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Adenoidectomy and nasopharyngeal carriage of *Streptococcus pneumoniae* in young children

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ABSTRACT

Objective The effect of adenoidectomy on nasopharyngeal colonisation of pathogens has not previously been evaluated. The authors studied the effect of adenoidectomy on nasopharyngeal colonisation by bacteria causing otitis media and the effect of adenoidectomy on the development of pneumococcal capsular polysaccharide antibodies.

Design Randomised controlled study.

Setting Tertiary care centre.

Patients 217 children aged 12–48 months who had recurrent or persistent otitis media were randomised. 166 children were followed up for 3 years.

Intervention Random allocation to undergo adenoidectomy or not to undergo adenoidectomy. All the children underwent insertion of tympanostomy tubes.

Main outcome measures Nasopharyngeal colonisation by pneumococci, *Haemophilus influenzae* and *Moraxella catarrhalis* 1, 2 and 3 years after randomisation. Serum IgG antibodies against pneumococcal capsular polysaccharide serotypes 6B, 14, 19F and 23F 3 years after randomisation.

Results After the first year of randomisation adenoidectomy increased nasopharyngeal carriage of pneumococci (RR, 1.47; 95% CI 1.04 to 2.07) but it did not influence the carriage of *H influenzae* or *M catarrhalis*. Among carriers of serotype 6B pneumococci, adenoidectomy resulted in lower concentrations of pneumococcal serotype 6B polysaccharide antibodies (ratio of geometric means of antibody concentrations, 0.37; 95% CI 0.16 to 0.85). Concentrations of serotype 14, 19F and 23F antibodies seemed not to be influenced by adenoidectomy. Despite this, adenoidectomy resulted in a significant increase in nasopharyngeal carriage of serotype 19F pneumococci.

Conclusions Adenoidectomy increases the risk of nasopharyngeal carriage of pneumococci in children younger than 4 years of age. This may be independent of the development of serum IgG capsular polysaccharide antibodies.

INTRODUCTION

The adenoid is located in the nasopharynx and is mainly composed of lymphatic tissue. It is covered by an epithelium that forms specialised invaginated crypts that are thought to convey nasopharyngeal antigens inside the adenoid.¹ The adenoid is thought to participate in immune responses in the upper respiratory tract but its exact contribution in the maturation of the overall immune system is not known. The characteristic feature of the adenoid is that it is present at birth and it is largest at 7–10 years of age, whereafter it gradually decreases in size and is usually rudimentary in adults.² The

What is already known on this topic

- It is not known how adenoidectomy influences nasopharyngeal colonisation of *Streptococcus pneumoniae*, *Haemophilus influenzae* or *Moraxella catarrhalis*.
- The natural function of the adenoid is unknown.

What this study adds

- Adenoidectomy in children younger than 4 years may increase the risk of nasopharyngeal carriage of pneumococci.
- The adenoid may have a function in the clearance and prevention of pneumococcal colonisation. This may be independent of the production of IgG capsular polysaccharide antibodies.

function of the adenoid is probably not insignificant, as the adenoid has persisted through human evolution. Despite this, children who have undergone adenoidectomy are apparently healthy and adenoidectomy is not known to cause any severe long-term side effects.

A usual reason for adenoidectomy is nasopharyngeal obstruction, which can result in continuous mouth breathing, sleep disturbances and long-term effects on the growth of facial skeleton and teeth.³ Chronic adenoidal infection may be associated with otitis media by transmission of the infection through the eustachian tubes into the middle ears.⁴ Removal of enlarged or chronically infected adenoid by adenoidectomy has been reported to be effective in the resolution of chronic otitis media with effusion (COME) in children who are older than 4 years of age.^{5–7} Adenoidectomy has also been reported to be effective in the treatment of children with recurrent otitis media who had previously received tympanostomy tubes.⁸

These reports have encouraged implementing adenoidectomy to prevent of otitis media in children younger than 4 years of age.⁹ This has been tempting as this is the age range that has the highest prevalence of acute otitis media. The rationale has been that the adenoid could be chronically

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infected even in very young children predisposing to otitis media. Disappointingly, randomised studies have failed to prove any efficiency of adenoidectomy in preventing acute otitis media in children younger than 4 years of age^{10–12} as well as in older children when used as the first surgical treatment.¹³ Currently, adenoidectomy is not recommended as the primary treatment for otitis media unless an evident adenoidal pathology exists, such as enlarged adenoid causing nasopharyngeal obstruction.^{14 15}

Although adenoidectomy is among the most prevalent surgical operations in children, its effect on the nasopharyngeal carriage of pathogens causing otitis media has not previously been assessed. We have carried out a randomised study on the effect of adenoidectomy that showed that adenoidectomy was inefficient in preventing acute otitis media.¹² We have subsequently followed these children for a total of 3 years and reported that adenoidectomy did not influence IgE mediated allergy, bronchial hyper-reactivity as measured by oscillometry after an exercise test or exhaled nitric oxide concentrations, which are surrogate markers predicting the risk of asthma.¹⁶ The aim of the present study was to assess the impact of adenoidectomy on nasopharyngeal carriage of pathogens causing acute otitis media as assessed by yearly nasopharyngeal swabs.

MATERIALS AND METHODS

Participants

The study children were enrolled from children who were referred to our Department of Otorhinolaryngology in Helsinki between March 2001 and December 2002. The inclusion criteria were age 1–4 years, and ≥ 3 episodes of acute otitis media during the past 6 months or ≥ 5 during the past 12 months or COME as judged by examination with a pneumatic otoscope 2–3 months before tympanostomy and at the time of recruitment. The exclusion criteria were previous adenotonsillar surgery, previous placement of tympanostomy tubes, asthma, cleft palate, diabetes or children judged to require removal of enlarged adenoid because of symptoms of nasopharyngeal obstruction.

The effect of adenoidectomy on otitis media during the first follow-up year¹² and the effect of adenoidectomy on respiratory function at the third year of follow-up visit and on otitis media during the 3-year follow-up have¹⁶ previously been reported. The ethics review committee of the Helsinki University Central Hospital had approved the study.

Of note is that the study children had not received any vaccination against pneumococci.

Objectives

The primary outcome was to evaluate the effect of adenoidectomy on nasopharyngeal colonisation of *Streptococcus pneumoniae* as evaluated by nasopharyngeal swabs taken during scheduled follow-up visits 1, 2 and 3 years after randomisation.

The secondary outcome was to evaluate the effect of adenoidectomy on nasopharyngeal carriage of *Haemophilus influenzae* and *Moraxella catarrhalis* as well as on the nasopharyngeal carriage of pneumococci of distinct capsular polysaccharide serotypes.

The secondary outcomes also included the evaluation of the effect of adenoidectomy on the development of serum IgG antibodies to pneumococcal capsular polysaccharides. Serum samples taken 3 years after the randomisation were analysed for antibodies against serotypes 6B, 14, 19F and 23F. These four antibodies were selected as they represented the most

common pneumococcal serotypes found in nasopharyngeal swabs.

As the development of these antibodies depends on a previous encounter with the corresponding antigen, we evaluated the effect of adenoidectomy on the development of antibodies in children who had been exposed to the respective pneumococcal serotypes. We also evaluated whether antibodies at the third year follow-up visit would be inversely associated with nasopharyngeal colonisation at that time.

Evaluation of nasopharyngeal carriage

The children had scheduled visits to our hospital after the first, second and third year of follow-up. During these visits nasopharyngeal swabs were taken. Analysis of the swabs was done as previously described.^{17 18} The swabs were immersed in medium containing skimmed milk, tryptone, glucose and glycerol, transported to the microbiological laboratory of the National Institute for Health and Welfare in Oulu (previously National Public Health Institute), and analysed for growth of *Streptococcus pneumoniae*, *H influenzae* and *M catarrhalis*. The isolated pneumococci were serotyped as previously described.¹⁷ The laboratory personnel who studied the nasopharyngeal swabs were blinded as to the adenoidectomy status.

Evaluation of serum antibodies to pneumococcal capsular polysaccharides

Serum samples were taken at the third year visit after randomisation. Pneumococcal capsular polysaccharide IgG antibody concentrations were measured at the National Institute for Health and Welfare in Helsinki. The laboratory personnel who studied the antibody concentrations were blinded to the age of the child, the adenoidectomy status and the nasopharyngeal carriage status. The concentrations of IgG antibodies to pneumococcal capsular polysaccharides 6B, 14, 19F and 23F were measured by a standardised enzyme immunoassay with heterologous polysaccharide (22F) absorption.¹⁹

Sample size analysis

We estimated that nasopharyngeal carriage of pneumococci in children with recurrent otitis media might reach 50% ($p_1=0.50$). Our assumption was that if adenoidectomy had a clinically significant impact on nasopharyngeal carriage of pneumococci, it should change the rate of carriage by 25% ($p_2=0.25$ or $p_2=0.75$). Based on these assumed frequencies and on the limits of risks of false-positive and false-negative results of $\alpha=0.05$ and $\beta=0.10$, respectively, we estimated that approximately 77 children were needed in each treatment group.

Randomisation

Altogether 296 children met the eligibility criteria. The parents of 217 children gave written consent to participate in the study. These children were randomised to undergo adenoidectomy or not to undergo adenoidectomy. All the children received tympanostomy tubes. The randomisation was revealed to the parents only after written consent.

Statistical analysis

Risk of nasopharyngeal carriage was estimated by relative risk and statistical significance was estimated by Fisher test. The Mantel-Haenszel test was used to test significance of the difference between randomisation groups of the combined frequencies of carriage at first, second and third follow-up visits.

Multivariate analysis of the risk of carriage was done by multivariate logistic regression. Comparison of the geometric means of IgG antibody concentrations between the randomisation groups was done by the Student *t* test. Analysis of variance was used to analyse the relation of nasopharyngeal carriage and adenoidectomy status to IgG antibody concentrations.

RESULTS

Randomisation and follow-up

Altogether 217 children were recruited. Of these, 109 were randomised to undergo adenoidectomy and 108 were randomised not to undergo adenoidectomy. All the children received tympanostomy tubes. There were no significant differences between the randomisation groups in any baseline measures. The mean number of otitis media episodes prior to randomisation was similar in the two randomisation groups (table 1). The numbers of children who had COME, defined as having middle ear effusion both at the time of referral to our hospital (which occurred 2–3 months before randomisation) as well as at the time of surgery, was 30 (28%) in the adenoidectomy group and 26 (24%) in the no-adenoidectomy group (table 1).

Of the 109 children in the adenoidectomy arm, nasopharyngeal swabs were obtained from 102 children (94%) during the first year follow-up visit, from 94 children (86%) during the second year follow-up visit and from 85 children (78%) during the third follow-up visit (figure 1). These numbers were somewhat smaller in the no-adenoidectomy group. Of the 108 children in the no-adenoidectomy arm the corresponding numbers were 94 (87%), 83 (77%) and 74 (67%) during the first, second and third follow-up visits, respectively. At the third follow-up visit serum samples were obtained from 87 (80%) children in the adenoidectomy arm and from 73 (68%) in the no-adenoidectomy arm (figure 1). As we had no follow-up data of the children who were withdrawn or who were lost to follow-up, we were not able to perform a full intention-to-treat analysis. Children who were first randomised not to undergo adenoidectomy, but who underwent adenoidectomy during the follow-up for whatever reason, were excluded from the analysis.

As there were more dropouts in the no-adenoidectomy group than in the adenoidectomy group, we assessed whether this had resulted in a bias selecting for infection prone children in one of the randomisation groups. To study this, we analysed the numbers of otitis media episodes prior to randomisation. The mean numbers of otitis media episodes in children who had a nasopharyngeal swab taken at the third year follow-up

visit were 5.6 (n=85, SD=4.2) in the adenoidectomy arm and 5.6 (n=74, SD=3.6) in the no-adenoidectomy arm. The corresponding mean numbers in children of whom no nasopharyngeal swab was available at the third year follow-up visit were 6.0 (n=24, SD=4.1) in the adenoidectomy arm and 5.6 (n=34, SD=3.8) in the no-adenoidectomy arm. These mean numbers of otitis media prior to randomisation were quite close to each other. Thus, the pattern of loss to follow-up in this study appears not to have introduced any clear bias selecting for infection-prone children in one of the two randomisation groups.

Influence of adenoidectomy on nasopharyngeal carriage

Altogether 532 nasopharyngeal swabs were taken during the follow-up visits (figure 1). Of the swabs 39% (209/532) grew pneumococci. Nasopharyngeal carriage of *S pneumoniae* was more frequent among children who had undergone adenoidectomy. During the first follow-up year visit, the relative risk of nasopharyngeal carriage by *S pneumoniae* was increased approximately 50% among children who had undergone adenoidectomy (RR 1.47, 95% CI 1.04 to 2.07; 51 (50%) of 102 children vs 32 (34%) of 94 children; *p*=0.03) (table 2). The risk of carriage of pneumococci seemed to be less markedly increased at the second and third year follow-up visits (table 2). Analysis

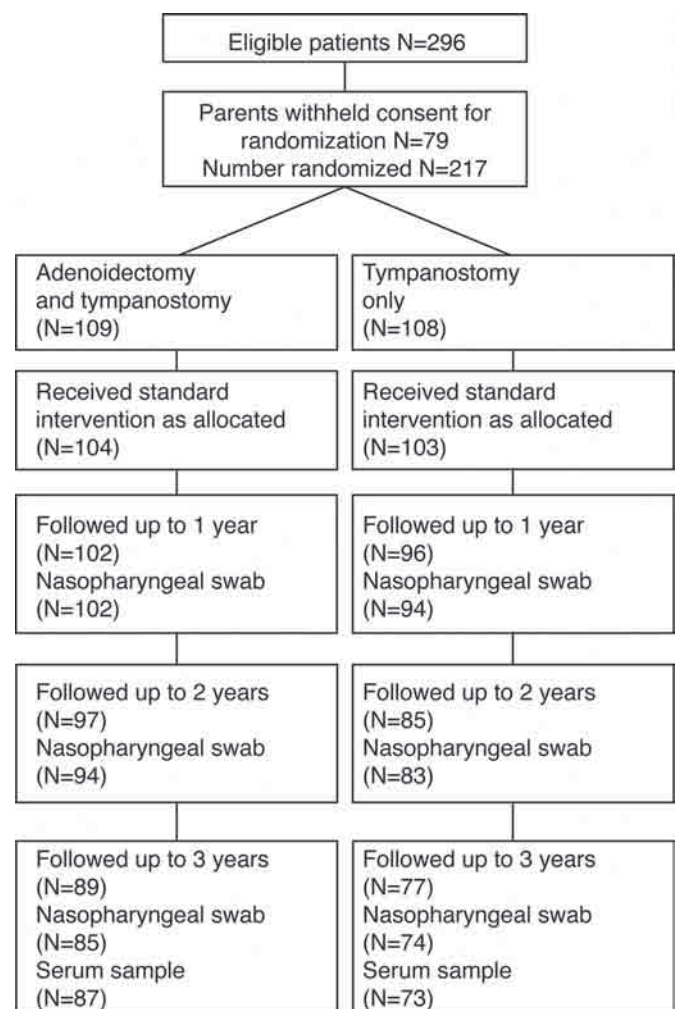


Figure 1 Flow of participants who were randomised to the two treatment groups: (1) adenoidectomy or (2) no adenoidectomy. All the children received tympanostomy tubes to both ears.

Table 1 Baseline characteristics of treatment groups

	Adenoidectomy (n=109)	No adenoidectomy (n=108)
Age (years)*	1.9 (1.0–3.9)	1.9 (1.0–3.9)
Age distribution		
12–24 months	72	73
24–36 months	25	26
36–48 months	12	9
Male/female	54/55	60/48
No of siblings*	1.1 (0–7)	0.9 (0–5)
No of otitis media episodes 12 months before surgery*	5.7 (1–10)	5.7 (1–10)
Mother or father smokes (%)	61 (56%)	54 (50%)
Diagnosis of COME (%)	30 (28%)	26 (24%)

*Values are means with range in parenthesis.

COME, chronic otitis media with effusion.

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of all the data of the first, second and third year follow-up visits using the Mantel-Haenszel test showed a significant association between adenoidectomy and nasopharyngeal carriage of pneumococci ($p=0.02$, $\chi^2=5.53$).

Of the nasopharyngeal swabs 11% (57/532) grew *H influenzae* and 38% (202/532) *M catarrhalis*. We could not observe any significant differences between the randomisation groups in the nasopharyngeal carriage of *H influenzae* or *M catarrhalis* (Mantel-Haenszel test, $p=0.63$, $\chi^2=0.49$; and $p=0.99$, $\chi^2=0.00$, respectively) (table 2). *S pyogenes* was found in only three nasopharyngeal swabs (0.6%). All these three were isolated in children who had not undergone adenoidectomy but the numbers were too low to assess if the difference was statistically significant.

To test whether the association between pneumococcal carriage and adenoidectomy was independent of the carriage of *H influenzae* or *M catarrhalis*, we performed multivariate logistic regression analysis. The analysis was performed using the data of the first year follow-up visit, as nasopharyngeal

carriages of all the three pathogens were the most frequent at this time point. In the multivariate analysis carriage of *S pneumoniae*, *H influenzae* and *M catarrhalis* (yes/no) as well as gender and age of the child were simultaneously entered as independent variables. The analysis showed that adenoidectomy increased pneumococcal carriage (OR 1.95, 95% CI 1.07 to 3.57, $p=0.03$) independent of the carriage by *H influenzae* (OR 0.70, 95% CI 0.31 to 1.60, $p=0.40$) or *M catarrhalis* (OR 1.01, 95% CI 0.55 to 1.84, $p=0.99$).

Of the cultured *S pneumoniae* isolates serotypes 6B, 23F and 19F were the most frequent (table 3). Adenoidectomy resulted in a statistically significant increase in the carriage of 19F serotype pneumococci (21 (7.5%) of 281 swabs vs 8 (3.2%) of 251 swabs; $p=0.04$). Adenoidectomy appeared to increase the carriage of many other pneumococcal serotypes, but the numbers of the isolates were too small to address whether adenoidectomy influenced the carriage of each serotype or whether it had a preference for only certain pneumococcal serotypes.

Table 2 Nasopharyngeal carriage of *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* at the first, second and third year follow-up visits by adenoidectomy status

	Adenoidectomy	No adenoidectomy	Relative risk of carriage (95% CI)	p Value
<i>Streptococcus pneumoniae</i>				
1st year	51/102 (50.0)	32/94 (34.0)	1.47 (1.04 to 2.07)	0.03
2nd year	43/94 (45.7)	31/83 (37.3)	1.22 (0.86 to 1.75)	0.29
3rd year	30/85 (35.3)	22/74 (29.7)	1.19 (0.75 to 1.87)	0.50
<i>Haemophilus influenzae</i>				
1st year	13/102 (12.7)	15/94 (16.0)	0.80 (0.40 to 1.59)	0.55
2nd year	13/94 (13.8)	5/83 (6.0)	2.30 (0.85 to 6.17)	0.13
3rd year	7/85 (8.2)	4/74 (5.4)	1.52 (0.46 to 5.00)	0.54
<i>Moraxella catarrhalis</i>				
1st year	45/102 (43.6)	38/94 (40.4)	1.09 (0.79 to 1.52)	0.66
2nd year	36/94 (38.3)	32/83 (38.6)	0.99 (0.68 to 1.44)	0.99
3rd year	25/85 (29.4)	26/74 (35.1)	0.84 (0.54 to 1.32)	0.50

Data are proportion (%) of children, unless otherwise indicated.

Relation of nasopharyngeal carriage history on serum concentrations of pneumococcal capsular polysaccharide IgG antibodies at the third year follow-up visit

To assess whether the concentrations of pneumococcal polysaccharide antibodies at the third year follow-up visit reflected prior exposure to pneumococci, we analysed the relation of pneumococcal carriage history to serum concentration of pneumococcal IgG antibodies. Carriage history was defined as being a carrier of the specific pneumococcal serotype at least once during the first, second or third follow-up visits (yes/no). Serum IgG antibodies against pneumococcal capsular polysaccharides serotypes 6B, 14, 19F and 23F were measured as these serotypes represented the most common pneumococcal serotypes in nasopharyngeal swabs.

We found that nasopharyngeal carriage of pneumococcal serotypes 6B and 23F was significantly associated with elevated serum concentrations of specific IgG polysaccharide antibodies against the respective serotypes (ratio of geometric means

Table 3 Serotypes of pneumococci isolated in 532 nasopharyngeal swabs taken at the first, second and third follow-up visits by adenoidectomy status

Serotype	Carriage at the 1st-year follow-up visit		Carriage at the 2nd-year follow-up visit		Carriage at the 3rd-year follow-up visit		Carriage at the 1st, 2nd and 3rd year follow-up visits combined	
	AT (n=102)	T (n=94)	AT (n=94)	T (n=83)	AT (n=85)	T (n=74)	AT (n=281)	T (n=251)
6B	7	7	10	5	6	6	23	18
23F	7	8	12	3	4	1	23	12
19F	10	2	8	4	3	2	21	8*
6A	8	4	2	5	1	2	11	11
15	3	3	2	1	2	4	7	8
14	2	2	2	1	5	1	9	4
11	2	0	2	3	2	1	6	4
35	1	0	2	3	2	1	5	4
18C	1	2	1	3	0	0	2	5
9N	2	1	1	2	0	0	3	3
19A	0	1	0	0	1	2	1	3
23A	2	1	0	0	0	1	2	2
3	0	1	2	0	0	0	2	1
35B	3	0	0	0	0	0	3	0
Other	5	4	2	1	5	3	12	8
All†	51	32*	43	31	30	22	124	85*

* $p<0.05$.

†The number of all swabs positive for pneumococci, this was less than the sum of each serotype as some swabs grew two different serotypes simultaneously.

AT, adenoidectomy and tympanostomy; T, tympanostomy without adenoidectomy; Other, serotypes 9V, 4, 21, 22, 33, 34, 35F, 37, 38 and unencapsulated pneumococci were isolated only once or twice.

of antibody concentrations, 1.63; 95% CI 1.01 to 2.65 and ratio of geometric means, 2.09; 95% CI 1.24 to 3.51, respectively). A similar trend, although not statistically significant, was found for carriage of serotype 14 pneumococci and serotype 14 antibodies (ratio of geometric means, 1.45; 95% CI 0.69 to 3.04). Carriage of serotype 19F seemed not to be connected with the concentration of serum type 19F polysaccharide antibodies (ratio of geometric means, 0.99; 95% CI 0.55 to 1.77). Thus, previous exposure to pneumococcal serotypes 6B and 23F and probably to 14 was associated with increased serum IgG antibodies to the respective serotype capsular polysaccharides at the third year follow-up visit.

Assessment if the development of IgG serum pneumococcal capsular polysaccharide antibodies at the third year follow-up visits could inhibit pneumococcal colonisation

As capsular polysaccharide antibodies may confer protection from nasopharyngeal colonisation, we evaluated whether capsular serotype specific IgG antibodies at the third year of follow-up visit would confer protection from nasopharyngeal colonisation at this time point. We could not find evidence for this. Carriage of a certain pneumococcal serotype at the third year follow-up time point tended, on the contrary, to be connected with an increased concentration of IgG antibodies against the respective serotype specific capsular polysaccharide. When the child was a nasopharyngeal carrier of serotype 6B pneumococci at the third year follow-up visit, the serum serotype 6B polysaccharide antibodies tended to be twice as high compared with children who were not carriers (ratio of geometric means 2.00, 95% CI 0.97 to 4.12). The corresponding values for serotype 14, 19F and 23F antibodies were 1.19 (95% CI 0.42 to 3.35), 1.30 (95% CI 0.34 to 4.91) and 2.36 (95% CI 0.64 to 8.73), respectively.

Influence of adenoidectomy on serum IgG pneumococcal capsular polysaccharide antibodies at the third follow-up visit

Analysis of variance revealed a significant association between adenoidectomy and the concentration of serotype 6B IgG antibodies ($p=0.05$), when the carrier status of serotype 6B pneumococci (carrier during any of the first, second and third year follow-up visits, yes/no) was entered in the analysis.

Adenoidectomy was associated with more than 50% lower serum concentration of serotype 6B capsular polysaccharide IgG antibodies (ratio of geometric means, 0.37; 95% CI 0.16 to 0.85, $p=0.02$) (table 4) among children who had been nasopharyngeal carriers of serotype 6B pneumococci. We could not observe any statistically significance differences between the randomisation groups in serum concentrations of IgG antibodies against serotypes 14, 19F and 23F polysaccharides (table 4).

DISCUSSION

Adenoidectomy did not prevent nasopharyngeal colonisation by *Streptococcus pneumoniae*, *Haemophilus influenzae* or *Moraxella catarrhalis*. On the contrary, in children, who were on average 2 years old at the time of the operation, adenoidectomy resulted in an increased frequency of nasopharyngeal colonisation by *S pneumoniae* 1 year after adenoidectomy.

The weakness of our result was that our analysis was not based on an intention-to-treat analysis as no data could be recovered from children who were lost to follow-up. This causes an uncertainty in our results, as it is possible that those children, who were prone to be carriers of pneumococci, could have been lost to follow-up more often in the no-adenoidectomy group than in the adenoidectomy group. Another weakness of the study was that antibody concentrations were measured only in serum samples taken during the third follow-up visit. As the effect on pneumococci colonisation seemed to be most evident during the first follow-up visit, measurements of antibody concentrations in samples taken during the first follow-up visit might have given more information.

Although we cannot completely rule out a possibility of selection bias due to not performing intention-to-treat analysis, there are arguments against a selection bias. First, the numbers of otitis media episodes prior to randomisation seemed to be quite similar between the randomisation groups irrespective whether the child had been lost to follow-up or not, suggesting that the dropouts may have not selected for infection prone children in one of the randomisation groups. Second, there appeared to be no gross difference in the frequency of nasopharyngeal carriage of *H influenzae* and *M catarrhalis*, implying that if a bias had occurred, it would have been specific

Table 4 Geometric mean concentrations (GMC) of IgG antibodies to pneumococcal serotypes 6B, 14, 19F and 23F by adenoidectomy status

Serotype	Adenoidectomy		No adenoidectomy		Ratio of the geometric means of antibody concentrations (95% CI)	p Value
	GMC ($\mu\text{g/ml}$) (95% CI)	No	GMC ($\mu\text{g/ml}$) (95% CI)	No		
6B						
All	0.17 (0.02 to 1.78)	87	0.21 (0.02 to 2.55)	73	0.81 (0.55 to 1.19)	0.29
Non-carrier	0.17 (0.02 to 1.80)	70	0.17 (0.01 to 2.01)	59	0.98 (0.64 to 1.49)	0.91
Carrier	0.18 (0.02 to 1.80)	17	0.48 (0.06 to 3.65)	14	0.37 (0.16 to 0.85)	0.02
14						
All	0.26 (0.03 to 2.43)	87	0.25 (0.03 to 2.52)	73	1.05 (0.74 to 1.51)	0.78
Non-carrier	0.25 (0.03 to 2.50)	79	0.25 (0.03 to 2.52)	71	1.01 (0.69 to 1.49)	0.94
Carrier	0.39 (0.11 to 1.42)	8	0.28 (0.01 to 5.75)	2	1.39 (0.31 to 6.25)	0.63
19F						
All	1.08 (0.08 to 15.3)	87	1.42 (0.11 to 17.9)	73	0.76 (0.50 to 1.15)	0.20
Non-carrier	1.07 (0.07 to 17.44)	69	1.41 (0.11 to 18.73)	67	0.76 (0.48 to 1.22)	0.25
Carrier	1.12 (0.14 to 8.97)	18	1.53 (0.20 to 11.54)	6	0.74 (0.26 to 2.04)	0.54
23F						
All	0.27 (0.02 to 3.21)	87	0.34 (0.02 to 4.81)	73	0.78 (0.52 to 1.78)	0.23
Non-carrier	0.21 (0.02 to 2.15)	68	0.33 (0.02 to 4.67)	63	0.65 (0.42 to 1.00)	0.05
Carrier	0.60 (0.05 to 7.29)	19	0.45 (0.03 to 6.28)	10	1.33 (0.47 to 3.70)	0.58

GMCs are given of all children and separately of children according to nasopharyngeal carriage of the corresponding pneumococcal serotype.

for pneumococci. Third, when only those children who had been carriers of serotype 6B pneumococci were analysed, adenoidectomy was associated with a decreased concentration of serotype 6B serum antibodies at the third year follow-up visit despite the fact that the carriage history of serotype 6B pneumococci was associated with an increased concentration of serotype 6B antibodies. A possible selection bias caused by children who were lost to follow-up, which would lead to a difference in the nasopharyngeal carriage rate of pneumococci, could not easily explain this. Instead, our results suggest that immune responses to pneumococci may be somewhat impaired by adenoidectomy, which could lead to an increased frequency of pneumococcal colonisation.

Although adenoidectomy may impair the development of pneumococcal IgG antibodies, adenoidectomy may increase the risk of pneumococcal colonisation by a mechanism that is independent of the production of IgG capsular polysaccharide antibodies. This notion may be raised as adenoidectomy increased the carriage rate of serotype 19F pneumococci although it did not seem to attenuate the generation of serotype 19F polysaccharide IgG antibodies. Also, in our study protection of nasopharyngeal carriage was not connected with the presence of specific polysaccharide IgG antibodies in serum although nasopharyngeal carriage augmented the development of these antibodies. Previous reports have indicated that capsular polysaccharide antibodies alone do not explain the development of natural pneumococcal immunity. It has been reported that protection of pneumococcal carriage in children can occur before the development of measurable pneumococcal polysaccharide antibodies.²⁰ In adults susceptibility to experimental colonisation by pneumococci has been reported to be independent of serum levels of antibodies to pneumococcal capsular polysaccharides.²¹ Thus, mechanisms other than capsular polysaccharide IgG antibodies are important in protection against pneumococcal carriage.

Although other antibodies such as antibodies to pneumococcal protein²¹ may have a role in the clearance of pneumococcal colonisation, antibodies alone may have a restricted role in the prevention of carriage. Antibodies have even been reported to have a very limited role in the clearance of pneumococcal colonisation as demonstrated in transgenic mice that are unable to produce antibodies.²² The antibody-independent acquired immunity to pneumococci in mice has been found to be mediated by CD4 T cells.^{23–25} CD4 T cells have a role in immunity to pneumococci in humans also, as pneumococcal pneumonia is greatly increased in patients with AIDS.²⁶ Studies in mice have shown that interleukin-17A has an essential role in T cell-mediated pneumococcal immunity.^{27,28} The CD4 interleukin-17 producing T_H17 cells can initiate an attack against extracellular pathogens by inducing the production of antimicrobial peptides by epithelial cells and by recruiting neutrophils.²⁹ In mice, neutrophil-mediated degradation of pneumococci enhances uptake of pneumococcal antigens inside the nasal associated lymphoid tissue (NALT) that may further promote pneumococcal immunity.³⁰ These antibody-independent mechanisms of acquired immunity observed in mice may operate in adenoid-mediated clearance and prevention of pneumococcal carriage in children.

The nasopharynx seems to have a special role in children as pneumococcal colonisation in children is best detected by swabs taken in the nasopharynx, implying that the nasopharynx is the primary reservoir of pneumococci in children.³¹ This is contrary to adults in whom oropharyngeal swabs yield higher carriage rates than nasopharyngeal swabs.^{32,33} One

may presume that the colonisation of pneumococci in the nasopharynx of the child may promote pneumococcal immunity, and that the adenoid located in the nasopharynx may have a special role in this.

The function of the adenoid in the prevention of nasopharyngeal colonisation by pneumococci is reminiscent of the function of the spleen, which protects against invasive disease caused by pneumococci.³⁴ Adenoidectomy may thus have significant adverse effects as nasopharyngeal colonisation increases the risk of invasive pneumococcal disease³⁵ that especially affects children younger than 5 years of age.^{36,37}

It should be noted that adenoidectomy seemed to increase pneumococcal carriage significantly only during the first year after adenoidectomy and that our medium-sized study did not definitively resolve whether the rate of pneumococcal carriage would be influenced later on. Thereby, adenoidectomy at an early age may not result in any long-term adverse effects, but rather may increase the risk of pneumococcal infections only during the first year after adenoidectomy. However, our findings suggest that adenoidectomy should not be performed in children younger than 4 years of age unless there is an apparent adenoidal pathology.

The possible role of the adenoid in the clearance of pneumococcal colonisation implies that significant immune responses may occur in the nasopharynx of children, which in turn suggests that intranasal vaccines might be effective in preventing pneumococcal disease in young children. Intranasal challenge with killed pneumococci or by purified pneumococcal antigens has proved to be effective in preventing pneumococcal colonisation and infections in mice.^{24,27,28,38,39} If successful in children, intranasal vaccination would be easier to administer and possibly cheaper than conventional systemic pneumococcal conjugate vaccines.

Our results suggest that the adenoid of young children may function by enhancing immunity against pneumococci. Previously, the natural function of the adenoid and the reasons for its evolution has been obscure. Our study is the first to suggest that the adenoid may be directly involved in promoting immunity to pneumococci in children younger than 4 years of age.

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