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Effect of Pneumococcal Vaccination on Quality of Life in Children With Recurrent Acute Otitis Media: A Randomized, Controlled Trial

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ABSTRACT. *Background.* **Limited effectiveness of current treatment strategies for recurrent acute otitis media (RAOM) and increasing antibiotic resistance have diverted attention to prevention of AOM by vaccination. Pneumococcal vaccination for AOM seems to have only modest clinical efficacy. Thus far, the effects on health-related quality of life (HRQoL) or functional health status (FHS) have not been studied.**

Objective. **To assess the effect of vaccination on HRQoL or FHS.**

Methods. **In a double-blind, randomized, controlled trial, 383 children 1 to 7 years old with RAOM were vaccinated with either heptavalent pneumococcal conjugate vaccine followed by pneumococcal polysaccharide vaccine (pneumococcal group: $n = 190$) or with hepatitis A or B vaccines (control group: $n = 193$). Parents completed validated Dutch versions of 8 HRQoL and FHS instruments assessing generic FHS (Rand, Functional Status Questionnaire specific, and Functional Status Questionnaire generic), otitis media–specific FHS (OM-6), otitis media–specific child HRQoL (Numerical Rating Scale for Child), family functioning (Family Functioning Questionnaire), and otitis media–specific caregiver HRQoL (Numerical Rating Scale for Caregiver). Scores were compared at baseline and at 14 and 26 months' follow-up.**

Results. **At baseline, the average AOM incidence in the pneumococcal and control group was 5.0 (SD: 2.8) and 4.9 (SD: 2.6) episodes per year, respectively, with 38.4% and 36.8% having suffered from ≥6 episodes per year. AOM frequency decreased 4.4 episodes per year in both groups, with a considerable and comparable improvement in HRQoL and FHS. No substantial differences in HRQoL or FHS were found between the pneumococcal and the control group at baseline or at 14 or 26 months' follow-up.**

Conclusion. **Pneumococcal vaccination has no beneficial effect compared with control vaccination on either HRQoL or FHS in children 1 to 7 years old with RAOM.** *Pediatrics* **2005;115:273–279;** ***health-related quality of life, acute otitis media, recurrent acute otitis media, functional health status, pneumococcal vaccination.***

ABBREVIATIONS. OM, otitis media; AOM, acute otitis media; RAOM, recurrent acute otitis media; HRQoL, health-related quality of life; FHS, functional health status; Rand, Rand general health rating index for children; FSQ, Functional Status Questionnaire; FFQ, Family Functioning Questionnaire; NRS Caregiver, Numerical Rating Scale for Caregiver; NRS Child, Numerical Rating Scale for Child; MANOVA, multivariate analysis of variance.

Acute otitis media (AOM) is one of the most common infectious diseases in childhood[1–4] and has considerable impact on daily functioning and health-related quality of life (HRQoL) of the affected child and his or her family.[5–8] Because the benefit of both medical treatment and surgery has proved to be limited[9–13] and with resistance against common antibiotics still on the increase,[14–17] there is much interest in developing alternative methods to prevent AOM. Because pneumococcus is the most common bacterial cause of otitis media (OM), research over the past decade has focused on pneumococcal vaccination.[18–22] Pneumococcal conjugate vaccination in infancy has been shown to be (highly) effective in preventing invasive disease.[23–25] Regarding AOM, the clinical efficacy seems modest (6–7%). A larger effect has been found in the preven-

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tion of recurrent AOM (RAOM) episodes, with up to a 12% reduction of ≥4 AOM episodes per year.[23,26,27] Children at risk for RAOM are assumed to benefit most through priming of their deficient immune response by pneumococcal conjugate vaccination.[23,27–29]

Because previous studies mainly addressed the clinical efficacy of pneumococcal vaccination regarding AOM, little is known about the effects of vaccination on functional health status (FHS) and HRQoL. Assessment of such outcome is important, especially because RAOM may be considered a chronic illness, and HRQoL and FHS are assumed to be particularly relevant as outcome measures.[30–32]

In 1998 we started a randomized, controlled trial on the effects of pneumococcal versus control vaccination in children 1 to 7 years old who had suffered from RAOM. This article focuses on the effects of pneumococcal vaccination versus control vaccination on FHS and HRQoL.

METHODS

Patients

The current study is part of a double-blind, randomized, controlled trial studying the effect of pneumococcal vaccination on FHS and HRQoL of children with RAOM alongside its clinical efficacy. The trial was conducted at the pediatric outpatient departments of a general hospital (Spaarne Hospital, Haarlem, Netherlands) and an academic hospital (University Medical Center, Utrecht, Netherlands) from April 1998 to December 2001. Children were referred by general practitioners, pediatricians, and otolaryngologists or were enrolled on the caregiver's own initiative.

Inclusion criteria were: 1 to 7 years old and a history of RAOM, defined as having had at least 2 physician-diagnosed episodes of AOM in the preceding year. Exclusion criteria were immunodeficiency other than IgA or IgG_2 subclass deficiency; cystic fibrosis; immotile cilia syndrome; cleft palate; chromosomal abnormalities such as Down syndrome; or severe adverse reaction to previous vaccinations. Informed consent was obtained from the caregivers of all children before participation in the trial. The medical ethics committees of both participating hospitals approved the study protocol.

Intervention and Follow-up

After inclusion in the trial, 383 children were assigned randomly to vaccination with either a 7-valent pneumococcal conjugate vaccine (Prevnar) followed 6 months later by a 23-valent polysaccharide vaccine (Pneumune) (pneumococcal vaccine group: $n = 190$) or with a control vaccine (recombinant hepatitis B vaccine, Engerix-B [AE Junior], in children 12–24 months old or hepatitis A vaccine, Havrix [AE Junior], in children 24–48 months old) (control vaccine group: $n = 193$) (Fig 1). Randomization was balanced over age (12–24 vs 24–84 months old) and number of AOM episodes in the year before enrollment (2–3 vs ≥4 episodes). Figure 2 reflects the flow of the study participants. Only the 2 study nurses who vaccinated the children were informed on the type of vaccine a child received; ie, the research physicians, parents, and children were unaware of the treatment received. Demographic data and clinical indices of the severity of OM were recorded at enrollment. Children were seen at the outpatient department at 7, 14, 20, and 26 months' follow-up. At each visit, data on episodes of physician-diagnosed AOM (based on predefined criteria) and other upper respiratory tract infections, as well as data on medical and surgical treatment of AOM, were collected.[33] Furthermore, otoscopy and tympanometry were performed by the 2 study physicians (C.N.M.B. and R.H.V.). At enrollment and during follow-up visits at 14 and 26 months, parents completed questionnaires assessing general FHS (Rand General Health Rating Index for Children [Rand] and Functional Status Questionnaire [FSQ] generic and specific) and disease-specific FHS (OM-6) of their child and a questionnaire addressing family functioning related to the child's ear infections (Family Functioning Questionnaire [FFQ]). Global HRQoL of the child and of the caregiver with respect to the child's ear infections was assessed by 2 numerical rating scales (Numerical Rating Scale for Child [NRS Child] and Numerical Rating Scale for Caregiver [NRS Caregiver]). Details of characteristics of these instruments (Table 1) as well as data on their reliability and validity have been described elsewhere.[46] The instruments generally were demonstrated to be reliable and valid.

Data Analysis

The study sample size was based on expected clinical benefit of pneumococcal vaccinations. Based on data from previous studies in the Netherlands, 55% of patients in the control group were estimated to have at least 1 recurrence of AOM during the 18 months of follow-up after completion of vaccinations. In view of the multifactorial cause of AOM and assuming a potential benefit of vaccinations similar to that of antibiotic prophylaxis and tympanostomy tubes, a reduction of 25%, resulting in an AOM recurrence rate of 40% in the pneumococcal vaccine group, was judged clinically relevant.[33] To detect this reduction, with α (2-sided) = .05 and power 80%, 352 patients would have to be randomized.

All analyses were done on the basis of intention to treat. At baseline, the pneumococcal group and control vaccine group were compared for differences in clinical and demographic characteristics.

To limit the number of comparisons, the Rand (generic questionnaire) and the OM-6 (disease-specific questionnaire) were considered as primary outcome measures, based on their face validity, reliability, and responsiveness.[5,37,38,45,46] Consequently, the other questionnaires were considered secondary outcome measures.

Because questionnaire scores generally were skewed, Mann-Whitney tests were used to assess differences in FHS and HRQoL scores between the pneumococcal and control vaccine groups at baseline and at 14 and 26 months' follow-up.

A multivariate analysis of variance (MANOVA) was performed to detect a treatment effect for all questionnaires combined.[47] MANOVA is an extension of the common analysis of variance to situations in which ≥2 dependent variables (HRQoL and FHS scores) are included; combining data increases the power to detect a difference. For this analysis we modeled the scores at 14 and 26 months' follow-up.

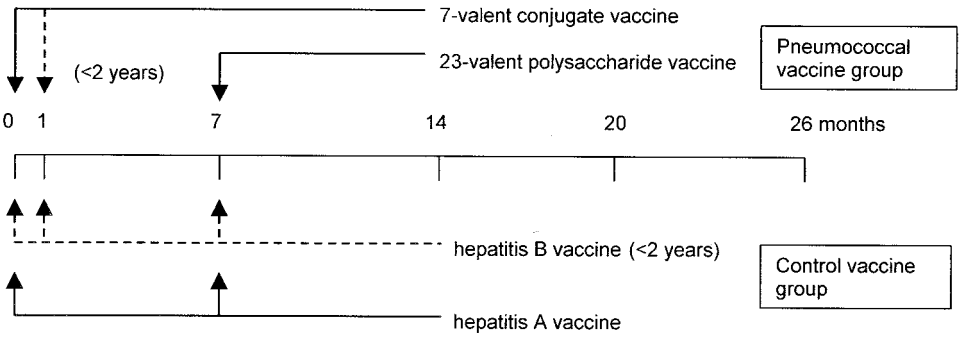

Fig 1. Vaccination schedules.

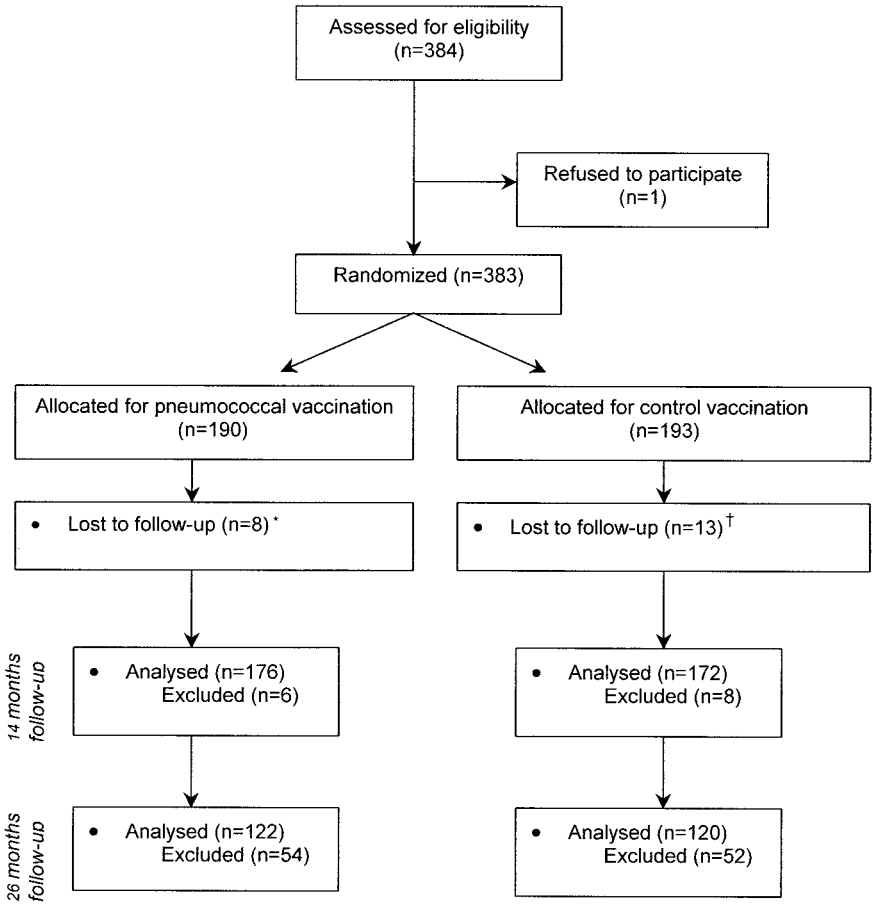

Fig 2. Flowchart of trial participants. * Reasons for loss to follow-up in the pneumococcal vaccine group were family circumstances (2), patient burden (too high) (3), disappointing effect from vaccination (1), and for unknown reasons (2). † In the control vaccine group, loss to follow-up was due to family circumstances (1), movement to an unknown address (1), disappointing effect from vaccination (2), patient burden (4), "prick fear"(2), dissatisfaction with staff (1), and development of late-onset hypogammaglobulinemia (1).

TABLE 1. Characteristics of HRQoL and FHS Instruments Used in the Study

Instruments	Type	No. of Items	Scale	Construct(s) Measured	Application in Other Studies
Generic					
Rand	FHS	7	Likert	General health: current health, previous health, resistance to illness	Low birth weight children,[34,35] survivors of childhood cancer,[36] asthmatic children[37,38]
FSQ generic	FHS	14	Likert	Age-appropriate functioning and emotional behavior	Low birth weight children,[34,39] survivors of childhood cancer,[40] asthmatic children[38,41–43]
FSQ specific	FHS	14	Likert	Impact of illness on functioning and behavior	Same as FSQ generic
Disease specific					
OM-6	FHS	6	Likert	Physical suffering, hearing loss, speech impairment, emotional distress, activity limitations, caregiver concerns	Children with RAOM,[5] children with chronic OME[5,44,45]
FFQ	FHS	7	Likert	Parents: sleep deprivation, change of daily or social activities, emotional distress; family: canceling family plans or trips; siblings: feeling neglected, demanding extra attention	None
NRS Child	HRQoL	1	Index	Global well-being of child related to AOM episodes	Children with RAOM or chronic OME[5]
NRS Caregiver	HRQoL	1	Index	Global well-being of parent related to child's AOM episodes	None

Finally, the variables considered as possible effect modifiers were age at inclusion (12–24 vs 24–84 months), number of AOM episodes in the year before enrollment (2–3 vs ≥4 episodes), number of upper respiratory tract infections other than AOM in the preceding year (<6 vs ≥6 episodes), symptoms of hearing-impairment (yes/no) or language difficulties in the preceding year (yes/no), previous ear, nose, or throat surgery (yes/no), previous adenoidectomy (yes/no), previous tympanostomy tube insertion (yes/no), history of antimicrobial prophylaxis (yes/no), atopy (yes/no), number of siblings, and educational level of the caregivers (high school or higher [yes/no]). The variables were tested by linear regression models to find potential modifiers of effect of the intervention (independent variables) on HRQoL or FHS outcome (dependent variable) at 14 months' follow-up.

TABLE 2. Characteristics of Study Population at Inclusion

	Pneumococcal Vaccine Group		Control Vaccine Group	
	(n = 190)	SD or 95% Confidence Interval	(n = 193)	SD or 95% Confidence Interval
Age, mo	32.8	19.3	34.8	20.1
Male gender	62.1%	(55.2–69.0)	61.7%	(54.8–68.6)
Age at first AOM, mo	11.2	9.4	10.8	8.4
No. of siblings	1.05	0.8	1.11	0.9
Caregiver's education ≥ high school*	54.4%	(47.1–61.3)	52.6%	(45.6–59.6)
In the year prior to inclusion				
Mean number of AOM episodes per y	5.0	2.8	4.9	2.6
≥6 episodes of upper respiratory tract infections per y	38.4%	(31.5–45.3)	36.8%	(30.0–43.6)
Pneumonia	10.0%	(5.7–14.3)	16.6%	(11.4–21.8)
Hearing difficulties	36.3%	(29.5–43.1)	33.2%	(26.6–39.8)
Speech or language difficulties	25.3%	(19.1–31.5)	19.2%	(13.6–24.8)
History of				
Chronic airway problems or atopy†	49.5%	(42.4–56.6)	51.8%	(44.8–58.8)
Adenoidectomy ± tonsillectomy	47.4%	(40.3–54.5)	46.4%	(39.4–53.4)
Tympanostomy tubes	52.6%	(45.5–59.7)	48.9%	(41.8–56.0)
Antimicrobial prophylaxis	15.8%	(10.6–21.0)	14.5%	(9.5–19.5)
Speech therapy	7.4%	(3.6–11.1)	10.4%	(6.1–14.7)

* Minimum educational level was high school for at least 1 of the caregivers.
† Asthma, wheezing, hay fever, or eczema.

For all analyses the statistical package of SPSS 10.1 (SPSS Inc, Chicago, IL) was used. Questionnaire scores were transformed into 0-to-100 scales to enhance comparability.

RESULTS

Population Characteristics

At baseline, demographic and clinical characteristics of the pneumococcal and control vaccine groups were similar (Table 2), as were the mean baseline scores on the measures of FHS and HRQoL (Table 3).

Clinical Efficacy of Pneumococcal Vaccination

After 14 and 26 months' follow-up, no differences between the pneumococcal vaccine and control vaccine groups were observed with respect to reduction of AOM episodes and associated use of analgesics or antibiotics. Furthermore, the number of children receiving tympanostomy tubes was comparable in both groups.[33]

Efficacy of Pneumococcal Vaccination on HRQoL and FHS

After 14 months' follow-up, the Rand showed no significant difference between the pneumococcal and control vaccine groups (score: 23.5 vs 23.8; P = .45). A small but statistically significant difference was found on the OM-6 in favor of the control vaccine group compared to the pneumococcal vaccine group (score: 22.3 vs 21.3; P = .002, respectively). Subsequent comparison of scores on the secondary generic and disease-specific HRQoL and FHS instruments showed no significant differences between both intervention groups. After 26 months' follow-up, HRQoL and FHS scores of the pneumococcal and control vaccine groups did not differ at all (Fig 3 and Table 3).

The MANOVA on all questionnaires combined showed a marginal significant difference at the expense of pneumococcal vaccination at 14 months' follow-up (P = .04 with the Hotelling-Lawley Trace test). At 26 months' follow-up, no association was found between the scores on all questionnaires combined and type of vaccination (P = .89).

None of the possible effect modifiers showed a significant interaction effect at 14 or 26 months' follow-up.

Figure 3 shows considerable improvements in FHS and HRQoL in both the pneumococcal and control vaccine groups simultaneous with a decrease in

TABLE 3. HRQoL and FHS Scores and AOM Frequency at 0, 14, and 26 Months' Follow-up in the Pneumococcal Versus Control Vaccine Groups

	0 mo			14 mo			26 mo		
	Pnc	Ctrl	P Value*	Pnc	Ctrl	P Value	Pnc	Ctrl	P Value
Generic									
Rand	20.2	20.1	.63	23.5	23.8	.45	25.0	24.3	.34
FSQ generic	73.9	73.7	.85	81.6	83.6	.10	87.2	86.1	.59
FSQ specific	80.9	79.9	.57	90.0	91.5	.16	92.9	91.3	.42
Disease specific									
OM-6	17.6	17.5	.93	21.3	22.3	.002	22.1	22.2	.41
NRS Child	5.3	5.4	.94	7.9	8.2	.14	8.3	8.4	.50
FFQ	25.2	25.4	.87	31.3	31.3	.78	32.1	31.9	.81
NRS Caregiver	6.1	6.6	.20	8.3	8.3	.88	7.9	8.3	.45
AOM episodes/child-year	5.0	4.9		1.4	1.0		0.6	0.5	

Pnc indicates pneumococcal vaccine group; Ctrl, control vaccine group.
* Mann-Whitney test.

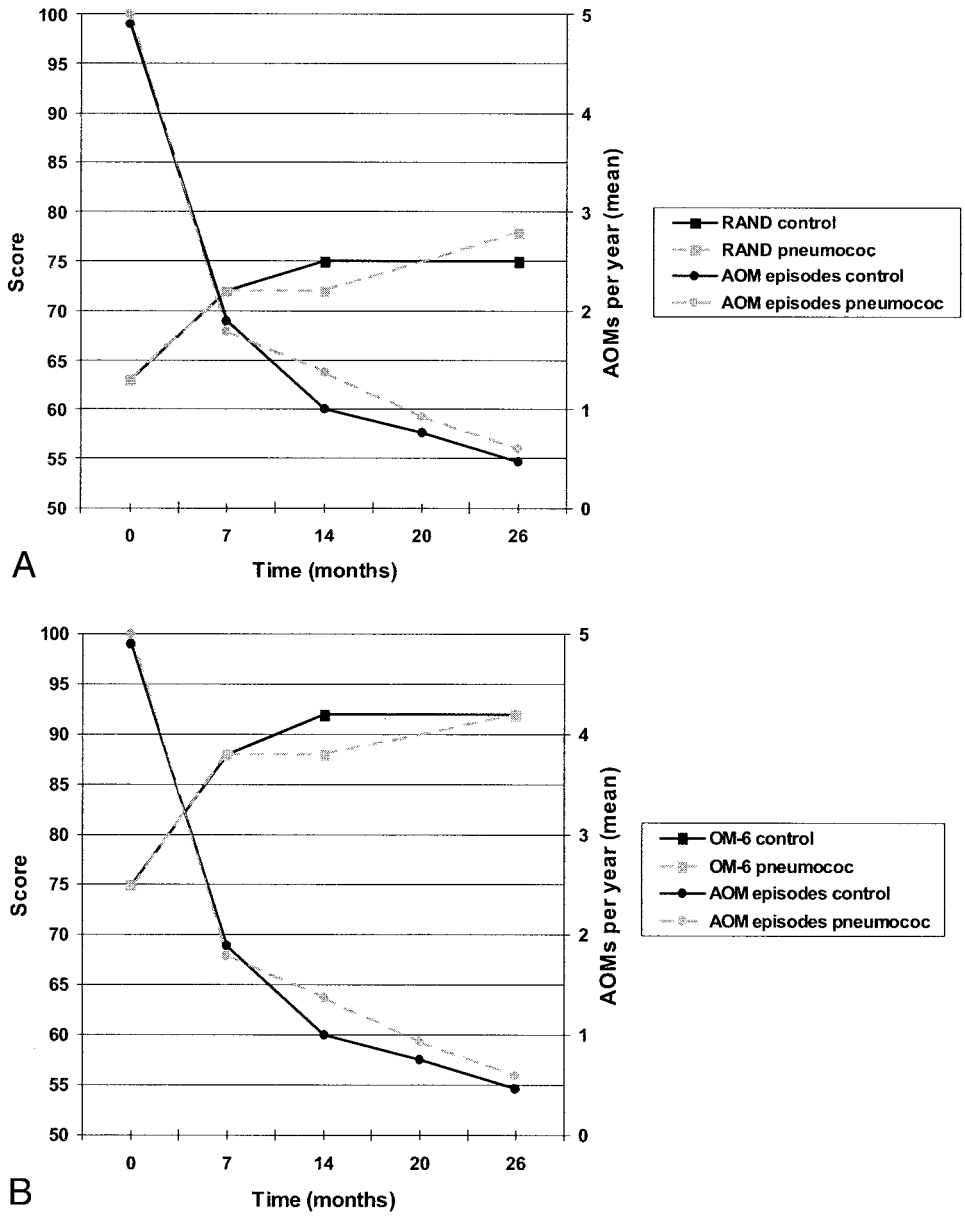

Fig 3. a, Rand scores and AOM frequency in pneumococcal versus control vaccinees. b, OM-6 scores and AOM frequency in pneumococcal versus control vaccinees.

AOM incidence (from 5.0 to 0.60 and 4.9 to 0.47 AOM episodes in the pneumococcal and control groups, respectively).

Loss to Follow-up and Missing Data

In the pneumococcal and control vaccine groups, 8 and 13 children were lost to follow-up, respectively (Fig 2). Exclusion from analysis (n = 106) was due to incomplete questionnaires and, for assessment at 26 months' follow-up, due to end of the study before follow-up of the participant was completed.

DISCUSSION

In this double-blind, randomized, controlled trial on the effect of pneumococcal vaccination on HRQoL and FHS in children with RAOM, no substantial difference between the 2 intervention groups could be found, nor could subgroups be identified that benefited either more or less from pneumococcal vaccination. FHS and HRQoL improved substantially in both the pneumococcal and control vaccine groups.

This study is the first to assess the effect of pneumococcal vaccination on HRQoL and FHS of older children with RAOM. Previous clinical trials in infants have shown significantly larger, albeit modest, reductions in the number of AOM episodes and tympanostomy tube placements by pneumococcal vaccination.[23,26] Clinical results of our trial, however, indicate that pneumococcal vaccination in children >1 year old with previous RAOM is not efficacious in the prevention of AOM episodes.[33] Our results regarding HRQoL and FHS are in agreement with these clinical results. Moreover, these study results complete the full spectrum from clinical to HRQoL effects of RAOM. In addition, they enabled us to show that there were no indirect positive effects from vaccination on HRQoL (eg, through reduction of

AOM severity or frequency of upper respiratory tract infections).

The current study is not the first to assess FHS in children with OM. In particular, several studies have been published investigating the effect of tympanostomy tube placement on their FHS, with some showing a positive effect[5,45,48,49] and others not.[50] Trials on tympanostomy tube placement, however, are hampered by the inability to blind caregivers and children for treatment, which means that treatment effects may be at least in part biased by their expectations.

The difference in effectiveness of pneumococcal conjugate vaccination between previous studies[23,26] and ours may be explained by the age at which children were vaccinated. When vaccination is started as early as at 2 months of age,[23,26] pneumococcal carriage of vaccine serotypes, and thereby the onset of pneumococcal AOM episodes, may be delayed until a later age, at which the child is immunologically and anatomically more mature to surmount these infections. By starting vaccination at a later age, especially after children have experienced RAOM, changes in nasopharyngeal and middle ear conditions may predispose them to additional AOM episodes and thus reduce the influence of vaccination on pneumococcal carriage and AOM.[33]

Several issues in this trial need to be considered. First, a small but statistically significant difference in favor of the control group was found for the OM-6 at 14 months' follow-up. This difference coincides with the largest difference in the incidence of AOM episodes between both intervention groups. The OM-6 is a disease-specific questionnaire and may accordingly be most sensitive to real changes in OM-related FHS. However, the clinical relevance of the difference in AOM frequency at 14 months' follow-up might be questioned, because there seems to be no reasonable explanation for it, and it did not persist through follow-up.

Second, the influence of various patient characteristics on treatment outcome was evaluated to identify subgroups that might benefit more from pneumococcal vaccination than others. No such effect modifiers, however, could be identified. Although this could be due to a lack of power, it is unlikely that relevant effect modifiers are present, because no overall beneficial effect of pneumococcal vaccination was observed. Therefore, for 1 subgroup of children to have benefited more from pneumococcal vaccination, another should have deteriorated.

Finally, during the trial, 8 children (4.2%) in the pneumococcal vaccine group and 13 (6.7%) in the control vaccine group were lost to follow-up. One child switched from the control to the pneumococcal vaccine group. It is unlikely that these small numbers of dropouts and crossovers influenced the trial results.

Although there are no overall differences between the pneumococcal vaccine and control vaccine groups in HRQoL and FHS after vaccination, there was a striking improvement of FHS and HRQoL in both intervention groups, especially during the first 7 months of follow-up. This improvement coincides with a marked reduction of AOM episodes and most likely may be explained by the fact that AOM frequency at enrollment was based on caregiver report, whereas during the trial only physician-diagnosed AOM episodes were counted. Caregivers may have overestimated the number of AOM episodes, something that has been reported before in children with RAOM.[51] If such a caregiver-recall bias regarding AOM incidence was in fact present, it obviously may also have influenced caregivers' reflection on subjective measures such as HRQoL and FHS.

Furthermore, the reduction might be an example of regression to the mean. The children we studied, with relatively serious RAOM (ie, at the extreme ends of AOM frequency distribution), are more likely to improve by chance alone. The reduction in AOM frequency also may result partly from a favorable natural course of RAOM. Similar but spontaneous reductions in AOM incidence in children with RAOM have been described.[2] Finally, there is growing evidence that medical and HRQoL outcomes may improve substantially by trial participation in itself, which is assumed to be related to the expectation of future benefit, better clinical follow-up, and other aspects of management of the condition.[52–55]

CONCLUSION

Pneumococcal vaccination in children 1 to 7 years old with previous recurrent episodes of AOM does not improve their HRQoL or FHS compared with control vaccination.

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