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Effect of Combined Pneumococcal Conjugate and Polysaccharide Vaccination on Recurrent Otitis Media With Effusion

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ABSTRACT

BACKGROUND. Otitis media with effusion (OME) is very common during childhood. Because *Streptococcus pneumoniae* is one of the most common bacterial pathogens involved in OME, pneumococcal vaccines may have a role in the prevention of recurrent OME.

OBJECTIVE. We sought to assess the effect of combined pneumococcal conjugate and polysaccharide vaccinations on the recurrence of OME.

METHODS. A randomized, controlled trial was performed with 161 children, 2 to 8 years of age, with documented persistent bilateral OME. All subjects were treated with tympanostomy tubes (TTs). One half of the subjects were assigned randomly to additional vaccination with a 7-valent pneumococcal conjugate vaccine 3 to 4 weeks before and a 23-valent pneumococcal polysaccharide vaccine 3 months after tube insertion. Blood samples were drawn at the first vaccination, at the time of TT placement, and 1 and 3 months after the second vaccination. Levels of IgA and IgG serum antibody against the 7-valent pneumococcal conjugate vaccine serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F were measured with enzyme-linked immunosorbent assays. All children were monitored for recurrence of OME for 6 months after spontaneous extrusion of the TTs.

RESULTS. The overall recurrence rate of bilateral OME was 50%. Pneumococcal vaccinations induced significant 4.6- to 24.4-fold increases in the geometric means of all conjugate vaccine serotype antibody titers but did not affect recurrence of OME.

CONCLUSIONS. Combined pneumococcal conjugate and polysaccharide vaccination does not prevent recurrence of OME among children 2 to 8 years of age previously known to have persistent OME. Therefore, pneumococcal vaccines are not indicated for the treatment of children suffering from recurrent OME.

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Key Words

otitis media, effusion, pneumococcal, conjugate vaccine

Abbreviations

OME—otitis media with effusion

TT—tympanostomy tube

PCV7—7-valent pneumococcal conjugate vaccine

PPV23—23-valent pneumococcal polysaccharide vaccine

CI—confidence interval

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OTTIS MEDIA WITH effusion (OME) is highly prevalent during childhood.¹ It is a self-limiting condition in most cases, but recurrences are frequent, with a cumulative recurrence rate of 50% within 24 months.² The pathogenesis of OME is multifactorial. Eustachian tube dysfunction,³⁻⁵ immunologic immaturity, or most likely a combination of these 2 factors is assumed to play a central role, especially in the pathogenesis of recurrent OME.⁶ Acquisition of viruses and bacteria in the nasopharynx is considered to be the first essential step in the pathogenesis of OME. If circumstances are favorable, that is, if Eustachian tube and/or immunologic dysfunction preexists, then these pathogens may enter the middle-ear cavity and induce inflammation of the middle-ear mucosa, resulting in OME.

Although there is still discussion about the long-term sequelae of OME, impairments of speech, language, and cognitive development have been reported to occur,⁷⁻⁹ especially among children with recurrent or persistent OME and associated hearing loss.¹⁰ Therefore, treatment should be focused on these children. The effectiveness of currently available treatment strategies (antibiotic therapy, adenoidectomy, and insertion of tympanostomy tubes [TTs]) is limited, and recurrences of OME are frequent; therefore new therapeutic approaches for OME are needed.

Streptococcus pneumoniae is the most common bacterial pathogen causing middle-ear effusion.¹¹⁻¹³ Vaccination against this pathogen for children prone to OME may be effective in preventing additional recurrences. Although previous studies addressed the effectiveness of pneumococcal vaccines against acute otitis media,¹⁴⁻¹⁶ no study has been published on the effectiveness of vaccination among children who are most at risk to develop long-term sequelae (ie, children with recurrent OME). The aim of this randomized, controlled trial was to establish the effect of combined pneumococcal conjugate and polysaccharide vaccine among children 2 to 8 years of age who were already known to be prone to recurrent OME and therefore most at risk to develop long-term sequelae.

METHODS

Study Subjects

Ear/nose/throat surgeons of 5 general hospitals and 2 academic hospitals participated in this multicenter trial. Between April 2000 and March 2002, all children referred by their general practitioner because of documented OME for ≥ 3 months were screened for eligibility to participate in the trial. Inclusion criteria were ages between 2 and 8 years and persistent (ie, for > 3 months) bilateral OME diagnosed with either a type B (flat) tympanogram or a type C2 (middle-ear pressure of less than -200 daPa) tympanogram with otoscopic evidence of

middle-ear effusion.¹⁷ Exclusion criteria were signs of acute otitis media, cleft palate, Down syndrome, known immune disorder other than IgA or IgG deficiency, chronic inhalation corticosteroid therapy, or use of anti-allergic drugs.

Permission for the study was obtained from the ethical committees of all participating hospitals. After written informed consent was obtained, all participating children were assigned randomly to 1 of 2 treatment groups, that is pneumococcal vaccinations in addition to TTs (vaccination plus TT group) or TTs only (TT group); age, previous adenoidectomy, previous episodes of persistent OME, and hospital were used as balancing factors, because these characteristics may affect the recurrence of OME (Fig 1). A computer program that allocated treatment on the basis of minimization was developed (ie, balanced allocation procedure). This program calculated a measure of imbalance based on the current number of treatment assignments and the prognostic factor composition of the treatment group. Before the next treatment assignment was made, the imbalance that would result when the child was assigned to either treatment was calculated. The treatment assignment that yielded the smallest imbalance was chosen, and the treatment was communicated to the ear/nose/throat surgeon. Treatment was not blinded.

This study was designed to detect a 20% reduction in recurrence of OME with a power of 80%, a 1-sided significance level of 5%, and a recurrence rate of 30% for the unvaccinated group. For that situation, 73 subjects per trial arm should complete the study. A target of 85 children in each group was set because of loss to follow-up monitoring.

Vaccines

The 7-valent pneumococcal conjugate vaccine (PCV7) (Prevenar; Wyeth Lederle Vaccines, Pearl River, NY) contains 2 μg of capsular polysaccharides of pneumococcal serotypes 4, 9V, 14, 19F, and 23F, 4 μg of serotype 6B polysaccharide, and 2 μg of serotype 18C oligosaccharide, each conjugated individually to the non-toxic diphtheria toxin analog CRM197. Two 23-valent pneumococcal polysaccharide vaccine (PPV23) forms (Pneumune; Wyeth Lederle Vaccines; and Pneumovax; Aventis Pasteur MSD, Lyon, France) were used for booster immunization. Both PPV23 forms contain 25 μg of purified type-specific capsular polysaccharides of pneumococcal serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 20, 22F, 23F, and 33F. All children in the vaccination plus TT group were immunized with PCV7, administered intramuscularly, 21 to 28 days before placement of TTs. PPV23 was administered intramuscularly 4 months after the conjugate vaccine (ie, ~ 3 months after insertion of the TTs).

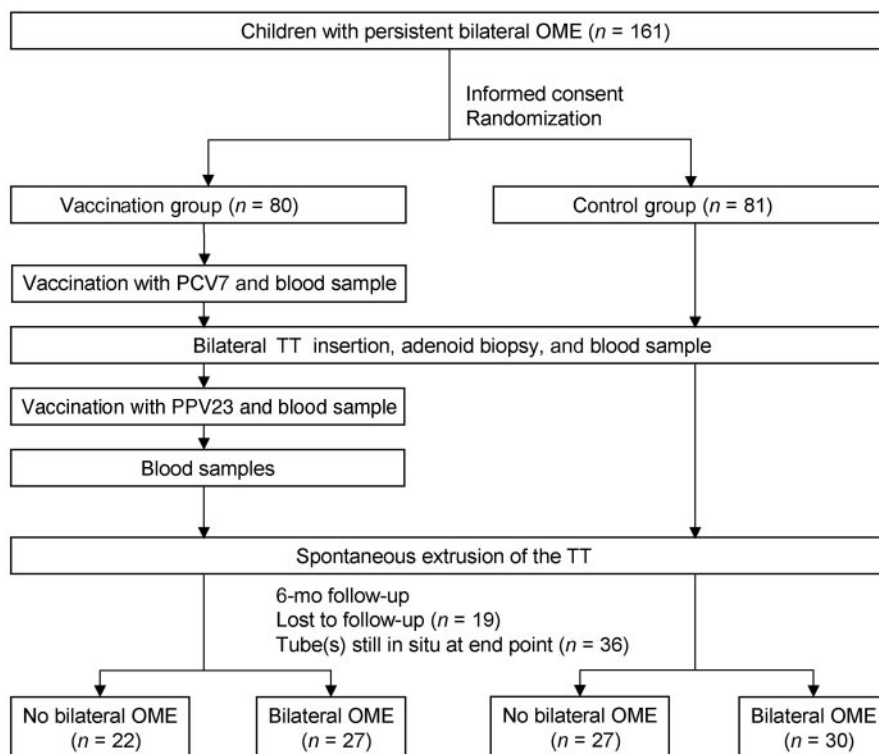


FIGURE 1
Flowchart outlining all stages of the randomized, controlled trial.

Procedures

For all children, fluoroplastic, Bevel Bobbin-type TTs (TympoVent; AtosMedical, Hörby, Sweden) were inserted bilaterally. The presence or absence of middle-ear effusion was documented, and a sample of the effusion was collected. A biopsy of the adenoid (or its remnant, in cases of previous adenoidectomy) was obtained, and blood samples were drawn (Fig 1). For the vaccination plus TT group, blood samples were also drawn at the time of first vaccination (PCV7), that is 1 month before TT insertion, and 1 and 3 months after booster vaccination (PPV23). For a random sample of 25 children in the TT group, blood samples were also drawn 6 months after insertion of TTs. The adenoid biopsy and middle-ear effusion were processed for bacteriologic culture, to determine the presence of *S pneumoniae* (see below). The blood samples were used for enzyme-linked immunosorbent assay determination of levels of IgA and IgG antibodies against the PCV7 serotypes of *S pneumoniae* (see below).

Follow-up Monitoring

The main end point of the trial was the recurrence of bilateral OME during the follow-up period of 6 months after spontaneous extrusion of the TTs. Follow-up visits were scheduled 1 week after insertion of TTs and then every 3 months. At these visits, symptoms of otorrhea during the previous 3 months, as well as adverse events resulting from the vaccinations, were recorded. Otoscopy was performed to determine whether the tube was

still in place and patent. The presence of otorrhea was documented. The incidence of otorrhea after insertion of TTs was calculated as the total number of either unilateral or bilateral episodes during the follow-up period. If otorrhea was present during one of the follow-up visits, no culture swabs were obtained and spontaneous recovery was awaited. Persistent otorrhea was treated with various antibiotic eardrops. Active and passive Eustachian tube function was measured with the pressure equilibration test and the forced response test, respectively. These tests are described in detail elsewhere.¹⁸ If the tube was found to be extruded, then the presence or absence of recurrent OME was recorded. Recurrent OME was defined as either a type B tympanogram or a type C2 tympanogram with otoscopic evidence of middle-ear effusion.¹⁷ All children were monitored until recurrent bilateral OME was determined, until 6 months after spontaneous extrusion of the ventilation tubes, or until the predetermined closing date of the study.

Laboratory Methods

Levels of IgA and IgG serum antibodies against serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F were measured with enzyme-linked immunosorbent assays, as described elsewhere.¹⁹ Samples of middle-ear fluid were diluted with 0.9% NaCl and centrifuged. The pellet was plated immediately on blood agar for bacterial cultures. The adenoid biopsy was also cultured on blood agar. *S pneumoniae* was identified on the basis of colony morphologic features and with conventional determination methods.

Statistical Analyses

All analyses were performed according to the intention-to-treat principle. To adjust for possible confounders, multivariate regression models were constructed. Vaccine effectiveness was expressed as an estimate of the relative risk, with 95% confidence interval (CI) (Proc Genmod procedure with SAS software [SAS Institute, Cary, NC]). χ^2 tests were used to assess differences in occurrence of otorrhea between the 2 intervention groups. Antibody levels were expressed as geometric means. Fold increases in antibody levels were calculated by dividing antibody levels from paired postimmunization and preimmunization samples. All analyses were performed with SAS 8.1.

RESULTS

Baseline Characteristics

One hundred sixty-one children were enrolled in the trial; 80 were assigned to the vaccination plus TT group and 81 to the TT group. The 2 groups were comparable with respect to demographic characteristics and known risk factors for OME, except for the number of siblings (Table 1). On average, children in the TT group had more younger siblings and fewer older siblings.

Total serum IgA and IgG titers, as well as serotype-specific antibody titers, were similar in the 2 groups at study entry. No differences in active or passive Eustachian tube function between the 2 groups were found.

For practical reasons, adenoid biopsies and middle-ear effusions were collected in 5 of the 7 participating hospitals. *S pneumoniae* was cultured from 54 of 123 adenoids (44%) and from only 7 of 101 effusions (7%). No differences were found between the 2 treatment groups in the proportions of pneumococcus-positive ad-

enoid or effusion cultures at the time of surgery ($P = .7$ and $.5$, respectively). *S pneumoniae* was found in the middle-ear effusion for none of the children with a negative adenoid culture. Other frequently cultured pathogens were *Haemophilus influenzae* and *Moraxella catarrhalis*.

Vaccine Effectiveness

One hundred six children completed follow-up assessments; 19 children were lost to follow-up monitoring, and one or both TTs were still present at the predetermined closing date of the study for 36 children. These reasons for incomplete follow-up monitoring were randomly distributed among the groups. The duration of middle-ear ventilation was the same for the 2 groups (median: 9 months; range: 1.5–22.5 months).

As shown in Table 2, vaccination with PCV7 followed by booster vaccination with PPV23 induced a significant 4.6- to 24.4-fold increase in the geometric mean of all serotype-specific antibody titers 1 month after vaccination. The greatest increases were found for IgA antibodies against serotype 4 (22.7-fold increase) and IgG antibodies against serotypes 4 and 14 (18.0- and 24.4-fold increases, respectively). In the TT group, serotype-specific IgA and IgG antibody titers did not change.

The combined PCV7/PPV23 vaccination did not decrease the risk of recurrent bilateral OME, however (relative risk: 0.91; 95% CI: 0.60–1.38). In this study, a larger number of younger siblings was associated with a higher rate of recurrence of bilateral OME; therefore, the relative risk was adjusted for the difference in the number of younger siblings between the vaccination plus TT group and the TT group. This did not affect the outcome (adjusted relative risk: 1.05; 95% CI: 0.69–1.59). Regarding unilateral recurrence of OME, no differences between the 2 groups were found (Table 3).

The total number otorrhea episodes ranged from 0 to 7 per child. In the vaccination plus TT group, 110 otorrhea episodes were reported by the parents and 32 episodes were recorded at the follow-up visits. In the TT group, these numbers were 117 and 34 episodes, respectively.

Safety

Approximately 5% of the children developed signs of inflammation at the injection site (ie, redness, swelling, pain, or itching) and/or fever (temperature of $>38^\circ\text{C}$) after vaccination with both the pneumococcal conjugate and the polysaccharide vaccine. No serious adverse events were reported.

DISCUSSION

This prospective, randomized study is the first to establish the effects of pneumococcal vaccination on recurrences of OME among children already known to be prone to this condition. The recurrence rate of 50% was

TABLE 1 Demographic Characteristics and Risk Factors for Recurrent OME for Both Treatment Groups

	Vaccination + TT Group (N = 80)	TT Group (N = 81)
Age, mean, y	5.4	5.2
Male gender, %	59	54
Previous episode of persistent OME, %	78	78
Previous TTs, %		
1	33	33
2	31	23
3	14	14
Previous adenoidectomy, %	51	51
No. of children with younger siblings	36 ^{a,b}	50 ^{a,b}
No. of children with older siblings	53 ^b	42 ^b
Day care, %		
At study entry	18	14
In the past	59	53
Habitual sniffing, %	30	32

^a $P = .03$.

^b The total number exceeds total number of children because children might have both younger and older siblings.

TABLE 2 Geometric Mean IgA and IgG Antibody Levels for All 7 Vaccine Serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F) Before and 1 Month After Vaccination

Serotype	Antibody Levels, $\mu\text{g/mL}$				Fold Increase
	Before Vaccination	95% CI	After Vaccination ^a	95% CI	
IgA					
4	0.026	0.018–0.037	0.587	0.452–0.761	22.6
6B	0.009	0.007–0.012	0.058	0.043–0.078	6.4
9V	0.227	0.166–0.311	3.255	2.335–4.538	14.3
14	0.235	0.178–0.312	2.936	2.264–3.809	12.5
18C	0.009	0.006–0.013	0.076	0.057–0.100	8.4
19F	0.113	0.087–0.147	1.102	0.817–1.486	9.8
23F	0.048	0.039–0.060	0.311	0.227–0.426	6.5
IgG					
4	0.122	0.079–0.186	2.193	1.736–2.771	17.8
6B	0.248	0.177–0.353	1.145	0.833–1.574	4.6
9V	1.667	1.201–2.314	15.213	10.957–21.124	9.1
14	2.836	2.022–3.980	69.286	54.058–88.804	24.4
18C	0.735	0.496–1.088	6.060	4.513–8.138	8.2
19F	0.832	0.583–1.188	7.044	5.283–9.391	8.5
23F	0.491	0.352–0.686	2.992	2.087–4.288	6.1

^a No additional increase in antibody titers between 1 and 3 months after the booster vaccination was found; therefore, results at 3 months are not shown.

TABLE 3 Number of Children With Unilateral or Bilateral OME After Extrusion of TTs in the 2 Treatment Groups

	n (%)	
	Vaccination + TT Group	TT Group
No recurrent OME	12 (15)	10 (12)
Unilateral OME	10 (13)	17 (21)
Bilateral OME	27 (34)	30 (37)
Incomplete follow-up data	31 (39)	24 (30)

high in both groups, indicating that we indeed included children who were at risk for recurrent OME. For all children, combined vaccination with PCV7 and PPV23 resulted in a good serum antibody response to each of the 7 pneumococcal serotypes. However, this did not result in a reduced risk of recurrent OME. Pneumococcal vaccination also did not reduce the incidence of TT otorrhea. These results are generalizable to all children with persistent OME for ≥ 3 months who are referred to an ear/nose/throat surgeon for additional evaluation and/or treatment.

Previous studies addressed the effect of pneumococcal conjugate vaccinations on otitis media in general. Fireman et al²⁰ demonstrated that PCV7 moderately reduced “otitis visits,” but they did not discriminate between acute otitis media and OME. Straetemans et al¹⁶ analyzed the data from the Finnish Otitis Media Vaccine Trial to assess the effect of PCV7 on OME among infants up to 2 years of age. They found no protective effect of PCV7 on OME episodes. In the same study, PCV7 vaccination did not affect ventilation tube placement for persistent OME among children 2 to 5 years of age.²¹

The lack of a clinical effect despite good antibody responses may be explained in several ways. First, the phenomenon called “serotype replacement” may be responsible for the ineffectiveness of the vaccines.²² Serotype replacement occurs when vaccine-induced reductions in the prevalence of vaccine-type pneumococci increase the prevalence of pneumococci not included in the vaccine. Replacement phenomena were demonstrated in both the nasopharynx and the middle ear after vaccination with PCV7.^{15,23–25} Second, pneumococcal vaccination may also induce replacement by other pathogens involved in middle-ear disease, such as *Staphylococcus aureus*, *H influenzae*, or *M catarrhalis*.^{25,26} A third explanation for the lack of effectiveness of pneumococcal vaccination may be that recurrent OME is caused not by actual reinfection with pneumococci but by dead bacteria or nonbacterial substances causing ongoing inflammation of the middle-ear mucosa.²⁷ Our finding that only 7% of middle-ear effusion cultures, compared with 44% of adenoid cultures, were positive for *S pneumoniae* supports this hypothesis.

Pneumococcal vaccines have been included in the infant vaccination programs of several countries and will be in many others to prevent invasive pneumococcal disease and pneumonia. Whether such widespread vaccination of very young children will reduce the incidence and recurrence of OME in the community is not yet known, but the current study results suggest that it will not. Additional research should be focused on methods for identification and early treatment of children who are at risk to develop long-term sequelae (ie, children with recurrent OME).

CONCLUSIONS

Although combined pneumococcal conjugate and pneumococcal polysaccharide vaccination is very effective against invasive infections and pneumonia attributable to *S pneumoniae*, it does not protect children who are prone to OME against recurrences. Therefore, pneumococcal vaccines are not indicated for the treatment of children suffering from recurrent OME.

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