New conjugated pneumococcal vaccine
Does it decrease the incidence of acute otitis media?

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Research question
Does routine administration of the new conjugated pneumococcal vaccine significantly decrease the incidence of acute otitis media (AOM) in children?

Type of article and design
The Finnish Otitis Media Vaccine Trial was a prospective randomized, double-blind trial of the efficacy of heptavalent conjugated pneumococcal vaccine (PCV7). It lasted 3 years. It was initially designed to evaluate two different conjugated pneumococcal vaccines, but this article reports only on the efficacy of the heptavalent CRM197 conjugate vaccine.

Relevance to family physicians
In addition to being the leading cause of invasive bacterial infections in children in Canada, *Streptococcus pneumoniae* is also the leading cause of bacterial pneumonia, AOM, and sinusitis. Children make frequent visits to physicians for AOM; 32% of children younger than 5 years visit for AOM at least once a year. Pneumococcus has been isolated in 28% to 55% of middle ear aspirates of young children. Researchers estimate there are 360,000 visits to physicians a year in Canada for pneumococcal AOM and approximately 1.8 million visits for all cases of AOM.1

The long-term sequelae of AOM include hearing loss, speech delay, and the morbidity associated with surgical interventions. With the increasing occurrence of antibiotic-resistant strains of pneumococci in various communities,2 prevention of pneumococcal infections is also important on an epidemiologic basis.

Until recently, no effective pneumococcal vaccine for children younger than 2 years has been available. Administering the new conjugated pneumococcal vaccine, Prevnar®, might be an effective preventive measure for decreasing risk of pneumococcal disease in children.

Overview of study and outcomes
The study included 1662 infants randomized at 2 months old to receive either the new vaccine or the hepatitis B vaccine at 2, 4, 6, and 12 months old. At the 2-, 4-, and 6-month visits, all children also received the combination diptheria-tetanus-pertussis–*Haemophilus influenzae* Type b vaccine in the contralateral thigh.

A total of 786 of 831 children in the vaccination group and 794 of 831 in the control group completed the protocol. The groups were similar, especially with respect to factors known to affect incidence of AOM, such as breastfeeding >6 months (53% of both groups) and attendance at day care at 12 months (16% in the new vaccine group and 12% in the control group).

Follow up took place at eight participating clinics at 2, 4, 6, 7, 12, 13, 18, and 24 months old. Aside from these scheduled follow-up visits, parents also brought their children to the clinics with any symptoms suggesting AOM or respiratory infection. As well, parents recorded any adverse reactions at 24, 48, and 72 hours after vaccination.

Outcomes included all cases of AOM categorized into those confirmed by culture and those pathogen-specific cases caused by various pneumococcal strains. Acute otitis media was defined clinically by an abnormal tympanic membrane and at least one other symptom suggesting AOM. Myringotomy and aspiration of middle ear fluid were performed in 93% of clinically diagnosed cases of AOM.

Results
Among the 1662 children in the study, 2596 episodes of AOM were diagnosed according to clinical criteria. The primary endpoint of the study, risk of culture-confirmed pneumococcal AOM, was significantly lower...
in the treatment group than in the control group (271 cases versus 414 cases, 95% confidence interval [CI] 21% to 45%). The vaccine also appeared to protect against AOM caused by a number of serotypes that cross-reacted with the seven serotypes included in the vaccine. The number of episodes due to serotypes not covered by the vaccine increased by 33% in the treatment group.

The overall incidence of AOM was not significantly reduced: 1251 cases in the treatment group (1.16 cases per child per year); 1345 cases in the control group (1.24 cases per child per year). The relative risk reduction was 7% (95% CI –4% to 16%). The CI indicates that the differences between the groups were not significant.

The study vaccine caused local reactions more frequently than the control hepatitis B vaccine did, but less frequently than the combination DTP–H influenza vaccine did. Three cases of urticaria, one rash, one transient granulocytopenia, and one episode of excessive crying occurred in the treatment group and were thought to be related to the vaccine.

Analysis of methodology
This well run, multicentre, prospective, randomized, double-blind controlled trial has some methodologic problems that should be considered in interpreting the results. The study population was self-referred, so the parent population might have been biased to parents more likely to seek care and might not be representative of the general population; however, the authors did enrol 55% of the eligible patients in the study areas.

Adverse events were largely based on parents’ reports, so the incidence of adverse events could have been overestimated or underestimated. As to the accuracy of AOM diagnosis, diagnostic criteria were fairly well standardized, and the clinicians were successful in obtaining middle ear fluid for culture in 93% of cases. Outside of scheduled follow-up appointments, however, the investigators relied on parents to initiate visits for potential cases of AOM based on their children’s symptoms.

Application to clinical practice
The authors of this study conclude that their primary end point, risk of pneumococcal AOM, was significantly reduced by administration of the PCV7 vaccine. The far more clinically relevant secondary end point, risk of all cases of AOM, however, showed no significant reduction. Other studies have shown only a modest decrease in risk of AOM in infants receiving the vaccine. One American trial of 37,830 healthy children found a 7% reduction in all episodes of AOM in the vaccinated group; frequent AOM (five episodes in 6 months, or six episodes a year) was reduced by 12.3% in the intention-to-treat analysis (22.8% in the per-protocol analysis), and use of ventilation tubes was reduced by 20.3%. Hence, the vaccine might be more efficacious for some high-risk children.

For most children, it seems that administration of the PCV7 vaccine would not be appropriate for reducing risk of AOM. In 1999, the United States Food and Drug Administration did not accept use of this vaccine for AOM prevention. A better strategy for reducing antibiotic resistance could be more selective prescribing because AOM is often a self-limited illness that does not require antibiotics. For prevention, a better choice might be the influenza vaccine, which is associated with a 36% decrease in incidence of AOM.

With mounting evidence that the PCV7 vaccine significantly decreases risk of invasive pneumococcal disease, the National Advisory Committee on Immunization (NACI) has recommended the vaccine for all infants aged 2 to 23 months (grade A recommendation) and for all high-risk children aged 24 to 59 months (grade B recommendation). Thus, parents should be offered the vaccine for their children according to these recommendations, but should be told that the reduction in episodes of AOM is modest at best, and that the purpose of the vaccine is to decrease risk of severe invasive disease caused by *S. pneumoniae*.

**Bottom line**
- In this study, administration of heptavalent pneumococcal conjugate vaccine did not significantly reduce risk of AOM in children.
- The vaccine appears to be safe and to have a relatively low incidence of local side effects.
- The vaccine is effective for prevention of other rarer, but possibly more invasive, pneumococcal infections beyond AOM. The NACI has recommended that the new vaccine be administered to all children younger than 2 years and to high-risk children between 24 and 59 months old for prevention of invasive pneumococcal disease.
- About 1800 children need to be vaccinated per year to prevent one case of invasive disease (absolute risk reduction of 1.9 cases over 3 1/2 years per 1000 vaccinated children).
- To avoid raising expectations among patients and physicians regarding prevention of AOM, advertising should not imply that the vaccine is effective for preventing AOM.
- The price for a series of four vaccinations is about $400; this could be a barrier for some parents. To ensure universal vaccination, governments should consider coverage. Also, if it is effective and tolerated, the vaccine should be incorporated into the standard pentavalent vaccine to reduce the number of injections needed.
**Points saillants**

- Dans la présente étude, l’administration du vaccin conjugué antipneumococcique heptavalent n’a pas réduit de manière significative le risque d’OMA chez les enfants.
- Le vaccin semble sûr et présente une faible incidence d’effets secondaires locaux.
- Le vaccin est efficace dans la prévention d’autres infections à pneumocoques plus rares mais plus envahissantes, mis à part l’OMA. Le CCNI a recommandé que le nouveau vaccin soit administré à tous les enfants de moins de deux ans et aux enfants à risque élevé de 24 à 59 mois pour prévenir les infections envahissantes à pneumocoques.
- Il faut vacciner environ 1 800 enfants par année pour prévenir un cas d’infection envahissante (réduction du risque absolu de 1,9 cas pendant 3/2 ans par 1 000 enfants vaccinés).
- Pour éviter d’accroître les attentes chez les patients et les médecins quant à la prévention de l’OMA, la publicité ne devrait pas sous-entendre que le vaccin est efficace à cet égard.
- Le prix d’une série de quatre vaccins s’élève à environ 400 $; cela pourrait poser un obstacle à certains parents. Pour assurer la vaccination universelle, les gouvernements devraient envisager d’en assumer les frais. De plus, s’il est efficace et toléré, le vaccin pourrait être incorporé au vaccin pentavalent standard pour réduire le nombre d’injections requises.

**References**