Effect of conjugate pneumococcal vaccine followed by polysaccharide pneumococcal vaccine on recurrent acute otitis media: a randomised study

Reinier Veenhoven, Debby Bogaert, Cuno Uiterwaal, Carole Brouwer, Herma Kiezebrink, Jacob Bruin, Ed IJzerman, Peter Hermans, Ronald de Groot, Ben Zegers, Wietse Kuis, Ger Rijkers, Anne Schilder, Elisabeth Sanders

Summary

Background Pneumococcal conjugate vaccine prevents recurrent acute otitis media (AOM) in infants immunised at 2, 4, 6, and 12–15 months of age. We aimed to find out whether this vaccine also prevents AOM in older children who have had previous episodes of AOM.

Methods In this double-blind, randomised study, we enrolled 383 patients aged 1–7 years who had had two or more episodes of AOM in the year before entry. Randomisation was stratified in four groups according to age (12–24 months vs 25–84 months) and the number of previous AOM episodes (two or three episodes vs four or more episodes). Children received either 7-valent pneumococcal conjugate vaccine followed by 23-valent pneumococcal polysaccharide vaccine, or hepatitis A or B vaccines. They were followed up for 18 months for recurrence of AOM. We also cultured samples of middle-ear fluid and nasopharyngeal swabs to assess association of pneumococcal serotypes with AOM after vaccination.

Findings We noted no reduction of AOM episodes in the pneumococcal vaccine group compared with controls (intention-to-treat analysis: rate ratio 1.25, 95% CI 0.99–1.57). Although nasopharyngeal carriage of pneumococci of serotypes included in the conjugate-vaccine was greatly reduced after pneumococcal vaccinations, immediate and complete replacement by non-vaccine pneumococcal serotypes took place.

Interpretation These data do not lend support to the use of pneumococcal conjugate vaccine to prevent otitis media in previously unvaccinated toddlers and children with a history of recurrent AOM.

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Department of Paediatrics, Spaarne Hospital, Haarlem, Netherlands (R Veenhoven MD, C Brouwer MD, H Kiezebrink MD); Department of Paediatrics, Sophia Children’s Hospital, Erasmus University, Rotterdam, Netherlands (D Bogaert MD, P Hermans PhD, Prof R de Groot MD); Julius Center for Health Sciences and Primary Care, Utrecht, Netherlands (C Uiterwaal MD); Regional Laboratory of Public Health, Haarlem (J Bruin MSc, E IJzerman MD); Department of Otorhinolaryngology (A Schilder MD), Laboratory of Paediatric Immunology (G Rijkers PhD, Prof B Zegers PhD), and Department of Paediatric Immunology (Prof W Kuis MD, E Sanders MD), Wilhelmina Children’s Hospital, University Medical Center, Utrecht

Correspondence to: Dr E A M Sanders, Department of Paediatric Immunology, Wilhelmina Children’s Hospital, University Medical Center Utrecht, PO Box 85090, 3508 AB Utrecht, Netherlands. (e-mail: eam.sanders@planet.nl)

Introduction

The American Academy of Pediatrics has recommended immunisation with 7-valent pneumococcal conjugate vaccine (PCV7) for children with recurrent or severe acute otitis media (AOM) and children who have tympanostomy tubes because of recurrent AOM. This advice was based on the results of two clinical trials with PCV7. The trials included almost 40 000 healthy infants, who were immunised at 2, 4, and 6 months of age, and had booster vaccinations at 12–15 months of age. These children were followed up for the occurrence of AOM up to their second birthday. The pneumococcal vaccine reduced the number of infants with recurrent episodes of AOM by 9%. The largest effect was a reduction of 23% in the number of children developing a severely otitis-prone condition (five episodes in 6 months or six episodes per year). Furthermore, the number of children receiving tympanostomy tubes was reduced by 20%.

However, the benefits of pneumococcal conjugate vaccine have not been investigated in previously unvaccinated toddlers and older children who have documented episodes of AOM before vaccination. Assessment of the vaccine’s effectiveness is especially important in this group, since children with recurrent AOM can have subtle immunodeficiencies that alter the vaccine’s immunogenicity. Genetically determined factors in innate and adaptive immunity may also affect the effectiveness of the vaccine. Furthermore, vaccine effectiveness in older children might differ from that in infants due to differences in pneumococcal serotype coverage and environmental factors. Therefore, the efficacy of pneumococcal conjugate vaccine needs to be assessed in randomised trials to support recommendations that these children should also be immunised.

We investigated whether combined vaccination with PCV7 followed by 23-valent pneumococcal polysaccharide vaccine (PPSV23) could prevent AOM in children aged 1–7 years, with two or more documented episodes of AOM before vaccination. This combination was chosen because of the booster effect of the polysaccharide vaccine after priming with conjugate vaccine both in infants and in children prone to otitis. Furthermore, the broad pneumococcal serotype coverage by the 23-valent vaccine could benefit children older than 2 years of age. We assessed the protective efficacy of pneumococcal vaccination against recurrent AOM, and the effect of vaccination on culture-confirmed pneumococcal AOM and nasopharyngeal carriage.

Methods

We did a randomised, double-blind trial between April, 1998, and January, 2002, at a general hospital (Spaarne Hospital, Haarlem) and a tertiary care hospital (Wilhelmina Children’s Hospital of the University Medical Center Utrecht) in the Netherlands. Parents were informed about the study by primary care physicians,
paediatricians, and otolaryngologists from across the Netherlands. Parents who were willing to participate signed a consent form to enrol their child in the study.

Inclusion criteria for the study were two or more episodes of AOM in the year before study entry, and age 1–7 years. The number of previous AOM episodes was based both on parental report—with AOM defined as having one or more of the symptoms: acute earache, new-onset otorrhea, irritability, and fever—and on clinical confirmation of the diagnosis by a physician. Exclusion criteria were primary or secondary immunodeficiency, cystic fibrosis, immotile cilia syndrome, craniofacial abnormalities such as cleft palate, chromosomal abnormalities such as Down’s syndrome, and severe adverse events during previous vaccinations.

The children were randomised to receive either PCV7 followed by PPSV23, or hepatitis A or B vaccines. PCV7 (Prevnar, Wyeth, Rochester, NY, USA) consisted of 2 µg each 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 CRM197 protein. PPSV23 (Pneumune, Wyeth) consisted of 25 µg of capsular polysaccharides of each of the pneumococcal serotypes 1, 2, 3, 4, 5B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, and 33F. Control vaccines were recombinant hepatitis B vaccine (Engerix-B=AE Junior, GlaxoSmithKline, Rixenart, Belgium) and hepatitis A vaccine (Havrix=AE Junior, GlaxoSmithKline).

Since we expected that age at baseline and the number of episodes of AOM in the year before study entry would be important prognostic indicators for AOM, we randomised the children within four groups according to age (12–24 months vs 25–84 months) and number of previous AOM episodes per year (two or three episodes vs four or more episodes). The children were assigned a number from a table of random numbers that identified the vaccine scheme. The vaccine was administered to the child by a study nurse, so that parents and physicians were unaware of treatment. Children aged 12–24 months in the pneumococcal vaccine group were immunised with PCV7 twice (with a 1-month interval between immunisations) followed 6 months later by PPSV23. The control vaccine group aged 12–24 months received three hepatitis B vaccinations according to a similar time schedule. Children aged 25–84 months in the pneumococcal vaccine group received one dose of PCV7, followed 7 months later by PPSV23. The control group aged 25–84 months received hepatitis A vaccine twice.

The primary endpoint was the efficacy of pneumococcal vaccination against clinical episodes of AOM during a follow-up period of 18 months, starting 1 month after completion of the vaccination schedule. AOM episodes occurring during the 6–7 month period beginning 1 month after PCV7 or control vaccinations and ending 1 month after the last vaccination were also recorded. We instructed parents to visit the study clinics or their family physician, otolaryngologist, or paediatrician to assess symptoms suggesting AOM. Physicians registered signs and symptoms of every AOM episode on standard registration forms. Guidelines issued by the Dutch College of General Practitioners define AOM as the presence of an abnormal tympanic membrane on otoscopy (red, dull, or bulging), or otorrhoea and at least one of these signs or symptoms of acute infection: acute earache, new-onset otorrhea, irritability, or fever greater than 38.5°C rectally or 38.0°C axillary.† New episodes of AOM were recorded after a minimum 7-day interval free of AOM-related symptoms and treatment.

Additional outcomes in our study included number of AOM episodes due to the seven pneumococcal serotypes included in the conjugate vaccine and nasopharyngeal carriage of conjugate vaccine serotypes. Bacterial cultures from middle-ear fluid were obtained only once in every child, at the time of the first AOM episode arising at least 1 month after the last vaccination. Parents had been asked to bring their child to the study clinic within 24 h after the onset of symptoms suggesting AOM. After clinical confirmation of the diagnosis of AOM, middle-ear fluid was collected by myringotomy or by spontaneous drainage near the perforation site with an aspirator (Juhn Tym-Tap collector, Xomed, Jacksonville, USA) or sterile dry cotton-wool swab (Coban Italia, Transwab, Medical Wire and Equipment Company, Corsham, England). At study entry and follow-up visits, we took nasopharyngeal samples transnasally with a flexible, sterile, dry cotton-wool swab. After sampling, we immediately placed swabs in 388 assessed for eligibility
5 excluded: 3 did not meet inclusion criteria
2 refused to participate
383 randomised
190 allocated pneumococcal vaccine
193 allocated control
4 discontinued treatment* 46
190 received pneumococcal vaccine
193 allocated control vaccine
186 assessed in per protocol analysis
181 assessed in per protocol analysis
190 assessed in intention-to-treat analysis
193 assessed in intention-to-treat analysis
1 lost to follow-up† 11 discontinued treatment‡

*One child discontinued treatment because of gastroenteritis directly after first vaccination (link with vaccination questionable); three discontinued because parents were not motivated. The patient moved and we did not know his new address.‡Four discontinued treatment because of symptoms suggesting AOM during the 6–7 month period beginning 1 month after PCV7 or control vaccinations and ending 1 month after the last vaccination were also recorded. We instructed parents to visit the study clinics or their family physician, otolaryngologist, or paediatrician to assess symptoms suggesting AOM. Physicians registered signs and symptoms of every AOM episode on standard registration forms. Guidelines issued by the Dutch College of General Practitioners define AOM as the presence of an abnormal tympanic membrane on otoscopy (red, dull, or bulging), or otorrhoea and at least one of these signs or symptoms of acute infection: acute earache, new-onset otorrhea, irritability, or fever greater than 38.5°C rectally or 38.0°C axillary. New episodes of AOM were recorded after a minimum 7-day interval free of AOM-related symptoms and treatment.

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who were unaware of treatment allocation. Plates were incubated at 37 °C for 48 h; the blood agar with 5 mg/L gentamicin, and a chocolate agar plate. Agar 5% sheep blood agar plates, a 5% sheep blood agar plate and nasopharyngeal swabs were plated within 6 h onto two transport medium. Samples of middle-ear fluid

The study was undertaken in accordance with the European standards for good clinical practice, which includes the provisions of the Declaration of Helsinki of 1989. The medical ethics committees of both participating hospitals approved the study protocol.

Statistical analysis

On the basis of data from previous studies in the Netherlands, we estimated that 55% of our high-risk patients in the control group would have at least one episode of AOM during the 18 months of follow-up after completion of vaccinations. In view of the multifactorial causes of AOM and comparison of the expected benefit of that of antibiotic prophylaxis and tympanostomy tubes, we judged a reduction of at least 25% to a recurrence rate of 40% of one or more AOM episodes in the pneumococcal vaccine group to be clinically relevant. In order to detect such a reduction, with α (2-sided) 0·05 and power 80%, 176 patients would have to be included in each group. To compensate for an estimated dropout of about 10%, 388 patients would have to be randomised.

Vaccine efficacy was assessed with Cox-type proportional hazards regression models, including a frailty term allowing for differences between individuals in numbers of recurrent AOM episodes. We undertook this analysis in S-plus, version 2000; all other analyses were done with SPSS 10·1. Results are presented as rate ratios with 95% CI; we judged significance to be reached when α (2-sided) 0·05 and power 80%, 176 patients would have to be included in each group. To compensate for an estimated dropout of about 10%, 388 patients would have to be randomised.

The differences in conjugate and non-conjugate nasopharyngeal pneumococcal carriage between the treatment groups were assessed as follows: children were classified as having had a positive culture for any pneumococcal serotype included in PCV7 or any pneumococcal serotype not included in PCV7 if they had had such a positive culture at any of the scheduled follow-up visits after complete vaccination. Proportional differences in pneumococcal carriage and pathogens causing AOM were analysed with χ² tests or Fisher’s exact tests when appropriate. We judged p<0·05 to be significant.

Differences in diary data between groups were assessed with the Mann-Whitney U test.

Results

We enrolled 383 children between April, 1998, and January, 2001; 190 children were randomised to receive pneumococcal vaccinations and 193 to receive control hepatitis vaccinations (figure 1). Age, sex, number of previous AOM episodes, and other risk factors for AOM did not differ between the groups (table 1). In the pneumococcal vaccine group, 186 of 190 children (98%) completed the vaccination scheme, as did 181 of 193 controls (94%). The median follow-up after complete vaccination was similar in the pneumococcal vaccine group (18·1 months, range 2·4–23·0) and control group (18·0 months, range 0·5–23·0). One patient was lost to follow-up immediately after the first vaccination. No serious adverse events were noted after pneumococcal or hepatitis vaccinations.

Of the 475 AOM episodes diagnosed during follow-up after the final vaccination, 275 episodes were recorded in 107 of 186 children (56%) in the pneumococcal vaccine group who completed all vaccinations (recurrence rate 1·1 episodes per person-year) and 200 episodes in 101 of 181 controls (56%; recurrence rate 0·83 episodes per person-year). In this per-protocol analysis after complete vaccination, the rate ratio of recurrence of AOM for the
pneumococcal vaccine group versus controls was 1·29 (95% CI 1·02–1·62). The results of the intention-to-treat analysis did not differ from those of the per-protocol analysis over the same period (rate ratio 1·25, 95% CI 0·99–1·57). The cumulative hazard function for AOM of the fully vaccinated pneumococcal vaccine group and controls is shown in figure 2. Subgroup analysis suggested a slightly higher rate ratio of recurrence of AOM in the pneumococcal vaccine group than in controls in children older than 2 years at the time of first vaccination (rate ratio 1·45, 95% CI 1·09–1·94), compared with the group aged 1–2 years (1·07, 0·72–1·60). The rate ratio also seemed higher in children who had two or three episodes of AOM in the year preceding the study (1·66, 1·11–2·49) compared with those who had four or more episodes (1·20, 0·92–1·56). However, since neither of the interactions between age and treatment effect (1·37, 0·87–2·14) and between previous AOM episodes and treatment effect (0·74, 0·45–1·22) was significant, we were not able to conclude that rate ratios differed across subgroups. Excluding the severely otitis-prone children with six or more AOM episodes in the year before study entry from the analyses did not change the outcome of the study (1·30, 0·83–2·06).

We recorded a total of 840 episodes of AOM during the investigation, including those that arose in the period of 6–7 months between first study vaccinations and 1 month after the last vaccination. 445 episodes were in 135 of the 190 children (71%) in the pneumococcal vaccine group (recurrence rate 1·23 episodes per person-year), and 395 episodes in 139 of the 192 controls (72%; recurrence rate 1·08 episodes per person-year). During this whole period, the intention-to-treat analysis also showed no decrease of AOM in the pneumococcal vaccine group compared with controls (rate ratio 1·11, 95% CI 0·92–1·33).

We used data from the diaries to assess the severity and duration of the AOM episodes. Parents of 179 of 208 children with AOM during follow-up completed diaries for 399 of the 475 episodes. We noted no differences between pneumococcal vaccine group and controls in median days per episode for ear-related symptoms such as earache, otorrhea, irritability, and fever, and ear-related treatment such as use of analgesics, antibiotics, and ototopical medications. The number of children treated with tympanostomy tubes during follow-up was similar in the pneumococcal vaccine and control groups (33 and 39, respectively; p = 0·36).

Nasopharyngeal swabs were taken at baseline, just before the last vaccination, and at 7, 13, and 19 months after complete vaccinations in 375, 358, 346, 282, and 240 of the children, respectively. At baseline, nasopharyngeal carriage of S pneumoniae was found in 49% of all children, regardless of age. Of these nasopharyngeal pneumococcal serotypes, 53% had been included in PCV7; these were serotypes 19F (13%), 6B (12%), 23F (11%), 14 (9%), 9V (5%), 18C (1%), and 4 (1%). In the pneumococcal vaccine group the nasopharyngeal carriage of the conjugate vaccine serotypes fell substantially after complete vaccination.
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**Discussion**

Our results show that combined pneumococcal conjugate and polysaccharide vaccination is not effective in prevention of AOM in children older than 1 year of age with recurrent AOM. Exclusion of children who were severely prone to otitis from the analysis did not change the outcome of the investigation.

During the trial we saw a marked reduction in AOM episodes both in the pneumococcal vaccine and control groups to an average of one episode per child per year. This decrease could be the result of overestimation of the number of AOM episodes by parents before study entry; such overestimation has been reported previously in studies of children with recurrent AOM. Furthermore, spontaneous recovery of recurrent AOM with increasing age would have had a role in our investigation, since the recurrence rate of AOM episodes per person-year decreased in the total group of patients from 1.63 in the interval between first and last vaccination to 0.97 between the last vaccination and the end of the study. Finally, evidence suggests that medical outcomes can improve substantially due to trial participation itself, which is assumed to be related to expectation of future benefit, improved clinical follow-up, and other aspects of management of the condition.

In accord with our assumptions, 101 of 181 (56%) children in the control group had at least one episode of AOM during follow-up. On the basis of results from previous trials with PCV7 in healthy infants, we assumed the efficacy of the vaccine to be higher in children with increased baseline risk of AOM. The children in our study had already had recurrent episodes of AOM and were followed up for a sufficiently long period to detect the reduction of AOM episodes by PCV7 that we intended. Our results do not show any beneficial effect of this vaccination scheme in terms of reduction of AOM. Since randomisation was successful, loss to follow-up was very low, and AOM episodes were meticulously recorded, we believe that this outcome is valid and that a further increase of precision (more included children) would be unlikely to change these estimates.

We noted very good IgG antibody responses to pneumococcal antigen. These responses were measured for 126 randomly selected children, 24 from each of the four randomisation groups who received pneumococcal vaccines and 30 controls. Geometric mean concentrations of these antibodies were consistently higher in the pneumococcal vaccine group than in controls, and reached values far above 1·5 mg/L, apart from concentrations of serotype 6B, which remained below 0·2 mg/L (table 3).

**Table 3: Geometric mean concentrations (mg/L) of IgG anti-pneumococcal antibodies against conjugate vaccine pneumococcal serotypes**

<table>
<thead>
<tr>
<th>Pathogens cultured at the first AOM episode after completion of the vaccination scheme</th>
<th>Number of children with at least one AOM episode</th>
<th>Number of AOM episodes at which MEF obtained</th>
<th>Pneumococcal serotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>S aureus</td>
<td>107</td>
<td>101</td>
<td>Pneumococcal serotype</td>
</tr>
<tr>
<td>M catarrhalis</td>
<td>92</td>
<td>89</td>
<td>4</td>
</tr>
<tr>
<td>S pneumoniae</td>
<td>13</td>
<td>19</td>
<td>6B</td>
</tr>
<tr>
<td>PCV7 pneumococcal serotypes</td>
<td>4</td>
<td>8</td>
<td>9V</td>
</tr>
<tr>
<td>Other pneumococcal serotypes</td>
<td>9</td>
<td>11</td>
<td>23</td>
</tr>
<tr>
<td>M catarrhalis</td>
<td>8</td>
<td>6</td>
<td>38</td>
</tr>
<tr>
<td>Group A streptococcus</td>
<td>6</td>
<td>4</td>
<td>67</td>
</tr>
<tr>
<td>Negative cultures</td>
<td>32</td>
<td>35</td>
<td>67</td>
</tr>
<tr>
<td>Others (all from spontaneously draining ears)</td>
<td>26</td>
<td>9</td>
<td>6002</td>
</tr>
</tbody>
</table>

MEF=middle ear fluid.

**Table 2: Pathogens cultured at the first AOM episode after completion of the vaccination scheme**

**Table 3: Geometric mean concentrations (mg/L) of IgG anti-pneumococcal antibodies against conjugate vaccine pneumococcal serotypes**

**Discussion**

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Furthermore, spontaneous recovery of recurrent AOM with increasing age would have had a role in our investigation, since the recurrence rate of AOM episodes per person-year decreased in the total group of patients from 1.63 in the interval between first and last vaccination to 0.97 between the last vaccination and the end of the study. Finally, evidence suggests that medical outcomes can improve substantially due to trial participation itself, which is assumed to be related to expectation of future benefit, improved clinical follow-up, and other aspects of management of the condition.

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We noted very good IgG antibody responses to pneumococcal antigen. These responses were measured for 126 randomly selected children, 24 from each of the four randomisation groups who received pneumococcal vaccines and 30 controls. Geometric mean concentrations of these antibodies were consistently higher in the pneumococcal vaccine group than in controls, and reached values far above 1·5 mg/L, apart from concentrations of serotype 6B, which remained below 0·2 mg/L (table 3).
protection against AOM caused by serotype 19F.\textsuperscript{24} The deficient response to serotype 6B in our study might be due to a subtle immune deficiency, which is characteristic of children who are prone to otitis.\textsuperscript{19} Results of other studies have shown that when healthy infants and toddlers were vaccinated with PCV, they were less likely to carry serotype 6B and cross-reactive serotype 6A or have AOM caused by these pathogens.\textsuperscript{20,22,24} By contrast, we found a low effect of pneumococcal vaccination against carriage of serotype 6B and no effect against 6A. This finding is probably the result of the low titres of antibody against serotype 6B, and might have influenced the outcome of our study, since serotypes 6B and 6A are among the most common AOM serotypes.\textsuperscript{1}

Our findings of no beneficial effect of pneumococcal vaccinations contrast with those of the two landmark studies on prevention of AOM by PCV\textsuperscript{7} in infants.\textsuperscript{2,3} These investigations both showed a small but beneficial effect on AOM and improved results in prevention of frequent recurrent AOM. Apart from the booster vaccination with PPSV23, the most important difference between these two studies and ours is that the former studies include healthy infants, who were vaccinated as early as 2 months of age. At this age the child has not yet developed an immune response and does not have fully established nasopharyngeal pneumococcal carriage.\textsuperscript{21} \textit{S pneumoniae} is a frequent pathogen in early AOM.\textsuperscript{1} Because of inflammation and subsequent damage to the middle-ear mucosa and eustachian tube, early pneumococcal AOM could predispose infants to recurrent AOM caused by other pathogens such as \textit{H influenzae}, which was shown to become increasingly important in recurrent AOM episodes.\textsuperscript{4} Arguably, conjugate vaccination at infant age might prohibit or delay nasopharyngeal acquisition of the most frequent pneumococcal serotypes, preventing or delaying pneumococcal AOM until a later age, at which time the child is immunologically and anatomically more mature and more capable of handling an AOM infection than in infancy. Thus, prevention of early pneumococcal AOM could be especially important for the prevention of the otitis-prone condition.

In our study, pneumococcal carriage was noted in 50% of children at study entry. This proportion remained constant throughout follow-up, both in the pneumococcal vaccine group and in controls. Although pneumococcal vaccinations did reduce nasopharyngeal carriage of the seven conjugate vaccine serotypes, including serotype 6B, this reduction was accompanied by an increase in pneumococcal serotypes not included in the conjugate vaccine. This shift in nasopharyngeal pneumococcal carriage after conjugate vaccination is consistent with observations in other studies\textsuperscript{24,25} and is most probably the result of replacement.\textsuperscript{24,25} The finding that replacement by serotypes 11 and 15 cannot be prevented by PPSV23, which includes these serotypes, lends support to previous results showing that polysaccharide vaccine did not affect nasopharyngeal carriage.\textsuperscript{26,27} Although children aged 2–7 years showed better responses to the polysaccharides 11 and 15 compared with the younger group, nasopharyngeal carriage was still unaffected by vaccination (data not shown). By induction of nasopharyngeal replacement with non-conjugate pneumococcal serotypes, PCV could even induce recurrence of AOM, because newly acquired carriage is associated with an increased risk for AOM in children with the established risk factor.\textsuperscript{28} This risk might account for the increased number of AOM episodes in the pneumococcal vaccine group in our study. The potentially pathogenic capacity of non-conjugate-vaccine pneumococcal serotypes was previously shown in the Finnish infant study on AOM;\textsuperscript{3} the conjugate vaccine reduced AOM caused by conjugate-vaccine-type pneumococci by 57%, but AOM caused by non-conjugate-vaccine pneumococcal serotypes was increased by 34%.

We were not able to confirm that replacement took place in middle-ear fluid. For ethical reasons, we obtained middle-ear fluid only in the first episode of AOM after vaccination. Therefore, the number of middle-ear fluid cultures investigated was small. We noted a 51% reduction in AOM caused by conjugate-vaccine-serotype pneumococci, and overall pneumococcal AOM was reduced by 34%; this finding was similar to that of the Finnish study.\textsuperscript{3} We noted no difference between the groups in presence of other middle ear pathogens, apart from \textit{S aureus}. This species was noted more often in middle-ear fluid cultures from the pneumococcal vaccine group, although only in samples taken from spontaneously draining ears. Whether \textit{S aureus} is a true AOM pathogen or is the result of contamination from the external ear canal is uncertain,\textsuperscript{29,30} but the double-blind nature of our study suggests that AOM and pneumococcal vaccination has an effect on the isolation of \textit{S aureus} in samples from spontaneously draining ears.

To summarise, we found that pneumococcal conjugate vaccination combined with pneumococcal polysaccharide vaccination does not prevent AOM in children older than 1 year who have had recurrent episodes of AOM before vaccination. Therefore, pneumococcal vaccinations are not indicated in the management of recurrent AOM in toddlers and older children. In view of the results of other studies, we might conclude that to prevent pneumococcal AOM in general, and to protect children from developing the otitis-prone condition, pneumococcal vaccinations should be given early in life, at least before 12 months of age and preferably before two or more episodes of AOM have occurred.

**Contributors**

R Veenhoven coordinated the study, did recruitment, obtained data, did follow-up, and analysed data. D Bogaert undertook pneumococcal serotyping. C Uiterwaal helped to design the study and did statistical analyses. C Brouwer and H Kiezebrink supervised the trial. All authors helped to interpret and write up the results of the study and helped to plan the trial. G Rijkers helped to design the trial and supervised pneumococcal serotyping. B Zegers and W Kuis helped to design the study and did statistical analyses. C Brouwer and H Kiezebrink recruited the study participants, obtained data and did follow-up. J Bruijn did bacterial cultures. E IJzerman supervised microbiology laboratory work at the Regional Laboratory of Public Health, Haarlem. P Hermans and R de Groot supervised pneumococcal serotyping. B Zegers and W Kuis helped to plan the trial. G Rijkers helped to design the trial and supervised humoral immune essays. A Sch¨{o}lder and E Sanders designed and supervised the trial. All authors helped to interpret and write up the findings. Other members of the Dutch Otitis Media Study Group include: study nurses—J Weens, A Haan; paediatric residents—A Jamieson, Y van de Berg; clinical laboratory workers—J Adelmayer, M van Schaik; bacteriology laboratory workers—M Sluiter, M Sonke; data management—B Slotboom.

**Conflict of interest statement**

None declared.

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