Pneumococcal conjugate vaccines for preventing otitis media
(Review)

Jansen AGSC, Hak E, Veenhoven RH, Damoiseaux RAMJ, Schilder AGM, Sanders EAM


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Pneumococcal conjugate vaccines for preventing otitis media

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ABSTRACT

Background

Acute otitis media (AOM) is a very common early infancy and childhood disease. The marginal benefits of antibiotics on AOM, the increasing problem of bacterial resistance to antibiotics, and the huge estimated direct and indirect annual costs associated with otitis media (OM) have prompted a search for effective vaccines to prevent AOM.

Objectives

To assess the effect of pneumococcal conjugate vaccines (PCVs) in preventing AOM in children up to 12 years of age.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2007, issue 2), which contains the Cochrane Acute Respiratory Infections Group’s Specialised Register; MEDLINE (January 1995 to November 2007); and EMBASE (January 1995 to November 2007).

Selection criteria

Randomised controlled trials of PCVs to prevent AOM in children aged 12 years or younger, with a follow up of at least six months after vaccination.

Data collection and analysis

Three review authors independently assessed trial quality and two review authors extracted data.

Main results

We included seven trials on 7- to 11-valent PCV (with different carrier proteins). There was large heterogeneity regarding study population, type of conjugate vaccine, and outcome measures between trials, therefore, results were not pooled. The only currently licensed 7-valent PCV Prevenar® with CRM197 as carrier protein (CRM197-PCV7) administered during infancy was in two studies associated with a 6% (95% confidence interval (CI) -4% to 16%) and 7% (95% CI 4% to 9%) relative reduction in risk of AOM episodes. Another 7-valent PCV with the outer membrane protein complex of Neisseria meningitidis (N. meningitidis) serogroup B as carrier protein, administered in infancy, did not reduce overall AOM episodes, while an 11-valent PCV with Haemophilus influenzae
(H. influenzae) protein D as carrier protein was associated with a relative reduction in risk of AOM episodes of 34% (95% CI 21% to 44%). 9-valent PCV (with CRM197 carrier protein) administered in healthy toddlers was associated with a 17% (95% CI 2% to 33%) relative reduction in risk of OM episodes. CRM197-PCV7 followed by 23-valent pneumococcal polysaccharide vaccination administered after infancy in older children with a history of AOM showed no beneficial effect on further AOM episodes.

Authors’ conclusions

Based on current evidence of the effectiveness of PCVs for the prevention of AOM, the currently licensed 7-valent PCV administered during infancy has marginal beneficial effects. Discrete reductions of 6% to 7% may mean substantial reductions from a public health perspective. Administering PCV7 in older children with a history of AOM appears to have no benefit in preventing further episodes.

Plain Language Summary

Pneumococcal conjugate vaccines for preventing otitis media

Acute otitis media (AOM) is the infection of the middle ear and is one of the most common diseases in childhood. Infection with pneumococci (a type of bacterium) is a frequent cause of AOM. Pneumococcal conjugate vaccines (PCVs) aim to immunise young children against pneumococcal infections. This review of seven trials with 46,885 participating children aimed to assess the effects of PCV in preventing AOM. The only currently licensed 7-valent PCV given in infancy reduced the occurrence of AOM episodes by 6% to 7%. This means only a marginal decrease in AOM episodes for the individual, but this may have a substantial impact on the healthcare burden of AOM. Children with a history of AOM do not seem to benefit from 7-valent PCV when immunised at an older age (outside infancy).

Background

Description of the condition

Acute otitis media (AOM), defined as effusion in the middle ear accompanied by one or more signs of acute inflammation in the middle ear, such as otalgia, otorrhoea, fever, or irritability, is one of the most common diseases in childhood, posing a large burden on public health. It has a peak incidence in six- to 11-month-olds (Teele 1989). By the age of one year, 62% of infants have experienced at least one episode of AOM, and by the age of two years up to 5% of all children have experienced recurrent episodes of AOM, defined as at least four AOM episodes within one year (Kvaerner 1997; Teele 1989). The three main bacterial pathogens isolated from the middle ear fluid of children with AOM are Streptococcus pneumoniae (S. pneumoniae) (25% to 39%), (non-typeable) Haemophilus influenzae (H. influenzae) (12% to 23%), and Moraxella catarrhalis (M. catarrhalis) (4% to 15%) (Bluestone 1992; Heikkinen 1999; Jacobs 1998; Luotonen 1981).

How the intervention might work

With pneumococcus being the most common bacterial cause of AOM and childhood pneumonia, and one of the most common causes of invasive bacterial disease such as meningitis, research has focused on the prevention of pneumococcal infections with pneumococcal vaccines. Pneumococcal polysaccharide vaccines (PPVs) have been available for decades, but have shown to be poorly immunogenic in children below the age of two years which are most prone to pneumococcal infections. The first pneumococcal conjugate vaccines (PCVs) in which the pneumococcal capsular serotypes are covalently conjugated to carrier proteins were developed in the 1990s and proved to be adequately immunogenic in infants and toddlers (Dagan 1997; Eskola 1999; Shinefield 1999). The focus in research shifted from the use of PPVs to PCVs in children, and the role of PPVs in the prevention of AOM in chil-
children has merely been assessed following PCVs and not as a primary intervention anymore. Therefore, the focus of the current review has shifted from the effect of PPVs to the effect of PCVs on AOM. No further attention will be paid to the effect of PPVs, which was described in prior versions of this review (Straetemans 2003).

OBJECTIVES

The aim of this review was to assess the effect of PCVs in preventing AOM in children up to 12 years of age.

METHODS

Criteria for considering studies for this review

Types of studies
Randomised controlled clinical trials of PCVs with prevention of AOM as an outcome in children aged 12 years or younger, and a follow up after vaccinations of at least six months.

Types of participants
Children up to 12 years of age.

Types of interventions
Multivalent PCVs.

Types of outcome measures
The primary outcomes considered are the frequency of all AOM episodes, pneumococcal AOM, and serotype-specific AOM, and the proportion of children with frequent AOM (defined as at least three episodes in the last six months or at least four episodes in the last year).

Search methods for identification of studies

Electronic searches
We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2007, issue 2), which contains the Cochrane Acute Respiratory Infections Group’s Specialised Register; MEDLINE (January 1995 to November 2007); and EMBASE (January 1995 to November 2007).

We used the following search strategy for searching MEDLINE and CENTRAL, and modified terms for searching EMBASE.

MEDLINE
#1 explode 'bacterial-vaccine' / all subheadings
#2 explode 'bacterial AND vaccine' / all subheadings
#3 explode 'Pneumococcus-vaccine' / all subheadings
#4 pneumococc* near immunity*
#5 pneumococc* near vaccin*
#6 #1 or #2 or #3 or #4 or #5
#7 explode 'otitis media' / all subheadings
#8 (otitis media in ti) or (otitis media in ab)
#9 #7 or #8
#10 #6 or #9
#11 explode 'randomised-controlled-trial' / all subheadings
#12 explode 'controlled-study' / all subheadings
#13 explode 'randomisation' / all subheadings
#14 explode 'single-blind-procedure' / all subheadings
#15 explode 'double-blind-procedure' / all subheadings
#16 explode 'crossover-procedure' / all subheadings
#17 explode 'phase-3-clinical-trial' / all subheadings
#18 (control* near trial*) in ti
#19 (control* near trial*) in ab
#20 (singl* or doubl* or trebl* or tripl*) near ((blind* or mask*) in ti
#21 (singl* or doubl* or trebl* or tripl*) near ((blind* or mask*) in ab
#22 random* near ((allocat* or assign*) in ti
#23 random* near ((allocat* or assign*) in ab
#24 #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23
#25 #10 and #24

Searching other resources
We also identified studies by checking the bibliographies of all studies and review articles retrieved. We imposed no language restrictions on the searches.

Data collection and analysis

Study quality and data extraction
Three review authors (AJ, LS and EH) assessed quality of the included studies using a three-item quality scale with a score range from zero to five (Jadad 1996). According to the Jadad criteria, one point was allocated for randomisation, double blinding and description of withdrawals and dropouts; an extra point was added for methods of randomisation and blinding that are well described and adequate. Studies that used a clearly inadequate method of
randomisation or blinding lost the point allocated. We resolved disagreement by discussion. The Jadad score may vary from zero to five, equalising the minimal and maximal quality score accomplished. The same authors performed data extraction independently, and resolved differences by consensus.

Data analysis

Meta-analysis by pooling the results of the different studies is only useful and justified when studies show satisfactory clinical homogeneity in terms of study population, setting, intervention and outcome measures. We assessed clinical heterogeneity between studies by reviewing the differences across trials. There was considerable clinical heterogeneity in the trials in terms of the study populations, outcome measures, and the type of PCV regarding carrier protein and valency (see ‘Description of studies’ below). Therefore, we decided a meta-analysis was not appropriate. We briefly describe the methods we would have used if we pooled the results. The generalised Cox proportional hazard method proposed by Anderson and Gill (Andersen 1982) is regarded as the most appropriate to assess the effect of PCVs on AOM (Jahn-Eimermacher 2007). Under the assumptions that the hazard rate is proportional between both groups over time, and that the risk of AOM is not affected by previous episodes (although this assumption is most likely not true), this model takes all available information into account; that is, all episodes (also the recurrent ones), differences in individual patient follow-up time, and time until a case of AOM (Jahn-Eimermacher 2007). However, information on individual follow-up time until the first, second, third, etc case of AOM is hard to obtain for each study to be included in the meta-analysis. Poisson regression is based on the assumptions of a constant risk of AOM over time and that this risk is not affected by previous episodes of AOM. This method only requires the total follow-up time and total number of episodes and appears therefore a more feasible method to meta-analyse. Furthermore, Poisson regression seems not to be affected by the deviation from a constant risk over time, having very similar results for the effect of PCVs on AOM to the Anderson-Gill approach (Jahn-Eimermacher 2007). For Poisson regression, the treatment effect is measured as a rate ratio defined as follows: (total AOM episodes in pneumococcal vaccination group multiplied by the number of children in the pneumococcal vaccination group divided by the follow-up time in months) divided by (total AOM episodes in control group divided by the number of children in the pneumococcal vaccination group multiplied by the follow-up time in months) (McCullagh 1989).

Description of studies

The MEDLINE search yielded eight potentially relevant randomised trials after screening of the title and abstract (Black 2000; Dagan 2001; Eskola 2001; Fireman 2003; Kilpi 2003; Prymula 2006; Van Kempen 2006; Veenhoven 2003). We found no additional potentially relevant trials in either CENTRAL or the Cochrane Acute Respiratory Infections Group Specialised Register. The EMBASE search also did not yield any additional potentially relevant studies.

The eight included papers in this review concerned seven studies in total. Two of these studies (Black 2000/Fireman 2003 and Dagan 2001) had all types of OM (including but not exclusively AOM) as an outcome. Since the effect of PCVs on AOM may be influenced by the age at which the PCV was administered, we will describe the studies accordingly, that is, those with vaccination in infancy and those with vaccination later in childhood. In all studies the control group received a control vaccine. See also the ‘Characteristics of included studies’ table.

PCV administered in infancy

Three trials including healthy infants studied the effect of PCV administered in infancy on OM. In the Northern California Kaiser Permanente (NCKP) trial (Black 2000/Fireman 2003) and the Finnish Otitis Media (FinOM) trial (Eskola 2001) the treatment group was administered the 7-valent PCV, containing the polysaccharides of seven serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F coupled to the carrier protein CRM197 (a non-toxic mutant of diphtheria toxin) (CRM197-PCV7), at the age of two, four and six months, and 12 to 15 months. In the NCKP trial, infants were enrolled over a period of almost three years and had a follow-up time varying from about eight months to 3.5 years. The trial was originally designed to investigate the effect of CRM197-PCV7 on invasive pneumococcal disease, and OM was a secondary outcome. Clinical diagnoses of OM were obtained from a computerised database collecting department-specific diagnosis checklists routinely marked by emergency physicians and paediatricians in the NCKP population. All clinical diagnoses of ‘otitis media’, ‘otitis media, acute’, ‘middle ear effusion’, ‘otitis media, serous’, or ‘otitis media with effusion’ were included. The FinOM trial primarily aimed to assess the effect on AOM. Infants were followed until the age of 24 months, and parents were encouraged to bring their child to the study clinic (established specifically for the purpose) for evaluation of symptoms suggesting respiratory infection or AOM. The diagnosis of AOM was standardised.

Kilpi 2003 describes another part of the FinOM trial in which the index group was administered another 7-valent PCV, containing capsular polysaccharides of the same seven serotypes as CRM197-PCV7 conjugated to the outer membrane protein complex of Neisseria meningitidis (N. meningitidis) serogroup B (OMPC-PCV7). Additionally, 22% of the children assigned to OMPC-PCV7 received PPV23 at the age of 12 months instead of a fourth OMPC-
PCV7 dose. The follow up and outcome measure was similar to Eskola 2001. Finally, in Prymula 2006 (POET trial) an 11-valent PCV was administered at the ages of two, four, five months, and 12 to 15 months, containing the capsular polysaccharides of serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19F; and 23F, conjugated to protein D, which is a surface lipoprotein of *H. influenzae*. Protein D is highly conserved in both encapsulated and non-encapsulated *H. influenzae* strains and therefore has the potential to provide protection against any *H. influenzae* strain that causes OM (Forsgren 2008; Prymula 2006). Follow up continued until the age of 24 to 27 months. The primary aim of the trial was to assess the effect on AOM, and parents were advised to consult their paediatrician if their child was sick, had ear pain, or had spontaneous ear discharge. The diagnosis of AOM was standardised.

**PCV administered at a later age**

Three trials assessed the effects of PCV administered at a later age on AOM. Dagan 2001 assessed the effect of a 9-valent PCV (containing the capsular polysaccharides of serotypes 1 and 5 besides those included in CRM197-PCV7, conjugated to CRM197) on AOM in healthy daycare attendees aged 12 to 35 months. The vaccine was administered twice in 12- to 17-month-olds and once in 18- to 35-month-olds. The study was undertaken to examine the effect on respiratory infections. In 18 encounters during the two-year follow-up period that started one month after complete immunisation, parents were questioned about illness episodes, including OM episodes. The OM diagnosis was not physician confirmed and not standardised. Van Kempen 2006 and Veenhoven 2003 assessed the effect of pneumococcal vaccination on AOM in children aged one to seven years with a history of at least two AOM episodes in the year prior to study entry. CRM197-PCV7 was administered twice in one- to two-year-olds and once in two- to seven-year-olds followed by PPV23 (containing capsular polysaccharides of the serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, and 33F) six to seven months later. Children with underlying illnesses including immunocompromising conditions were excluded. Both studies had a similar design, were conducted in parallel but were analysed separately due to differences in study population (children included in Van Kempen 2006 had a more severe history of AOM and more often tympanostomy tube placement prior to study entry). Follow-up lasted about 24 months. Parents were instructed to visit the study clinics or their family physician, otolaryngologists, or paediatrician for assessment in case of symptoms suggesting AOM. Physicians registered signs and symptoms of every AOM episode on standard registration forms. The diagnosis of AOM was standardised.

**Risk of bias in included studies**

Table 1 shows the results of the quality assessment by the Jadad method (Jadad 1996). Dagan 2001, Van Kempen 2006 and Veenhoven 2003 had a maximum quality score of five. Kilpi 2003 scored four points because this article failed to report withdrawals and dropouts, while adequately reporting the randomisation and double-blinding methods. Prymula 2006 scored four points and missed one point due to not reporting of double-blinding methods. Black 2000 and Fireman 2003 had a quality score of two. Both articles failed to report withdrawals and dropouts, and no additional points could be given for adequate reporting of the method to generate the sequence of randomisation and the method of double blinding. Eskola 2001 had a score of two for similar reasons. Although this study reported the number of withdrawals and dropouts, no reasons were given for them. This review will present the results of the trials as reported in the published papers since meta-analysis was decided to be inappropriate due to heterogeneity in study population, intervention and outcome measure. Therefore the statistical methods by which the data were analysed in each study are shortly assessed. Black 2000, Eskola 2001, Fireman 2003, Kilpi 2003, Prymula 2006, Van Kempen 2006 and Veenhoven 2003 all used the generalised Cox proportional hazard method proposed by Anderson and Gill 1982 (Andersen 1982), currently regarded most optimal to analyse this kind of data (see ‘Data collection and analysis’ section above). Dagan 2001 compared rates of AOM, but rather than comparing them by Poisson regression (which would presumably yield results similar to those obtained with the Anderson and Gill approach), the chi-square test was used, which is suboptimal for comparing rates.

**Effects of interventions**

In total, we included seven trials with 46,885 participating children, ranging from 74 to 37,868 participants per study. Four studies included infants who received primary vaccinations before six months of age (46,164 participants in total) (Black 2000; Fireman 2003; Eskola 2001; Kilpi 2003; Prymula 2006); one study included daycare attendees aged 12 to 35 months (264 participants) (Dagan 2001), and two included one- to seven-year-olds with a history of AOM (457 participants in total) (Van Kempen 2006; Veenhoven 2003).

In four studies the licensed CRM197-PCV7 was used as intervention (Black 2000; Fireman 2003; Eskola 2001; Veenhoven 2003; Van Kempen 2006), and in two of these studies boosting with 23-valent PPV was given (Van Kempen 2006; Veenhoven 2003). The other three studies each had different interventions, i.e. a 9-valent PCV with CRM197 as protein carrier (Dagan 2001), a 7-valent PCV with the outer membrane complex of *N. meningitidis* serogroup B as protein carrier (Kilpi 2003), and an 11-valent PCV with protein D as protein carrier (Prymula 2006).
All studies had a control group that was given a control vaccine (meningococcus type C conjugate vaccine, hepatitis A vaccine or hepatitis B vaccine). Five studies applied a standardised diagnosis of AOM (Eskola 2001; Kilpi 2003; Prymula 2006; Van Kempen 2006; Veenhoven 2003), whereas in one study, AOM episodes were extracted from a computerised data source containing all visits registered by physicians (Black 2000/Fireman 2003) and another study assessed parent-reported AOM episodes (Dagan 2001). Five studies additionally assessed the effect of PCVs on pneumococcal AOM (Black 2000/Fireman 2003; Eskola 2001; Kilpi 2003; Prymula 2006; Veenhoven 2003). Three studies cultured middle ear fluid from all AOM episodes (Eskola 2001; Kilpi 2003; Prymula 2006), whereas one study only cultured it from the first AOM episode (Veenhoven 2003), and another study assessed the effect on reported cultures that were taken in cases of spontaneously draining ears (Black 2000/Fireman 2003). Three studies reported on the effects of PCVs on recurrent AOM (Black 2000/Fireman 2003; Eskola 2001; Prymula 2006). It should be noted that we have presented the results of the trials included in this review as reported in the published papers and that the presentation of results varied between trials. Where possible we have reported the incidences of the various outcomes in the study arms together with the efficacy estimates with 95% CIs. However, due to limitations of the data, we have reported alternative statistical measures in some instances. Most studies reported efficacy estimates on the basis of per-protocol-analysis with or without noting that estimates on the basis of intention-to-treat-analysis were similar. See also Table 2, Table 3, and Table 4 for the efficacy estimates of PCVs on all AOM episodes, pneumococcal AOM, and recurrent AOM respectively.

Effect of PCV administered in infancy

The NCKP and FinOM trials in which CRM197-PCV7 was administered during infancy showed that CRM197-PCV7 reduced overall AOM episodes by 6% to 7% (Eskola 2001; Fireman 2003), whereas OMPC-PCV7 appeared to have no effect on overall AOM episodes (Kilpi 2003). The administration of protein D PCV11 during infancy was associated with a 34% reduction in AOM episodes (Prymula 2006). Efficacy of PCVs administered in infancy against pneumococcal AOM varied from 25% for OMPC-PCV7 (Kilpi 2003), 34% for CRM197-PCV7 (Eskola 2001), to 52% for protein D PCV11 (Prymula 2006). The reduction of vaccine-type pneumococcal AOM was fairly similar with 56% to 67% (Black 2000; Eskola 2001; Kilpi 2003; Prymula 2006). Administration of CRM197-PCV7 and protein D PCV11 also seemed to reduce AOM caused by the so-called cross-reactive serotypes which are non-vaccine serotypes with a serogroup that is included in the vaccine (Eskola 2001; Prymula 2006), while OMPC-PCV7 failed to show cross-protection (Kilpi 2003). Although not statistically significant, the administration of CRM197-PCV7 and OMPC-PCV7 was associated with an increase in non-vaccine-type AOM (replacement) (Eskola 2001; Kilpi 2003) and H. influenzae AOM while the protein D PCV11 did not show pneumococcal replacement and showed vaccine efficacy of 35% against H. influenzae AOM (Prymula 2006).

CRM197-PCV7 seemed to reduce recurrent AOM by 9% (Black 2000; Eskola 2001), whereas the administration of protein D PCV11 was associated with a statistically non-significant decrease of 56% in recurrent AOM (Prymula 2006).

Effect of PCV administered at a later age

9-valent PCV administered in healthy 12- to 35-month-olds appeared to reduce overall OM episodes by 17% (Dagan 2001), while CRM197-PCV7 followed by PPV23 in one- to seven-year-olds with a history of AOM did not reduce the occurrence of further AOM episodes (Van Kempen 2006; Veenhoven 2003). With respect to pneumococcal AOM, only one study reported the effect of CRM197-PCV7 followed by PPV23 on pneumococcal AOM (Veenhoven 2003): pneumococcal AOM was reduced by 33%, vaccine-type AOM by 56%, and non-vaccine type AOM by 17%, although none of the estimates was statistically significant (small numbers). None of the three trials in older children reported the effect of the PCV on recurrent AOM.

DISCUSSION

The trials on the effect of PCV on AOM in children show large heterogeneity regarding study population (age of administration of PCV), intervention (vaccine valency (7-/9-/11-valent vaccines), carrier protein (CRM197, OMPC or protein D), presence or absence of additional booster immunisation with PCV or PPV23, and outcomes (active surveillance for standardised physician-diagnosed AOM, passive collection of diagnoses of AOM or parent-reported AOM). Furthermore, in the infant studies on AOM focusing on bacteriology (Eskola 2001; Kilpi 2003; Prymula 2006) the control groups varied markedly in the proportions of S. pneumoniae, H. influenzae and M. catarrhalis in middle ear fluid, possibly related to time and geographic region as well as case definition which will affect the result of overall AOM episodes prevented by pneumococcal vaccines. Additionally, two studies (Van Kempen 2006; Veenhoven 2003) included older otitis-prone children with tympanostomy tubes, so the intervention was aimed at secondary or even tertiary, not primary prevention.

The currently licensed CRM197-PCV7, a 7-valent pneumococcal conjugate vaccine with CRM197 as carrier protein, administered in infancy was associated with a 6% to 7% reduction in AOM episodes (Eskola 2001; Fireman 2003). The 7-valent PCV with OMPC as carrier protein appeared to have less effect on
AOM episodes overall than CRM197-PCV7 (Kilpi 2003). This despite the fact that both 7-valent vaccines appeared to have a similar effect on vaccine-serotype pneumococcal AOM of 56% and 57% (Eskola 2001; Kilpi 2003). However, CRM197-PCV7 also showed cross-protection to vaccine-related serotypes, in particular to the very common vaccine-related 6A serotype (Eskola 2001), while OMPC-PCV7 showed no efficacy at all against vaccine-related serotypes like 6A (Kilpi 2003). For both 7-valent vaccines, there was a tendency of replacement disease by non-vaccine pneumococci as well as by other otopathogens like H. influenzae. Furthermore, in the OMPC-PCV7 arm of the FinOM trial, the proportion of AOM caused by M. catarrhalis also increased (Kilpi 2003). This means that PCVs are effective against vaccine-serotype pneumococci, but in AOM there is high potential for replacement by other pathogens that are common colonisers of the nasopharynx. CRM197-PCV7 is known to affect nasopharyngeal carriage of pneumococci, with a shift from vaccine-type pneumococci to non-vaccine-type pneumococci and other bacterial pathogens that may have pathogenic potential (Block 2006; Eskola 2001; Obaro 1996; Veenhoven 2003; Veenhoven 2004). The middle ear is directly connected to the nasopharynx and by lowering the carriage of vaccine-type pneumococci, a niche is created for other bacteria with a pathogenic potential (Block 2006; Veenhoven 2003; Veenhoven 2004).

Although the vaccine-related serotypes, mostly notably 6A and 19A, were reduced after CRM197-PCV7 in the FinOM trial (Eskola 2001), the name ‘cross-protection’ by the vaccine should probably be abandoned. In post-marketing studies after licensure of CRM7-PCV7 in the US in 2000, an increase in serotype 19A in invasive pneumococcal disease as well as an increase in serotype 6A and 19A involved in AOM was observed (Block 2004; Hicks 2007; McEllistrem 2005; Pichichero 2007). Both upcoming ear pathogens (pneumococcal serotypes 6A and 19A) are included in a 13-valent CRM197-conjugate vaccine that is under development.

The POET trial with an 11-valent PCV with protein D as carrier protein administered to infants, reported the largest reduction in overall AOM episodes of 34% (Prymula 2006). Compared to the 6% to 7% reduction in studies with CRM197-PCV, this effect is rather large and may not be solely explained by the four additional serotypes covered by the 11-valent PCV compared to CRM197-PCV7. Part of the effect may be related to the protein D to which the polysaccharides are conjugated in the vaccine. Protein D has the potential to provide protection against any H. influenzae strain that causes OM (Forsgren 2008; Prymula 2006). Indeed, the 11-valent PCV with protein D as carrier protein was demonstrated to reduce non-typeable H. influenzae by 35% (95% CI 2 to 57) (Prymula 2006). Furthermore, an effect against vaccine-related serotypes was observed in the POET trial and remarkably, no replacement by non-vaccine serotypes was demonstrated. It should be noted that in the POET trial children diagnosed with AOM by the paediatrician were subsequently referred to the otorhinolaryngologist for confirmation and collection of middle ear fluid, while in the FinOM trial middle ear fluid was collected from every child with a diagnosis of AOM during the same visit. This may have contributed to the large difference in AOM incidence between these studies with incidence rates reported by Prymula 2006 being about ten times lower than the incidence reported by Eskola 2001. It might be that in the POET trial the more severe episodes of AOM were identified and consequently the effect may only apply to these more severe episodes. The case definition potentially also introduced a different selection of pathogens.

Only one trial reported on the effects of PCV on AOM in older healthy children, daycare attendees (Dagan 2001). After administration of a 9-valent PCV with CRM197 as carrier protein, a 17% reduction in AOM was observed. However, in this study the outcome measure (parent-reported AOM) and the statistics were suboptimal. The other studies in older children aged one to seven years concern children with a history of AOM (Van Kempen 2006; Veenhoven 2003). In these studies, the administration of CRM197-PCV7 was followed by PPV23, and both showed no beneficial effect on further AOM episodes overall after the PPV booster. In contrast, in the infant studies with CRM197-PCV7 but without the PPV23 booster, a protective effect on the number of children developing recurrent episodes of AOM up to 16% was demonstrated. This was also reflected in a 20% reduction of tympanostomy tube placement (Black 2000; Fireman 2003). The point estimate of vaccine efficacy in the children vaccinated at an older age but after previous AOM episodes indicated a similar reduction of AOM caused by vaccine-serotypes to the FinOM study with CRM197-PCV7 (Eskola 2001; Kilpi 2003; Veenhoven 2003). Furthermore, a significant and adequate nasopharyngeal carriage reduction of vaccine-type pneumococci was observed (Veenhoven 2004). The reduced efficacy of CRM197-PCV7 in children already with a history of AOM may be explained by an increased susceptibility to subsequent infections, not only with non-vaccine type pneumococci but also other nasopharyngeal colonisers, due to ‘damages’ already suffered by the middle ear mucosa caused by prior AOM (Veenhoven 2003). Thus, it appears that the age at which PCV is administered and/or a history of AOM episodes modifies the effect of PCV on AOM, despite the fact that age alone could not be identified as a statistically significant effect modifier (Fireman 2003; Veenhoven 2003).

The real-world experience gained with widespread CRM197-PCV7 vaccination in infants after 2000 in the United States suggests that the impact on AOM may be much greater than that seen in the clinical studies. Post-licensure studies comparing rates of ambulatory visits and antibiotic prescriptions related to AOM in the immediate years before and following widespread implementation of routine CRM197-PCV7 vaccination in children younger than two years of age, found a reduction of 42.7% and 41.9% respectively (Zhou 2008), and another study found a decline in frequent OM of 17% and 28% in birth cohorts from Tennessee.
and upstate New York (Poehling 2007). These much higher benefits might be due to indirect herd effects and may have important implications for the cost-effectiveness analyses for conjugate vaccines. However, in a recent study in the Boston area, the decline of uncomplicated AOM, as well as (OM) treatment failure and AOM relapse showed that the decline was at least as much in the period 1996 to 2000 as from 2000 to 2004 and therefore the role of PCV implementation for OM may be modest (Sox 2008).

Whether the decline in OM will continue or wane with time is relevant and deserves ongoing monitoring. A waning effect in OM incidence after implementation of conjugate vaccinations may be explained by replacement by other otopathogens like H. influenzae or an increase in the proportion of OM caused by non-vaccine serotypes including serotypes 3, 6A and 19A (Block 2004; McEllistrem 2005; Pichichero 2007). As previously mentioned, two infant studies found an increase in non-vaccine-type pneumococcal AOM after administration of 7-valent PCV, albeit not statistically significant, as well as an increase of H. influenzae (Eskola 2001; Kilpi 2003). An increase in H. influenzae was also observed in the postmarketing studies on AOM in the United States (Block 2004; Casey 2004). In addition, the study in older children with previous AOM episodes demonstrated an increase of AOM caused by Staphylococcus aureus (S. aureus) (Veenhoven 2003). Continuing research after the effects of PCV on nasopharyngeal carriage and on AOM before and after the introduction of CRM197-PCV7 in national infant immunisation protocols is therefore of utmost importance.

**Authors’ conclusions**

**Implications for practice**

When administered in infancy, PCVs appear to have some protective effect against AOM, depending on the type of PCV used. At present, CRM197-PCV7, a 7-valent PCV with CRM197 as carrier protein, is the only PCV licensed for use in young children. The prevention of invasive pneumococcal disease has been the primary reason for many Western countries to introduce CRM197-PCV7 into their national infant immunisation protocol. The beneficial effect on overall AOM episodes with the currently licensed 7-valent vaccine appears marginal with a 6% to 7% reduction, and therefore promoting CRM197-PCV7 solely to reduce AOM for the individual does not seem justified. However, from a public health perspective, because AOM is so common, even such small reductions may substantially reduce the health care burden caused by AOM.

For countries that have not yet implemented CRM197-PCV7 into the immunisation protocol and for countries that did not implement a catch-up vaccination programme for older children up to five years of age, the question is whether it would be beneficial to administer the vaccine to older children with a history of AOM. The two trials in older children with a history of AOM suggested no beneficial effect of CRM197-PCV7 on all further episodes of AOM (Van Kempen 2006; Veenhoven 2003), and consequently, there is no reason at present to administer older children with a history of previous AOM episodes the vaccine in order to protect them against further AOM episodes. In fact, early vaccination before the first AOM episode may be required for prevention of middle ear mucosal damage.

**Implications for research**

The Jadad quality analysis is very sensitive to written information from published manuscripts. Most studies included in this review lost points because the method of randomisation or blinding was not described. Also, often points were lost because the reasons for withdrawals and dropouts were not described. Future publications of trials should clearly report these items.

In view of the ongoing development of new PCVs and studies on these, we emphasise the need for uniform outcome measures (case definitions of AOM) and presentation of results to allow for meta-analysis by pooling the results in future. Reporting of the total number of AOM episodes in the different study arms, together with the total follow-up time in person-months is required. These figures should also be available on the basis of intention-to-treat analysis and not only on the basis of per-protocol-analysis.

Eleven-valent PCV with protein D as carrier protein appears promising in the prevention of AOM, and currently trials are initiated to determine the effect of this vaccine on pneumococcal disease. Also the newly developed 13-valent PCV (with CRM197 as carrier protein and the additional serotypes 1, 3, 5, 6A, 7F, and 19A besides those included in CRM197-PCV7) may mean an improvement in the protection against pneumococcal infections, including AOM.

In view of the effects of PCVs on nasopharyngeal carriage of pathogens, awareness of the possibility of infections caused by replacing pathogens is warranted. Besides reduction of nasopharyngeal vaccine-type serotypes which is presumed to induce herd effects, replacing pneumococcal serotypes may not only lead to replacement disease in vaccinees but also in the population. Continuing surveillance of pneumococcal disease in different settings and geographic locations is therefore of utmost importance.

**Acknowledgements**

We would like to thank Masja Straetemans and Gerhard Zielhuis for their contributions to prior versions of this review. We would also like to thank the following people for commenting on the update of this review: Barbara Loe Fisher, Morio Aihara, Mark Jones, and Paul Glazziu.
References to studies included in this review

Black 2000  {published data only}

Dagan 2001  {published data only}

Eskola 2001  {published data only}

Fireman 2003  {published data only}


Kilpi 2003  {published data only}

Prymula 2006  {published data only}

Van Kempen 2006  {published data only}

Veenhoven 2003  {published data only}

Additional references

Andersen 1982

Arason 1996

Block 2004

Block 2006

Bluestone 1992

Casey 2004

Dagan 1997

Dagan 2000

Del Castillo 1998

Eskola 1999
Pneumococcal conjugate vaccines for preventing otitis media (Review)

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McEllistrem 2005

Niemela 1999

Obaro 1996

Pichichero 2007

Poehling 2007

Rovers 2006

Shinefield 1999

Sax 2008

Spiro 2008

Teele 1989

Veenhoven 2004
Zhou 2008

References to other published versions of this review

Straetemans 2003

Straetemans 2004

* Indicates the major publication for the study
## CHARACTERISTICS OF STUDIES

### Characteristics of included studies  [ordered by study ID]

#### Black 2000

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised controlled, double-blind trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>US multicentre trial of 37,868 healthy infants aged 2 months</td>
</tr>
<tr>
<td>Interventions</td>
<td>7-valent pneumococcal conjugate vaccine (containing the polysaccharides of serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F conjugated to the carrier protein CRM197) at 2, 4, 6, and 12 to 15 months of age versus meningococcus type C conjugate vaccine at similar ages</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Recurrent episodes/visits of otitis media - episodes extracted from a computerised data source containing all visits registered by physicians</td>
</tr>
<tr>
<td>Notes</td>
<td>These were secondary outcomes; the trial was originally designed to assess the effect of the vaccine on invasive pneumococcal disease</td>
</tr>
</tbody>
</table>

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
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</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear risk</td>
<td>B - Unclear</td>
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</table>

#### Dagan 2001

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised controlled, double-blind trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Israeli trial of 264 healthy 12- to 35-month-olds attending eight daycare centres</td>
</tr>
<tr>
<td>Interventions</td>
<td>9-valent pneumococcal conjugate vaccine (containing saccharides of nine serotypes 1, 4, 5, 6B, 9V, 14, 18C, 19F and 23F conjugated to CRM197) twice in 12- to 17-month-olds and once in 18-to 35-month-olds versus meningococcus type C vaccination at similar ages</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Otitis media episodes, parent-reported</td>
</tr>
<tr>
<td>Notes</td>
<td>This was a secondary outcome; primary outcome of the trial was nasopharyngeal carriage of <em>S. pneumoniae</em></td>
</tr>
</tbody>
</table>

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
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<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Low risk</td>
<td>A - Adequate</td>
</tr>
</tbody>
</table>
### Eskola 2001

**Methods**  
Randomised controlled, double-blind trial

**Participants**  
Finland, multicentre trial of 1662 infants aged 2 months

**Interventions**  
7-valent pneumococcal conjugate vaccine (containing polysaccharides of serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F conjugated to the carrier protein CRM197) at 2, 4, 6, and 12 to 15 months of age versus hepatitis B vaccine at similar ages

**Outcomes**  
Recurrent AOM episodes + AOM due to *S. pneumoniae*/non-vaccine type pneumococcal AOM  
AOM diagnosed by otoscopy (presence of abnormal tympanic membrane in terms of colour, position, or mobility, suggesting middle-ear effusion, plus at least one of the following symptoms or signs of acute infection (fever, earache, irritability, diarrhoea, vomiting, acute otorrhoea not caused by otitis externa, and other symptoms of respiratory infection)

**Notes**  
This trial was part of a study including Kilpi 2003. Both Eskola 2001 and Kilpi 2003 used the same control group but a different index group, each with a different type of 7-valent pneumococcal conjugate vaccine

### Risk of bias

<table>
<thead>
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<td>Unclear risk</td>
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### Fireman 2003

**Methods**  
see Black 2000

**Participants**  
see Black 2000

**Interventions**  
see Black 2000

**Outcomes**  
see Black 2000

**Notes**

### Risk of bias

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<tbody>
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<td>Unclear risk</td>
<td>B - Unclear</td>
</tr>
</tbody>
</table>
### Kilpi 2003

**Methods**
Randomised controlled, double-blind trial

**Participants**
Finland, multicentre trial of 1666 infants aged 2 months

**Interventions**
7-valent pneumococcal conjugate vaccine (containing polysaccharides of serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F conjugated to the outer membrane protein complex of *N. meningitidis* serogroup B) at 2, 4, 6, and 12 months of age versus hepatitis B vaccine at similar ages. 22% of the children assigned to receive the 7-valent pneumococcal conjugate vaccine received 23-valent pneumococcal polysaccharide vaccination instead (containing saccharides of the serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, and 33F) at the age of 12 months

**Outcomes**
See Eskola 2001

**Notes**

### Risk of bias

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<tr>
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<td>Low risk</td>
<td>A - Adequate</td>
</tr>
</tbody>
</table>

### Prymula 2006

**Methods**
Randomised controlled, double-blind trial

**Participants**
Czech Republic/Slovakian multicentre trial of 4,968 infants aged between 6 weeks and 5 months

**Interventions**
11-valent pneumococcal conjugate vaccine (containing polysaccharides of the serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F conjugated to protein D (surface lipoprotein of *H. influenzae*) at ages of ~ 2, 4, 5, and 12 to 15 months versus hepatitis A vaccines at similar ages

**Outcomes**
Recurrent AOM episodes + AOM due to *S. pneumoniae*, (non) vaccine type pneumococcal AOM AOM diagnosed by either the visual appearance of the tympanic membrane (i.e. redness, bulging, loss of light reflex) or the presence of middle-ear effusion (as shown by simple or pneumatic otoscopy or by microscopy). The presence of at least two of the following signs or symptoms was required: earache, ear discharge, hearing loss, fever, lethargy, irritability, anorexia, vomiting or diarrhoea (these symptoms had to have started within the 14 days preceding the clinical diagnosis)

**Notes**

### Risk of bias

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<tr>
<td>Methods</td>
<td>Randomised controlled, double-blind trial</td>
<td></td>
</tr>
<tr>
<td>--------------------------</td>
<td>------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Participants</td>
<td>Belgian trial of 74 one- to seven-year-olds with at least two acute otitis media episodes in the year before study entry</td>
<td></td>
</tr>
<tr>
<td>Interventions</td>
<td>7-valent pneumococcal conjugate vaccine (containing polysaccharides of serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F conjugated to the carrier protein CRM197) twice in 12- to 24-month-olds and once in 2- to 7-year-olds followed by 23-valent pneumococcal polysaccharide vaccination (containing polysaccharides of the serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, and 33F) respectively 6 and 7 months later versus hepatitis A vaccination in a similar time schedule</td>
<td></td>
</tr>
<tr>
<td>Outcomes</td>
<td>AOM episodes diagnosed 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: earache, acute otorrhoea, irritability, or fever (greater than 38.5°C rectally)</td>
<td></td>
</tr>
<tr>
<td>Notes</td>
<td>Performed in parallel with the study of Veenhoven 2003 but analysed separately due to differences in study population</td>
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### Risk of bias

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</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Dutch trial of 383 1- to 7-year-olds with at least two acute otitis media (AOM) episodes in the year before study entry</td>
</tr>
<tr>
<td>Interventions</td>
<td>7-valent pneumococcal conjugate vaccine (containing polysaccharides of serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F conjugated to the carrier protein CRM197) twice in 12- to 24-month-olds and once in 2- to 7-year-olds followed by 23-valent pneumococcal polysaccharide vaccination (containing saccharides of the serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, and 33F) respectively 6 and 7 months later versus respectively hepatitis B or hepatitis A vaccination in a similar time schedule</td>
</tr>
<tr>
<td>Outcomes</td>
<td>AOM episodes + AOM due to Streptococcus pneumoniae (non) vaccine type pneumococcal AOM AOM diagnosed 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 otorrhoea, irritability, or fever greater than 38.5°C rectally or 38.0°C axillary</td>
</tr>
<tr>
<td>Notes</td>
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### Risk of bias

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### ADDITIONAL TABLES

#### Table 1. Methodological quality of included studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Randomised</th>
<th>R appropriate?</th>
<th>Double blinded</th>
<th>DB appropriate?</th>
<th>Withdrawals/dropouts</th>
<th>Total score</th>
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<tbody>
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<td>Black (2000)</td>
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<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Eskola (2001)</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Dagan (2001)</td>
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<td>+1</td>
<td>1</td>
<td>+1</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Fireman (2003)</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Kilpi (2003)</td>
<td>1</td>
<td>+1</td>
<td>1</td>
<td>+1</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Veenhoven (2003)</td>
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<td>+1</td>
<td>1</td>
<td>+1</td>
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<td>5</td>
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<tr>
<td>Van Kempen (2006)</td>
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<td>1</td>
<td>+1</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Prymula (2006)</td>
<td>1</td>
<td>+1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>

R = Randomisation  
DB = Double blinding

#### Table 2. The effect of pneumococcal conjugate vaccination on acute otitis media episodes

<table>
<thead>
<tr>
<th>Pneumococcal conjugate vaccination administered in infancy</th>
<th>Episodes/person year</th>
<th>Relative reduction in risk (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Index</td>
<td>Control</td>
</tr>
<tr>
<td>Intention-to-treat analysis</td>
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</table>
Table 2. The effect of pneumococcal conjugate vaccination on acute otitis media episodes  
(Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Episodes/person year</th>
<th>Index</th>
<th>Control</th>
<th>Relative reduction in risk (95% confidence interval)</th>
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</thead>
<tbody>
<tr>
<td>Firemean 2003</td>
<td>not reported</td>
<td>not reported</td>
<td>6% (4 to 8)</td>
<td></td>
</tr>
<tr>
<td>Eskola 2001</td>
<td>not reported</td>
<td>not reported</td>
<td>not reported</td>
<td></td>
</tr>
<tr>
<td>Kilpi 2003</td>
<td>not reported</td>
<td>not reported</td>
<td>not reported</td>
<td></td>
</tr>
<tr>
<td>Prymula 2006</td>
<td>not reported</td>
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**Per-protocol analysis**

<table>
<thead>
<tr>
<th>Study</th>
<th>Episodes/person year</th>
<th>Index</th>
<th>Control</th>
<th>Relative reduction in risk (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Firemean 2003</td>
<td>not reported</td>
<td>not reported</td>
<td>7% (4 to 9)</td>
<td></td>
</tr>
<tr>
<td>Eskola 2001</td>
<td>1.16</td>
<td>1.24</td>
<td>6% (-4 to 16)</td>
<td></td>
</tr>
<tr>
<td>Kilpi 2003</td>
<td>not reported</td>
<td>not reported</td>
<td>-1% (-12 to 10)</td>
<td></td>
</tr>
<tr>
<td>Prymula 2006</td>
<td>0.08</td>
<td>0.13</td>
<td>34% (21 to 44)</td>
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</table>

**Pneumococcal conjugate vaccination administered at a later age**

<table>
<thead>
<tr>
<th>Study</th>
<th>Episodes/person year</th>
<th>Index</th>
<th>Control</th>
<th>Relative reduction in risk (95% confidence interval)</th>
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</thead>
<tbody>
<tr>
<td>Dagan 2001</td>
<td>0.66</td>
<td>0.79</td>
<td>17% (-2 to 33)</td>
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<tr>
<td>Veenhoven 2003</td>
<td>not reported</td>
<td>not reported</td>
<td>-25% (-57 to 1)</td>
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</tr>
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<td>Van Kempen 2006</td>
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<td>not reported</td>
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**Per-protocol analysis**

<table>
<thead>
<tr>
<th>Study</th>
<th>Episodes/person year</th>
<th>Index</th>
<th>Control</th>
<th>Relative reduction in risk (95% confidence interval)</th>
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</thead>
<tbody>
<tr>
<td>Dagan 2001</td>
<td>Not reported</td>
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</tr>
<tr>
<td>Veenhoven 2003</td>
<td>1.1</td>
<td>0.83</td>
<td>-29% (-62 to -2)</td>
<td></td>
</tr>
<tr>
<td>Van Kempen 2006</td>
<td>0.78</td>
<td>0.67</td>
<td>-16% (-96 to 31)</td>
<td></td>
</tr>
</tbody>
</table>

Note: negative values represent an increase in the risk for AOM
### Pneumococcal conjugate vaccination administered in infancy

<table>
<thead>
<tr>
<th></th>
<th>Relative reduction in risk (95% confidence interval); P-value</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pneumococcal AOM</td>
<td>Vaccine-type AOM</td>
</tr>
<tr>
<td><strong>Intention-to-treat analysis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black 2000</td>
<td>not reported</td>
<td>65%, P = 0.035</td>
</tr>
<tr>
<td>Eskola 2001</td>
<td>not reported</td>
<td>54% (41 to 64)</td>
</tr>
<tr>
<td>Kilpi 2003</td>
<td>not reported</td>
<td>not reported</td>
</tr>
<tr>
<td>Prymula 2006</td>
<td>not reported</td>
<td>not reported</td>
</tr>
<tr>
<td><strong>Per-protocol analysis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black 2000</td>
<td>not reported</td>
<td>67%, P = 0.077</td>
</tr>
</tbody>
</table>
| Eskola 2001             | 34% (21 to 45)   | 57% (44 to 67)  | cross-reactives: 51% (27 to 67)
|                         |                 |                 | others: -33% (-80 to 1) |
| Kilpi 2003              | 25% (11 to 37)   | 56% (44 to 66)  | cross-reactives: -5% (-47 to 25)
|                         |                 |                 | others: -27% (-70 to 6) |
| Prymula 2006            | 52% (37 to 63)   | 58% (41 to 69)  | cross-reactives: 66% (22 to 85)
|                         |                 |                 | others: 9% (-64 to 49) |

### Pneumococcal conjugate vaccination administered at a later age

<table>
<thead>
<tr>
<th></th>
<th>Relative reduction in risk (95% confidence interval); P-value</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pneumococcal AOM</td>
<td>Vaccine-type AOM</td>
</tr>
<tr>
<td><strong>Intention-to-treat analysis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dagan 2001</td>
<td>not reported</td>
<td>not reported</td>
</tr>
<tr>
<td>Veenhoven 2003</td>
<td>not reported</td>
<td>not reported</td>
</tr>
<tr>
<td>Van Kempen 2006</td>
<td>not reported</td>
<td>not reported</td>
</tr>
<tr>
<td><strong>Per-protocol analysis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dagan 2001</td>
<td>not reported</td>
<td>not reported</td>
</tr>
</tbody>
</table>
Table 3. The effect of pneumococcal conjugate vaccination on pneumococcal acute otitis media (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Reduction</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Veenhoven 2003</td>
<td>34%, P = 0.22</td>
<td>52%, P = 0.21</td>
</tr>
<tr>
<td>Van Kempen 2006</td>
<td>not reported</td>
<td>not reported</td>
</tr>
</tbody>
</table>

Note: negative values represent an increase in the risk for AOM.

Table 4. The effect of pneumococcal conjugate vaccination on recurrent acute otitis media

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Reduction</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pneumococcal conjugate vaccination administered in infancy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intention-to-treat analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black 2000</td>
<td>9% (4 to 14)</td>
<td></td>
</tr>
<tr>
<td>Eskola 2001</td>
<td>9% (-12 to 27)</td>
<td></td>
</tr>
<tr>
<td>Kilpi 2003</td>
<td>not reported</td>
<td></td>
</tr>
<tr>
<td>Prymula 2006</td>
<td>not reported</td>
<td></td>
</tr>
<tr>
<td>Per-protocol analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black 2000</td>
<td>9% (3 to 15)</td>
<td></td>
</tr>
<tr>
<td>Eskola 2001</td>
<td>16% (-6 to 35)</td>
<td></td>
</tr>
<tr>
<td>Kilpi 2003</td>
<td>not reported</td>
<td></td>
</tr>
<tr>
<td>Prymula 2006</td>
<td>56% (-2 to 81)</td>
<td></td>
</tr>
</tbody>
</table>

**Pneumococcal conjugate vaccination administered at a later age**

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Reduction</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dagan 2001</td>
<td>not reported</td>
<td></td>
</tr>
<tr>
<td>Veenhoven 2003</td>
<td>not reported</td>
<td></td>
</tr>
<tr>
<td>Van Kempen 2006</td>
<td>not reported</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Reduction</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Dagan 2001</td>
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</tr>
<tr>
<td>Veenhoven 2003</td>
<td>not reported</td>
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</tr>
<tr>
<td>Van Kempen 2006</td>
<td>not reported</td>
<td></td>
</tr>
</tbody>
</table>
Table 4. The effect of pneumococcal conjugate vaccination on recurrent acute otitis media (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dagan 2001</td>
<td>not reported</td>
</tr>
<tr>
<td>Veenhoven 2003</td>
<td>not reported</td>
</tr>
<tr>
<td>Van Kempen 2006</td>
<td>not reported</td>
</tr>
</tbody>
</table>

**WHAT’S NEW**

Last assessed as up-to-date: 14 November 2007.

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 September 2010</td>
<td>Amended</td>
<td>Contact details updated.</td>
</tr>
</tbody>
</table>

**HISTORY**

Protocol first published: Issue 2, 1999

Review first published: Issue 2, 2002

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>29 April 2008</td>
<td>New citation required but conclusions have not</td>
<td>New review authors.</td>
</tr>
<tr>
<td></td>
<td>changed</td>
<td></td>
</tr>
<tr>
<td>15 November 2007</td>
<td>New search has been performed</td>
<td>Searches conducted</td>
</tr>
<tr>
<td>28 April 2008</td>
<td>Amended</td>
<td>Converted to new review format</td>
</tr>
<tr>
<td>26 November 2003</td>
<td>New citation required and conclusions have changed</td>
<td>Substantive amendment</td>
</tr>
<tr>
<td>29 June 2003</td>
<td>New search has been performed</td>
<td>Searches conducted</td>
</tr>
<tr>
<td>19 August 2000</td>
<td>New search has been performed</td>
<td>Searches conducted</td>
</tr>
</tbody>
</table>
CONTRIBUTIONS OF AUTHORS

AJ, LS co-ordinated the review.
AJ, LS, EH were involved in data collection, quality assessment and analysis of data.
All review authors (AJ, LS, EH, RV, AS, RD) were involved in designing and writing the review and interpreting the data.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources
- Department of Pediatric Immunology and Infectious Diseases, UMC Utrecht, Wilhelmina Children’s Hospital Utrecht, Netherlands.
- Julius Center for Health Sciences and Primary Care, UMC Utrecht, the Netherlands, Netherlands.
- Department of Pediatrics, Spaarne Hospital Haarlem, Netherlands.
- Department of Otorhinolaryngology, UMC Utrecht, Wilhelmina Children’s Hospital Utrecht, Netherlands.

External sources
- No sources of support supplied

NOTES

The focus in research shifted from the use of PPVs to PCVs in children, and the role of PPVs in the prevention of AOM in children has merely been assessed following PCVs and not as a primary intervention anymore. Therefore, the focus of the current review has shifted from the effect of PPVs to the effect of PCVs on AOM. No further attention will be paid to the effect of PPVs, which was described in prior versions of this review (Straetemans 2003).

INDEX TERMS

Medical Subject Headings (MeSH)
Acute Disease; Otitis Media [microbiology; *prevention & control]; Pneumococcal Vaccines [*therapeutic use]; Randomized Controlled Trials as Topic; Vaccines, Conjugate [therapeutic use]
MeSH check words
Child; Child, Preschool; Humans; Infant