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Pneumococcal conjugate vaccines for preventing otitis media

Fortanier, Alexandre C.; Venekamp, Roderick P.; Boonacker, Chantal W. B.; Hak, Eelko; Schilder, Anne G. M.; Sanders, Elisabeth A. M.; Damoiseaux, Roger A. M. J.

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Pneumococcal conjugate vaccines for preventing otitis media (Review)

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[Intervention Review]

Pneumococcal conjugate vaccines for preventing otitis media

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ABSTRACT

Background

Acute otitis media (AOM) is a very common respiratory infection in early infancy and childhood. The marginal benefits of antibiotics for AOM in low-risk populations in general, 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 CENTRAL (2013, Issue 11), MEDLINE (1995 to November week 3, 2013), EMBASE (1995 to December 2013), CINAHL (2007 to December 2013), LILACS (2007 to December 2013) and Web of Science (2007 to December 2013).

Selection criteria

Randomised controlled trials (RCTs) 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

Two review authors independently assessed trial quality and extracted data.

Main results

We included 11 publications of nine RCTs (n = 48,426 children, range 74 to 37,868 per study) of 7- to 11-valent PCV (with different carrier proteins). Five trials (n = 47,108) included infants, while four trials (n = 1318) included children aged one to seven years that were either healthy (one study, n = 264) or had a previous history of upper respiratory tract infection (URTI), including AOM. We

Pneumococcal conjugate vaccines for preventing otitis media (Review)

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judged the methodological quality of the included studies to be moderate to high. There was considerable clinical diversity between studies in terms of study population, type of conjugate vaccine and outcome measures. We therefore refrained from pooling the results.

In three studies, the 7-valent PCV with CRM197 as carrier protein (CRM197-PCV7) administered during early infancy was associated with a relative risk reduction (RRR) of all-cause AOM ranging from -5% in high-risk children (95% confidence interval (CI) -25% to 12%) to 7% in low-risk children (95% CI 4% to 9%). 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 a precursor 11-valent PCV with *Haemophilus influenzae* (*H. influenzae*) protein D as carrier protein was associated with a RRR of all-cause AOM episodes of 34% (95% CI 21% to 44%).

A 9-valent PCV (with CRM197 carrier protein) administered in healthy toddlers was associated with a RRR of (parent-reported) OM episodes of 17% (95% CI -2% to 33%). 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 first occurrence and later AOM episodes. In a study in older children with a previously diagnosed respiratory tract infection, performed during the influenza season, a trivalent influenza vaccine combined with placebo (TIV/placebo) led to fewer all-cause AOM episodes than vaccination with TIV and PCV7 (TIV/PCV7) when compared to hepatitis B vaccination and placebo (HBV/placebo) (RRR 71%, 95% CI 30% to 88% versus RRR 57%, 95% CI 6% to 80%, respectively) indicating that CRM197-PCV7 after infancy may even have negative effects on AOM.

Authors' conclusions

Based on current evidence of the effects of PCVs for preventing AOM, the licensed 7-valent CRM197-PCV7 has modest beneficial effects in healthy infants with a low baseline risk of AOM. Administering PCV7 in high-risk infants, after early infancy and in older children with a history of AOM, appears to have no benefit in preventing further episodes. Currently, several RCTs with different (newly licensed, multivalent) PCVs administered during early infancy are ongoing to establish their effects on AOM. Results of these studies may provide a better understanding of the role of the newly licensed, multivalent PCVs in preventing AOM. Also the impact on AOM of the carrier protein D, as used in certain pneumococcal vaccines, needs to be further established.

PLAIN LANGUAGE SUMMARY

Vaccination against a bacterium called pneumococcus for preventing middle ear infection

Review question

We reviewed the evidence about the effect of vaccination against pneumococcus (a type of bacterium) on preventing middle ear infections in children.

Background

Middle ear infection, or otitis media, is one of the most common respiratory infections in childhood. Infection with *Streptococcus pneumoniae* (pneumococcus) is a frequent cause of middle ear infection. Vaccination against pneumococcus with pneumococcal conjugate vaccines (PCVs) is primarily introduced to protect young children against severe pneumococcal infections, such as meningitis and pneumonia. We wanted to discover whether vaccination with PCV also leads to fewer middle ear infections in children.

Study characteristics

This review included evidence up to 3 December 2013. Nine trials with a total of 48,426 children were included; five trials included 47,108 infants, while four trials included 1318 children at a later age, i.e. aged one to seven years, who were either healthy (one trial, 264 children) or had previous upper respiratory tract infections, including middle ear infections. All trials had a long follow-up, varying from 6 to 40 months.

Key outcomes

When vaccinating against seven different serotypes of pneumococcus (7-valent PCV) during early infancy, the occurrence of middle ear infections either increased by 5% or decreased by 6% to 7%. One study in infants used 11 serotypes of pneumococcus together with a carrier protein from another bacterium (*Haemophilus influenzae*); this decreased the occurrence of middle ear infections by 34%.

Children with a history of middle ear infections do not seem to benefit from 7-valent PCV when immunised at an older age (after infancy).

Quality of the evidence

We judged the quality of the evidence for 7-valent PCV in early infancy to be high (further research is very unlikely to change our confidence in the estimate of effect), while we judged the quality of the evidence for multivalent (more than seven different serotypes) PCV to be moderate (further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate), as this evidence is derived from only one trial. We judged the quality of the evidence for 7-valent PCV in older children with a history of middle ear infections to be high.

Future studies on the effects of PCV in infants, with broader serotype coverage (more than seven different serotypes), are likely to provide more understanding of the role of PCV in preventing middle ear infections.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Pneumococcal conjugate vaccine compared with control intervention for preventing acute otitis media				
<p>Patient or population: children aged 12 years or younger and a follow-up after vaccinations of at least 6 months</p> <p>Settings: open population</p> <p>Intervention: multivalent PCVs</p> <p>Comparison: control treatment</p>				
Outcomes	VE - relative effect (95% CI)*	No of participants (studies)	Quality of the evidence (GRADE)	Comments
<p>Frequency of all-cause AOM <i>PCV7 administered in early infancy</i> Follow-up 6 to 42 months</p>	RRR: -5% to 7%	42,140 (4)	⊕⊕⊕⊕ high	<p>Results are derived from 1 very large trial (Black 2000/Fireman 2003) and 3 trials of approximately equal size (944 to 1666 participants) (Eskola 2001; Kilpi 2003; O'Brien 2008)</p> <p>Lowest efficacy was found in high-risk children (O'Brien 2008)</p>
<p>Frequency of all-cause AOM <i>PD-PCV11 administered in early infancy</i> Follow-up 27 months</p>	RRR 34% (21 to 44)	4968 (1)	⊕⊕⊕○ moderate	<p>Results derived from 1 high-quality trial (Prymula 2006)</p> <p>Part of the effect may be related to the protein D to which the polysaccharides are conjugated in the vaccine PD-PCV11, demonstrated to reduce non-typeable <i>H. influenzae</i> by 35% (95% CI 2 to 57)</p> <p>AOM incidence rate in control group was low compared to the other studies on the effect on PCV7 in infants and the absolute risk difference was small (Table 1)</p>
<p>Frequency of all-cause AOM <i>CRM197-PCV9 administered in healthy toddlers</i> Follow-up 24 months</p>	RRR 17% (-2 to 33)	264 (1)	⊕⊕⊕○ moderate	<p>Results derived from 1 trial of moderate methodological quality (Dagan 2001). Uncertainty about the effect size (statistically non-significant effect) and outcome measure (parent-reported OM)</p>

Frequency of all-cause AOM <i>PCV7 administered in older children with a known history of AOM</i> Follow-up 6 to 26 months	RRR -29% to 57%	1054 (3)	⊕⊕⊕⊕ high	Results are derived from 2 high-quality trials (Veenhoven 2003 ; Van Kempen 2006) and 1 trial of moderate methodological quality (Jansen 2008). The 2 high-quality trials found no beneficial effect of PCV in preventing AOM recurrences, while the other trial found PCV7/TIV not to be superior to TIV/placebo in preventing AOM during the influenza season
Frequency of pneumococcal AOM <i>PCV7 administered in early infancy</i> Follow-up 6 to 42 months	RRR 20% to 34%	1233 (2)	⊕⊕⊕⊕ high	Results are derived from 2 high-quality trials (Eskola 2001 / Palmu 2009 ; Kilpi 2003)
Frequency of pneumococcal AOM <i>PD-PCV11 administered in early infancy</i> Follow-up 27 months	RRR 52% (37 to 63)	281 (1)	⊕⊕⊕○ moderate	Results derived from 1 high-quality trial in which myringotomy was performed in all children (Prymula 2006)

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

*Results include both ITT and PP results; 95% CI lacking in case of multiple studies (range of effect estimates presented as we refrained from pooling)

AOM: acute otitis media

CI: confidence interval

ITT: intention-to-treat

OM: otitis media

PCV: pneumococcal conjugate vaccine

PP: per-protocol

RRR: relative reduction in risk

TIV: trivalent inactivated influenza vaccine

VE: vaccine efficacy

BACKGROUND

Description of the condition

Acute otitis media (AOM), defined as middle ear effusion 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, imposing a large burden on public health. It has a peak incidence in six to 11-month-old infants (Teele 1989). By the age of one year, approximately 60% of infants have experienced at least one AOM episode and by the age of two years up to 5% of all children have experienced recurrent episodes of AOM, defined as three or more AOM episodes in six months or four or more in one year (Kvaerner 1997; Teele 1989). The three main bacterial pathogens isolated from the middle ear fluid of children with AOM, collected before the widespread use of pneumococcal conjugate vaccines (PCVs), were *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). Recent studies have shown that nationwide implementation of PCVs may have changed the frequency of the causative otopathogens involved in AOM towards pneumococcal serotypes not included in the vaccines and non-typeable *H. influenzae* (ntHi) (Casey 2013; Coker 2010; Somech 2011; Wiertsema 2011).

Description of the intervention

The marginal benefits of antibiotics for AOM in low-risk populations (Rovers 2006; Spiro 2008; Venekamp 2013), the increasing problem of bacterial resistance against antibiotics (Arason 1996; Del Castillo 1998; Dagan 2000; Goossens 2007) and the high estimated direct and indirect annual costs associated with otitis media (OM) (Boonacker 2011; Kaplan 1997; Niemela 1999) have prompted a search for effective vaccines to prevent AOM.

How the intervention might work

With *S. pneumoniae* (pneumococcus) being the prime 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 been shown to be poorly immunogenic in children below two years of age, who 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). No further attention will be paid to the effect of PPVs, which were described in a prior version of this review (Straetmans 2003).

Why it is important to do this review

With AOM being amongst the most common diseases in early childhood, the need for a vaccine to prevent effectively AOM is high. Over the past decades various randomised controlled trials (RCTs) have been performed to assess the effects of pneumococcal vaccination to prevent AOM. From 2009 onwards, two multivalent PCVs (10- and 13-valent PCVs) have been licensed and are being implemented in nationwide immunisation programmes worldwide (WHO 2012). These new vaccines may have an increased benefit in preventing AOM (Marom 2014; O'Brien 2009). As such, it is important to provide an up-to-date systematic review on the effects of pneumococcal vaccination on preventing AOM. This review is an update of a Cochrane review first published in 2002 (Straetmans 2002), and updated in 2004 (Straetmans 2004) and 2009 (Jansen 2009).

OBJECTIVES

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

METHODS

Criteria for considering studies for this review

Types of studies

RCTs of PCVs with prevention of AOM as an outcome in children aged 12 years or younger and a follow-up for at least six months.

Types of participants

Children up to 12 years of age.

Types of interventions

Multivalent PCVs.

Types of outcome measures

Primary outcomes

Frequency of all-cause AOM episodes defined as AOM irrespective of causative pathogen, as we considered this to be most relevant for children, parents and physicians.

Secondary outcomes

1. Frequency of pneumococcal AOM.
2. Frequency of pneumococcal serotype-specific AOM.
3. Frequency of recurrent AOM (defined as three or more episodes in the last six months or four or more in the last year).

Search methods for identification of studies

Electronic searches

For this update we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (2013, Issue 11), which contains the Cochrane Acute Respiratory Infections Group's Specialised Register; MEDLINE (1995 to November week 3, 2013); EMBASE (1995 to December 2013); CINAHL (2007 to December 2013); LILACS (2007 to December 2013) and Web of Science (2007 to December 2013).

We used the following search strategy to search CENTRAL and MEDLINE. We combined the MEDLINE search with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision); Ovid format (Lefebvre 2011). We adapted the search strategy to search EMBASE (Appendix 2), CINAHL (Appendix 3), LILACS (Appendix 4) and Web of Science (Appendix 5).

MEDLINE (Ovid)

- 1 exp Otitis Media/
- 2 otitis media.tw.
- 3 aom.tw.
- 4 or/1-3
- 5 Pneumococcal Vaccines/
- 6 Vaccines, Conjugate/
- 7 Bacterial Vaccines/

- 8 (pneumococ* adj5 (vaccin* or conjugat* or immuni*)).tw,nm.
- 9 pcv*.tw,nm.
- 10 or/5-9
- 11 4 and 10

Searching other resources

To increase the yield of relevant studies we reviewed the reference lists of all studies and review articles retrieved. We imposed no language restrictions on the searches. We checked ClinicalTrials.gov (<http://clinicaltrials.gov/>) and WHO ICTRP (<http://www.who.int/trialsearch>) for completed and ongoing trials (3 December 2013).

Data collection and analysis

Selection of studies

Three review authors (ACF, RPV, CWB) independently screened titles and abstracts obtained from the database searches and reviewed the full text of the potentially relevant titles and abstracts against the inclusion criteria. We resolved disagreements by discussion.

Data extraction and management

Two review authors (ACF, RPV) independently extracted data from the included studies. We resolved disagreements by discussion.

Assessment of risk of bias in included studies

Two review authors (ACF, RPV) independently assessed the methodological quality of the included trials. We resolved any disagreements by discussion. We assessed the methodological quality of included studies using the 'Risk of bias' tool as described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We judged the following domains as high, low or unclear risk of bias: random sequence generation (selection bias), concealment of allocation (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other bias. We presented the results of the 'Risk of bias' assessment in a 'Risk of bias' graph (Figure 1) and a 'Risk of bias' summary (Figure 2).

Figure 1. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

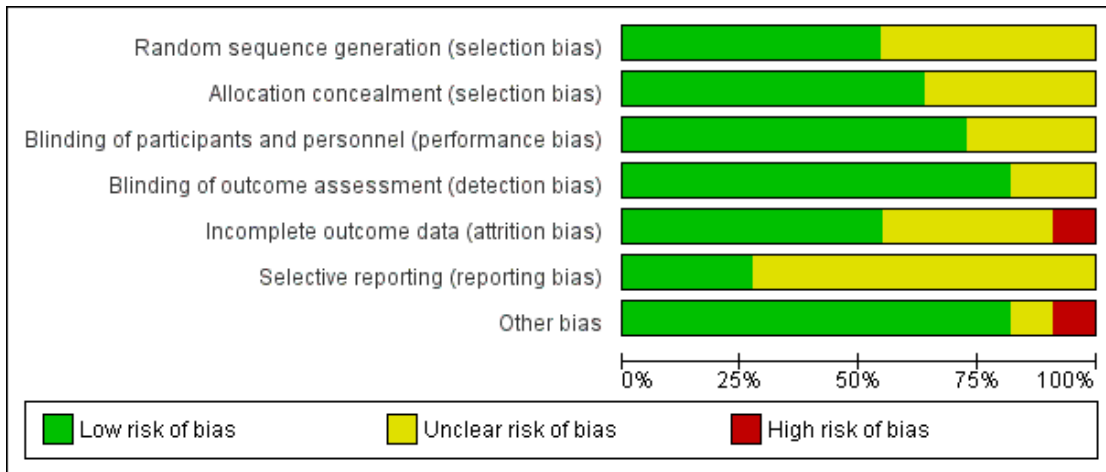


Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Black 2000	?	?	?	+	?	?	+
Dagan 2001	?	+	+	?	+	?	+
Eskola 2001	+	+	+	+	+	?	+
Fireman 2003	?	?	?	+	-	?	+
Jansen 2008	?	?	+	+	?	+	-
Kilpi 2003	+	+	+	+	+	?	?
O'Brien 2008	+	+	+	?	?	+	+
Palmu 2009	+	+	+	+	?	?	+
Pymula 2006	+	+	?	+	+	+	+
Van Kempen 2006	?	+	+	+	+	?	+
Veenhoven 2003	+	?	+	+	+	?	+

Measures of treatment effect

For both our primary and secondary outcomes we extracted the relative risks and their accompanying 95% CIs. Vaccine efficacy was estimated as 1 minus the relative risk (relative risk reduction (RRR)).

Unit of analysis issues

We included all types of RCTs. In case of cluster-randomised trials, we considered potential differences between the intervention effects being estimated.

Dealing with missing data

We primarily presented data based on the intention-to-treat (ITT) principle, i.e. all data were analysed in the group to which the participants were originally allocated. As a secondary analysis, we presented data based on the per-protocol analysis. For each trial, we determined the number of missing data and whether the authors took duration of follow-up (and censoring) of individual participants into account in their statistical analyses.

Assessment of heterogeneity

Meta-analysis by pooling the results of the different trials is only useful and justified when trials show satisfactory clinical homogeneity in terms of study population, setting, intervention and outcome measures. We assessed clinical diversity between trials by reviewing the differences across trials. There was considerable clinical diversity between trials. First, there were differences in the timing of PCV administration, i.e. trials administering PCV during infancy and trials administering PCV later in life. As such, study populations varied from healthy infants to those at high risk of AOM. Second, the number of pneumococcal serotypes present in the vaccines, the type of conjugate method used and co-administration of non-bacterial vaccines differed across trials. For example, the protein D carrier, as used in one trial assessing the effect of PD-PCV11 (Prymula 2006), has been shown to be beneficial in reducing AOM caused by non-typeable *H. influenzae* (ntHi) (Prymula 2006), and as such may have an impact on all-cause AOM beyond pneumococcal AOM. Furthermore, co-administration of a trivalent flu vaccine with CRM197-PCV7, as used in another trial (Jansen 2008), may have substantial impact on all-cause AOM. Finally, large differences in outcome assessments and AOM definitions were observed, varying from 'passive' (chart review at end of the trial) versus 'active' (parents were instructed to visit a physician in case of AOM symptoms) outcome assessments. As a consequence, AOM incidence in the control groups varied widely across the studies administering PCV during infancy, i.e.

from 0.13 to 1.3 episodes per person-year. Therefore, we decided that a meta-analysis was not appropriate.

Assessment of reporting biases

For each study, we searched the Internet and ClinicalTrials.gov (<http://clinicaltrials.gov/>) for available study protocols to determine whether all a priori defined outcomes have been reported in the publications.

Data synthesis

As we refrained from pooling (see [Assessment of heterogeneity](#) section), we reported the effect estimates as presented by the individual trials. Where possible we reported the incidences of the various outcomes in the study arms together with the vaccine efficacy estimates, with 95% confidence intervals (CIs). However, due to limitations of the data, we reported alternative statistical measures in some instances.

We will briefly describe the methods we would have used if we had pooled the results. The generalised Cox proportional hazard method proposed by Andersen 1982 is regarded as the most appropriate to assess the effect of PCVs on AOM (Jahn-Eimermacher 2007). Under the assumption 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 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 assumption 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 for meta-analysis. 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 divided by the number of children in the pneumococcal vaccination group multiplied by the follow-up time in months) divided by (total AOM episodes in control group divided by the number of children in the control group multiplied by the follow-up time in months) (McCullagh 1989).

Subgroup analysis and investigation of heterogeneity

Since the effect of PCVs on AOM may be influenced by the age at which the PCV was administered and the occurrence of previous AOM episodes, we described the studies accordingly, that is, those with vaccination in early infancy versus those with vaccination later in childhood.

Sensitivity analysis

As mentioned, the clinical diversity between the studies was large and therefore we decided not to meta-analyse the trials nor conduct a sensitivity analysis on, for example: risk status (age, number of previous episodes), outcome measurement or adjustments for clustering in the case of a cluster-randomised trial.

RESULTS

Description of studies

See the [Characteristics of included studies](#), [Characteristics of excluded studies](#) and [Characteristics of ongoing studies](#) tables.

Results of the search

This is an update of a Cochrane review first published in 2002 (Straetemans 2002) and updated in 2004 (Straetemans 2004) and 2009 (Jansen 2009). In the 2009 review, which included studies up to November 2007, eight publications were found eligible, concerning a total of seven RCTs (Black 2000/Fireman 2003; Dagan 2001; Eskola 2001; Kilpi 2003; Prymula 2006; Van Kempen 2006; Veenhoven 2003). The studies of Eskola 2001 and Kilpi 2003 are part of the FinOM Vaccine Trial (three parallel-group trials using the same control group (hepatitis B vaccine) but two different treatment groups, each with a different type of 7-valent pneumococcal conjugate vaccine) and we therefore regarded them as two 'separate' trials in this review.

With the updated search (November 2007 to December 2013) we retrieved 171 records. Removing duplicates left 165 records. After screening titles and abstracts, we identified seven potentially eligible studies. After obtaining the full text of these papers, we excluded two studies as they studied the effect of pneumococcal vaccination on either otitis media with effusion (OME) (Le 2007) or suppurative otitis media (Roy 2011). Furthermore, one RCT studying the effect of PCV on (recurrent) AOM was excluded as the children in the control group did not receive any type of vaccination (PCV versus no vaccination), while for outcome assessment non-blinded parents were instructed to visit the ear, nose and throat (ENT) department whenever they suspected an episode of AOM; the parental threshold to consult ENT departments may be lower in children allocated to the control treatment

(no vaccination) than in those allocated to PCV, which may have introduced (detection) bias (Gisselsson Solen 2011). Finally, one trial was excluded (Jokinen 2012), as this study was a re-analysis of the Eskola 2001 study and did not include new outcome data useful to this review. This left three new publications eligible for inclusion (Jansen 2008; O'Brien 2008; Palmu 2009). One study (Palmu 2009) was an additional analysis of the previously included Eskola 2001 study. We did not identify any additional eligible trials after scanning the reference lists of the full-text papers and relevant systematic reviews. In searching ClinicalTrials.gov, we identified five ongoing RCTs (NCT00466947; NCT00861380; NCT01545375; NCT01735084; NCT01174849) (see also the [Characteristics of ongoing studies](#) table).

Included studies

The 11 included trials in this review originate from nine RCTs in total: (1) Black 2000/Fireman 2003; (2) Dagan 2001; (3) Eskola 2001/Palmu 2009; (4) Jansen 2008; (5) Kilpi 2003; (6) O'Brien 2008; (7) Prymula 2006; (8) Van Kempen 2006; (9) Veenhoven 2003.

Study designs

Of these trials, eight were standard, individually randomised trials, while one trial was a cluster-randomised trial (O'Brien 2008).

Study populations (early infancy versus later in life)

Five trials (Black 2000/Fireman 2003; Eskola 2001/Palmu 2009; Kilpi 2003; O'Brien 2008; Prymula 2006) included healthy infants and studied the effect of PCV administered in early infancy (first dose before the age of 12 months) on otitis media (OM), while the other four trials (Dagan 2001; Jansen 2008; Van Kempen 2006; Veenhoven 2003) assessed the effects of PCV administered at a later age on OM in either healthy infants (Dagan 2001), or in children with a known history of respiratory disease, including OM (Jansen 2008; Van Kempen 2006; Veenhoven 2003).

Interventions (type of PCV used)

In all nine RCTs the control group received a control vaccine. In six trials 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) was used as the intervention (Black 2000/Fireman 2003; Eskola 2001/Palmu 2009; Jansen 2008; O'Brien 2008; Van Kempen 2006; Veenhoven 2003). In two of these studies a booster dose with 23-valent PPV (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) was given to all children (Van Kempen 2006; Veenhoven 2003), while in one trial CRM197-PCV7 was administered with

a trivalent inactivated influenza vaccine (TIV) (Jansen 2008). The other three studies (Dagan 2001; Kilpi 2003; Prymula 2006) used different interventions, i.e. a 9-valent PCV containing the capsular polysaccharides of serotypes 1 and 5 besides those included in CRM197-PCV7, conjugated to CRM197 (CRM197-PCV9) (Dagan 2001), a 7-valent PCV with the outer membrane complex of *N. meningitidis* serogroup B as protein carrier (OMPC-PCV7) (Kilpi 2003) and a subgroup of these children received a PPV23 as a booster dose and an 11-valent PCV 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* (PD-PCV11) (Prymula 2006).

Outcomes

Five studies applied a standardised diagnosis of AOM (Eskola 2001/Palmu 2009; Kilpi 2003; Prymula 2006; Van Kempen 2006; Veenhoven 2003), one study used standardised AOM registration forms to be completed by GPs (Jansen 2008), whereas in two studies AOM episodes were extracted from a computerised data source containing all visits registered by physicians (Black 2000/Fireman 2003; O'Brien 2008). Another study assessed parent-reported AOM episodes (Dagan 2001). Six studies additionally assessed the effect of PCVs on (serotype-specific) pneumococcal AOM (Black 2000/Fireman 2003; Eskola 2001; Kilpi 2003; O'Brien 2008; 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 by myringotomy or from spontaneously draining ears (Veenhoven 2003). Two other studies assessed the effect on reported cultures that were taken in cases of spontaneously draining ears (Black 2000/Fireman 2003; O'Brien 2008). Three studies reported on the effects of PCVs on recurrent AOM (Black 2000/Fireman 2003; Eskola 2001; Prymula 2006). Three of the included studies had all types of OM (including but not exclusively AOM) as an outcome (Black 2000/Fireman 2003; Dagan 2001; O'Brien 2008). Since the effect of PCVs on AOM may be influenced by the age at which the PCV was administered and the occurrence of previous episodes of AOM, we will further describe the studies accordingly; that is, those with vaccination in infancy versus those vaccinated later in childhood.

PCV administered in early infancy (first dose before the age of 12 months)

In the Northern California Kaiser Permanente (NCKP) trial (Black 2000/Fireman 2003), the Finnish Otitis Media (FinOM) trial (Eskola 2001/Palmu 2009) and the trial among Navajo and White Mountain Apache children (O'Brien 2008), the treatment group was administered CRM197-PCV7, at the age of two, four and six months and 12 to 15 months. In the NCKP trial (Black 2000/Fireman 2003), infants were enrolled over a period of almost three years and had a follow-up time varying from about

eight months to 30 months (Black 2000) and 42 months (Fireman 2003), respectively. The trial was originally designed to investigate the effect of CRM197-PCV7 on invasive pneumococcal disease, with OM as 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 of CRM197-PCV7 on AOM (Eskola 2001/Palmu 2009). 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. In recent years, an additional analysis was performed as part of the Eskola 2001 trial, including pneumolysin-PCR positive AOM (Palmu 2009). The trial among Navajo and White Mountain Apache children was a cluster-randomised trial primarily aiming to assess the safety and efficacy of CRM197-PCV7 on invasive pneumococcal disease (O'Brien 2003). These children have some of the highest rates of invasive pneumococcal disease and otitis media in the world. Clinical and culture-proven OM were secondary outcomes measured in this trial and were assessed, at trial completion, by retrospective chart review. OM visits, as in every visit made by the study children through to two years of age and documented by their treating physician, were evaluated. An OM visit was defined as a visit for 'otitis media', 'acute otitis media', 'bilateral OM', 'chronic OM', 'OM with perforation', 'otorrhoea', 'pressure equalising tube placement', 'perforation tympanic membrane', 'serous OM' and 'bullous myringitis'. Further sub-categorisation was performed on AOM (either 'acute otitis media' or 'bilateral otitis media'), severe episodes, number of medical visits and pressure equalising tube placement.

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 used in the Eskola 2001 study, i.e. 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 three, four, five months and 12 to 15 months, conjugated to protein D (PD-PCV11). 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 (first dose administered

after 12 months of age)

[Dagan 2001](#) assessed the effect of CRM197-PCV9 on AOM in healthy day-care 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 six to seven months later. Children with underlying illnesses, including immuno-compromising conditions, were excluded. Both studies had a similar design and 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 frequent 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.

In [Jansen 2008](#), children aged between 18 and 72 months were randomly assigned in blocks of three in a 1:1:1 ratio to either (1) two doses of CRM197-PCV7 (six months apart) administered together with a trivalent inactivated influenza vaccine (TIV), (2) TIV plus placebo or (3) hepatitis B virus vaccine plus placebo. The main outcome measure was febrile respiratory tract infections including AOM during the influenza season. All children were eligible if they had a previous history of physician-diagnosed respiratory tract infections (RTI). This history included 'acute otitis media', 'cough', acute upper RTI, 'sinusitis', 'acute tonsillitis', 'acute laryngitis/tracheitis', 'acute bronchitis/bronchiolitis', 'influenza', 'pneumonia', 'pleurisy/pleural effusion' and 'other respiratory infections', all recorded according to the International Classification of Primary Care (ICPC). Each parent was instructed to keep a daily diary, recording signs or symptoms associated with RTI that began 14 days after the second dose and continued for six to 18 months (depending on year of inclusion). The parent was also instructed to measure the child's body temperature with a validated tympanic thermometer provided by the study centre. All GP visits were recorded as well and the GP was instructed to complete a form including diagnosis and treatment.

Excluded studies

Four studies were excluded for various reasons ([Gisselsson Solen 2011](#); [Jokinen 2012](#); [Le 2007](#); [Roy 2011](#)) (see also [Characteristics of excluded studies](#) table).

Risk of bias in included studies

We judged the methodological quality of the included studies to be moderate to high. For further details on the risk of bias in included studies see the 'Risk of bias' graph ([Figure 1](#)) and 'Risk of bias' summary ([Figure 2](#)).

Allocation

Concealment of allocation was adequately described in six of the nine included trials, while in the other three trials it was unclear due to insufficient information ([Black 2000/Fireman 2003](#); [Jansen 2008](#); [Veenhoven 2003](#)). We judged random sequence generation to be adequate in five of the nine trials, while in four trials insufficient information was provided on the method of random sequence generation used ([Black 2000/Fireman 2003](#); [Dagan 2001](#); [Jansen 2008](#); [Van Kempen 2006](#)).

Blinding

Authors of all studies indicated that the studies were double-blinded, but for two of the nine trials insufficient information was provided on how blinding was performed ([Black 2000/Fireman 2003](#); [Prymula 2006](#)).

Incomplete outcome data

Overall, we judged the risk of bias due to incomplete outcome data to be low. In the [Fireman 2003](#) study (extension of [Black 2000](#)), we judged the risk of attrition bias to be high, as 27% in the PCV group and 26% in the control group did not stay in the Kaiser Permanente healthcare database to the end of follow-up (April 1999), while missing data were either substantial or unclear in two trials ([Jansen 2008](#); [Palmu 2009](#)), and in one trial the distribution across treatment groups of those who were not included in the primary efficacy analysis was unclear ([O'Brien 2008](#)). Almost all trials did take duration of follow-up of individuals into account by using either the generalised Cox proportional hazard method ([Black 2000/Fireman 2003](#); [Eskola 2001](#); [Kilpi 2003](#); [Prymula 2006](#); [Van Kempen 2006](#); [Veenhoven 2003](#)), or Poisson regression analyses ([Jansen 2008](#); [O'Brien 2008](#)). One trial used a Chi² test to compare rates of AOM, which is considered suboptimal ([Dagan 2001](#)).

Selective reporting

In three trials, we judged the risk of reporting bias to be low as prespecified (primary and secondary) outcomes were listed in

ClinicalTrials.gov (Jansen 2008; O'Brien 2008; Prymula 2006). O'Brien 2008 used a subset of the 4476 children that were included in the cluster-randomised trial to estimate the efficacy of PCV on the main outcome of the trial, i.e. invasive pneumococcal disease for a retrospective chart review on OM. Of the 4476 children that were included in the main study (O'Brien 2003), 944 were randomly selected and 856 met the chart review criteria (O'Brien 2008). In four trials no study protocol was identified (Black 2000/Fireman 2003; Dagan 2001; Van Kempen 2006; Veenhoven 2003), while in two trials the study protocol was uploaded at ClinicalTrials.gov but after the completion of the study (Eskola 2001/Palmu 2009; Kilpi 2003).

Other potential sources of bias

In four trials we detected no other potential sources of bias (Dagan 2001; Eskola 2001/Palmu 2009; Van Kempen 2006; Veenhoven 2003). In three trials study enrolment was stopped as a result of interim analyses (Black 2000/Fireman 2003; O'Brien 2008; Prymula 2006). These interim analyses were prespecified and performed by independent data safety monitoring boards; we therefore judged the risk of bias as low. In one trial a sample of the children (22%) assigned to OMPC-PCV7 received PPV23 at the age of 12 months instead of a fourth OMPC-PCV7 dose. However, it was unclear how it was known that only those particular children should receive that intervention. Moreover, in one trial PCV was administered together with a influenza vaccine (CRM197-PCV7/TIV) (Jansen 2008). As such, it is not possible to determine the effect of PCV only in this study.

Effects of interventions

See: [Summary of findings for the main comparison](#)

The main results are described in [Summary of findings for the main comparison](#).

In total, we included nine trials with 48,426 children, ranging from 74 to 37,868 participants per study. Five trials included infants who received primary vaccinations before six months of age (47,108 participants in total) (Black 2000/Fireman 2003; Eskola 2001/Palmu 2009; Kilpi 2003; O'Brien 2008; Prymula 2006); one study included day-care attendees aged 12 to 35 months (264 participants) (Dagan 2001), two trials included one to seven year-olds with a history of acute otitis media (AOM) (457 participants) (Van Kempen 2006; Veenhoven 2003), and one trial included children aged 18 to 72 months with a previously diagnosed respiratory tract infection (RTI) (597 participants) (Jansen 2008).

We present the results of the individual trials as reported in the published papers since meta-analysis was inappropriate due to substantial differences between studies. Therefore, the statistical methods by which the data were analysed in each study are briefly assessed. Black 2000/Fireman 2003, Eskola 2001, Kilpi 2003, Prymula

2006, Van Kempen 2006 and Veenhoven 2003 all used the generalised Cox proportional hazard method proposed by Andersen 1982, currently regarded as the most optimal for analysing this kind of data (see [Data synthesis](#)). 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 approach), the Chi² test was used, which is suboptimal for comparing rates. Jansen 2008 used Poisson regression to compare rates of AOM, accounting for the potential dependency of observations between individuals. O'Brien 2008 was a cluster-randomised trial. The incidence rate ratio was calculated with a Poisson regression with sandwich variance estimation to account for within-community correlation.

Effect estimates of pneumococcal conjugate vaccines (PCVs) on all AOM episodes, pneumococcal AOM and recurrent AOM are summarised in [Table 1](#), [Table 2](#) and [Table 3](#), respectively.

Primary outcome

1. Frequency of all-cause AOM episodes (defined as AOM irrespective of causative pathogen)

Effect of PCV administered in early infancy

CRM197-PCV7 reduced overall AOM episodes by -5% in high-risk children to 6% in low-risk children in intention-to-treat (ITT) analyses and by 0% in high-risk children to 7% in low-risk children in per-protocol analyses (Black 2000/Fireman 2003; Eskola 2001; O'Brien 2008), whereas OMPC-PCV7 appeared to have no effect on overall AOM episodes (Kilpi 2003). In a per-protocol analysis, PD-PCV11 led to a 34% (95% confidence interval (CI) 21% to 44%) relative reduction in AOM episodes (Prymula 2006). However, the AOM incidence rate in the control group was low compared to the other studies and the absolute risk difference was small ([Table 1](#)).

Effect of PCV administered at a later age

In per-protocol analyses, CRM197-PCV9 administered in healthy 12- to 35-month-olds reduced overall otitis media (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). CRM197-PCV7 administered together with a trivalent influenza vaccine (CRM197-PCV7/TIV) reduced overall AOM episodes by 57% (95% CI 6% to 80%) in per-protocol analysis (Jansen 2008), as compared to hepatitis B (HBV)/placebo vaccination. However, the vaccine efficacy of trivalent influenza vaccine (TIV)/placebo, as compared to HBV/placebo, on overall AOM, appeared to be even larger, i.e. 71% (95% CI 30% to 88%).

Secondary outcomes

1. Frequency of pneumococcal AOM

Effect of PCV administered in early infancy

The efficacy of PCVs for pneumococcal AOM varied from 25% for OMPC-PCV7 (Kilpi 2003), 20% to 34% for CRM197-PCV7 (Eskola 2001/Palmu 2009), to 52% for PD-PCV11 (Prymula 2006). CRM197-PCV7 and PD-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, CRM197-PCV7 and OMPC-PCV7 were associated with an increase in non-vaccine-type AOM (replacement) (Eskola 2001; Kilpi 2003) and *H. influenzae* AOM, while PD-PCV11 did not show pneumococcal replacement and showed a vaccine efficacy of 35% against AOM caused by *H. influenzae* (Prymula 2006).

Effect of PCV administered at a later age

Only one study reported the effect of CRM197-PCV7 followed by PPV23 on pneumococcal AOM (Veenhoven 2003). In per-protocol analysis, pneumococcal AOM was reduced by 34%, while non-vaccine-type AOM was reduced by 21%, although none of the estimates was statistically significant (because of small numbers).

2. Frequency of pneumococcal serotype-specific AOM

Effect of PCV administered in early infancy

The effect of CRM197-PCV7 on vaccine-type pneumococcal AOM varied from 54% to 65% in ITT analyses (Black 2000/Fireman 2003; Eskola 2001; O'Brien 2008), and from 57% to 67% in per-protocol analyses (Black 2000/Fireman 2003; Eskola 2001). In per-protocol analyses, OMPC-PCV7 appeared to reduce vaccine-type AOM by 56% (Kilpi 2003), while PD-PCV11 led to a 58% relative reduction in vaccine-type AOM (Prymula 2006).

Effect of PCV administered at a later age

In per-protocol analysis, CRM197-PCV7 followed by PPV23 reduced pneumococcal serotype-specific AOM by a statistically non-significant 52% (Veenhoven 2003). None of the other trials reported on pneumococcal (serotype-specific) AOM.

3. Frequency of recurrent AOM (defined as three or more episodes in the last six months or four or more in the last year)

Effect of PCV administered in early infancy

CRM197-PCV7 seemed to reduce recurrent AOM by 9% to 10% in ITT analyses (Black 2000/Fireman 2003; Eskola 2001), whereas the administration of PD-PCV11 was associated with a statistically non-significant decrease of 56% in recurrent AOM in per-protocol analysis (Prymula 2006).

Effect of PCV administered at a later age

None of the four trials in older children reported the effect of PCV on recurrent AOM.

DISCUSSION

Summary of main results

Clinical diversity between the nine included randomised controlled trials (RCTs), in terms of study population, number of pneumococcal serotypes present in the vaccines, type of conjugate method used, co-administration of non-bacterial vaccines and outcome measures, was considerable and we therefore did not pool results. The main findings are summarised in the [Summary of findings for the main comparison](#).

Based on current evidence of the effects of pneumococcal conjugate vaccines (PCVs) for preventing acute otitis media (AOM), the licensed 7-valent PCV has modest beneficial effects in healthy infants; in the studies in healthy infants, the licensed CRM197-PCV7 was associated with a relative risk reduction (RRR) of overall AOM of -5% (in high-risk children) to 7% (in low-risk children) and OMPC-PCV7 did not reduce overall AOM episodes. PD-PCV11 showed a large reduction in all-cause AOM episodes, i.e. 34%, compared to the PCV7 studies. In healthy toddlers, CRM197-PCV9 was associated with a non-significant RRR of 17% of parent-reported OM episodes. Administering PCV7 in older children with a history of AOM appears to have no beneficial effect on preventing further AOM episodes.

In infants, PCV led to a substantial reduction in AOM caused by *S. pneumoniae* (RRR ranging from 20% to 52%). This beneficial effect seems to be mainly driven by the large effect of PCV on vaccine-type pneumococcal AOM (RRR ranging from 54% to 67%). In contrast, no or even a negative contribution of PCV was observed for non-vaccine-type pneumococcal AOM (RRR ranging from -33% to 9%). For PCV7, there was a tendency toward replacement disease by non-vaccine pneumococci as well as

by other otopathogens, such as *H. influenzae*. OMPC-PCV7 appeared to increase the proportion of AOM caused by *M. catarrhalis* (Kilpi 2003). This means that while PCVs are effective against vaccine-serotype pneumococcal AOM, there is high potential for replacement by other pathogens. Although we are confident in the effect estimate for PCV7 administered in infancy on all-cause AOM and pneumococcal AOM, uncertainty exists about the effect of conjugate vaccines that include more than seven pneumococcal serotypes and the impact of replacement by non-vaccine-type pneumococci or other otopathogens (Summary of findings for the main comparison).

The large effect of PD-PCV11 on all-cause AOM found in the trial of Prymula 2006 may not be solely explained by the four additional serotypes covered by PD-PCV11 compared to PCV7. Part of the effect might be related to the protein D, which has the potential to provide protection against *H. influenzae* strains causing AOM (Forsgren 2008), or may be secondary to the prevention of pneumococcal AOM in the first place with nHi as a pathogen more frequently observed in previously inflamed middle ears (Dagan 2013; Kaur 2013). Furthermore, Prymula 2006 used a stringent outcome definition for AOM (children diagnosed with AOM by the paediatrician were subsequently referred to the otorhinolaryngologist for confirmation of diagnosis), which may have contributed to the low AOM incidence rate observed in Prymula 2006; this is about 10 times lower than the incidence reported by other studies in infancy. It might be that in Prymula 2006 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 as early findings suggest that *S. pneumoniae* was associated with more severe episodes (Howie 1970). However, a subsequent post hoc analysis of Eskola 2001, using a case definition of AOM very close to the Prymula 2006 definition, showed only a slight impact on the vaccine efficacy estimates compared to the original case definitions (Palmu 2008).

The effect of a multivalent PCV, i.e. CRM197-PCV9, on AOM was evaluated in healthy toddlers attending day-care (Dagan 2001). As such, the effect of PCV9 in early life remains uncertain. In toddlers, PCV9 led to a non-statistically significant RRR of all-cause AOM of 17%. However, this result should be interpreted with caution as the outcome measure (parent-reported AOM) and the statistics were suboptimal.

In AOM there is a 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 bacteria that may have pathogenic potential (Block 2006; Casey 2013; Coker 2010; Eskola 2001; Obaro 1996; Somech 2011; Veenhoven 2003; Wiertsema 2011). Nasopharyngeal carriage results from a recent RCT with a commercially available 10-valent protein D pneumococcal conjugate vaccine (PD-PCV10) show similar bacterial

colonisation patterns of vaccine-type and non-vaccine-type pneumococci (*H. influenzae*, *M. catarrhalis* and *Staphylococcus aureus* (*S. aureus*)) to CRM197-PCV7 in healthy Dutch children up to two years of age (Van den Bergh 2013). 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). Future studies may provide more precise information about the extent and impact of such replacement in AOM when administering conjugate vaccines that include more than seven pneumococcal serotypes.

Overall completeness and applicability of evidence

The nine RCTs included in this review on the effect of PCV on AOM in children show large heterogeneity regarding study design (standard, individually randomised trials versus group randomised trial), population (age of administration of PCV and baseline risk of AOM), intervention (vaccine valency (7-/9-/11-valent vaccines), carrier protein (CRM197, OMPC or PD), presence or absence of additional booster immunisation with PCV or PPV23, co-administration of non-bacterial vaccines and outcome assessment and definition (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 all-cause AOM episodes prevented by pneumococcal vaccines. Additionally, three studies included older otitis-prone children, so the intervention was aimed at secondary or even tertiary prevention and not primary prevention (Jansen 2008; Van Kempen 2006; Veenhoven 2003). 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 'damage' already suffered by the middle ear mucosa caused by prior AOM (Veenhoven 2003). Another explanation, although debated, could be the non-protective, impaired antibody responses of children who are otitis-prone (Pichichero 2013; Wiertsema 2012). Thus, it appears that the age at which PCV is administered, a history of AOM episodes, or both, 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).

Quality of the evidence

We judged the methodological quality of the included studies to be moderate to high. Although we were not able to pool the results of the separate trials due to substantial clinical diversity, the overall results were consistent.

Potential biases in the review process

In this review, we strictly adhered to the prespecified review protocol. Three review authors independently searched all relevant electronic databases by using a search syntax comprising all relevant synonyms for PCV and AOM. Additionally, we performed a broad Internet search to identify potentially relevant articles. To increase the yield of relevant studies, we reviewed the reference lists of all identified studies and systematic reviews or meta-analyses.

Agreements and disagreements with other studies or reviews

Our main findings are in agreement with two other systematic reviews on the effect of PCV in children, indicating that PCV may provide some protection against otitis media, but that other factors could also have contributed to the observed effect estimates (Pavia 2009; Taylor 2012).

AUTHORS' CONCLUSIONS

Implications for practice

The prevention of invasive pneumococcal disease has been the primary reason for many Western countries to introduce pneumococcal conjugate vaccine (PCV) into their national infant immunisation protocol. The beneficial effect on overall acute otitis media (AOM) episodes with CRM197-PCV7 appears to be modest in healthy, low-risk infants and therefore promoting PCV solely to reduce AOM for the individual does not seem justified. For countries that have not yet implemented PCV in the immunisation protocol and for countries that do 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. In two trials in older children with a history of AOM, no beneficial effect of CRM197-PCV7 on further episodes of AOM was observed (Van Kempen 2006; Veenhoven 2003), while in a third trial CRM197-PCV7 administered together with a trivalent influenza vaccine (CRM197-PCV7/TIV) reduced overall AOM episodes by 57% during the influenza season, compared to hepatitis B vaccination (HBV)/placebo vaccination (Jansen 2008). However, the vaccine efficacy of trivalent influenza vaccine (TIV)/placebo, compared to HBV/placebo, on overall AOM appeared to be even larger (i.e.

71%), indicating that CRM197-PCV7 after infancy may even have negative effects on AOM. As such, there is at present no reason to administer the vaccine to older children with a history of previous AOM episodes in order to protect them against further AOM episodes. In fact, early vaccination before the first AOM episode might be required for prevention of middle ear mucosal damage.

Implications for research

Uncertainty exists nowadays about 1) the effect of widespread implementation of pneumococcal conjugate vaccination on AOM in everyday practice, 2) the effect of conjugate vaccines that include more than seven pneumococcal serotypes and 3) the impact of replacement by non-vaccine-type pneumococci or other otopathogens. Although the beneficial effect of CRM197-PCV7 on all-cause AOM in randomised controlled trials (RCTs) seems modest, 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 (Taylor 2012). Post-licensure studies, comparing rates of ambulatory visits related to AOM in the immediate years before and after widespread implementation of routine CRM197-PCV7 vaccination in children younger than 12 years of age, have reported a substantial decrease (mean decrease in ambulatory visits of 19%). Quickly after the introduction of PCV in the United States decreases in AOM visits and antibiotic prescriptions were reported in children below two years of age (43% and 42%, respectively (Zhou 2008)), a decline in the frequency of otitis media of 17% and 28% in birth cohorts from Tennessee and upstate New York (Poehling 2007) and an overall downward trend in otitis media-related health care use in children aged below six years over the years 2001 to 2011 (Marom 2014). A recent non-US observational study showed a decline of AOM in Norwegian children aged 12 to 18 months and 18 to 36 months of 14% and 8%, respectively (Magnus 2012). These larger benefits found in observational studies, compared to the effects reported in RCTs, might be due to indirect herd effects and may have important implications for the cost-effectiveness analyses for PCV. However, the findings of the observational studies must be interpreted with caution as variability in baseline incidence, study population, case definition and implementation of AOM treatment guidelines could have influenced the AOM incidences reported. For example, results from Boston in the US showed that the decline in uncomplicated AOM, treatment failure and AOM relapse was at least as large in the 2000 to 2004 period compared to 1996 to 2000 (Sox 2008). Therefore the 'true' contribution of PCV to reducing AOM incidence remains uncertain (Sox 2008).

Whether the decline in AOM will continue or wane with time is relevant and deserves ongoing monitoring. A waning effect in AOM incidence after implementation of PCV may be explained by replacement by other otopathogens such as *H. influenzae* or

an increase in the proportion of AOM caused by non-CRM197-PCV7 pneumococcal serotypes, including serotypes 3, 6A and 19A (Alonso 2013; Block 2004; Casey 2013; Coker 2010; Couloigner 2012; McEllistrem 2005; Pichichero 2007). As previously mentioned, two infant studies found an increase in non-vaccine-type pneumococcal AOM after administration of CRM197-PCV7, albeit not statistically significant, as well as an increase in *H. influenzae* (Eskola 2001; Kilpi 2003). An increase in *H. influenzae* was also observed in the post-marketing studies on AOM in the US (Block 2004; Casey 2004). In addition, the study in older children with previous AOM episodes demonstrated an increase in AOM caused by *S. aureus* (Veenhoven 2003). In view of the effects of PCVs on nasopharyngeal carriage of pathogens, awareness of the possibility of infections caused by replacement pathogens is warranted. Besides a reduction of nasopharyngeal vaccine-type serotypes, which is presumed to induce herd effects, replacing pneumococcal serotypes may not only lead to replacement disease in vaccines but also in the population. Continuing surveillance of pneumococcal disease in different settings and geographic locations is therefore of utmost importance. Currently, several RCTs with different (newly licensed, multivalent) PCVs administered during early infancy are ongoing to establish their effects on AOM (Characteristics of ongoing studies). The results of these studies may provide a better understanding of the role of PCVs in preventing all-cause AOM (Hausdorff 2013), including mixed *S. pneu-*

moniae and *H. influenzae* infections (Dagan 2013), bacterial-bacterial interactions (Van den Bergh 2012) and long-term effects of shifts in pneumococcal serotypes (Spijkerman 2012).

We emphasise the need for uniform outcome measures (case definitions of AOM) and uniform 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 preferred. These figures should also be available on the basis of intention-to-treat analysis and not only on the basis of per-protocol analysis.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Black 2000

Methods	<p>Randomised - yes, at individual level</p> <p>Design - standard parallel-group design</p> <p>Intention-to-treat (ITT) - yes</p> <p>Follow-up - 6 to 31 months</p>
Participants	<p>N - 37,868 healthy infants</p> <p>Age - 2 months</p> <p>Setting - 23 medical centres within Northern California Kaiser Permanente (NCKP), USA</p> <p>Inclusion criteria - healthy children aged 2 months</p> <p>Exclusion criteria - children with sickle cell disease, known immunodeficiency, any serious chronic or progressive disease, a history of seizures or a history of either pneumococcal or meningococcal disease</p> <p>Baseline characteristics - not described</p>
Interventions	<p>Children were randomly allocated to either a 7-valent pneumococcal conjugate vaccine (PCV7) or a meningococcus type C conjugate vaccine (MenC) at 2, 4, 6 and 12 to 15 months of age</p> <p>Tx - PCV7 (containing the polysaccharides of serotypes 4, 6B, 9V, 14, 18C, 19F and 23F conjugated to carrier protein CRM197); N = 18,927 received 1 dose or more of the vaccine (unclear how many children were included in otitis media analyses)</p> <p>C - MenC (10 µg of group C oligosaccharide conjugated to carrier protein CRM197); N = 18,941 received 1 dose or more of the vaccine (unclear how many children were included in otitis media analyses)</p> <p>Additional vaccines - routine childhood vaccines were administered at the recommended ages: diphtheria-tetanus toxoid-whole cell pertussis vaccine (DTwP) or diphtheria-tetanus toxoid-acellular pertussis vaccine (DTaP); oral poliovirus vaccine or inactivated poliovirus vaccine; <i>Haemophilus influenzae</i> type B; hepatitis B; measles-mumps-rubella vaccine; varicella. Initially all participants received a vaccine combining <i>Haemophilus b</i> conjugate and DTwP into the opposite leg and oral poliovirus vaccine concurrently. When recommendations changed the protocol was amended to allow administration of DTaP and inactivated poliovirus vaccine. Vaccines not given concomitantly were given at least 2 weeks apart from study vaccine</p>
Outcomes	<p>Primary outcome - protective efficacy of PCV7 against invasive pneumococcal disease caused by vaccine serotypes</p> <p>Secondary outcomes - effect of PCV7 on (a) number of otitis media episodes in fully vaccinated per-protocol; (b) number of otitis media visits; (c) time to frequent otitis media (defined as 3 or more episodes in 6 months or 4 or more in 12 months); (d) number of tympanostomy tubes placements; (e) number of cases of spontaneous draining ruptured tympanic membranes with culture of a vaccine serotype pneumococcus</p> <p>Clinical diagnoses of acute otitis media were obtained from computerised data sources using diagnoses registered by emergency physicians and paediatricians in the NCKP population. Each clinic visit constituted a new episode unless it was classified as a follow-</p>

Black 2000 (Continued)

	up visit. A visit < 21 days after another otitis media visit was always considered a follow-up visit. A visit 42 days or more after the most recent otitis media visit was considered a new episode. Visits occurring between 21 and 42 days, if the appointment was made < 3 days in advance, were considered new episodes	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not described
Allocation concealment (selection bias)	Unclear risk	No method of allocation concealment was described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Indicated to be double-blind study but insufficient details provided to ensure blinding of participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Clinical diagnoses of AOM were obtained from computerised data sources using diagnoses registered by emergency physicians and paediatricians (non-trialists)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear how many children were included in otitis media analyses
Selective reporting (reporting bias)	Unclear risk	Study protocol is not available. Otitis media endpoint (efficacy against otitis media episodes) is reported as a secondary endpoint
Other bias	Low risk	Control group was vaccinated against MenC disease, but meningococci are not a causative pathogen in otitis media. Study enrolment was stopped as a result of pre-specified interim analysis

Methods	<p>Randomised - yes, at individual level</p> <p>Design - standard parallel-group design</p> <p>Intention-to-treat (ITT) - no, per- protocol analysis</p> <p>Follow-up - 2 years starting 1 month after complete immunisation</p>	
Participants	<p>N - 264 healthy infants (261 children were included in clinical follow-up)</p> <p>Age - 12 to 35 months</p> <p>Setting - 8 day-care centres in Beer-Sheva, Israel</p> <p>Inclusion criteria - healthy children aged 12 to 35 months</p> <p>Exclusion criteria - children that received any vaccine within a 4-week period before, or were scheduled to receive any vaccine during the 4 weeks after the administration of the study vaccines, or received immunoglobulin within 8 weeks of study vaccination, known or suspected impairment of immunologic functions, major congenital malformation or serious chronic disease, known hypersensitivity to any components of the study vaccine, previous severe vaccine-associated adverse reaction, previous vaccination with any pneumococcal or meningococcal vaccine, febrile illness (rectal temperature, 38 °C) within 72 h before vaccination</p> <p>Baseline characteristics - described and balanced (Table 1)</p>	
Interventions	<p>Children were randomly allocated to either a 9-valent pneumococcal conjugate vaccine (PCV9) or a meningococcus type C conjugate vaccine (MenC). Children aged 12 to 17 months at time of enrolment received 2 intramuscular injections 2 to 3 months apart and those 18 to 35 months at time of enrolment received 1 intramuscular injection</p> <p>Tx - PCV9 (containing the polysaccharides of serotypes 1, 4, 5, 6B, 9V, 14, 18C, 19F and 23F conjugated to carrier protein CRM197); N = 131</p> <p>C - MenC (10 µG of group C oligosaccharide conjugated to carrier protein CRM197); N = 130</p> <p>Additional vaccines - not described</p>	
Outcomes	<p>Primary outcome - effect of PCV9 on nasopharyngeal carriage of <i>S. pneumoniae</i> of the serotypes found in the vaccines in general and antibiotic-resistant <i>S. pneumoniae</i> in particular</p> <p>Secondary outcomes - effect of PCV9 on parent-reported respiratory infections including otitis media</p> <p>18 encounters were planned for each child during the 2-year follow-up period. During the first year encounters were planned to take place monthly and during the second year bimonthly. At each visit the parents were questioned about illness and antibiotic use since the last visit. Illness episodes were divided into 4 categories:</p> <p>(1) upper respiratory infections; (2) lower respiratory problems; (3) otitis media; and (4) other illnesses. Only episodes starting 1 month after complete immunisation were counted</p>	
Notes	<p>Participants lost to follow-up during first 12 months - total: 32/261 (12.3%)</p> <p>Participants lost to follow-up during first 12 months - Tx: 16/131 (12.2%)</p> <p>Participants lost to follow-up during first 12 months - C: 16/130 (12.3%)</p>	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement

Dagan 2001 (Continued)

Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not described. Block randomisation (n = 6) stratified by DCC and age
Allocation concealment (selection bias)	Low risk	Randomisation list provided in a sealed envelope by Wyeth-Lederle Vaccines
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Appearance of PCV9 and MenC vaccines was not similar. 2 nurses not belonging to the study team injected the vaccines. They were not allowed reveal the child's allocation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Parental interview. A positive report of OM was defined as an episode
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up rates reported in Table 1. 12% of children followed up for < 12 months
Selective reporting (reporting bias)	Unclear risk	Study protocol is not available
Other bias	Low risk	

Eskola 2001

Methods	<p>This trial was part of a study including Kilpi 2003 (FinOM Vaccine Trial). Both Eskola 2001 and Kilpi 2003 used the same control group (hepatitis B vaccine) but a different treatment group, each with a different type of 7-valent pneumococcal conjugate vaccine. Eskola 2001 used a PCV7 containing the polysaccharides of serotypes 4, 6B, 9V, 14, 18C, 19F and 23F conjugated to carrier protein CRM197, while Kilpi 2003 used a PCV7 containing polysaccharides of serotypes 4, 6B, 9V, 14, 18C, 19F and 23F conjugated to the outer membrane protein complex of <i>N. meningitidis</i> serogroup B</p> <p>Randomised - yes, at individual level Design - standard parallel-group design Intention-to-treat (ITT) - yes, both ITT and per-protocol analysis described Follow-up - 22 consecutive months (children were followed up to 24 months of age)</p>
Participants	<p>N - 1662 healthy infants Age - 2 months Setting - 8 study clinics in the communities of Tampere, Kangsala and Nokia, Finland Inclusion criteria - healthy children aged 2 months Exclusion criteria - not described Baseline characteristics - described and balanced (Table 1)</p>
Interventions	<p>Children were randomly allocated to either a 7-valent pneumococcal conjugate vaccine (PCV7) or a hepatitis B at 2, 4, 6 and 12 to 15 months of age Tx - PCV7 (containing the polysaccharides of serotypes 4, 6B, 9V, 14, 18C, 19F and</p>

	<p>23F conjugated to carrier protein CRM197); N = 831 (N = 786 completed the follow-up as specified in the protocol)</p> <p>C - hepatitis B vaccine (containing 5 µg of recombinant hepatitis B surface protein); N = 831 (N = 794 completed the follow-up as specified in the protocol)</p> <p>Additional vaccines - a combination vaccine containing whole-cell DTP and <i>Haemophilus influenzae</i> type B was given in the child's opposite thigh at the same visit as the pneumococcal vaccine at 2, 4 and 6 months of age. In half of the study clinics, the carrier protein in the DTP and <i>H. influenzae</i> vaccine was CRM197 and in the other half it was tetanus toxoid. Inactivated poliovirus vaccine was given at 7 months of age and again at the same time as the fourth dose of the study vaccine at 12 months of age. Measles-mumps-rubella vaccine was administered at 18 months</p>	
Outcomes	<p>Primary outcome - effect of PCV7 on the number of acute otitis media (AOM) episodes due to the pneumococcal serotypes included in the vaccine</p> <p>Secondary outcomes - effect of PCV7 on the number of all-cause AOM episodes, culture-confirmed AOM episodes and pathogen-specific AOM episodes, preventing first and subsequent AOM episodes, number of children with recurrent AOM episodes (defined as 3 or more AOM episodes in last 6 months or 4 or more in the last 12 months), serious adverse events</p> <p>All children attended 1 of the study clinics for enrolment at 2 months of age and thereafter at 4, 6, 7, 12, 13, 18 and 24 months. Parents were encouraged to bring their child to the study clinic for evaluation of symptoms suggesting respiratory infection or AOM. AOM was diagnosed by otoscopy (visibly abnormal tympanic membrane in terms of colour, position or mobility, suggesting middle ear effusion) and the presence of at least 1 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</p> <p>For the overall and pathogen-specific AOM episodes, a new episode was considered to have started if at least 30 days had elapsed since the beginning of the previous episode. For AOM episodes according to serotype, a new episode was considered to have started if 30 days had elapsed since the beginning of an episode due to the same serotype, or if any interval had elapsed since the beginning of an episode due to a different serotype. If more than 1 serotype was recovered from the middle ear fluid at the same time, only 1 episode was considered to have started</p>	
Notes	<p>Participants lost to follow-up - total: 82/1662 (4.9%) did not complete the follow-up period according to protocol</p> <p>Participants lost to follow-up - Tx: 45/831 (5.4%) did not complete the follow-up period according to protocol</p> <p>Participants lost to follow-up - C: 37/831 (4.5%) did not complete the follow-up period according to protocol</p>	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	6 letters corresponding to the 3 treatment options were randomly allocated to consecutive subject identification numbers, using

Eskola 2001 (Continued)

		an allocation of 1:1:1 and a block size of 12 (see Kilpi 2003)
Allocation concealment (selection bias)	Low risk	Individual treatment assignments were kept in sealed envelopes until vaccination (see Kilpi 2003)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Use of vaccinators who were not otherwise involved in the trial follow-up. Letter code was destroyed immediately after vaccination (see Kilpi 2003)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessment of the outcome was done according to a strict definition of AOM. Assessment was done by other personnel than those that vaccinated the children (vaccinators were not otherwise involved in the trial follow-up) (see Kilpi 2003)
Incomplete outcome data (attrition bias) All outcomes	Low risk	No reporting of reasons for drop-out and/or lost to follow-up. Not expected to have major impact on outcome since 94.6% in the PCV7 and 95.5% in the control group completed the follow-up as specified in the protocol
Selective reporting (reporting bias)	Unclear risk	Prespecified outcomes (primary and secondary) are listed in ClinicalTrials.gov (although uploaded after study end)
Other bias	Low risk	

Fireman 2003

Methods	This study is an extension of Black 2000 (data updated to 1999). Follow-up continued until children left Northern California Kaiser Permanente (NCKP) or until 20 April 1999, when the study was unblinded and the control group was offered PCV7. For a detailed description of the characteristics of this study, see Black 2000
Participants	
Interventions	
Outcomes	
Notes	
<i>Risk of bias</i>	

Fireman 2003 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This study is an extension of Black 2000 Method of random sequence generation not described
Allocation concealment (selection bias)	Unclear risk	No method of allocation concealment was described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Indicated to be double-blind study but insufficient details provided to ensure blinding of participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Clinical diagnoses of AOM were obtained from computerised data sources using diagnoses registered by emergency physicians and paediatricians (non-trialists)
Incomplete outcome data (attrition bias) All outcomes	High risk	Substantial number of randomised children did not stay in the Kaiser Permanente healthcare database to the end of follow-up (April 1999), i.e. 27% in the PCV group and 26% in the control group
Selective reporting (reporting bias)	Unclear risk	Study protocol is not available but trial includes all expected outcomes (including OM visits, frequent OM, tube procedures and Ab prescriptions)
Other bias	Low risk	Control group was vaccinated against MenC disease, but meningococci are not a causative pathogen in otitis media. Study enrolment was stopped as a result of pre-specified interim analysis

Jansen 2008

Methods	<p>Randomised - yes, at individual level</p> <p>Design - standard parallel-group design</p> <p>Intention-to-treat (ITT) - yes</p> <p>Follow-up - follow-up started 14 days after the second set of vaccinations and continued for 6 to 18 months, depending on the year of inclusion</p>
Participants	<p>N - 597 children with a previously diagnosed respiratory tract infection (RTI)</p> <p>Age - 18 to 72 months</p> <p>Setting - general practitioners (GPs) in the centre of the Netherlands selected children</p> <p>Inclusion criteria - children aged 18 to 72 months with a previously diagnosed respiratory tract infection (RTI) registered according to the International Classification of</p>

	<p>Primary Care (ICPC), i.e. acute otitis media (AOM); cough (with fever); acute upper RTI; acute laryngitis/tracheitis; acute bronchitis/bronchiolitis; influenza; pneumonia; pleurisy/pleural effusion</p> <p>Exclusion criteria - children with chronic asthma or recurrent wheezing (for longer than 3 months) treated with corticosteroids; craniofacial abnormalities; clinically significant hypersensitivity to eggs; previous serious adverse reactions to vaccines; previous influenza, pneumococcal or hepatitis B vaccinations and those with conditions for which these vaccinations are already recommended, such as chronic cardiac and respiratory conditions</p> <p>Baseline characteristics - described and balanced (Table 1)</p>
Interventions	<p>Children were randomly allocated to either trivalent influenza plus 7-valent pneumococcal conjugate vaccination (TIV/PCV7), trivalent influenza plus placebo vaccination (TIV/placebo) or hepatitis B virus vaccination plus placebo vaccination (HBV/placebo) Children received 2 vaccinations 4 to 8 weeks apart in the first year of inclusion and the first 2 cohorts of children received a subsequent vaccination in the subsequent year</p> <p>Tx - TIV (strains in the 2003-2004 formulation were H1N1, H3N2 and B/HongKong/330/01; strains in the 2004-2005 formulation were H1N1, H3N2 and B/Shanghai/361/2002; strains in the 2005-2006 formulation included H1N1, H3N2 and B/Shanghai/361/2002/PCV7 (containing the polysaccharides of serotypes 4, 6B, 9V, 14, 18C, 19F and 23F conjugated to carrier protein CRM197); N = 197 (N = 163 completed; 67,867 person-days analysed, 14% missing)</p> <p>C1 - TIV/placebo (standard diluent (0.9% phosphate buffered NaCl)); N = 187 (N = 148 completed; 60,515 person-days analysed, 20% missing)</p> <p>C2 - HBV (recombinant HBV vaccine; Engerix-B Junior)/placebo; N = 195 (N = 160 completed; 67,679 person-days analysed, 15% missing)</p> <p>Additional vaccines - not described</p>
Outcomes	<p>Primary outcome - effect of the TIV/PCV7 on febrile RTI, defined as fever (tympanic temperature 38.0 °C) for at least 2 consecutive days accompanied by 1 or more of the aforementioned signs or symptoms of RTI with a moderate or severe severity score</p> <p>Secondary outcomes - effect of the TIV/PCV7 on febrile RTI-related polymerase chain reaction (PCR)-confirmed influenza, GP visits, antibiotic prescriptions or a physician-diagnosed episode of AOM</p> <p>Each parent was instructed to keep a daily diary, recording any clinical signs or symptoms associated with RTI and to characterise their severity on a scale of 1 (mild) to 3 (severe). The parent also was instructed to measure the child's body temperature using a validated electronic tympanic thermometer. The parent also was asked to record all GP visits due to their child's RTI-related complaints. For each such visit, the GP was instructed to complete a form including information on the diagnosis and possible antibiotic prescriptions</p> <p>During influenza seasons, the parent was instructed to contact the trial centre for evaluation for influenza if the child had fever (tympanic temperature 38.0 °C) for more than 1 day accompanied by at least 1 RTI-associated sign or symptom of severity score 2. Within 4 days of onset of fever and symptoms, a trained research assistant obtained a nasopharyngeal swab for viral determination. Each sample was analysed by real-time PCR for the presence of influenza A and B viruses</p>
Notes	<p>Participants lost to follow-up - total: 108/579 (18.7%) completely (n = 41) or partially (n = 67) lost to follow-up</p>

Participants lost to follow-up - Tx: 34/197 (17.3%) completely (n = 8) or partially (n = 26) lost to follow-up; 67,867 person-days analysed, 14% missing
Participants lost to follow-up - C1: 39/187 (20.8%) completely (n = 19) or partially (n = 20) lost to follow-up; 60,515 person-days analysed, 20% missing
Participants lost to follow-up - C2: 35/195 (17.9%) completely (n = 14) or partially (n = 21) lost to follow-up; 67,679 person-days analysed, 15% missing
 2 of the 3 treatment arms received an additional vaccination in the second year of the study. To evaluate blinding, parents of these cohorts of children were asked which vaccinations that they thought their child had received just after the vaccinations were given and at the end of the study. Just after the vaccination, 87% of the parents either did not know or identified the wrong set of vaccinations; at the end of the study, this percentage was 80%, indicating successful blinding

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not described; children were randomly assigned in blocks of 3 in a 1:1:1 ratio
Allocation concealment (selection bias)	Unclear risk	No method of allocation concealment was described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The injections were administered by non-blinded research nurses who were not involved in subsequent follow-up and were instructed to not reveal the intervention allocation. The treatment group assignments were not revealed to parents, investigators, research personnel conducting the follow-up or health care providers, all of whom remained blinded throughout the study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The parents were asked to record all GP visits due to their child's RTT-related complaints. For each such visit, the GP was instructed to complete a form including information on the diagnosis and possible antibiotic prescriptions. The treatment group assignments were not revealed to parents, investigators, research personnel conducting the follow-up or health care providers, all of whom remained blinded throughout the study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Substantial loss to follow-up (< 14% in both groups)

Jansen 2008 (Continued)

Selective reporting (reporting bias)	Low risk	Prespecified outcomes (primary and secondary) are listed in ClinicalTrials.gov
Other bias	High risk	Co-administered with influenza vaccine in influenza season. Pivotal role of influenza viruses acknowledged by the authors

Kilpi 2003

Methods	<p>This trial was part of a study including Eskola 2001 (FinOM Vaccine Trial). Both Eskola 2001 and Kilpi 2003 used the same control group (hepatitis B vaccine) but a different treatment group, each with a different type of 7-valent pneumococcal conjugate vaccine. Eskola 2001 used a PCV7 containing the polysaccharides of serotypes 4, 6B, 9V, 14, 18C, 19F and 23F conjugated to carrier protein CRM197, while Kilpi 2003 used a PCV7 containing polysaccharides of serotypes 4, 6B, 9V, 14, 18C, 19F and 23F conjugated to the outer membrane protein complex of <i>N. meningitidis</i> serogroup B</p> <p>Randomised - yes, at individual level Design - standard parallel-group design Intention-to-treat (ITT) - no, per-protocol analysis Follow-up - 22 consecutive months (children were followed up to 24 months of age)</p>
Participants	<p>N - 1666 healthy infants Age - 2 months Setting - 8 study clinics in the communities of Tampere, Kangsala and Nokia, Finland Inclusion criteria - healthy children aged 2 months Exclusion criteria - not described Baseline characteristics - described and balanced (Table 1)</p>
Interventions	<p>Children were randomly allocated to either a 7-valent pneumococcal conjugate vaccine (PCV7) or a hepatitis B at 2, 4, 6 and 12 to 15 months of age. From 3 November 1997 onward, for the children randomised to receive OMPC-PCV7, the fourth dose of the conjugate vaccine was replaced by a 23-valent pneumococcal polysaccharide vaccine (PPV-23) that consisted of serotypes 1, 2, 3, 4, 5, 6B, 7E, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F and 33F (Pneumovax23)</p> <p>Tx - PCV7 (containing the polysaccharides of serotypes 4, 6B, 9V, 14, 18C, 19F and 23F conjugated to the outer membrane protein complex of <i>N. meningitidis</i> serogroup B (OMPC)); N = 835 (N = 805 completed the follow-up as specified in the protocol) C - hepatitis B vaccine (containing 5 µg of recombinant hepatitis B surface protein); N = 831 (N = 794 completed the follow-up as specified in the protocol) Additional vaccines - a diphtheria-tetanus toxoids-pertussis vaccine with a whole-cell pertussis component, combined with a <i>Haemophilus influenzae</i> type b conjugate vaccine (DTP-Hib), was administered concomitantly with the first 3 doses of the study vaccine and an inactivated poliovirus vaccine was administered with the fourth dose. In 4 study clinics, the carrier protein in the DTP-Hib conjugate combination was CRM197 and in the other 4 it was tetanus toxoid</p>
Outcomes	See Eskola 2001

Notes	<p>Participants lost to follow-up - total: 67/1,666 (4.0%) did not complete the follow-up period according to protocol</p> <p>Participants lost to follow-up - Tx: 30/835 (3.6%) did not complete the follow-up period according to protocol</p> <p>Participants lost to follow-up - C: 37/831 (4.5%) did not complete the follow-up period according to protocol</p>	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	6 letters corresponding to the 3 treatment options were randomly allocated to consecutive subject identification numbers, using an allocation of 1:1:1 and a block size of 12
Allocation concealment (selection bias)	Low risk	Individual treatment assignments were kept in sealed envelopes until vaccination
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Use of vaccinators who were not otherwise involved in the trial follow-up. Letter code was destroyed immediately after vaccination
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessment of the outcome was done according to a strict definition of AOM. Assessment was done by other personnel than those who vaccinated the children (vaccinators were not otherwise involved in the trial follow-up)
Incomplete outcome data (attrition bias) All outcomes	Low risk	No reporting of reasons for drop-out and/or loss to follow-up. Not expected to have a major impact on outcome since 96.0% in the PCV7 OMPC and 95.5% in the control group completed the follow-up as specified in the protocol
Selective reporting (reporting bias)	Unclear risk	Prespecified outcomes (primary and secondary) are listed in ClinicalTrials.gov (although uploaded after study end)
Other bias	Unclear risk	Mixed schedule with 187 children boosted with PPV-23. How was it known that only the children allocated to PCV7 OMPC should receive PPV-23 after November 1997?

Methods	<p>The design of this cluster-randomised trial has been described extensively in Moulton 2001, while the findings on invasive pneumococcal disease (main outcome of the trial) have been published in O'Brien 2003</p> <p>Randomised - yes, at group level</p> <p>Design - cluster-randomised design</p> <p>Intention-to-treat (ITT) - no, per-protocol analysis</p> <p>Follow-up - depending on time of inclusion, maximum duration of follow-up 40 months</p>
Participants	<p>N - 944 (944 of the 4476 children were randomly selected for chart review. This sample size was determined by logistic feasibility and expected frequency of healthcare events. Of these 944 children, 856 were found to have strictly met the chart review criteria)</p> <p>Age - below 2 years of age</p> <p>Setting - Navajo and White Mountain Apache region</p> <p>Inclusion criteria - Navajo and White Mountain Apache children below 2 years of age</p> <p>Exclusion criteria - no exclusion criteria described</p> <p>Baseline characteristics - balanced but data not shown</p>
Interventions	<p>Children were randomly allocated to either a 7-valent pneumococcal conjugate vaccine (PCV7) or a meningococcus type C conjugate vaccine (MenC). For each of the study and control vaccines, 3 immunisation schedules were designed according to age of entry into the trial: 6 weeks to 6 months (3 doses, ideally at 2, 4 and 6 months of age and a booster at 12 to 15 months of age), 7 months to 11 months (2 doses 1 month apart and a booster at 12 to 15 months of age) and 12 months to 23 months (2 doses separated by at least 2 months). Over the course of the trial, the great majority of new enrollees are in the first group, which is referred to as the primary efficacy cohort</p> <p>Tx - PCV7 (containing the polysaccharides of serotypes 4, 6B, 9V, 14, 18C, 19F and 23F conjugated to carrier protein CRM197); N = unknown (N = 424 analysed in primary efficacy group)</p> <p>C - MenC (10 µg of group C oligosaccharide conjugated to carrier protein CRM197); N = unknown (N = 432 analysed in primary efficacy group)</p> <p>Additional vaccines - not described</p>
Outcomes	<p>Primary outcome - effect of PCV7 on clinically diagnosed episodes of OM</p> <p>Every medical visit made by study children was evaluated through 2 years of age. OM visits, as documented by the patients' treating physician, were recorded</p> <p>A new OM episode was counted if any of the following were recorded as the diagnosis: OM, AOM, bilateral OM, chronic OM, OM with perforation, otorrhoea, pressure equalising tube placement, perforated tympanic membrane, serous OM and bullous myringitis</p> <p>An episode of AOM was categorised as either AOM or bilateral AOM. An OM episode was categorised as severe if there were 3 or more OM visits for the episode. A child's first medical visit for OM was considered their first episode. OM visits occurring less than 21 days after the immediately prior otitis-related visit and visits noted as a follow-up to a previous otitis-related visit were counted as follow-up visits, not as OM episodes</p>
Notes	<p>Participants lost to follow-up - total: 88/944 (9.3%) not included in primary efficacy analysis</p> <p>Participants lost to follow-up - Tx: unknown</p> <p>Participants lost to follow-up - C: unknown</p>

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation using 38 independent randomisation units, stratified using 3 blocks of 4 units and 13 blocks of 2 units
Allocation concealment (selection bias)	Low risk	6 labels were assigned to the vaccines (B, E, H, M, T, U), with 3 labels for PCV7 and 3 for MenC. The grouping of these codes was known only to a statistician employed by the manufacturer (who had no other responsibilities with respect to the trial other than handling treatment allocation and randomisation issues. No loss of clusters
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Masked treatment assignment (vaccines were labelled). In addition, field staff were blinded as to serotype of the invasive disease cases and thus did not know which ones would be likely to be prevented by an effective vaccine
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Every medical visit made by study children was evaluated through 2 years of age. OM visits, as documented by the patients' treating physician, were recorded. Treating physicians were blinded to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	88 of the 944 children (9.3%) not included in primary efficacy analysis; no information provided on the distribution across treatment groups
Selective reporting (reporting bias)	Low risk	Study design was described extensively in Moulton 2001 and O'Brien 2003
Other bias	Low risk	Study enrolment was stopped as a result of prespecified interim analysis

Palmu 2009

Methods	This study is an additional analysis of Eskola 2001 , which is part of the FinOM Vaccine Trial and studies the effect of PCV7 containing the polysaccharides of serotypes 4, 6B, 9V, 14, 18C, 19F and 23F conjugated to carrier protein CRM197 as compared to a hepatitis B vaccine. For a detailed description of the characteristics of this study, see Eskola 2001
Participants	
Interventions	
Outcomes	Primary outcome - effect of PCV7 on PCR-positive AOM The aetiology of AOM attacks was determined by bacterial culture of middle ear fluid samples obtained by myringotomy. In addition, PCR was performed from the middle ear fluid samples. Samples with a positive PCR result were reanalysed using Ply-PCR followed by microwell hybridisation using a Europium-labelled probe Definitions of 30-day episodes were used in the analysis, for example, a new episode of PCR-positive AOM was considered to start if 30 days had elapsed since the start of the previous PCR-positive AOM episode
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	This is an additional analysis of Eskola 2001 6 letters corresponding to the 3 treatment options were randomly allocated to consecutive subject identification numbers, using an allocation of 1:1:1 and a block size of 12
Allocation concealment (selection bias)	Low risk	Individual treatment assignments were kept in sealed envelopes until vaccination
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Use of vaccinators who were not otherwise involved in the trial follow-up. Letter code was destroyed immediately after vaccination
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessment of the outcome was done according to a strict definition of AOM. Assessment was done by other personnel than those that vaccinated the children (vaccinators were not otherwise involved in the trial follow-up)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear how many children were lost to follow-up. In Eskola 2001 , 94.6% in the PCV7 and 95.5% in the control group

Palmu 2009 (Continued)

		completed the follow-up as specified in the protocol
Selective reporting (reporting bias)	Unclear risk	Prespecified outcomes (primary and secondary) are listed in ClinicalTrials.gov (although uploaded after study end)
Other bias	Low risk	

Prymula 2006

Methods	<p>Randomised - yes, at individual level</p> <p>Design - standard parallel-group design</p> <p>Intention-to-treat (ITT) - yes, both ITT and per-protocol analysis described</p> <p>Follow-up - efficacy follow-up started on the day of the first dose of study vaccine (for ITT analysis) or 2 weeks after the third vaccine dose (for the per-protocol analysis) and continued until 24 to 27 months of age</p>
Participants	<p>N - 4968 healthy infants</p> <p>Age - between 6 weeks and 5 months</p> <p>Setting - 27 paediatric centres in the Czech Republic and 23 in Slovakia</p> <p>Inclusion criteria - healthy children aged between 6 weeks and 5 months with no acute illness</p> <p>Exclusion criteria - use of any investigational or non-registered drug or vaccine other than the study vaccines within 30 days preceding the study vaccines' first dose; previous vaccination against <i>S. pneumoniae</i>; fever (defined as a rectal temperature of 38 °C or higher or temperature by other routes of 37.5 °C or higher); history of allergic disease or reactions likely to be exacerbated by any component of the study vaccines; other conditions that might have potentially interfered with the interpretation of study outcomes according to the investigator</p> <p>Baseline characteristics - described and balanced (Table 1)</p>
Interventions	<p>Children were randomly allocated to either an 11-valent pneumococcal conjugate vaccine (PCV11) or a hepatitis A at the ages of about 3, 4, 5 and 12 to 15 months of age</p> <p>Tx - PCV11 (containing the polysaccharides of serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F conjugated to protein D (surface lipoprotein of <i>H. influenzae</i>)); N = 2489 (N = 2455 included in per-protocol cohort for efficacy)</p> <p>C - hepatitis A vaccine (containing 720 ELISA units of inactivated hepatitis A virus antigen (strain HM 175)); N = 2479 (N = 2452 included in per-protocol cohort for efficacy)</p> <p>Additional vaccines - a concomitant hexavalent diphtheria-tetanus-3-component acellular pertussis-hepatitis B-inactivated poliovirus types 1, 2 and 3 <i>H. influenzae</i> type b (DTPa-HBV-IPV/Hib) vaccine was offered to all study participants, followed by a booster dose at age 15 to 18 months</p>
Outcomes	<p>Primary outcome - effect of PCV11 on first episode of acute otitis media (AOM) caused by vaccine pneumococcal serotypes</p> <p>Secondary outcomes - effect of PCV11 on first episode of AOM caused by non-typeable</p>

	<p><i>Haemophilus influenzae</i></p> <p>There was no active surveillance. Unscheduled doctor visits could take place any time during follow-up according to standard local practice (parents consulting their local paediatrician in case of illness of their child). Parents were advised to consult their paediatrician if their child was sick, had ear pain or had spontaneous ear discharge. Children with suspected AOM were immediately referred to ENT surgeons</p> <p>AOM was defined as either abnormal findings of the tympanic membrane at otoscopy (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 together with at least 2 of the following signs or symptoms: ear pain, ear discharge, hearing loss, fever, lethargy, irritability, anorexia, vomiting or diarrhoea. These signs or symptoms had to be present for a maximum of 14 days</p> <p>For patients with repeated doctor visits, a new episode of AOM was judged to have started if more than 30 days had elapsed since the beginning of the previous episode. Additionally, for categories defined according to bacterial pathogen or serotype, a new episode was judged to have started if any interval had elapsed since the beginning of an episode caused by a different bacterial pathogen or serotype</p> <p>Recurrent AOM was defined as 3 or more AOM episodes in the last 6 months or 4 or more in the last 12 months</p>	
Notes	<p>Participants lost to follow-up - total: 61/4968 (1.2%) did not complete the follow-up period according to protocol</p> <p>Participants lost to follow-up - Tx: 34/2489 (1.4%) did not complete the follow-up period according to protocol</p> <p>Participants lost to follow-up - C: 27/2479 (1.1%) did not complete the follow-up period according to protocol</p>	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random list
Allocation concealment (selection bias)	Low risk	Randomisation (1:1) was done with a study-specific central randomisation system via the Internet which, on receipt of the infant's initials and birth date, determined the vaccine number to be used
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Indicated to be double-blinded study. Sponsor numbered the vaccine supplies. It was, however, unknown whether the appearance of the vaccines was similar at the time of administration
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Visits during efficacy follow-up were according to standard local clinical practice. When AOM was suspected children were

Prymula 2006 (Continued)

		referred to ENT surgeons
Incomplete outcome data (attrition bias) All outcomes	Low risk	No reporting of reasons for drop-out and/or loss to follow-up. Not expected to have a major impact on outcome since 98.6% in the PCV11 and 98.9% in the control group completed the follow-up as specified in the protocol
Selective reporting (reporting bias)	Low risk	Prespecified outcomes (primary and secondary) are listed in ClinicalTrials.gov
Other bias	Low risk	Study enrolment was stopped as a result of prespecified interim analysis

Van Kempen 2006

Methods	This study was performed in parallel with Veenhoven 2003 , but analysed separately due to differences in study population Randomised - yes, at individual level Design - standard parallel-group design Intention-to-treat (ITT) - unclear Follow-up - 26 months
Participants	N - 74 children with a history of frequent acute otitis media (AOM) Age - between 1 and 7 years Setting - ENT department of the Ghent University Hospital in Belgium Inclusion criteria - children aged 1 to 7 years with a history of frequent AOM defined as at least 2 separate clinically diagnosed AOM episodes in the past year Exclusion criteria - children with any underlying illnesses including immunocompromising conditions other than partial serum IgA and IgG2 deficiencies, craniofacial abnormalities, previous pneumococcal vaccination or documented hypersensitivity to any of the vaccine components Baseline characteristics - described and balanced (Table 1)
Interventions	Children were randomly allocated to either a 7-valent pneumococcal conjugate vaccine (PCV7) or a hepatitis A vaccine. Children aged 12 to 24 months received 2 intramuscular injections with a 1-month interval and those aged over 2 years received 1 intramuscular injection. Those allocated to PCV7 received an additional 23-valent pneumococcal polysaccharide vaccination (PPSV-23) respectively at 6 months (in children aged 12 to 24 months) and 7 months (in those aged above 2 years) later Tx - PCV7 (containing polysaccharides of serotypes 4, 6B, 9V, 14, 18C, 19F and 23F conjugated to the carrier protein CRM197)/PPSV23 (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); N = 38 (N = 35 completed the vaccination scheme) C - hepatitis A vaccine (containing 720 units of inactivated hepatitis A virus); N = 36 (N = 33 completed the vaccination scheme) Additional vaccines - not described

Outcomes	<p>Primary outcome - effect of PCV7/PPSV23 on the number of AOM episodes during 18 months follow-up</p> <p>Secondary outcomes - effect of PCV7/PPSV23 on immunogenicity; nasopharyngeal carriage of conjugate vaccine related serotypes; and antibiotic-resistant pneumococci</p> <p>At scheduled hospital visits at 7, 14, 20 and 26 months after randomisation, a medical history was taken, antibiotic usage noted and an otomicroscopic examination performed</p> <p>When, at least 1 month following complete vaccination, a new AOM episode was suspected, parents were asked to bring their sick child within 24 hours to the study centre for otoscopic diagnosis. In case of all other AOM episodes during follow-up, participants were allowed to visit the study centre, their family physician or a paediatrician who was asked to report otoscopic findings, diagnosis and treatment on an AOM registration form</p> <p>AOM was defined by an abnormal tympanic membrane on otomicroscopy (red, dull or bulging); plus at least 1 of the following symptoms or signs of acute infection: earache, acute otorrhoea, fever (> 38.5 °C rectally) or irritability</p>
Notes	<p>Participants lost to follow-up - total: 6/74 (8.1%) did not complete the follow-up period according to protocol</p> <p>Participants lost to follow-up - Tx: 3/38 (7.9%) did not complete the follow-up period according to protocol</p> <p>Participants lost to follow-up - C: 3/36 (8.3%) did not complete the follow-up period according to protocol</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not described, randomisation stratified according to age (12 to 24 months versus 25 to 84 months) and number of previous AOM episodes per year (2 to 3 versus 4 or more episodes)
Allocation concealment (selection bias)	Low risk	2 study nurses immunised all children according to a randomisation list provided to them in a sealed envelope by a third party (the Julius Center for Health Sciences, Utrecht, The Netherlands)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The nurses that vaccinated children were not allowed to reveal the child's allocation to either the study team or the parents
Blinding of outcome assessment (detection bias) All outcomes	Low risk	When a new AOM episode was suspected, parents were asked to bring their sick child within 24 hours to the study centre for otoscopic diagnosis. In case of all other

Van Kempen 2006 (Continued)

		AOM episodes during follow-up, participants were allowed to visit the study centre, their family physician or a paediatrician who was asked to report otoscopic findings, diagnosis and treatment on an AOM registration form
Incomplete outcome data (attrition bias) All outcomes	Low risk	In total 6 of the 74 children (8.1%) did not complete the follow-up period according to protocol (equally distributed across groups). Reasons for withdrawals are described in the Results section of the article
Selective reporting (reporting bias)	Unclear risk	No study protocol available
Other bias	Low risk	

Veenhoven 2003

Methods	<p>Randomised - yes, at individual level</p> <p>Design - standard parallel-group design</p> <p>Intention-to-treat (ITT) - yes</p> <p>Follow-up - 18 months, starting 1 month after completion of the vaccination scheme</p>
Participants	<p>N - 383 children with a history of frequent acute otitis media (AOM)</p> <p>Age - between 1 and 7 years</p> <p>Setting - a general hospital (Spaarne Hospital, Haarlem) and a tertiary care hospital (Wilhelmina Children's Hospital of the University Medical Centre Utrecht) in the Netherlands</p> <p>Inclusion criteria - children aged 1 to 7 years with a history of frequent AOM defined as 2 or more AOM episodes in the year before study entry. The number of previous AOM episodes was based on parental report and on clinical confirmation of the diagnosis by a physician</p> <p>Exclusion criteria - children with immunodeficiency, cystic fibrosis, immotile cilia syndrome, craniofacial abnormalities, chromosomal abnormalities such as Down's syndrome and severe adverse events during previous vaccinations</p> <p>Baseline characteristics - described and balanced (Table 1)</p>
Interventions	<p>Children were randomly allocated to either a 7-valent pneumococcal conjugate vaccine (PCV7) followed by a 23-valent pneumococcal polysaccharide vaccination (PPSV23) or a hepatitis A or B vaccine</p> <p>Children aged 12 to 24 months in the pneumococcal vaccination group received PCV7 twice with a 1-month interval followed 6 months later by PPSV23. The control vaccine group received 3 hepatitis B vaccinations according to a similar time schedule</p> <p>Children aged 25 to 84 months in the pneumococcal vaccine group received 1 dose of PCV7 followed 7 months later by PPSV23. The control group received hepatitis A vaccine twice</p> <p>Tx - PCV7 (containing polysaccharides of serotypes 4, 6B, 9V, 14, 18C, 19F and 23F conjugated to the carrier protein CRM197)/PPSV23 (containing polysaccharides of the</p>

	<p>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); N = 190 (N = 190 included in ITT analysis) C - hepatitis A vaccine (Havrix) or hepatitis B vaccine (Engerix-B); N = 193 (N = 193 included in ITT analysis) Additional vaccines - not described.</p>	
Outcomes	<p>Primary outcome - effect of PCV7/PPSV23 on the number of clinical episodes of AOM during 18 months follow-up Secondary outcomes - effect of PCV7/PPSV23 on the number of AOM episodes due to the 7 pneumococcal serotypes included in the PCV7 vaccine and nasopharyngeal carriage of conjugate vaccine serotypes Parents were instructed 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 and were unaware of treatment allocation. AOM was defined according to the guideline issued by the Dutch College of General Practitioners, i.e. presence of an abnormal tympanic membrane on otoscopy (red, dull or bulging), or otorrhoea and at least 1 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</p>	
Notes	<p>Participants lost to follow-up - total: 1/383 (0.3%); all children included in ITT analysis Participants lost to follow-up - Tx: 0/190 (0%) Participants lost to follow-up - C: 1/193(0.5%) Performed in parallel with the study of Van Kempen 2006, but analysed separately due to differences in study population</p>	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Table of random numbers that identified the vaccine scheme, randomisation stratified according to age (12 to 24 months versus 25 to 84 months) and number of previous AOM episodes per year (2 to 3 versus 4 or more episodes)
Allocation concealment (selection bias)	Unclear risk	No method of allocation concealment was described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Vaccine was administered to the child by a study nurse, so that parents and physicians were unaware of treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Parents were instructed to visit the study clinics or their family physician, otolaryngologist or paediatrician to assess symptoms suggesting AOM. Physicians regis-

Veenhoven 2003 (Continued)

		tered signs and symptoms of every AOM episode on standard registration forms and were unaware of treatment allocation. AOM was defined according to the guideline issued by the Dutch College of General Practitioners
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised children were included in ITT analysis
Selective reporting (reporting bias)	Unclear risk	No study protocol available
Other bias	Low risk	

Ab: antibiotics; AOM: acute otitis media; C: control; DCC: day-care centre; DTaP: diphtheria-tetanus toxoid-acellular pertussis vaccine; DTP: diphtheria-tetanus toxoid-pertussis vaccine; DTwP: diphtheria-tetanus toxoid-whole cell pertussis vaccine; ENT: ear, nose and throat; IgA: immunoglobulin A; IgG: immunoglobulin G; GP: general practitioner; ITT: intention-to-treat; NaCl: sodium chloride; OM: otitis media; PCR: polymerase chain reaction; PCV: pneumococcal conjugate vaccine; PPV: pneumococcal polysaccharide vaccine; RTI: respiratory tract infection; TIV: trivalent influenza vaccine; Tx: treatment

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Gisselsson Solen 2011	No control vaccination. As such, parents were not blinded to treatment allocation (children received either PCV or no vaccination). However, for outcome assessment, parents were instructed to visit the ENT department whenever they suspected an episode of AOM. Parental threshold to consult ENT may be lower in children allocated to control treatment (no vaccination) than in those allocated to PCV, which may have introduced (detection) bias
Jokinen 2012	Re-analysis of the Eskola 2001 study without new outcome data that could be used for our review
Le 2007	RCT studying the effect of PCV on OME
Roy 2011	RCT studying the effect of PCV on suppurative otitis media (abstract of conference meeting)

AOM: acute otitis media
 ENT: ear, nose and throat
 OME: otitis media with effusion
 PCV: pneumococcal conjugate vaccine
 RCT: randomised controlled trial

Characteristics of ongoing studies [ordered by study ID]

[NCT00466947](#)

Trial name or title	'COMPAS: Phase III, Double-blind, Randomized Study to Demonstrate Efficacy of GSK Biologicals' Pneumococcal Conjugate Vaccine (GSK1024850A) Against Community Acquired Pneumonia and Acute Otitis Media (AOM)'
Methods	Phase III, double-blind, randomised study
Participants	Healthy children aged 6 to 16 weeks
Interventions	Group A: pneumococcal conjugate vaccine GSK1024850A 4 doses, hepatitis A vaccine 2 doses, DTaP-IPV/Hib vaccine 1 dose Group B: hepatitis A vaccine 3 doses, hepatitis B vaccine 3 doses, DTaP-IPV/Hib vaccine 4 doses
Outcomes	Primary outcome: occurrence of likely bacterial community-acquired pneumonia (CAP) cases Secondary outcomes include occurrence of clinically confirmed acute otitis media (AOM) cases (in a subset), occurrence of bacteriologically confirmed AOM cases (B-AOM) caused by any bacterial pathogen (in a subset), bacteriologically confirmed AOM cases (B-AOM) caused by vaccine serotypes, cross-reactive and other pneumococcal serotypes (in a subset)
Starting date	June 2007; study complete date: June 2011
Contact information	GSK Clinical Trials Call Centre
Notes	NCT00466947

[NCT00861380](#)

Trial name or title	'Evaluation of Effectiveness of GSK Biologicals' Pneumococcal Conjugate Vaccine 1024850A Against Invasive Disease (FinIP)'
Methods	Cluster-randomised, double-blind trial
Participants	Healthy children aged younger than 19 months
Interventions	Infants aged younger than 7 months at the first vaccination received either a 3+1 or a 2+1 vaccination schedule, children aged 7 to 11 months received a 2+1 schedule and those 12 to 18 months of age received a 2-dose schedule. Children received PD-CV10 in 52 clusters or hepatitis vaccines as control in 26 clusters
Outcomes	Primary outcome: occurrence of culture-confirmed pneumococcal invasive diseases due to any of the vaccine-related pneumococcal serotypes Secondary outcomes include occurrence of tympanostomy tube placements, occurrence of upper and lower respiratory tract infections, including AOM (in a subset of vaccinated subjects in Turku area)
Starting date	March 2009; study complete date: January 2012
Contact information	GSK Clinical Trials Call Centre

NCT00861380 (Continued)

Notes	NCT00861380; published papers: effect PD-CV10 on primary outcome (Palmu 2013a) and secondary outcome, i.e. outpatient antimicrobial purchases (Palmu 2013b)
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NCT01174849

Trial name or title	'A Randomised Controlled Trial of Pneumococcal Conjugate Vaccines Synflorix and Prevenar13 in Sequence or Alone in High-risk Indigenous Infants (PREV-IX_COMBO): Immunogenicity, Carriage and Otitis Media Outcomes'
Methods	Open-label, randomised study
Participants	Indigenous infants 4 to 6 weeks of age
Interventions	3 doses of either PCV13 or PD-CV10 versus an early schedule of a combination of 3 doses of PD-CV10 and 1 dose of PCV13
Outcomes	Primary outcome: immunogenicity Secondary outcomes: nasopharyngeal carriage, otitis media
Starting date	August 2011
Contact information	Amanda J Leach, PhD; Menzies School of Health Research, Darwin, Northern Territory, Australia, 0810
Notes	NCT01174849

NCT01545375

Trial name or title	'Evaluation of a Vaccine for Reducing Ear and Lung Infections in Children: Study to Determine Protective Efficacy Against Otitis Media and Assess Safety of an Investigational Pneumococcal Vaccine 2189242A in Healthy Infants'
Methods	Double-blind, placebo-controlled, randomised study
Participants	A healthy American Indian infant between and including 6 and 12 weeks (42 to 90 days) of age at the time of the first vaccination
Interventions	GSK2189242A vaccine versus placebo co-administration of PCV13 and Hib-CV. Hib-CV will be given as study vaccine for infants of the immuno/reacto subgroup; for the other infants, this vaccine will be given as part of the routine vaccination schedule
Outcomes	Primary outcome: occurrence of any clinical AOM episodes diagnosed and verified against American Academy of Pediatrics (AAP) criteria Secondary outcomes include occurrence of any healthcare provider-diagnosed clinical AOM, occurrence of any clinical AOM episodes diagnosed and verified against modified AAP criteria, occurrence of any recurrent AOM (at least 3 episodes in 6 months or at least 4 episodes in 12 months)
Starting date	May 2012

NCT01545375 (Continued)

Contact information	GSK Clinical Trials Call Center
Notes	NCT01545375

NCT01735084

Trial name or title	'Pneumococcal Conjugate Vaccine (PCV) Schedules for the Northern Territory (NT): Randomised Controlled Trial of Booster Vaccines to Broaden and Strengthen Protection From Invasive and Mucosal Infections'
Methods	Single-blind (outcomes assessor), randomised study
Participants	Australian indigenous infants who were participants in PREV-IX_COMBO trial of primary course pneumococcal conjugate vaccines, age at least 2 months post final dose of primary course
Interventions	PCV13 versus PD-CV10
Outcomes	Primary outcome: immune response Secondary outcomes: nasopharyngeal carriage, any otitis media, episodes of respiratory illness and acute otitis media
Starting date	December 2012
Contact information	Amanda J Leach, PhD; Menzies School of Health Research, Darwin, Northern Territory, Australia, 0810
Notes	NCT01735084

AAP: American Academy of Pediatrics

AOM: acute otitis media

DTaP-IPV/Hib: diphtheria-tetanus toxoid-acellular pertussis-inactivated polio-haemophilus influenzae type B vaccine

Hib-CV: haemophilus influenzae type B conjugate vaccine

ADDITIONAL TABLES

Table 1. The effect of pneumococcal conjugate vaccination on all-cause acute otitis media episodes

	Intention-to-treat			Per-protocol		
	Episodes/person year		VE expressed as relative reduction in risk (95% CI)	Episodes/person year		Incidence rate difference - episodes per person year (95% CI)
	Treatment	Control		Treatment	Control	
PCV administered in early infancy						

Table 1. The effect of pneumococcal conjugate vaccination on all-cause acute otitis media episodes (Continued)

Black 2000	-	-	6% (4 to 9)	-	-	-	7% (4 to 10)
Fireman 2003	-	-	6% (4 to 8)	-	-	-	7% (4 to 9)
Eskola 2001	-	-	-	1.16	1.24	-0.08 ~	6% (-4 to 16)
Kilpi 2003	-	-	-	-	-	-	-1% (-12 to 10)
Prymula 2006	-	-	-	0.08	0.13	-0.04 ~	34% (21 to 44)
O'Brien 2008*	1.4	1.4	-5% (-25 to 12) [#]	1.3	1.3	0.0 (-0.13 to 0.14)	0% (-21 to 17)
PCV administered at a later age							
Dagan 2001	-	-	-	0.66	0.79	-0.14 (-0.29 to 0.02)	17% (-2 to 33)
Veenhoven 2003	-	-	-25% (-57 to 1)	1.1	0.83	0.27 ~	-29% (-62 to -2)
Van Kempen 2006	-	-	-	0.78	0.67	0.11 ~	-16% (-96 to 31)
Jansen 2008	-	-	-	-	-	-	57% (6 to 80) [^]

CI: confidence interval; HBV: hepatitis B vaccine; PCV: pneumococcal conjugate vaccine; TIV: trivalent influenza vaccine; VE: vaccine efficacy.

*Cluster-randomised trial.

[#]Defined as primary efficacy analysis. Analysis not entirely according to intention-to-treat principle as 88/944 children were not included in analysis because of not meeting strict chart review criteria.

[^]Index group: TIV/PCV7, control: HBV/placebo; VE TIV/placebo versus HBV/placebo: 71% (95% 30% to 88%), i.e. larger VE TIV/placebo versus HBV/placebo than TIV/PCV7 versus HBV/placebo.

~ 95% CI could not be calculated as person-time across treatment groups was not reported.

Note: negative values for VE expressed as relative reduction in risk represent an increase in the risk for AOM.

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

	Intention-to-treat				Per-protocol			
	VE expressed as relative reduction in risk (95% CI)				VE expressed as relative reduction in risk (95% CI)			
	Pneumo-coccal AOM	Vaccine-type AOM	Cross-re-active type AOM	Non-vaccine-type AOM	Pneumo-coccal AOM	Vaccine-type AOM	Cross-re-active type AOM	Non-vaccine-type AOM
PCV administered in infancy								

Table 2. The effect of pneumococcal conjugate vaccination on pneumococcal acute otitis media (Continued)

Black 2000 [#]	-	65% P = 0.	-	-	-	67% P = 0.	-	-
Fireman 2003	-	04	-	-	-	08	-	-
Eskola 2001	-	54% (41 to	-	-	34% (21 to	57% (44 to	51% (27 to	-33% (-80
Palmu 2009	-	64)	-	-	45)	67)	67)	to 1)
	-	-	-	-	20% (7 to	-	-	-
	-	-	-	-	31)	-	-	-
Kilpi 2003	-	-	-	-	25% (11 to	56% (44 to	-5% (-47 to	-27% (-70
	-	-	-	-	37)	66)	25)	to 6)
Prymula 2006	-	-	-	-	52% (37 to	58% (41 to	66% (22 to	9% (-64 to
	-	-	-	-	63)	69)	85)	49)
O'Brien 2008 ^{*#}	-	64% (-34 to	-	-	-	-	-	-
	-	90)	-	-	-	-	-	-
PCV administered at a later age								
Dagan 2001	-	-	-	-	-	-	-	-
Veenhoven 2003	-	-	-	-	34% P = 0.	52% P = 0.	-	21% P = 0.
	-	-	-	-	22	21	-	44
Van Kempen 2006	-	-	-	-	-	-	-	-
Jansen 2008	-	-	-	-	-	-	-	-

VE: vaccine efficacy; PCV: pneumococcal conjugate vaccine; MEF: middle ear fluid.

*Cluster-randomised trial.

[#]MEF collected from spontaneous draining ears; in the other studies MEF was routinely collected during AOM episodes through paracentesis.

[^]Additional analysis of [Eskola 2001](#) including pneumococcal AOM by a positive culture or PCR.

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

Table 3. The effect of pneumococcal conjugate vaccination on recurrent acute otitis media

	Intention-to-treat	Per-protocol
	VE expressed as relative reduction in risk (95% CI)	VE expressed as relative reduction in risk (95% CI)
PCV administered in infancy		

Table 3. The effect of pneumococcal conjugate vaccination on recurrent acute otitis media (Continued)

Black 2000	9% (4 to 14)	9% (3 to 15)
Fireman 2003	10% (7 to 13)	-
Eskola 2001	9% (-12 to 27)	16% (-6 to 35)
Kilpi 2003	-	-
Prymula 2006	-	56% (-2 to 81)
O'Brien 2008*	-	-
PCV administered at a later age		
Dagan 2001	-	-
Veenhoven 2003	-	-
Van Kempen 2006	-	-
Jansen 2008	-	-

PCV: pneumococcal conjugate vaccine; VE: vaccine efficacy.

*Cluster-randomised trial.

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

APPENDICES

Appendix I. Previous search

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 ((alocat* 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

Appendix 2. Embase.com search strategy

#14. #9 AND #13
 #13. #10 OR #11 OR #12
 #12. random*:ab,ti OR placebo*:ab,ti OR factorial*:ab,ti OR crossover*:ab,ti OR 'cross over':ab,ti OR 'cross-over':ab,ti OR volunteer*:ab,ti OR assign*:ab,ti OR allocat*:ab,ti OR ((singl* OR doubl*) NEAR/1 blind*):ab,ti
 #11. 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp
 #10. 'randomized controlled trial'/exp
 #9. #3 AND #8
 #8. #4 OR #5 OR #6 OR #7
 #7. pcv*:ab,ti
 #6. (pneumococ* NEAR/5 (vaccin* OR conjugat* OR immuni*)):ab,ti
 #5. 'bacterial vaccine'/de
 #4. 'pneumococcus vaccine'/de
 #3. #1 OR #2
 #2. 'otitis media':ab,ti OR aom:ab,ti
 #1. 'otitis media'/exp

Appendix 3. CINAHL (Ebsco) search strategy

S22 S11 and S20
 S21 S11 and S20
 S20 S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19
 S19 (MH "Quantitative Studies")
 S18 (MH "Placebos")
 S17 TI placebo* OR AB placebo*
 S16 TI random* OR AB random*
 S15 TI (singl* blind* or doubl* blind* or tripl* blind* or trebl* blind* or singl* mask* or doubl* mask* or tripl* mask* or trebl* mask*) OR AB (singl* blind* or doubl* blind* or tripl* blind* or trebl* blind* or singl* mask* or doubl* mask* or tripl* mask* or trebl* mask*)
 S14 TI clinic* trial* OR AB clinic* trial*
 S13 PT clinical trial
 S12 (MH "Clinical Trials+")
 S11 S3 and S10

S10 S4 or S5 or S6 or S7 or S8 or S9
 S9 TI pcv* OR AB pcv*
 S8 TI pneumococc* N5 immuni* OR AB pneumococc* N5 immuni*
 S7 TI pneumococc* N5 conjugat* OR AB pneumococc* N5 conjugat*
 S6 TI pneumococc* N5 vaccin* OR AB pneumococc* N5 vaccin*
 S5 (MH "Bacterial Vaccines")
 S4 (MH "Pneumococcal Vaccine")
 S3 S1 or S2
 S2 TI (otitis media or aom) OR AB (otitis media or aom)
 S1 (MH "Otitis Media+")

Appendix 4. LILACS (Brieme) search strategy

(mh:"otitis media" OR "otitis media" OR "Otite Média" OR mh:c09.218.705.663* OR aom) AND (mh:"Pneumococcal Vaccines" OR "Vacunas Neumococicas" OR "Vacinas Pneumocólicas" OR mh:"Vaccines, Conjugate" OR "Vacunas Conjugadas" OR "Vacinas Conjugadas" OR mh:"Bacterial Vaccines" OR "Vacunas Bacterianas" OR "Vacinas Bacterianas" OR "pneumococcal vaccine" OR "pneumococcal vaccines" OR "conjugate vaccines" OR "conjugate vaccine" OR pcv*) AND db:("LILACS") AND type of study: ("clinical trials")

Appendix 5. Web of Science (Thomson ISI) search strategy

# 6	40	#4 AND #3 Refined by: Publication Years=(2011 OR 2012 OR 2013) <i>Databases=SCI-EXPANDED, CPCI-S, CCR-EXPANDED, IC Timespan=All Years</i>
# 5	205	#4 AND #3 <i>Databases=SCI-EXPANDED, CPCI-S, CCR-EXPANDED, IC Timespan=All Years</i>
# 4	1,334,537	Topic=(random* or placebo* or allocat* or crossover* or "cross over" or ((doubl* or singl*) NEAR/1 (blind* or mask*))) OR Title=(trial) <i>Databases=SCI-EXPANDED, CPCI-S, CCR-EXPANDED, IC Timespan=All Years</i>
# 3	1,095	#2 AND #1 <i>Databases=SCI-EXPANDED, CPCI-S, CCR-EXPANDED, IC Timespan=All Years</i>
# 2	11,997	Topic=(pneumococc* NEAR/5 (vaccin* or conjugat* or immuni*)) OR Topic=(pcv*) <i>Databases=SCI-EXPANDED, CPCI-S, CCR-EXPANDED, IC Timespan=All Years</i>
# 1	17,113	TS=("otitis media" or aom) <i>Databases=SCI-EXPANDED, CPCI-S, CCR-EXPANDED, IC Timespan=All Years</i>

WHAT'S NEW

Last assessed as up-to-date: 3 December 2013.

Date	Event	Description
21 February 2014	New citation required and conclusions have changed	<p>With this update, more precise information on the effect of PCV7 for the prevention of otitis media has become available. We judged the quality of the evidence for PCV7 in both early infancy and older children to be high and further research is very unlikely to change our confidence in the estimate of effect</p> <p>Based on current evidence of the effects of pneumococcal conjugate vaccines (PCVs) for preventing acute otitis media (AOM), the licensed 7-valent PCV has modest beneficial effects in healthy infants with a low baseline risk of AOM. Administering PCV7 in high-risk infants, after early infancy and in older children with a history of AOM appears to have no benefit in preventing further episodes</p> <p>Currently, several randomised controlled trials (RCTs), with different (newly licensed, multivalent) PCVs administered during early infancy, are ongoing to establish their effects on AOM. The results of these studies may provide a better understanding of the role of the newly licensed, multivalent PCVs in preventing AOM. Also the impact of the carrier protein D, as used in certain pneumococcal vaccines for AOM, needs to be further established</p>
3 December 2013	New search has been performed	<p>Three new review authors joined the team to update this review</p> <p>With the updated search (November 2007 to December 2013) we retrieved 171 records. Removing duplicates left 165 records. After screening titles and abstracts, three new publications remained for inclusion (Palmu 2009; Prymula 2006; Van Kempen 2006). One study was an additional analysis of the previously included Eskola 2001 study.</p> <p>We identified five 'ongoing' RCTs (NCT00466947; NCT00861380; NCT01545375; NCT01735084; NCT01174849).</p> <p>The 11 included studies in this review concerned nine RCTs in total: (1) Black 2000/Fireman 2003; (2) Dagan 2001; (3) Eskola 2001/Palmu 2009; (4) Kilpi 2003; (5) Prymula 2006; (6) Van Kempen 2006; (7) Veenhoven 2003; (8) Jansen 2008 and (9) O'Brien 2008. Five trials (Black 2000/Fireman 2003; Eskola 2001/Palmu 2009; Kilpi 2003; O'Brien 2008; Prymula 2006) (n = 47,108) included healthy infants and studied the effect of PCV</p>

(Continued)

		administered in early infancy on otitis media (OM), while the other four trials (n = 1318) (Dagan 2001; Jansen 2008; Van Kempen 2006; Veenhoven 2003) assessed the effects of PCV administered at a later age on OM in either healthy infants (Dagan 2001) or in children with a known history of respiratory disease, including OM (Jansen 2008; Van Kempen 2006; Veenhoven 2003).
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HISTORY

Protocol first published: Issue 2, 1999

Review first published: Issue 2, 2002

Date	Event	Description
29 April 2008	New citation required but conclusions have not changed	New review authors
28 April 2008	Amended	Converted to new review format
15 November 2007	New search has been performed	Searches conducted
26 November 2003	New citation required and conclusions have changed	Substantive amendment
29 June 2003	New search has been performed	Searches conducted
19 August 2000	New search has been performed	Searches conducted

CONTRIBUTIONS OF AUTHORS

ACF, RPV co-ordinated the review.

ACF, RPV, CWB were involved in data collection.

ACF and RPV performed 'Risk of bias' assessment and analysis of data.

All review authors (ACF, ES, EH, RPV, CWB, AS, RD) were involved in designing and writing the review and interpreting the data.

DECLARATIONS OF INTEREST

During the initial phase of the review ACF was employed by the Medical Affairs department of GlaxoSmithKline B.V., the Netherlands. Currently ACF is an employee of the Bacterial Vaccines Discovery and Early Development group at Crucell. Neither company was involved in any aspect of the submitted work.

AS: My team at UCL is supported by an NIHR Research Professorship award to establish an infrastructure and programme of clinical trials in ENT, Hearing and Balance. My institution has received a grant from GSK for a study on the microbiology of acute tympanostomy tube otorrhoea.

EH: I have authored a paper on the design of the CAPITA study (Neth J Med), but have not been involved in the actual conduct of that study, nor does it pose a conflict of interest to the current work.

ES: For research on pneumococcal vaccines, carriage and surveillance studies, I received money paid by the institution, by governmental agencies and by pharmaceutical companies GSK and Pfizer and paid to the institution or collaborating institutions. Furthermore, I participate in Independent Data Monitoring Committees and Advisory Boards for pharmaceutical companies for vaccine studies and/or respiratory tract infections with fees paid to the institution. In general, all fees are always paid to the institution and used for research purposes.

RPV, CWB and RD declare no conflicts of interest in the current work.

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 Otorhinolaryngology, UMC Utrecht, Wilhelmina Children's Hospital Utrecht, Netherlands.
- University Center for Pharmacy, PharmacoEpidemiology & PharmacoEconomics, University of Groningen, Netherlands.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None.

NOTES

The focus in research has shifted from the use of pneumococcal polysaccharide vaccines (PPVs) to pneumococcal conjugate vaccines (PCVs) in children and the role of PPVs in the prevention of AOM in children has merely been assessed following PCVs and no longer as a primary intervention. Therefore, the focus of the current review has shifted from the effect of PPVs to the effect of PCVs on acute otitis media. No further attention will be paid to the effect of PPVs, which were 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