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.