children currently undergoing adeno-tonsillectomy for relatively mild tonsillar complaints, the operation resulted in a significant increase in costs without realising relevant clinical benefit. Additional research is required to identify subgroups in which surgery may be more (cost-)effective.

Introduction

In western countries tonsillectomy with or without adenoidectomy is among the most frequently performed surgical procedures in childhood. However, as may be inferred from the wide range of surgical rates observed across countries, its benefits are debated. In 1998, the Netherlands ranked high with 115 adenotonsillectomies per 10,000 children, whereas in England 65/10,000 children underwent this operation and in the United States 50/10,000.[1] Preference for antibiotic versus surgical management for upper respiratory infections may explain some of this variation.[2] Yet, the lack of sound evidence regarding the balance between costs and effects of adenotonsillectomy may also contribute to variability in indications.[3]

In the Netherlands, some 35% of the children undergoing adenotonsillectomy appear to suffer from very frequent throat infections (i.e. 7 or more episodes per year) or obstructive sleep apnoea. Accordingly, the remaining 65% is operated on for less frequent throat infections, milder symptoms of adenotonsillar hypertrophy, or other indications such as recurrent upper respiratory infections.[4] While very frequent throat infections and obstructive sleep apnoea (OSA) are generally considered adequate indications for (adeno)tonsillectomy,[5-8] for the majority of children the benefit of the operation is less clear.[4,9-12] To resolve this issue a randomised experimental design was chosen to compare the balance between costs and effects of adenotonsillectomy and watchful waiting in children with relatively mild symptoms of throat infections or adenotonsillar hypertrophy.

Material and Methods

The design of the study has previously been reported.[13] In brief, an open multi-center randomised controlled trial was conducted in 21 general hospitals and 3 academic centres in the Netherlands between March 2000 and February 2003. Information on the indication to perform adenotonsillectomy was recorded for every child aged 2 to 8 years. The indications included recurrent throat infections (3 or more per year) or other indications such as obstructive complaints or recurrent upper respiratory infections. Children with a history of very frequent throat infections,[5] and those with a Brouillette's OSA-score of more than 3.5, reflecting a high suspicion of obstructive sleep apnoea,[14] were excluded as these are generally considered adequate indications for adenotonsillectomy in children.[5-8] Patients with Down's syndrome, craniofacial

malformations, and documented immunodeficiency other than IgA or IgG2 deficiencies were also excluded.
After obtaining informed consent from the parents, the children were randomly assigned to prompt adenotonsillectomy, i.e. within 6 weeks, or watchful waiting.

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. Furthermore, the child's temperature was measured daily with a validated infrared tympanic membrane thermometer.[15] To avoid information bias, we had an electronic device built in to store the date of the 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.

Outcome measures
The primary measure of clinical effectiveness defined for the economic evaluation was the number of fever episodes avoided. 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. 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.
The secondary measures of clinical effectiveness defined for this economic evaluation were the number of throat infections and upper respiratory infections avoided. 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. 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. In children undergoing adenotonsillectomy, symptoms of sore throat and upper respiratory infections immediately following surgery were included in the outcomes.
For this economic evaluation, incremental costs per fever episode avoided, throat infection avoided and upper respiratory infection avoided were calculated.

In parallel to the clinical study, costs were estimated at the patient level for the year 2002. Resource uses, such as over the counter drug use and physician's visits, were recorded in the patient diaries. Similarly, out-of-pocket expenses such as for baby sitter and travel costs were recorded in the diaries. Diary entries were verified by the research physicians during the follow-up visits. Specific interventions such as

adenoidectomy or placement of tympanostomy tubes during follow-up were recorded by the research physician. The scheduled visits by the research physician were excluded from the cost analyses.
Relevant costs were retrieved from available sources where possible. In case unavailable, unit costs were estimated in a separate costing study to be able to estimate the actual costs from a societal perspective. The costs of adenotonsillectomy, adenoidectomy and placement of tympanostomy tubes were calculated, based on resource use and personnel input as estimated in 7 participating hospitals. The costs associated with surgical complications were based on the resource use, i.e. personnel and material input, multiplied by the unit costs. Costs of medication, inclusive of antibiotics, were derived from the Dutch formulary[16] increased with the pharmacist's charge. Costs of diagnostic test were derived from the Dutch diagnostic formulary[17] where relevant increased with a technician's charge. Costs of over the counter drugs and alternative medicines were based on average retail prices. Costs of consultation of a general practitioner or medical specialist, or other procedures and hospitalisations were based on current Dutch guidelines for Pharmaco-economic evaluation[18] or charges if no other estimates were available. Indirect costs to society associated with leave of absence were estimated using the friction cost method.[19]

Incremental cost-effectiveness ratios (iCERs) were calculated by dividing the estimated differences in costs by the differences in effects observed. Costs per episode of fever, throat infection and upper respiratory infection avoided were estimated. For all analyses only a short time horizon was used and therefore no time preference or discount rate was taken into account. Uncertainty was addressed by means of bootstrapping.[20] Based on the original trial data on costs and effects, 1000 bootstrap replications were obtained. Subsequently, the incremental cost and effects were estimated and plotted for each replicate.

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 measures of clinical effect were calculated as incidence rate difference (IRD) per person year with 95% confidence interval. Overall costs were compared across the

randomisation groups. Where relevant, differences were calculated, inclusive of 95% confidence intervals.
All analyses were performed on an intention-to-treat basis.

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.[21] The medical ethics committees of all participating hospitals approved the study protocol.

Results

Patients
Between March 2000 and August 2002, 300 children were enrolled; 151 were allocated to adenotonsillectomy and 149 to a watchful waiting strategy. Baseline characteristics did not differ between the adenotonsillectomy and watchful waiting group: e.g. mean age was 54 months and the median number of throat infections in the previous year was 3 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. parents moved to another town or considered participation too time-consuming); serious co-morbidity (N=1); or unknown (N=6). In addition, 50 children allocated to the watchful waiting group underwent adenotonsillectomy during follow-up and 7 children allocated to the adenotonsillectomy group did not undergo the operation. Median follow-up was similar in the adenotonsillectomy and watchful waiting group: 22.0 (range: 0.4 to 27.1) and 22.4 (range: 1.5 to 26.5) months, respectively.

Clinical effectiveness
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).

Table 1. Baseline demographic and clinical characteristics of 300 participants according to treatment allocation (data are numbers and (%) unless otherwise indicated).

Characteristic	**Adenotonsillectomy 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 ENT-surgeon		
recurrent throat infections	76 (50.3)	67 (45.0)
other indications	73 (48.3)	82 (55.0)
Mean number of throat infections (range) in the previous year (only for children selected 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 selected 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 previous year	12 (0 to 24)	10 (0 to 24)
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)

* 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.

Complications of surgery

Of the 195 children (145 in the adenotonsillectomy group and 50 in the watchful waiting group) who underwent adenotonsillectomy, 12 (6%) had surgery related complications. Seven children had a primary haemorrhage: 2 (1%) were managed surgically, and 5 (3%) non-surgically; 3 children (2%) were admitted for observation for one night. Five children (3%) suffered from postoperative nausea, which was managed by anti-emetic medication and intravenous hydration.

Costs

A detailed overview of the most relevant cost estimates is presented in table 2.

Overall, patients in the adenotonsillectomy group incurred €1,196 on average, whereas patients in the watchful waiting group incurred €804, i.e. adenotonsillectomy implied almost 1.5 times higher costs (49% increase). With regard to uncertainty, the bootstrap analyses indicated that adenotonsillectomy increases overall costs with 100%

certainty; all estimates on the y-axis are > 0 (figures 1a through 1c). In fact, adenotonsillectomy decreased costs associated with general practitioners visits and over the counter drug use by only €7 and €4, respectively compared to watchful waiting. Other costs did not differ or were higher for the adenotonsillectomy group than for the watchful waiting group.

Table 2. Resources used and cost estimates (year 2002).

Resources	**Cost estimate (€)**	**Source**
Adenoidectomy	320.84	Cost study
Adenoidectomy combined with myringotomy	365.93	Cost study
Adenoidectomy combined with tympanostomy tubes	683.56	Cost study
Adenotonsillectomy	361.32	Cost study
Adenotonsillectomy combined with myringotomy	365.93	Cost study
Adenotonsillectomy combined with tympanostomy tubes	724.04	Cost study
Tympanostomy tubes	362.72	Cost study
Re-operation for primary haemorrhage	1,212.55	Cost study
Consultation otorhinolaryngologist for minor heamorrhage	45.09	Cost study
Consultation otorhinolaryngologist	45.09	Guideline
Hospital day	240.00	Guideline
Day-case	120.00	Guideline
Consultation general practitioner	18.32	Guideline
Consultation paramedical professional	20.04	Guideline
Leave of absence (per hour based on friction costs)	21.66	Guideline

Cost-effectiveness

The balance between costs and effects, inclusive of uncertainty, was assessed by head to head comparison of costs and effects for the original trial data and for the 1000 bootstrap replicates of the trial. The incremental cost per episode of fever avoided, per throat infection avoided and per upper respiratory infection avoided were €2,333, €1,444 and €788, respectively. Incremental costs and effects for the adenotonsillectomy strategy as compared to the watchful waiting stragety of each of the replicates are depicted in figures 1a through 1c for fever episodes, throat infections and upper respiratory infections, respectively (y-axis of the figures).

Figure 1a. Incremental costs and effects for adenotonsillectomy as compared to watchful waiting for fever episodes.

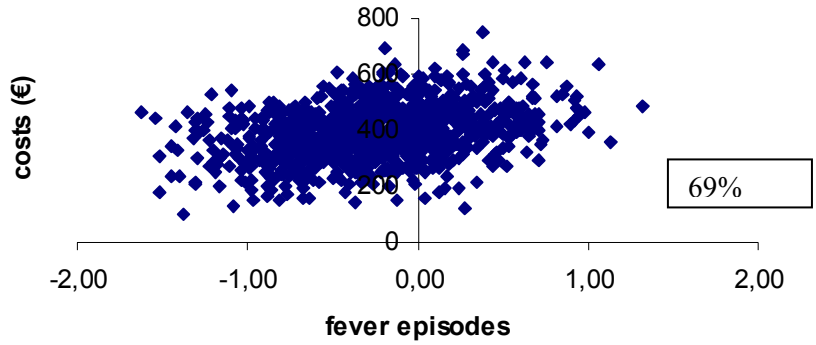


Figure 1b. Incremental costs and effects for adenotonsillectomy as compared to watchful waiting for throat infections.

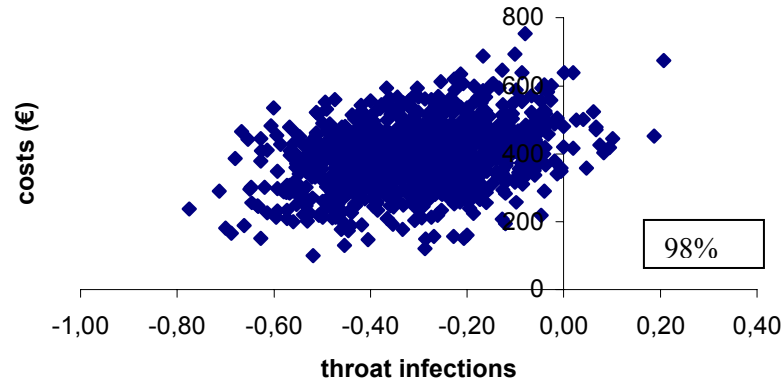
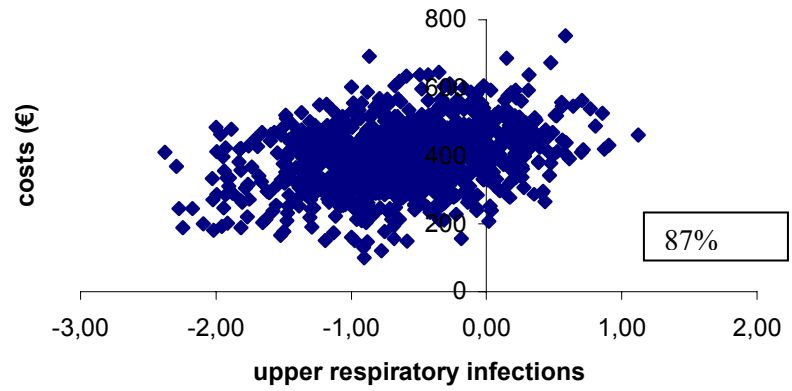


Figure 1c. Incremental costs and effects for adenotonsillectomy as compared to watchful waiting for upper respiratory infections.



The figures 1a through 1c show the proportion of bootstrap estimates where adenotonsillectomy resulted in fewer disease episodes than watchful waiting; for fever episodes 69% of the data points show advantage of adenotonsillectomy over watchful waiting, for throat infections 98% and for upper respiratory infections 87%, respectively (x-axis of the figures).

Discussion

In children selected for adenotonsillectomy for relatively mild symptoms of throat infections or adenotonsillar hypertrophy, surgery did, in comparison to watchful waiting, result in an overall increase of costs by 49% to over €390. This increase was not counterbalanced by a clinically relevant reduction in the number of fever episodes, throat infections and upper respiratory infections. Overall the balance between costs and effects in this population appeared unfavourable for adenotonsillectomy, with incremental cost-effectiveness ratios of over €780 per disease episode averted.

To our knowledge, we are the first to have performed an elaborate economic evaluation alongside a randomised clinical trial on adenotonsillectomy in children, yielding information readily applicable in policy decisions. To appreciate the results of our study, certain aspects need to be discussed in more detail.
First, children selected 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. Regarding cost-effectiveness of surgical intervention in children with very frequent throat infections no data have been published. In children with OSA adenotonsillectomy significantly reduces health care utilisation.[22]
Second, fifty children (34%) changed from watchful waiting to surgery during follow-up. Inappropriate handling of these data can lead to bias. In surgical trials like ours, per protocol analyses (excluding children who changed treatment groups or analysing children on the basis of the time spent in any treatment arm) will lead to either an under- or overestimation 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, with regard to the outcomes defined for the economic evaluation, i.e. incremental costs per episode of disease avoided, we deviated from the standard costs

per quality-adjusted life years (QALYs) gained. Consequently, our results cannot be directly compared to those of studies on other health care interventions in other patient categories. We chose not to use costs per QALY, as quality of life measurements in young children mainly rely on parental reports or other proxies and therefore restrict assessment to observational consequences of disease expressed in the child's functioning. The extent to which caregivers are able to judge emotional and cognitive responses in young children is under discussion.[23,24]

Fourth, another issue regarding the generalisability of our results is related to the unique adenotonsillectomy technique generally used in the Netherlands, i.e. Sluder's guillotine technique.[25] This technique is usually combined with inhalation anesthesia with a face mask using Sevoflurane gas and does not require endotracheal intubation. This combination of surgical and anesthetic techniques takes only about 15 minutes from the entry to the operation theatre until transfer to the recovery room. Almost all procedures are performed in day-case setting. This obviously has considerable consequences for the costs of the procedure. As compared to the cost incurred outside the Netherlands our cost estimates may be rather low.

Conclusion

For the majority of Dutch children currently undergoing adenotonsillectomy for relatively mild tonsillar complaints, the operation resulted in a significant increase in costs without realising relevant clinical benefit. Additional research is required to identify subgroups in whom the operation may be more (cost-)effective.

References

1 van den Akker EH, Hoes AW, Burton MJ, Schilder AG. Large international differences in (adeno)tonsillectomy rates. *Clin Otolaryngol* 2004;**29**:161-4.

2. Schilder AG, Lok W, Rovers MM. International perspectives on management of acute otitis media: a qualitative review. *Int J Pediatr Otorhinolaryngol* 2004;**68**:29-36.

3. Burton MJ, Towler B, Glasziou P. Tonsillectomy versus non-surgical treatment for chronic / recurrent acute tonsillitis. *Cochrane Database Syst Rev* 2000;CD001802.

4. van den Akker EH, Schilder AG, Kemps YJ, van Balen FA, Hordijk GJ, Hoes AW. Current indications for (adeno)tonsillectomy in children: a survey in The Netherlands. *Int J Pediatr Otorhinolaryngol* 2003;**67**:603-7.

5. Paradise JL, Bluestone CD, Bachman RZ, Colborn DK, Bernard BS, Taylor FH, et al. Efficacy of tonsillectomy for recurrent throat infection in severely affected children. Results of parallel randomized and nonrandomized clinical trials. *N Engl J Med* 1984;**310**:674-83.

6. Nieminen P, Tolonen U, Lopponen H. Snoring and obstructive sleep apnea in children: a 6-month follow-up study. *Arch Otolaryngol Head Neck Surg* 2000;**126**:481-6.

7. de Serres LM, Derkay C, Sie K, Biavati M, Jones J, Tunkel D, et al. Impact of adenotonsillectomy on quality of life in children with obstructive sleep disorders. *Arch Otolaryngol Head Neck Surg* 2002;**128**:489-96.

8. Flanary VA. Long-term effect of adenotonsillectomy on quality of life in pediatric patients. *Laryngoscope* 2003;**113**:1639-44.

9. Blair RL, McKerrow WS, Carter NW, Fenton A. The Scottish tonsillectomy audit. Audit Sub-Committee of the Scottish Otolaryngological Society. *J Laryngol Otol* 1996;**110 (Suppl 20)**:1-25.

10. Donnelly MJ, Quraishi MS, McShane DP. Indications for paediatric tonsillectomy GP versus Consultant perspective. *J Laryngol Otol* 1994;**108**:131-4.

11. Capper R, Canter RJ. Is there agreement among general practitioners, paediatricians and otolaryngologists about the management of children with recurrent tonsillitis? *Clin Otolaryngol* 2001;**26**:371-8.

12. Faulconbridge RV, Fowler S, Horrocks J, Topham JH. Comparative audit of tonsillectomy. *Clin Otolaryngol* 2000;**25**:110-7.

13. van Staaij BK, van den Akker EH, Rovers MM, Hordijk GJ, Hoes AW, Schilder AGM. Adentonsillectomy in children: a randomised trial. *BMJ* 2004. In press.

14. Brouilette R, Hanson D, David R, Klemka L, Szatkowski A, Fernbach S, et al. A diagnostic approach to suspected obstructive sleep apnea in children. *J Pediatr* 1984;**105**:10-4.

15. van Staaij BK, Rovers MM, Schilder AG, Hoes AW. Accuracy and feasibility of daily infrared tympanic membrane temperature measurements in the identification of fever in children. *Int J Pediatr Otorhinolaryngol* 2003;**67**:1091-7.

16 Farmacotherapeutisch Kompas 2002. Published by College voor zorgverzekeringen. ISBN 90-70918-24-2.

17 Diagnostisch Kompas 2002. Published by College voor zorgverzekeringen. ISBN 90-70918-30-7

18. Oostenbrink JB, Koopmanschap MA, Rutten FF. Standardisation of costs: the Dutch Manual for Costing in economic evaluations. *Pharmacoeconomics* 2002;**20**:443-54.

19. Koopmanschap MA, Rutten FF, van Ineveld BM, van Roijen L. The friction cost method for measuring indirect costs of disease. *J Health Econ* 1995;**14**:171-89.

20. Efron B and Tibshirani RJ. 1993. An introduction to the bootstrap. New York: Chapman & Hall.

21. World Medical Association declaration of Helsinki. World Medical Association declaration of Helsinki. Available from www.wma.net/e/policy/b3.htm (accessed 20-05-04).

22. Tarasiuk A, Simon T, Tal A, Reuveni H. Adenotonsillectomy in children with obstructive sleep apnea syndrome reduces health care utilization. *Pediatrics* 2004;**113**:351-6.

23. Theunissen NC, Vogels TG, Koopman HM, Verrips GH, Zwinderman KA, Verloove-Vanhorick SP, et al. The proxy problem: child report versus parent report in health-related quality of life research. *Qual Life Res* 1998;**7**:387-97.
24. le Coq EM, Boeke AJ, Bezemer PD, Colland VT, van Eijk JT. Which source should we use to measure quality of life in children with asthma: the children themselves or their parents? *Qual Life Res* 2000;**9**:625-36.
25. Homer JJ, Williams BT, Semple P, Swanepoel A, Knight LC. Tonsillectomy by guillotine is less painful than by dissection. *Int J Pediatr Otorhinolaryngol* 2000;**52**:25-9.

Chapter 9

General discussion

Doctor and parent: consensus in dealing with upper respiratory infections in children?

Case history

On a busy Monday morning consulting hour 4-year-old Kevin visits your family practice, accompanied by his mother. You have known the family for quite some years. Their family includes father Ron, mother Annabel, Kevin and his 2-year-old sister Lisette. You have seen Kevin 3 times this year for an aspecific upper respiratory infection and 2 times for a throat infection. Most of these episodes were treated symptomatically with analgesics or a cough mixture. Kevin is a heavy snorer, but otherwise sleeps well. Six weeks ago you prescribed Kevin antibiotics because his mother felt that at that time the symptoms were not resolving spontaneously. Kevin is now again suffering from a sore throat with fever and has been absent from school for the last 3 days. Friends told the mother that their child had had the same problems as Kevin and that adenotonsillectomy (T&Ads) "made him a different child". She wants your opinion. On examination you see an otherwise healthy 4-year-old boy, who is suffering from an acute throat infection. No alarming signs are present. You decide to treat this episode with penicillin for 7 days. You have just read the results of a recent trial on adenotonsillectomy in children and tell the mother that adenotonsillectomy in children with recurrent upper respiratory infections is unlikely to reduce the number of throat infections or other upper respiratory infections materially and that you do not think referral is appropriate. You advice her on how to deal with these upper respiratory infections and when to contact you. She tells you she is glad an operation is not needed (yet) and leaves your practice. Six weeks later you see her again with Kevin, who is again suffering from an aspecific upper respiratory infection. She, as well as her family and friends, believe a referral to the ENT-surgeon is now necessary.

State of the art on the effectiveness of adenotonsillectomy in children

Children with very frequent throat infections

For children with very frequent throat infections (i.e. 7 or more in the preceding year; 5 or more in each of the 2 preceding years; or 3 or more in each of the 3 preceding years) (adeno)tonsillectomy compared to a non-surgical management reduces the number of throat infections by 1.2 (95% CI 0,8 tot 1.7) episodes per person year.[1,2] Most doctors agree that (adeno)tonsillectomy is beneficial for this very selective group of children with very frequent throat infections. However, even in these children a spontaneous reduction of the incidence of throat infections can be expected.

Children with obstructive sleep apnoea
Children with obstructive sleep apnoea (OSA) due to adenotonsillar hypertrophy generally benefit from T&Ads. The effectiveness of adenotonsillectomy for obstructive sleep apnoea has not been ascertained in a randomised trial, but several uncontrolled studies have shown considerable postoperative improvement of objective sleep parameters and obstructive complaints.[3-5]

Children with relatively mild symptoms of throat infections or adenotonsillar hypertrophy.
Children with very frequent throat infections or a high suspicion of OSA constitute approximately 35% of the children currently undergoing T&Ads in The Netherlands, whereas 65% are operated for non-evidence based indications like less frequent throat infections and milder symptoms of adenotonsillar hypertrophy, or for other indications such as upper respiratory infections. To assess the effectiveness of adenotonsillectomy in these children, we performed our randomised trial. Its results show that many of the children with relatively mild symptoms of throat infections or adenotonsillar hypertrophy will derive only modest benefits from an operation over watchful waiting.

Since Kevin, the boy in our case history, is suffering from relatively mild symptoms of throat infections and recurrent upper respiratory infections, the results of our trial are applicable to him. You therefore decide that referral is, at this moment, not indicated.

The doctor

In the Netherlands, throat infections and other upper respiratory infections are primarily managed by the general practitioner. If our trial results are to be implemented in daily practice, the GP - and ENT surgeon - should be familiar with the trial results and agree with its conclusions.[6] Currently, many general practitioners and ENT surgeons believe that adenotonsillectomy is not only effective in children with very frequent throat infections and OSA but also in children with less severe throat infections or other indications such as recurrent upper respiratory infections and milder symptoms of adenotonsillar hypertrophy.[7-10] The question is whether our trial results will change these beliefs.

The parents

When consulting a doctor, parents of children with recurrent upper respiratory infections have certain views about the problem and expectations for treatment, such as effectiveness of antibiotics or surgery.[11-14] Prior expectations of parents in the beneficial effect of adenotonsillectomy are usually strong. However, the available trial results are not in agreement with these common expectations and it may be difficult to change them.

Given the growing evidence that patients wish to be involved in decision-making, particularly when the condition is not life threatening, it is important to be aware of patients' (in this case parents') views and expectations.[15,16] It is also important to realise that the expectations of parents of children with upper respiratory infections influence the doctor's decision.[9,12,17]

It is obvious that the help-seeking behaviour in the presented case history did not begin in the general practitioners office, but started much earlier in parents' conversations with friends and relatives. The factors that influence patients help-seeking behaviour include 1) signs and symptoms; 2) social interference; 3) medical beliefs; and 4) lay referral network.

Signs and symptoms

The interpretation of the symptoms by the parents affects help-seeking behaviour and is influenced by previous experiences, the perceived seriousness of the symptoms and their duration and/or frequency. As Howel et al.[18] have shown, parental worry and eagerness for surgery were significantly associated with the duration of episodes of throat infections and the number of episodes in the previous year.

Social interference

When valued activities or social demands, such as school or work, are affected by a condition, parents are more likely to seek prompt medical attention. Also if the illness of the child leads to disagreements between the parents regarding the need for therapeutic interventions, medical professionals are often consulted.[19] Two recent studies have shown that recurrent throat infections have a considerable impact on children and their families, especially if a child misses school, or if parents have to take time off work.[18,20]

Medical beliefs

People have concepts of health and illness that influence how they react to physical symptoms. These medical beliefs are acquired through personal previous experiences, from family and friends, and through the media.[19] In families where parents or siblings have undergone adenotonsillectomy, a higher proportion of parents preferred adenotonsillectomy,[18] and similarly, the probability of a child having a tonsillectomy increased significantly, compared with families were no family members had been treated surgically.[21,22]

Lay referral network

The lay referral network has an important influence on the help-seeking behaviour for upper respiratory infections.[23] Most people have an informal network of family and friends who offer their own interpretation of the symptoms and ideas about how they should be treated well before any professional medical help is sought. As Burton recently stated, "The word on the street is still this – if you are having trouble with your throat, you should have your tonsils out".[23]

Interaction between doctor and parents

According to current best evidence a referral of Kevin to an ENT-surgeon is not yet indicated. Which tools does the general practitioner have to provide care to such children and to inform the parents so that they agree on evidence-based management of his symptoms?

Education

- *health education*

In the Netherlands the general practitioner is an important source of medical information for many families. As such, he/she should be aware that patients' knowledge of the usual presentation of upper respiratory infections, their natural course, and appropriate treatment is incomplete or inaccurate.[24] In particular, the self-limiting character of upper respiratory tract symptoms is often not recognised by patients.[13,25] Many patients consider antibiotics as necessary treatment for upper respiratory symptoms,[24-26] 54% believes that bacteria are the cause of upper respiratory infections, only 28% knows that upper respiratory infections are usually caused by viruses and the majority of lay public does not know the difference between bacteria and viruses.[13,27]

General practitioners therefore have an important task to inform the parents that the natural history of the disease is favourable and that with growing age the incidence of upper respiratory infections will decrease. The latter is probably attributable to maturation of the immune system with growing age. Furthermore, children are often referred for adenotonsillectomy when their complaints are most severe and these are likely to become less severe in time, whether surgery is being performed or not (regression to the mean). This expected reduction in complaints might explain the high parental satisfaction with the surgical procedure.[28-30] These phenomena emphasise the need for a control group in effectiveness studies. In our randomised trial -including a non-surgical control group- children allocated to the adenotonsillectomy group experienced fewer fever episodes and more improvement of sleeping and eating patterns in the first 6 months after surgery than those in the watchful waiting group. During the remaining follow-up of the trial, however, these differences gradually disappeared. The early difference regarding the objective outcome fever between the surgical and non-surgical group can only be explained by the effectiveness of adenotonsillectomy; the early difference regarding the subjective parameters might also be explained by the parental satisfaction with the surgical strategy (or dissatisfaction with the watchful waiting strategy).

- *encouragement of self management by e.g. supplying leaflets*

Several studies showed that interventions such as distribution of a leaflet with information on a medical condition may have a favourable, but small, impact on health care utilization.[31,32] Such educational material is usually appreciated by both patients and doctors.[33]

Management

- *shared-decision making*

In consultations in which disagreement might occur between parents and clinicians about the necessity of adenotonsillectomy (or antibiotics) a "shared-decision making" model could be applied.[34,35] This implies explicit exploration of expectations and explanation of possible options and risks. Applying such models improve satisfaction of parents with a non-surgical approach. In current practice, time constraints seriously hampers shared-decision making.

- *management guidelines*

Clinical practice guidelines that are based on valid evidence may facilitate evidence-based care. However, most studies evaluating the effect of clinical guidelines have shown that they lead to only limited changes in physician behaviour.[36-39] Several barriers are known to influence the implementation of trial results, notably lack of

awareness and of agreement, and external barriers such as lack of time and of other treatment options.[6] For example, a study by Rovers et al.[37] on the effect of tympanostomy tubes in children with bilateral otitis media with effusion showed that dissemination of their trial results did not change the prior beliefs of otorhinolaryngologists. If the expectations as to the effects of adenotonsillectomy on reducing upper respiratory infections remain high, even though trial results do not confirm these beliefs, daily practice is unlikely to change. Therefore, simple dissemination of a guideline is not sufficient. For successful implementation in daily practice, it is important to design implementation strategies.[40-42]

In 1999 the Dutch College of General Practitioners (NHG) has issued a guideline for the treatment of sore throat in general practice (NHG-Standaard Acute Keelpijn 1999, revised version from 1990).[43] Importantly, this guideline is inconclusive about the indications for (adeno)tonsillectomy. If such a guideline would be developed on the indications for adenotonsillectomy in children, and both individual general practitioners and ENT-surgeons would support this guideline, the chance of implementation of our trial results would increase.

- *other treatment options*

Upper respiratory infections are inevitable when growing up and young children experience on average 6 upper respiratory infections per year.[44,45] Cultural and social differences play a role in how these upper respiratory infections are managed internationally, such as a preference for antibiotics (e.g. US and UK) or for surgical management of upper respiratory infections (e.g. the Netherlands).[46] Regarding antibiotics for acute sore throat, recent studies have shown that antibiotics confer only relative benefits in the treatment of acute sore throat and that the absolute benefits are modest.[47,48] Protecting sore throat sufferers against suppurative and non-suppurative complications in modern western society can only be achieved by treating many children with antibiotics of whom most will derive no benefits from it.[47,48]

However, children like Kevin have serious complaints and need care. At present, the best available treatment for these children is watchful waiting with careful monitoring of the child and reassurance of parents. During sore throat episodes children should receive adequate symptomatic relief, in particular by sufficient administration of analgesics.[49,50] It is known that, especially in children, analgesics are often given "on demand" and that both the frequency and dosage are usually not optimal.[49,51]

Future research

Future research could focus on 3 issues:
1) Individual targeting of the available treatment options.
It is important to individualise the currently available treatment options on an individual basis, as there is no doubt that subgroup(s) exist in which an operation and/or antibiotics and/or watchful waiting are more effective. Unfortunately, these subgroups can not be identified as yet.[48,52]

- *IPD-meta-analyses.* The power of the available individual trials on adeno-tonsillectomy is too limited to identify subgroups of children that might benefit from the operation. To identify such subgroups larger numbers or specific groups of children should be studied. However, a more efficient approach to detect subgroups with differences in treatment effect might be to perform individual patient data (IPD) meta-analyses including the original data from all adenotonsillectomy trials performed so far.[53,54]
- *Prognostic research.* If it were possible to identify children at high-risk of developing frequent upper respiratory infections or complications, we could target our medical interventions, such as adenotonsillectomy, at these children. The prognostic study presented in this thesis is the only available study so far attempting to identify these children,[52] and showed that it is not possible to predict the development of chronic recurrent upper respiratory infections satisfactorily. Our study might be hampered by a limited sample size, and much larger studies, perhaps also combining individual study data, are necessary to assess whether it is possible –or simply impossible- to predict chronic recurrent upper respiratory infections.

2) Etiological research
Upper respiratory infections are known to be a complex, multifactorial disease resulting from interplay between host factors such as age, genetic predisposition, immunological response, and the microbial load (viral and bacterial), which is influenced by environmental factors such as siblings, group day care and season.[55,56] The relative importance of, and interactions between the various known etiological factors is still poorly understood. More insight into the pathogenesis of upper respiratory infections is urgently needed to answer the question why some children are more susceptible to infections of Waldeyer's ring than others and to develop more effective preventive and therapeutic approaches.

3) Preventive measurements and novel therapies

Research in the past decade has focused on the development of preventive strategies for upper respiratory infections, such as immunization with pneumococcal[57-59] and viral vaccines,[60] intranasally administered immunoglobulins,[61] probiotics,[62,63] α streptococci spray[46,64] and intranasal steroids.[65,66] Most of these studies, however, have shown limited benefits of these interventions. Future research should focus on new and more effective therapies that reduce the frequency and/or severity of upper respiratory infections. Most success is expected if such therapies focus on interactions between pathogenic factors.

References

1. Paradise JL, Bluestone CD, Bachman RZ, Colborn DK, Bernard BS, Taylor FH, et al. Efficacy of tonsillectomy for recurrent throat infection in severely affected children. Results of parallel randomized and nonrandomized clinical trials. *N Engl J Med* 1984;**310**:674-83.
2. van Staaij BK, van den Akker EH, van der Heijden GJMG, Schilder AG, Hoes AW. Adenotonsillectomy for upper respiratory infections. Evidence based? *Arch Dis Child* 2004. Accepted for publication.
3. Nieminen P, Tolonen U, Lopponen H. Snoring and obstructive sleep apnea in children: a 6-month follow-up study. *Arch Otolaryngol Head Neck Surg* 2000;**126**:481-6.
4. de Serres LM, Derkay C, Sie K, Biavati M, Jones J, Tunkel D et al., Impact of adenotonsillectomy on quality of life in children with obstructive sleep disorders. *Arch Otolaryngol Head Neck Surg* 2002;**128**:489-96.
5. Flanary VA. Long-term effect of adenotonsillectomy on quality of life in pediatric patients. *Laryngoscope* 2003;**113**:1639-44.
6. Cabana MD, Rand CS, Powe NR, Wu AW, Wilson MH, Abboud PA et al. Why don't physicians follow clinical practice guidelines? A framework for improvement. *JAMA* 1999;**282**:1458-65.
7. Blair RL, McKerrow WS, Carter NW, Fenton A. The Scottish tonsillectomy audit. Audit Sub-Committee of the Scottish Otolaryngological Society. *J Laryngol Otol* 1996;**110 Suppl 20**:1-25.
8. Donnelly MJ, Quraishi MS, McShane DP. Indications for paediatric tonsillectomy GP versus Consultant perspective. *J Laryngol Otol* 1994;**108**:131-4.
9. Capper R, Canter RJ. Is there agreement among general practitioners, paediatricians and otolaryngologists about the management of children with recurrent tonsillitis? *Clin Otolaryngol* 2001;**26**:371-8.
10. van den Akker EH, Schilder AG, Kemps YJ, van Balen FA, Hordijk GJ, Hoes AW. Current indications for (adeno)tonsillectomy in children: a survey in The Netherlands. *Int J Pediatr Otorhinolaryngol* 2003;**67**:603-7.
11. Macfarlane J, Holmes W, Macfarlane R, Britten N. Influence of patients' expectations on antibiotic management of acute lower respiratory tract illness in general practice: questionnaire study. *BMJ* 1997;**315**:1211-4.
12. Vinson DC, Lutz LJ. The effect of parental expectations on treatment of children with a cough: a report from ASPN. *J Fam Pract* 1993;**37**:23-7.
13. Chan CS. What do patients expect from consultations for upper respiratory tract infections? *Fam Pract* 1996;**13**:229-35.
14. Harbarth S, Albrich W, Brun-Buisson C. Outpatient antibiotic use and prevalence of antibiotic-resistant pneumococci in France and Germany: a sociocultural perspective. *Emerg Infect Dis* 2002;**8**:1460-7.
15. Rollnick S, Seale C, Kinnersley P, Rees M, Butler C, Hood K. Developing a new line of patter: can doctors change their consultations for sore throat? *Med Educ* 2002;**36**:678-81.
16. Coulter A. Managing demand at the interface between primary and secondary care. *BMJ* 1998;**316**:1974-6.
17. Webb S, Lloyd M. Prescribing and referral in general practice: a study of patients' expectations and doctors' actions. *Br J Gen Pract* 1994;**44**:165-9.
18. Howel D, Webster S, Hayes J, Barton A, Donaldson L. The impact of recurrent throat infection on children and their families. *Fam Pract* 2002;**19**:242-6.
19. Taylor SE. Health psychology; fourth edition. McGraw-Hill International editions 1999.
20. Stewart MG, Friedman EM, Sulek M, Hulka GF, Kuppersmith RB, Harrill WC et al. Quality of life and health status in pediatric tonsil and adenoid disease. *Arch Otolaryngol Head Neck Surg* 2000;**126**:45-8.

21. Katznelson D, Gross S. Familial clustering of tonsillectomies and adenoidectomies. *Clin Pediatr (Phila)* 1980;**19**:276-83.
22. Domenighetti G, Bisig BE. Tonsillectomy: a family-transmissible surgical procedure. *Lancet* 1995;**346**:1376.
23. Burton M. Tonsillectomy. *Arch Dis Child* 2003;**88**:95-6.
24. Mainous AGI, Zoorob RJ, Oler MJ, Haynes DM. Patient knowledge of upper respiratory infections: implications for antibiotic expectations and unnecessary utilization. *J Fam Pract* 1997;**45**:75-83.
25. van Duijn H, Kuyvenhoven M, Welschen I, den Ouden H, Slootweg A, Verheij T. Patients' and doctors' views on respiratory tract symptoms. *Scand J Prim Health Care* 2002;**20**:201-2.
26. Delbanco TL. Enriching the doctor-patient relationship by inviting the patient's perspective. *Ann Intern Med* 1992;**116**:414-8.
27. Butler CC, Rollnick S, Pill R, Maggs-Rapport F, Stott N. Understanding the culture of prescribing: qualitative study of general practitioners' and patients' perceptions of antibiotics for sore throats. *BMJ* 1998;**317**:637-42.
28. Wolfensberger M, Haury JA, Linder T. Parent satisfaction 1 year after adenotonsillectomy of their children. *Int J Pediatr Otorhinolaryngol* 2000;**56**:199-205.
29. Conlon BJ, Donnelly MJ, McShane DP. Improvements in health and behaviour following childhood tonsillectomy: a parental perspective at 1 year. *Int J Pediatr Otorhinolaryngol* 1997;**41**:155-61.
30. Faulconbridge RV, Fowler S, Horrocks J, Topham JH. Comparative audit of tonsillectomy. *Clin Otolaryngol* 2000;**25**:110-7.
31. Macfarlane JT, Holmes WF, Macfarlane RM. Reducing reconsultations for acute lower respiratory tract illness with an information leaflet: a randomized controlled study of patients in primary care. *Br J Gen Pract* 1997;**47**:719-22.
32. Macfarlane J, Holmes W, Gard P, Thornhill D, Macfarlane R, Hubbard R. Reducing antibiotic use for acute bronchitis in primary care: blinded, randomised controlled trial of patient information leaflet. *BMJ* 2002;**324**:91-4.
33. Roland M, Dixon M. Randomized controlled trial of an educational booklet for patients presenting with back pain in general practice. *J R Coll Gen Pract* 1989;**39**:244-6.
34. Elwyn G, Gwyn R, Edwards A, Grol R. Is 'shared decision-making' feasible in consultations for upper respiratory tract infections? Assessing the influence of antibiotic expectations using discourse analysis. *Health Expect* 1999;**2**:105-17.
35. Butler CC, Kinnersley P, Prout H, Rollnick S, Edwards A, Elwyn G. Antibiotics and shared decision-making in primary care. *J Antimicrob Chemother.* 2001;**48**:435-40.
36. Donaldson LJ, Hayes JH, Barton AG, Howel D, Hawthorne M. Impact of clinical practice guidelines on clinicians' behaviour: tonsillectomy in children. *J Otolaryngol* 1999;**28**:24-30.
37. Rovers MM, Van Der BS, Ingels K, van der Wilt GJ, Zielhuis GA. Does a trial on the effects of ventilation tubes influence clinical practice? *Clin Otolaryngol* 2003;**28**:355-9.
38. Andrew Clement W, Dempster JH. Implementation by Scottish otolaryngologists of the Schottisch Intercollegiate Guidline Netwotk document *Management of Sore Throats and the Indications for Tonsillectomy*: four years on. J Laryngol Otol 2004;**118**:357-61
39. O'Connor PJ, Amundson G, Christianson J. Performance failure of an evidence-based upper respiratory infection clinical guideline. *J Fam Pract* 1999;**48**:690-7.
40. Moulding NT, Silagy CA, Weller DP. A framework for effective management of change in clinical practice: dissemination and implementation of clinical practice guidelines. *Qual Health Care* 1999;**8**:177-83.
41. Wensing M, van der WT, Grol R. Implementing guidelines and innovations in general practice: which interventions are effective? *Br J Gen Pract* 1998;**48**:991-7.
42. Cohen SJ, Halvorson HW, Gosselink CA. Changing physician behavior to improve disease prevention. *Prev Med* 1994;**23**:284-91.
43. NHG-standaard acute keelpijn. *Huisarts Wet* 1999;**42**:271-278.

44. Monto AS, Ullman BM. Acute respiratory illness in an American community. The Tecumseh study. *JAMA* 1974;**227**:164-9.
45. Kvaerner KJ, Nafstad P, Jaakkola JJ. Upper respiratory morbidity in preschool children: a cross-sectional study. *Arch Otolaryngol Head Neck Surg* 2000;**126**:1201-6.
46. Schilder AG, Lok W, Rovers MM. International perspectives on management of acute otitis media: a qualitative review. *Int J Pediatr Otorhinolaryngol* 2004;**68**:29-36.
47. Del Mar CB, Glasziou PP, Spinks AB. Antibiotics for sore throat. *Cochrane Database Syst Rev* 2000;CD000023.
48. Zwart S, Rovers MM, de Melker RA, Hoes AW. Penicillin for acute sore throat in children: randomised, double blind trial. *BMJ* 2003;**327**:1324.
49. Bertin L, Pons G, d'Athis P, Lasfargues G, Maudelonde C, Duhamel JF, et al. Randomized, double-blind, multicenter, controlled trial of ibuprofen versus acetaminophen (paracetamol) and placebo for treatment of symptoms of tonsillitis and pharyngitis in children. *J Pediatr* 1991;**119**:811-4.
50. Schachtel BP, Thoden WR. A placebo-controlled model for assaying systemic analgesics in children. *Clin Pharmacol Ther* 1993;**53**:593-601.
51. Medisch-farmaceutische mededelingen 1992;7:703-704.
52. van Staaij BK, Rovers MM, van den Akker EH, Schilder AG, Hoes AW. Is it possible to predict chronic recurrent upper respiratory infections in children? submitted 2004.
53. Stewart, LA. Palmer MKB. Meta-analysis of the literature or of individual patient data: is there a difference? *Lancet* 1993;**341**, 418-422.
54. Oxman AD, Clarke MJ, Stewart LA From science to practice. meta-analysis using individual patient data are needed. *JAMA* 1995;**274**:845-846.
55. Kvaerner KJ, Nafstad P, Jaakkola JJK. Upper respiratory morbidity in preschool children - A cross-sectional study. *Archives of Otolaryngology-Head & Neck Surgery* 2000;**126**:1201-6.
56. Selwyn BJ. The Epidemiology of Acute Respiratory-Tract Infection in Young-Children - Comparison of Findings from Several Developing-Countries. *Reviews of Infectious Diseases* 1990;**12**:S870-S888.
57. Straetemans M, Sanders EA, Veenhoven RH, Schilder AG, Damoiseaux RA, Zielhuis GA. Pneumococcal vaccines for preventing otitis media. *Cochrane Database Syst Rev* 2002;CD001480.
58. Dagan R, Sikuler-Cohen M, Zamir O, Janco J, Givon-Lavi N, Fraser D. Effect of a conjugate pneumococcal vaccine on the occurrence of respiratory infections and antibiotic use in day-care center attendees. *Pediatr Infect Dis J* 2001;**20**:951-8
59. Eskola J, Kilpi T, Palmu A, Jokinen J, Haapakoski J, Herva E, et al. Efficacy of a pneumococcal conjugate vaccine against acute otitis media. *N Engl J Med* 2001;**344**:403-9.
60. Hoberman A, Greenberg DP, Paradise JL, Rockette HE, Lave JR, Kearney DH, et al. Effectiveness of inactivated influenza vaccine in preventing acute otitis media in young children: a randomized controlled trial. *JAMA* 2003;**290**:1608-16.
61. Heikkinen T, Ruohola A, Ruuskanen O, Waris M, Uhari M, Hammarstrom L. Intranasally administered immunoglobulin for the prevention of rhinitis in children. *Pediatr Infect Dis J* 1998;**17**:367-72.
62. Hatakka K, Savilahti E, Ponka A, Meurman JH, Poussa T, Nase L, et al. Effect of long term consumption of probiotic milk on infections in children attending day care centres: double blind, randomised trial. *BMJ* 2001;**322**:1327.
63. Lodinova-Zadnikova R, Cukrowska B, Tlaskalova-Hogenova H. Oral administration of probiotic Escherichia coli after birth reduces frequency of allergies and repeated infections later in life (after 10 and 20 years). *Int Arch Allergy Immunol* 2003;**131**:209-11.
64. Falck G, Grahn-Hakansson E, Holm SE, Roos K, Lagergren L. Tolerance and efficacy of interfering alpha-streptococci in recurrence of streptococcal pharyngotonsillitis: a placebo-controlled study. *Acta Otolaryngol* 1999;**119**:944-8.

65. Ruohola A, Heikkinen T, Waris M, Puhakka T, Ruuskanen O. Intranasal fluticasone propionate does not prevent acute otitis media during viral upper respiratory infection in children. *J Allergy Clin Immunol* 2000;**106**:467-71.
66. Puhakka T, Makela MJ, Malmstrom K, Uhari M, Savolainen J, Terho EO, et al. The common cold: effects of intranasal fluticasone propionate treatment. *J Allergy Clin Immunol* 1998;**101**:726-31.

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 is 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. Partly, this variation is explained by cultural differences, such as a preference for antibiotic or surgical management of upper respiratory infections, but inconsistent guidelines on indications for this common procedure also play an important role. The main reason for the absence of generally accepted clinical guidelines is the poor quality of the scientific evidence of the effects of (adeno)tonsillectomy in children. In general, doctors agree that (adeno)tonsillectomy is beneficial for children with very frequent throat infections (i.e. 7 or more per year) and for those with obstructive sleep apnoea. However, there is no consensus for the benefits of (adeno)tonsillectomy in a large proportion of children currently undergoing this procedure for less frequent throat infections and milder symptoms of adenotonsillar hypertrophy or for other indications such as recurrent upper respiratory infections, i.e. 65% of the children underging (adeno)tonsillectomy in the Netherlands.

Not only is our knowledge of the effectiveness of the operation limited, the complaints of children undergoing adenotonsillectomy are also poorly studied. As De Melker stated in 1995 “Diseases: the more common the less studied.” Due to large gaps in our knowledge of so-called “common” diseases a scientific basis for their management is lacking. For example, we know little of the incidence of upper respiratory infections and associated fever episodes in “healthy” children versus children selected for (adeno)tonsillectomy. In addition, the pathogenesis of upper respiratory infections has not been fully elucidated. Many of the children who have recurrent throat and other upper respiratory infections will improve spontaneously and will not need surgical interventions like adenotonsillectomy, So far, however, physicians do not have tools to identify children at high risk of chronic recurrent upper respiratory infections and this may result in unnecessary interventions in children that would have recovered on their own.

To provide further evidence on these issues, we designed a randomised trial on the effectiveness of adenotonsillectomy in children selected for this operation according to current medical practice in the Netherlands and we initiated several additional cross-sectional and follow-up studies

In **Chapter 2** we investigated the age and sex-specific incidence and duration of fever episodes in children, the main symptoms experienced during fever episodes, and the

consequences in terms of physician consultation rates and antibiotic prescription rates. The study was undertaken in a cohort of 321 children aged 2 to 8 years selected for adenotonsillectomy for relatively mild symptoms of throat infections or adenotonsillar hypertrophy. During follow-up the child's temperature was measured daily with a validated infrared tympanic membrane thermometer and parents kept a standardised diary including details on upper respiratory and other symptoms, physician's visits and prescribed medication.
We found that the incidence rate of fever episodes in these children is high, i.e. 3.0 fever episodes per person year and that with growing age the incidence of fever episodes does not materially change. The median duration of a fever episode was 1 day (inter quartile range 1-2) and 60.4% of all fever episodes lasted only one day. During fever episodes one or more symptoms of upper respiratory infections were present in 55.9% of all fever epsisodes (rhinorrhea in 38.9% of fever episodes, sore throat in 20.5% and cough in 35.4%). Gastro-intestinal symptoms were reported in 11.1% of all fever episodes. Antibiotics were prescribed in 7% of all fever episodes and as much as 87.3% of fever episodes never reach medical attention.

In **Chapter 3** we present our attempt to develop and validate an easily applicable prediction rule that can be used by general practitioners as a tool to identify children at risk for developing chronic recurrent upper respiratory infections. Once it is possible to identify such high-risk children, medical resources can be targeted at this group. Two hundred and thirty children aged 2 to 8 years visiting the general practitioner with recurrent symptoms of upper respiratory infections were studied. They were part of a cohort participating in our randomised trial on the effectiveness of adenotonsillectomy. Univariate and multivariate logistic regression modelling were used to evaluate which information - obtained from medical history, physical examination, and laboratory tests - independently contributed to the prediction of chronic recurrent upper respiratory infections, defined as more than 84 days with upper respiratory symptoms per year (assuming an average incidence of 6 upper respiratory infections per year with a mean duration of 14 days). Independent predictors for the development of chronic recurrent upper respiratory infections were age, the number of upper respiratory infections in the previous year, the number of throat infections in the previous year and parental smoking. With these independent predictors we constructed a prediction rule (score = 4 + (–8 x age $\geq$ 4 years) + (–6 x $\geq$ 3 throat infections in previous year) + (7 x > 6 upper respiratory infections in previous year) + (–8 x parental smoking)). The predictive ability of this rule, however, was rather poor; the area under the curve of 0.68 (95% confidence interval 0.61-0.75), indicating a

moderate discriminability of the model. It was not possible to find a threshold in the risk score that classified the children satisfactorily. Expanding the model with simple laboratory measurements, i.e. haemoglobulin level, throat culture or IgA level, did not improve its predictive power. We therefore conclude that in children visiting the general practitioner with recurrent symptoms of upper respiratory infections, the development of chronic recurrent upper respiratory infections cannot be predicted satisfactorily by a set of variables that can be easily obtained in general practice.

In **Chapter 4** we investigated whether the tonsillar flora in children with adenotonsillar disease differs from that in children without such complaints. Tonsil surface swabs were taken from 218 children selected for adenotonsillectomy for recurrent throat infections (3-6 throat infections in the previous year), symptoms of adenotonsillar hypertrophy, or for other indications such as upper respiratory infections and from 100 children without symptoms of adenotonsillar disease who visited the ophthalmology outpatient clinic. Potential respiratory pathogens were found in 54% of the adenotonsillectomy group, compared to 41% of the control group (p=0.04). *Haemophilus influenzae* was the commonest pathogen in both groups, being found in 41% of the adenotonsillectomy group and 34% of the control group (p=0.27). *Moraxella catarrhalis* was also found more often in the adenotonsillectomy group compared to the control group: 7% vs 0% (p=0.004). *Haemophilus influenzae* was more often found in children selected for adenotonsillectomy for adenotonsillar hypertrophy, or for other indications such as upper respiratory infections than in children selected for adenotonsillectomy for recurrent throat infections: 48% versus 32%, respectively (p=0.03). We conclude that the prevalence of potential respiratory pathogens on the tonsillar surface of children with relatively mild symptoms of throat infections or adenotonsillar hypertrophy differs only slightly from that in children without such symptoms and that variation in the microbial flora does not seem to play an essential role in the predisposition of these children to tonsillar disease.

In **Chapter 5** of this thesis the current evidence regarding the effectiveness of tonsillectomy with or without adenoidectomy in children is presented. A meta-analysis of the existing 6 trials of (adeno)tonsillectomy shows that the operation compared to no surgery reduces the incidence of sore throat episodes by 1.2 episodes per person year (95% CI 1.1 to 1.3), sore throat associated days 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). 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 our randomised trial (presented in chapter 7) fever, measured by the parents with an infrared tympanic membrane thermometer, is the primary outcome. In the trial the parents measured their child's temperature daily. In **Chapter 6** we present the accuracy of the infrared tympanic membrane thermometer (Braun Pro 3000) and the feasibility of daily infrared tympanic membrane thermometer measurements at home. To establish the accuracy of the infrared tympanic membrane thermometer, rectal and tympanic membrane temperature measurements were performed in 41 children, aged 2 to 10 years. To establish the feasibility of daily infrared tympanic temperature measurements at home, parents of 21 children performed daily measurements for 2 weeks. With fever defined as a body temperature of ≥ 38.0 ºC, sensitivity was 93.3%, specificity 92.0%, positive predictive value 87.5%, negative predictive value 95.8%, and the concordance rate 92.5%. During the test period of 2 weeks the technique of the tympanic membrane temperature measurements remained adequate in 93% of the parents. We therefore conclude that the tympanic membrane temperature measured by the Braun Pro 3000 accurately reflects rectal temperature, validly assesses the presence of fever in children, and is easy to use, even on a daily basis.

In **Chapter 7**, the results of our trial (NATAN project: Nederlands Adenotonsillectomy project; Tonsillectomy and Adenoidectomy in the Netherlands) on the effectiveness of adenotonsillectomy in 300 Dutch children aged 2 to 8 years, selected for adenotonsillectomy according to current medical practice, are reported. Excluded from this trial were children with very frequent recurrent throat infections (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. 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. We conclude that in the children selected for adeno-tonsillectomy for relatively mild symptoms of throat infections or adenotonsillar hypertrophy, the operation had no relevant clinical benefits to offer over a watchful waiting policy.

In **Chapter 8** we assessed the balance between costs and effects of adenotonsillectomy in children with relatively mild symptoms of throat infections or adenotonsillar hypertrophy. The economic evaluation focussed on the incremental costs per fever episode, throat infection and upper respiratory infection avoided. Costs were estimated at the patient level for the year 2002. Uncertainty of the estimates was addressed by means of bootstrapping. Overall, patients in the adenotonsillectomy group incurred €1,196 on average, whereas patients in the watchful waiting group incurred €804, i.e. adenotonsillectomy implied almost 1.5 times higher costs (49% increase). With regard to uncertainty, the bootstrap analyses selected that adenotonsillectomy increases overall costs with 100% certainty**.** The incremental cost per episode of fever avoided, per throat infection avoided and per upper respiratory infection avoided were €2,333, €1,444 and €788, respectively. We therefore conclude that for the majority of Dutch children currently undergoing adenotonsillectomy for relatively mild symptoms of throat infections or adenotonsillar hypertrophy, the operation resulted in a significant increase in costs without relevant clinical benefit.

In **Chapter 9** we explore the potential impact of our trial results on daily general practice. The results of our trial suggest that referral for surgery of children with relatively mild symptoms of throat infections or adenotonsillar hypertrophy for surgery is usually not indicated. Many general practitioners and ENT surgeons, however, believe that adenotonsillectomy is an effective procedure in these children. Prior expectations of parents in the beneficial effect of surgery are also usually strong. The question is whether our trial results will change these beliefs. If the general practitioner agrees with our trial results and decides to implement them in daily practice, he/she has certain tools that can support this evidence-based management, such as health education, encouragement of self-management, shared decision-making, management guidelines and offering alternative treatment options.
Recommendations for future research:
1) IPD-meta-analysis. It is important to individualise the currently available treatment options better, as there is no doubt that subgroup(s) exist in which an operation and/or antibiotics are more effective. Unfortunately, these subgroups cannot be identified as

yet. The power of the available individual trials on adenotonsillectomy is too limited to identify subgroups of children that might benefit from the operation. To enable identification of these subgroups, an individual patient data (IPD) meta-analysis with original data from the available adenotonsillectomy trials, including those from the NATAN trial, should be performed.

2) Prognostic research. If it were possible to identify children at high-risk of developing chronic recurrent upper respiratory infections or complications, we could target our medical interventions, such as adenotonsillectomy, at these children. So far, however, it is not possible to predict that the child's symptoms will either persist or improve spontaneously without medical intervention.

3) Etiological research. Upper respiratory infections are known to be a multifactorial disease resulting from interplay between host factors such as age, genetic predisposition, immunological response, and the microbial load (viral and bacterial), which is influenced by environmental factors such as siblings, group day care and season. The relative importance of, and interactions between the various known etiological factors is still poorly understood. More insight into the pathogenesis of upper respiratory infections is urgently needed to answer the question why some children are more susceptible to infections of Waldeyer's ring than others and to develop more effective preventive and therapeutic approaches.

4) Preventive measurements and novel therapies. Future research should focus on new and more effective preventive measurements and therapies that reduce the frequency and/or severity of upper respiratory infections. Most success is expected if such interventions focus on interactions between pathogenic factors.

Het verwijderen van de keelamandelen (tonsillectomie), al dan niet gecombineerd met het verwijderen van de neusamandel (adenotomie), is één van de meest frequent uitgevoerde operaties bij kinderen in westerse landen. Opvallend is dat veel meer Nederlandse kinderen een (adeno)tonsillectomie ondergaan (115 per 10.000 kinderen per jaar) dan Britse (65 per 10.000) en Amerikaanse (50 per 10.000) kinderen. Deze variatie wordt deels verklaard door culturele verschillen zoals voorkeur voor een chirurgische dan wel een antibiotische behandeling van bovenste luchtweginfecties. Ook speelt het ontbreken van richtlijnen omtrent de indicatie voor deze ingreep een belangrijke rol. De belangrijkste oorzaak voor het ontbreken van algemeen geaccepteerde richtlijnen is het gebrek aan kwaliteit van het beschikbare wetenschappelijke onderzoek naar de effectiviteit van (adeno)tonsillectomie bij kinderen. Er is consensus onder artsen dat adenotonsillectomie (ATE) effectief is bij kinderen met zeer frequente keelontstekingen (7 of meer per jaar) en bij kinderen met obstructief slaap-apnoesyndroom. Er is echter geen consensus over het nut van (adeno)tonsillectomie bij de meerderheid (ongeveer 65% van alle ingrepen) van de kinderen die momenteel in Nederland geopereerd worden voor minder frequent recidiverende keelontstekingen, milde obstructieve klachten ten gevolge van tonsil en adenoid hypertrofie en andere indicaties zoals recidiverende bovenste luchtweginfecties.

Niet alleen is onze kennis over de effectiviteit van de ingreep beperkt, ook is weinig bekend over de klachten van kinderen, die in aanmerking komen voor adenotonsillectomie. Zoals de Melker al in 1995 verwoordde: “de meest frequent voorkomende ziekten worden het minst frequent bestudeerd.”. Zo is onderzoek naar de incidentie van bovenste luchtweginfecties en geassocieerde koortsepisoden bij “gezonde” kinderen en kinderen met een indicatie voor adenotonsillectomie nauwelijks voorhanden. Bovendien is de aetiologie van bovenste luchtweginfecties nog niet opgehelderd. Bij veel kinderen die last hebben van recidiverende keelontstekingen en andere bovenste luchtweginfecties zullen de klachten spontaan en op relatief korte termijn verdwijnen, terwijl bij andere kinderen de klachten aan zullen houden. Als het mogelijk zou zijn te voorspellen bij welke kinderen de klachten aan zullen houden en bij welke niet, zouden daardoor onnodige interventies kunnen worden voorkomen bij kinderen die ook spontaan op korte termijn minder klachten zouden krijgen.

Om meer inzicht te krijgen in de hierboven beschreven onderwerpen, hebben we een aantal studies opgezet. Naast een gerandomiseerde trial om de effectiviteit van adenotonsillectomie vast te stellen bij kinderen die volgens de gangbare praktijk in

Nederland in aanmerking komen voor deze operatie, zijn een aantal cross-sectionele en follow-up onderzoeken uitgevoerd.

In **Hoofdstuk 2** onderzochten we de leeftijd- en sexspecifieke incidentie en duur van koortsepisoden bij 321 kinderen in de leeftijd van 2 tot 8 jaar die in aanmerking kwamen voor adenotonsillectomie vanwege relatief milde klachten van recidiverende keelontstekingen en/of adenotonsillaire hypertrofie. Daarnaast werden de voornaamste symptomen die deze kinderen ondervonden gedurende deze koortsepisoden en de medische gevolgen, in het bijzonder artsenbezoek en antibioticavoorschriften beschreven. Gedurende de follow-up van 2 jaar werd de temperatuur van het kind dagelijks gemeten met een gevalideerde infrarood oorthermometer. Bovendien hielden de ouders een dagboek bij waarin klachten van de bovenste luchtwegen en andere klachten, alsmede artsenbezoek en gebruik van medicatie werden genoteerd.
We vonden een hoge incidentie van koortsepisoden bij deze kinderen, namelijk 3,0 koortsepisoden per persoonsjaar. Met het ouder worden veranderde de incidentie van de koortsepisoden niet wezenlijk. De mediane duur van de koortsepisoden was 1 dag (interkwartielafstand 1-2) en 60,4% van alle koortsepisoden duurde slechts 1 dag. Bij 55,9% van de koortsepisoden hadden kinderen klachten van de bovenste luchtwegen (loopneus in 38,9% van de koortsepisoden, keelpijn in 20,5% en hoest in 35,4%). Gastro-intestinale klachten werden gerapporteerd in 11,1% van alle koortsepisoden. Antibiotica werden voorgeschreven bij 7,0% van alle koortsepisoden en bij 87,3% van de koortsepisoden werd geen arts geraadpleegd.

In **Hoofdstuk 3** presenteren wij onze poging om een bruikbare predictieregel voor de huisarts te ontwikkelen, waarmee kinderen geïdentificeerd kunnen worden met een hoog risico op het ontwikkelen van chronisch recidiverende bovenste luchtweginfecties. Als het mogelijk zou zijn deze kinderen te identificeren, zouden onze medische interventies, zoals adenotonsillectomie, vooral op deze groep kinderen kunnen worden gericht. We bestudeerden 230 kinderen in de leeftijd van 2 tot 8 jaar, die hun huisarts bezochten vanwege recidiverende bovenste luchtwegklachten. Deze kinderen maakten deel uit van het cohort kinderen, dat deelnam aan onze gerandomiseerde trial naar de effectiviteit van adenotonsillectomie. Univariate en multivariate regressie modellen werden gebruikt om te evalueren welke informatie, verkregen uit de anamnese, lichamelijk onderzoek en laboratorium bepalingen, onafhankelijk bijdroegen aan het voorspellen van chronisch recidiverende bovenste luchtweginfecties. De uitkomst chronisch recidiverende bovenste luchtweginfecties was gedefinieerd als meer dan 84 dagen met bovenste luchtwegklachten. Deze

uitkomstmaat was gebaseerd op een gemiddelde incidentie bij kinderen van 6 bovenste luchtweginfecties per jaar met een gemiddelde duur van 14 dagen. Onafhankelijke voorspellers voor het ontwikkelen van chronisch recidiverende bovenste luchtwegklachten waren leeftijd, het aantal bovenste luchtweginfecties in het voorafgaande jaar, het aantal keelontstekingen in het voorafgaande jaar, en rokende ouders. Met deze onafhankelijke voorspellers construeerden wij een predictieregel (score = 4 + (–8 x leeftijd ≥ 4 jaar) + (–6 x ≥ 3 keelontstekingen in het voorafgaande jaar) + (7 x > 6 bovenste luchtweginfecties in het voorafgaande jaar) + (–8 x rokende ouders). De oppervlakte onder de ROC curve was 0,68 (95% betrouwbaarheidsinterval 0,61-0,75), hetgeen betekent dat de predictieregel een matig discriminerend vermogen heeft. Uitbreiding van de regel met laboratoriumbepalingen, zoals haemoglobuline gehalte, IgA waarde, of keelkweek vergrootte het voorspelende vermogen niet. Wij concluderen dat de huisarts met behulp van eenvoudig vast te stellen parameters in de praktijk onvoldoende kan voorspellen, welke kinderen chronisch recidiverende bovenste luchtweginfecties zullen ontwikkelen.

In **Hoofdstuk 4** onderzochten wij of de tonsillaire flora van kinderen met een indicatie adenotonsillectomie verschilt van die van kinderen zonder indicatie adeno-tonsillectomie. Bij 218 kinderen die in aanmerking kwamen voor adenotonsillectomie vanwege relatief milde klachten van recidiverende keelontstekingen, milde obstructieve klachten ten gevolge van tonsil en adenoid hypertrofie of recidiverende bovenste luchtweginfecties werd een uitstrijk van het tonsiloppervlak afgenomen. Bij 100 controle kinderen zonder deze klachten, die de polikliniek oogheelkunde bezochten werd ook een uitstrijk van het tonsiloppervlak afgenomen. Bij 54% van de kinderen van de adenotonsillectomie groep werden potentieel respiratoire pathogenen gekweekt, en bij 41% van de controlegroep (p=0,04). *Haemophilus influenzae* was in beide groepen de meest frequent geïsoleerde bacterie: bij 41% in de adenotonsillectomie groep en bij 34% in de controlegroep (p=0,27). *Moraxella catarrhalis* werd vaker gekweekt bij de adenotonsillectomie groep dan bij de controlegroep: 7% versus 0% (p=0,004). *Haemophilus influenzae* werd vaker gevonden bij kinderen die in aanmerking kwamen voor adenotonsillectomie vanwege milde obstructieve klachten ten gevolge van tonsil en adenoid hypertrofie of recidiverende bovenste luchtweginfecties dan bij kinderen met klachten van recidiverende keelonstekingen, respectievelijk 48% versus 32% (p=0,03). Wij concluderen dat het voorkomen van potentieel respiratoire pathogenen bij kinderen met relatief milde klachten van keelontstekingen of adenotonsilaire hypertrofie nauwelijks verschilt van die in kinderen zonder zulke klachten. Variatie in de

microbiologische flora op het tonsiloppervlak lijkt daarom geen belangrijke rol te spelen bij de aanleg van kinderen tot relatief milde klachten van keelontstekingen en/of adenotonsillaire hypertrofie.

In **Hoofdstuk 5** van dit proefschrift worden de beschikbare studies 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 1,1 tot 1,3), een afname van keelpijn-gerelateerd schoolverzuim met 2,8 dagen per persoonsjaar (95% betrouwbaarheidsinterval 1,6 tot 3,9) en een afname van bovenste luchtweginfecties met 0,5 episoden per persoonsjaar (95% betrouwbaarheidsinterval 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. Klaarblijkelijk neemt de frequentie van deze infecties af met het ouder worden, en wordt het beloop nauwelijks beïnvloedt door het wel of niet ondergaan van een adenotonsillectomie.

In onze gerandomiseerde trial (zie hoofdstuk 7) is koorts, gemeten met een infrarood oorthermometer, gekozen als de primaire uitkomstmaat. Daartoe werd door de ouders dagelijks de temperatuur gemeten met een infrarood oorthermometer. In **Hoofdstuk 6** presenteren we de betrouwbaarheid van de infrarood oorthermometer (Braun Pro 3000) en haalbaarheid van dagelijkse temperatuurmetingen met een oorthermometer in de thuissituatie. Om de betrouwbaarheid van de infrarood oorthermometer te bepalen, werden zowel rectale als tympanale (in het oor) temperatuurmetingen verricht bij 41 kinderen in de leeftijd van 2 tot 10 jaar. Om de haalbaarheid van dagelijkse temperatuurmetingen met de oorthermometer in de thuissituatie te onderzoeken, namen 21 ouders gedurende 2 weken dagelijks de temperatuur op bij hun kind. Bij een definitie van koorts als een lichaamstemperatuur van ≥ 38 °C was de sensitiviteit 93,3%, de specificiteit 92,0%, de positief voorspellende waarde 87,5%, de negatief voorspellende waarde 95,8% en de concordantie ratio 92,5%. De technische uitvoering van de temperatuurmetingen door de ouders werd aan het einde van de 2 weken durende testperiode beoordeeld door de onderzoeksarts; deze bleek bij 93% van de

ouders goed te zijn. Wij concluderen dat de Braun Pro 3000 betrouwbaar de lichaamstemperatuur weergeeft en dat de thermometer gemakkelijk is in het gebruik.

In **Hoofdstuk 7** wordt verslag gedaan van de resultaten van het NATAN project (Nederlands Adenotonsillectomy project; Tonsillectomy and Adenoidectomy in the Netherlands) naar de effectiviteit van adenotonsillectomie bij 300 Nederlandse kinderen van 2 tot 8 jaar die volgens de huidige klinische praktijk in aanmerking kwamen voor adenotonsillectomie. 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). 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 6,00 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. Deze resultaten geven aan dat bij kinderen met relatief milde klachten van recidiverende keelontstekingen en/of adenotonsillaire hypertrofie en andere indicaties zoals recidiverende bovenste luchtweginfecties, de voordelen van een adenotonsillectomie gering zijn in vergelijking met een afwachtend beleid.

In **Hoofdstuk 8** onderzochten we de balans tussen kosten en effecten van adenotonsillectomie bij kinderen met relatief milde klachten van recidiverende keelontstekingen en/of adenotonsillaire hypertrofie. Parallel met de klinische studie werden de werkelijke kosten per behandelingsstrategie geschat vanuit een maatschappelijk perspectief. De balans tussen kosten en effecten werd geraamd door

een directe vergelijking van de kosten en effecten in de beide armen van de trial. De onzekerheid van de schattingen werd onderzocht met behulp van bootstrap technieken. De kosten per patiënt waren in de adenotonsillectomie groep gemiddeld €1.196 en in de niet-chirurgische groep gemiddeld €804; de kosten in de adenotonsillectomie groep waren dus 49% hoger dan in de niet-chirurgische groep. Op basis van bootstrapsimulaties kon met 100% zekerheid worden vastgesteld dat de kosten in de adenotonsillectomie-arm hoger uitvielen. De incrementele kosten per voorkomen koortsepisoden, per voorkomen keelontsteking en per voorkomen bovenste luchtweginfectie waren respectievelijk €2.333, €1.444 en €788. We concluderen daarom dat voor een aanzienlijk deel van de Nederlandse kinderen, die momenteel een adenotonsillectomie ondergaat voor relatief milde klachten van recidiverende keelontstekingen en/of adenotonsillaire hypertrofie, adenotonsillectomie resulteert in een significante verhoging van de kosten zonder relevante klinische effecten.

In **Hoofdstuk 9** exploreren we de potentiële invloed van onze trial op de dagelijkse praktijk. De resultaten van onze trial tonen aan dat een verwijzing voor chirurgie bij kinderen met relatief milde klachten van recidiverende keelontstekingen en/of adenotonsillaire hypertrofie over het algemeen niet geïndiceerd is. Echter, veel huisartsen en KNO-artsen zijn van mening dat adenotonsillectomie effectief is bij deze kinderen. Ouders hebben in het algemeen ook hoge verwachtingen ten aanzien van de effectiviteit van de ingreep. De vraag is of onze trialresultaten deze verwachtingen zal veranderen. Als de huisarts zich kan vinden in de resultaten van ons onderzoek en besluit deze toe te passen in zijn dagelijkse praktijkvoering, heeft hij enkele mogelijkheden om dit evidence-based beleid te ondersteunen. Voorbeelden zijn het geven van gezondheidsvoorlichting, het stimuleren van zelfredzaamheid bij de behandeling van bovenste luchtwegklachten, het in de spreekkamer gebruik maken van gesprekstechnieken zoals “shared desicion-making”, het gebruik maken van behandelingsrichtlijnen en het aanbieden van andere behandelingsmogelijkheden. Aanbevelingen voor toekomstig onderzoek:
1) IPD meta-analyse. Omdat er geen twijfel over bestaat dat er subgroepen kinderen zijn bij wie adenotonsillectomie effectiever is, zou het individualiseren van de reeds bestaande behandelingsmogelijkheden -adenotonsillectomie of een niet-chirurgisch beleid- één van de doelen van toekomstig onderzoek kunnen zijn. Omdat de patiëntenaantallen van de huidige beschikbare trials te klein zijn om subgroepen te identificeren, is het wenselijk een meta-analyse uit te voeren met individuele-patiënten-data. 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 hebben.

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

3) Aetiologisch onderzoek. Het is bekend dat bovenste luchtweginfecties 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 aetiologische factoren is onvoldoende bekend.

4) Preventieve en therapeutische maatregelen. Het verkrijgen van meer inzicht in de aetiologie 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.

Publications by the author

1. van Staaij BK, van den Akker EH, Poels PJ, Hoes AW, Schilder AG. Adenotonsillectomie bij kinderen: nog onvoldoende wetenschapelijk onderbouwd. [Adenotonsillectomy in children: not yet scientifically validated]. *Ned Tijdschr Geneeskd* 2002;**146**:8-12.
2. van Staaij BK, van den Akker EH, Van Dorsser EHMD, Fleer A, Hoes AW, Schilder AGM. Does the tonsillar surface flora differ in children with and without tonsillar disease? *Acta Oto-Laryngologica* 2003;**123**:873-8.
3. van Staaij BK, Rovers MM, Schilder AG, Hoes AW. Accuracy and feasibility of daily infrared tympanic membrane temperature measurements in the identification of fever in children. *Int J Pediatr Otorhinolaryngol* 2003;67(10):1091-1097.
4. van Staaij BK, van den Akker EH, van der Heijden GJMG, Schilder AGM, Hoes AW. Adenotonsillectomy for upper respiratory infections. Evidence based? *Arch Dis Child* 2004. Accepted for publication.
5. van Staaij BK, van den Akker EH, Rovers MM, Hordijk GJ, Hoes AW, Schilder AGM. Adentonsillectomy in children: a randomised trial. *BMJ* 2004. In press.
6. van den Akker EH, Rovers MM, van Staaij BK, Hoes AW, Schilder AG. Representativeness of trial populations: an example from a trial of adenotonsillectomy in children. *Acta Otolaryngol* 2003;**123**:297-301.

Vele mensen waren betrokken bij het tot stand komen van dit proefschrift. Ik wil hen hier graag bedanken voor hun enthousiasme, steun en begeleiding.

Allereerst wil ik alle kinderen en hun ouders bedanken, die hebben deelgenomen aan het NATAN project. Dankzij jullie enthousiaste en trouwe deelname is het NATAN project een groot succes geworden. Zonder jullie was dit onderzoek niet mogelijk geweest!

De KNO-artsen, poliverpleegkundigen en huisartsen, die de ouders en hun kinderen hebben geïnformeerd over en enthousiast gemaakt voor ons onderzoek, wil ik hartelijk bedanken. Het was voor de ouders belangrijk om te weten dat hun huisarts en KNO-arts achter het NATAN project stond.

Prof. Dr. AW Hoes (promotor), beste Arno, jouw vermogen om in korte tijd de vinger op de zere plek van een studieopzet of artikel te leggen, heb ik zeer leren waarderen. Tijdens onze besprekingen vuurde je in een rap tempo je suggesties op me af. Later, als ik alles nog eens rustig over las en het tot me door kon laten dringen, bleek daar zeer waardevolle informatie in te zitten. Ik denk met name met veel plezier terug aan die laatste paar maanden van het promotietraject, waarin we de resterende artikelen hebben afgeschreven en we beiden onze schouders eronder hebben gezet om het op tijd af te krijgen.

Dr. AGM Schilder (co-promotor), beste Anne, jouw niet aflatende enthousiasme en doorzettingsvermogen was één van de belangrijkste motors van het NATAN project. Zonder jouw drive was dit project niet zo succesvol geworden als het nu is. Altijd kritisch, want alles kan natuurlijk altijd net iets anders of beter. Jij bent iemand die een artikel helemaal blauw van de correcties terug kan geven en er dan vervolgens “wordt heel fraai” boven kan zetten. Wat ik enorm waardeer is jouw gedrevenheid om altijd voor het beste te gaan; dat krijg je dan ook meestal voor elkaar.

Jet van den Akker (mede-promovendus), lieve Jet, als ik aan jouw denk moet ik altijd denken aan dat halve glas; bij jouw is dat echt altijd half vol. Ik denk dat het heel bijzonder is hoe wij binnen het NATAN project hebben samengewerkt. Op momenten dat het nodig was vol gas en wetende dat je van de ander op aan kon. Met iemand samen door de bergen en dalen van een promotieonderzoek kunnen gaan, geeft er een extra dimensie aan. Dat we bij elkaars promotie paranimf zijn, zegt voldoende over onze samenwerking en vriendschap van de afgelopen 5 jaar.

Natuurlijk ook mijn hartelijke dank voor de veldwerkers van het NATAN onderzoek: het NATAN team. Met zijn allen deelden we dat kleine kamertje op de 4e verdieping van het WKZ. Naast dat er hard gewerkt werd, was er altijd ruimte voor gezelligheid, een kopje koffie en werden er (soms uitgebreid) de dagelijkse beslommeringen en belevenissen van "en route" besproken. Gedurende de gehele projecttijd was Nelly van Eden de projectsecretaresse. In de chaos die dit onderzoek soms met zich meebracht, bleef jij de orde bewaren. Samen met datamanagement bedacht jij een zeer werkzame database, die zijn waarde tijdens het schrijven van onze artikelen bewezen heeft. Je nuchterheid was vaak zeer verfrissend.
De artsen, die mee hebben gewerkt aan de dataverzameling wil ik hartelijk bedanken, te weten Patrick Poels, Ward Videler, Charlotte van Krevel en Wietske Richard. Jullie inzet om het includeren en vervolgen van de kinderen vloeiend te laten verlopen, is heel belangrijk geweest.
Ook de verpleegkundigen van het NATAN team wil ik bedanken voor hun samenwerking. Met veel bewondering denk ik aan de enorme hoeveelheid telefoontjes die jullie elke maand verrichtten en aan jullie betrokkenheid bij de andere zaken van het NATAN project. Els de Bruin, Ella Wijnia, Karry Meertens, Judith Koppelman, Fien Stern en Renate Wieman, hartelijke dank.

Dr. MM Rovers, beste Maroeska, jij kwam op een voor mijn promotieonderzoek belangrijk moment bij het Julius Centrum werken. Heel prettig om een vraagbaak één deur verder te hebben! Wat ik enorm in jouw waardeer, is dat je zeer benaderbaar bent voor vragen en eigenlijk altijd bereid bent om mee te denken over een oplossing. Met jouw heb ik me door de regressie analyses heen geworsteld, iets waarvan ik niet gedacht had het ooit te zullen begrijpen.

De ondersteuning van de mensen van datamanagement was erg belangrijk om de enorme hoeveelheid aan data, die zo'n groot onderzoek als het NATAN project met zich meebrengt, te stroomlijnen. Dank: Hanneke den Breeijen, Nicole Boekema, Robert Veen. In het bijzonder wil ik Frank Leus bedanken: na een "echt-laatste SPSS bestand" was je toch altijd weer bereid om een "nu-echt-laatste SPSS bestand" klaar te maken.

Alle leden van de stuurgroep wil ik bedanken voor het meedenken met de opzet en de uitvoering van NATAN project, in alfabetische volgorde Dr. AAA Bak, Dr. PPG van Benthem, Dr. A Fleer, Prof. Dr. DE Grobbee, Prof. Dr. GJ Hordijk, Prof. Dr. JLL

Kimpen, Prof. Dr. EAM Sanders, Prof. Dr. ThJM Verheij. In het bijzonder Dr. E Buskens, beste Erik, voor de begeleiding bij de KEA-artikel.

Dr GJMG van der Heijden, beste Geert, dank voor het wegwijs maken in de methodologie van de systematische reviews.

Ik wil ook de medewerkers van het microbiologisch laboratorium hartelijk bedanken voor de beoordelen van de vele tonsilkweken, die zij wekelijks van ons kregen. Heel fijn dat jullie na al die honderden kweekjes steeds kritisch op de beoordeling ervan bleven.

De leden van de beoordelingscommissie, die gedurende de warme zomermaanden mijn proefschrift beoordeeld hebben, wil ik hartelijk bedanken: Prof. Dr. MJM Bonten, Prof. Dr. J Kimpen, Prof. Dr. WJJ Assendelft, Prof. Dr. M Offringa, Prof. Dr. PB Van Cauwenberge

Lieve kamergenoten van de HAG: Wim Opstelten, Frans Rutten, Tjarda Scheltens, Paul Janssen, Ruud Oudega, Rykel van Bruggen, Hans Kelder, Pieta Bruggink, Frits Cleveringa en de andere ex-kamergenoten die mij reeds voorgingen. Een kamer vol huisartsen is bijzonder in het Stratenum. Ik heb het altijd inspirerend gevonden daar te kunnen werken. Veel dank voor de gezellige momenten en de motiverende gesprekken, die vaak gingen over de gebieden die ons allen boeien: het verrichten van onderzoek en/in de huisartsgeneeskunde.

Monique den Hartog, mijn hartelijke dank voor het beantwoorden van al mijn “edit” vraagstukken.

Hierbij wil ik ook mijn hartelijke dank uitspreken voor de huisartsen en assistenten van Huisartsenpraktijk de Bundeling. De afgelopen 2 jaar heb ik met veel plezier in jullie praktijk gewerkt. De open sfeer, die er in de Bundeling heerst, vind ik heel plezierig. Er is altijd ruimte voor een gezellig praatje, maar ook voor feedback.

Lieve papa en mama, lieve Claire, lieve Michiel en Hilde. Mijn hartelijke dank voor het vele inspringen in de laatste paar maanden van mijn onderzoek. Zonder jullie hulp was het waarschijnlijk niet op tijd afgekomen. Lieve Claire, geweldig dat je me terzijde wilt staan tijdens mijn verdediging. Even geen Warschau of Berlijn, maar gewoon Utrecht!

Lieve Matthijs, Boele en Karlijn, ik ben ontzettend trots op jullie. Jullie zijn vrolijke, lieve kinderen, die me elke dag weer ontzettend blij maken. Het is heerlijk jullie te zien ontwikkelen en opgroeien. Vanaf nu is dat "grote werk" van mamma afgelopen.
Lieve Stef, je bent enorm belangrijk voor me. Ik wil je hartelijk bedanken voor alle liefde, steun en ruimte die je me gegeven hebt en voor het vertrouwen dat we in elkaar hebben. Ons gezin, onze gezamenlijke zorg voor Matthijs, Boele en Karlijn, is het mooiste wat me kon overkomen.

Curriculum Vitae

Birgit van Staaij was born on 23 July 1965 in The Hague, The Netherlands. In 1983, after graduating secondary school at the Bisschoppelijk College in Weert (gymnasium beta), she started Medical School at the University of Utrecht, the Netherlands. On 7 November 1988 she obtained her doctor's degree with the certificate "clear pass". She obtained her MD degree in July 1991. During the following years she worked as a physician in department of surgery in Barnstaple, England and in Hospital Gooi-Noord in Blaricum, The Netherlands and in the nursing home St Elisabeth Verpleeg- en Gasthuis in Amersfoort, the Netherlands. In May 1994 she started with the 2-years general practitioners training at the Erasmus University of Rotterdam. From May 1996 till 1998 she worked as a general practioner. In April 1999 she started the work described in this thesis at the Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht (supervised by Prof. Dr. AW Hoes and Dr. AGM Schilder). The project was financial supported by the Dutch Health Care Insurance Board. Besides, she works as a general practitioner in Soest.