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Pneumococcal vaccination during pregnancy for preventing infant infection (Review)

Chaithongwongwatthana S, Yamasmit W, Limpongsanurak S, Lumbiganon P, Tolosa JE

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[Intervention Review]

Pneumococcal vaccination during pregnancy for preventing infant infection

Surasith Chaithongwongwatthana[1], Waralak Yamasmit[2], Sompop Limpongsanurak[1], Pisake Lumbiganon[3], Jorge E Tolosa[4]

[1]Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand. [2]Department of Obstetrics and Gynecology, Faculty of Medicine Vajira Hospital, Navamindradhiraj University, Bangkok, Thailand. [3]Department of Obstetrics and Gynaecology, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand. [4]Department of Obstetrics and Gynecology, Oregon Health and Science University, Portland, Oregon, USA

Contact: Surasith Chaithongwongwatthana, Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University, Rama IV Road, Pathumwan, Bangkok, 10330, Thailand. iamsurasith@gmail.com.

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ABSTRACT

Background

Approximately 450,000 children worldwide die of pneumococcal infections each year. The development of bacterial resistance to antimicrobials adds to the difficulty of treatment of diseases and emphasizes the need for a preventive approach. Newborn vaccination schedules could substantially reduce the impact of pneumococcal disease in immunized children, but do not have an effect on the morbidity and mortality of infants less than three months of age. Pneumococcal vaccination during pregnancy may be a way of preventing pneumococcal disease during the first months of life before the pneumococcal vaccine administered to the infant starts to produce protection.

Objectives

To assess the effect of pneumococcal vaccination during pregnancy for preventing infant infection.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (31 July 2014) and reference lists of retrieved studies.

Selection criteria

Randomized controlled trials in pregnant women comparing pneumococcal vaccine with placebo or doing nothing, or with another vaccine to prevent infant infections.

Data collection and analysis

Two review authors independently assessed trials for inclusion and risk of bias, extracted data and checked them for accuracy. We contacted study authors for additional information.

Main results

Seven trials were included, but only six trials (919 participants) contributed data. There was no evidence that pneumococcal vaccination during pregnancy reduces the risk of neonatal infection (risk ratio (RR) 0.66; 95% confidence interval (CI) 0.30 to 1.46; two trials, 241 pregnancies, *low quality evidence*). Although the data suggest an effect in reducing pneumococcal colonization in infants by 16 months of age (average RR 0.33; 95% CI 0.11 to 0.98; one trial, 56 pregnancies), there was no evidence of this effect in infants at two to three months

of age (average RR 1.13; 95% CI 0.46 to 2.78; two trials, 146 pregnancies, *low quality evidence*) or by six to seven months of age (average RR 0.67, 95% CI 0.22 to 2.08; two trials, 148 pregnancies, *low quality evidence*). None of the trials included in this review reported neonatal death as a result of pneumococcal infection.

Neonatal antibody levels were reported as geometric mean and 95% CI. There were inconsistent results between studies. Two studies showed significantly higher immunoglobulin G (IgG) levels in cord blood in the pneumococcal vaccine group when compared with the control group for all serotypes. In contrast, another trial showed no difference in neonatal antibody levels between the pneumococcal vaccine group and the control group.

Maternal antibody levels were also reported as geometric mean and 95% CI. One study showed significantly higher IgG levels in maternal serum in women immunized with pneumococcal vaccine when compared with control vaccine regardless of any serotypes. Another study showed significantly higher maternal antibody levels only for serotype 14, but no evidence of an effect for other serotypes.

The percentage of women with seroprotection was measured in one trial at delivery and at 12 months post-delivery. At delivery, results favored the intervention group for serotype 6 (RR 1.49, 95% CI 1.31 to 1.69), serotype 14 (RR 1.40, 95% CI 1.25 to 1.56) and serotype 19 (RR 2.29, 95% CI 1.89 to 2.76). There were no group differences seen at 12 months post-delivery for serotypes 6 or 14 (RR 1.06, 95% CI 1.00 to 1.12 and RR 1.06, 95% CI 0.98 to 1.15, respectively), but results favored the intervention group for serotype 19 (RR 1.59, 95% CI 1.37 to 1.85).

No significant difference for tenderness at the injection site between women who received pneumococcal vaccine and those who received control vaccine (average RR 3.20; 95% CI 0.32 to 31.54; two trials, 130 women).

The overall quality of evidence is low for primary outcomes. Most outcomes had wide confidence intervals crossing the line of no effect, and most of the included trials had small numbers of participants and few events which led to downgrading evidence for imprecision of findings.

Authors' conclusions

There is insufficient evidence to assess whether pneumococcal vaccination during pregnancy could reduce infant infections.

PLAIN LANGUAGE SUMMARY

Pneumococcal vaccination during pregnancy for preventing infant infection

There is not enough evidence to assess whether using pneumococcal vaccination during pregnancy can prevent infant infections.

Although the incidence of invasive pneumococcal disease is variable across the world, the rate of serious illness or death is high in children who get this infection. The *Streptococcus pneumoniae* (pneumococcus) organism colonizes the upper respiratory tract and can cause bacteremia, meningitis, pneumonia and other lower respiratory tract, and upper respiratory tract infections, including otitis media and sinusitis. Newborn vaccination schedules of three primary doses with a booster dose could reduce the impact of pneumococcal disease in immunized children, but these vaccinations have no protective effect in infants less than three months of age. Maternal pneumococcal immunization during pregnancy may be a way of preventing pneumococcal disease during the infant's first months of life. We included seven randomized controlled trials. A total of 919 pregnant women participated in the six randomized controlled trials that contributed data to this review. The trials compared 23-valent pneumococcal polysaccharide vaccine with control vaccine. All women received a single injection of pneumococcal or control vaccine (where used). The women's mean gestational age at the time of immunization was between 27 and 38 weeks, where stated. Only two trials with 241 pregnancies reported on neonatal infections. This was not enough information to say whether pneumococcal vaccination during pregnancy led to fewer infant infections. Two trials with 146 pregnancies reported on infant nasal carriage of pneumococci (pneumococcal colonization), which was not enough evidence to show an effect in reducing colonization at two to three months of age or six to seven months of age. The included trials were of reasonable quality. There was no difference between pneumococcal vaccine and control vaccine for tenderness at the injection site. No serious adverse events were reported in the trials.

Summary of findings for the main comparison. Pneumococcal vaccine versus control vaccine for preventing infant infection

Pneumococcal vaccine versus control vaccine for preventing infant infection

Patient or population: Pregnant women undergoing vaccination to prevent infant infection
Settings: Studies were located in Bangladesh, Brazil, The Gambia and the USA.
Intervention: Pneumococcal vaccine versus control vaccine

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Pneumococcal vaccine versus control vaccine				
Neonatal death due to pneumococcal infection			0	0	Not estimable	None of the included studies in this review measured the primary outcome of neonatal death due to pneumococcal infection.
Neonatal infection - Pneumonia Follow-up: 1 year	**Study population**		**RR 0.58** (0.18 to 1.9)	149 (1 study)	⊕⊕⊝⊝ **low** [1]	
	93 per 1000	**54 per 1000** (17 to 177)				
Neonatal infection - Meningitis Follow-up: 1 year	**Study population**		**RR 3.04** (0.13 to 73.44)	149 (1 study)	⊕⊕⊝⊝ **low** [1]	
	0 per 1000	**0 per 1000** (0 to 0)				
Neonatal infection - Otitis media Follow-up: 1 year	**Study population**		**RR 0.14** (0.01 to 2.75)	149 (1 study)	⊕⊕⊝⊝ **low** [1]	
	40 per 1000	**6 per 1000** (0 to 110)				
Neonatal infection - All infections	**Study population**		**RR 0.66** (0.3 to 1.46)	241 (2 studies)	⊕⊕⊝⊝ **low** [1]	

Follow-up: 3-12 months	**115 per 1000**	**76 per 1000** (34 to 168)			
Pneumococcal colonization - At 2-3 months of age Follow-up: 2-3 months	**Study population**		**RR 1.13** (0.46 to 2.78)	146 (2 studies)	⊕⊕⊝⊝ **low** [1]
	133 per 1000	**150 per 1000** (61 to 368)			
Pneumococcal colonization - By 6-7 months of age Follow-up: 6-7 months	**Study population**		**RR 0.67** (0.22 to 2.08)	148 (2 studies)	⊕⊕⊝⊝ **low** [1]
	271 per 1000	**181 per 1000** (60 to 563)			

*The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio.

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.

[1] Wide confidence interval crossing the line of no effect, few events and small sample size (-2).

BACKGROUND

Description of the condition

Infections caused by*Streptococcus pneumoniae* (pneumococcus) are a major cause of morbidity and mortality throughout the world (WHO 2012). Pneumococcus is a leading cause of illness in young children and causes illness and death among the elderly and persons who have certain underlying medical conditions. The organism colonizes the upper respiratory tract and can cause the following types of illnesses: (a) invasive pneumococcal infections, including bacteremia and meningitis; (b) pneumonia and other lower respiratory tract infections; and (c) upper respiratory tract infections, including otitis media and sinusitis. Invasive pneumococcal diseases are less common than non-invasive manifestations, but cause high mortality. Each year, approximately 330,000 to 529,000 children worldwide, mostly in low- to middle-income countries, die of pneumococcal infections (WHO 2012). The development of resistance to antimicrobials by the bacteria adds to the difficulty of treatment of diseases and emphasizes the need for a preventive approach.

Regional differences in incidence of invasive pneumococcal disease have been noted. A 10-year surveillance in the Oxfordshire region of England, found that the annual incidence of invasive pneumococcal disease among children under five years of age prior to implementation of the pneumococcal vaccine was 24.3 per 100,000 persons (95% confidence interval 21.0 to 27.7) (Foster 2008). A population-based study carried out in a rural area of Bangladesh estimated the incidence of invasive pneumococcal disease among children to be 86 cases per 100,000 person-years (Arifeen 2009). In the United States, the routine use of pneumococcal vaccine beginning in 2000 has had a substantial impact on the epidemiology of pneumococcal disease in children. In infants younger than five years, rates of invasive pneumococcal disease have decreased from 98.7 cases per 100,000 population during 1998 and 1999 to 23.6 cases per 100,000 population in 2007 (Pilishvili 2010). Similar findings were reported in European countries. After widespread pneumococcal vaccination, there was a mean decline in the incidence of invasive pneumococcal disease in children aged less than two years from 32.5 to 23.4/100,000 (Isaacman 2010).

Description of the intervention

There are two types of pneumococcal vaccine available, polysaccharide vaccines and polysaccharide/protein conjugate vaccines. The 23-valent polysaccharide vaccine (PPV23) contains polysaccharide antigen from 23 types of pneumococcal bacteria (serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B,17F, 18C, 19A, 19F, 20, 22F, 23F and 33F), which cause 85% to 90% of bacteremic pneumococcal disease in adults. More than 80% of healthy adults who receive PPV23 develop antibodies against the serotypes contained in the vaccine within two to three weeks after vaccination; however, the vaccine is relatively poor at producing immunity in children less than two years old (Klouwenberg 2008). The pneumococcal conjugated vaccine (PCV) is much better at producing immunity in infants than pure polysaccharide vaccines (Black 2000; Klouwenberg 2008). In 2000, the 7-valent pneumococcal conjugated vaccine (PCV7) was recommended in the United States for immunization of infants (CDC 2000). PCV-7 includes the seven most frequent polysaccharides (serotypes 4, 6B, 9V, 14, 18C, 19F, 23F) in pneumococcal infections of the young child. Newborn vaccination schedules consist of three primary doses routinely plus a booster dose. After four doses, more than 90% of healthy infants develop antibodies to all seven serotypes contained in the vaccine. In a large trial, PCV7 was shown to reduce invasive disease caused by vaccine serotypes by 97%; however, it was less effective against acute otitis media (Black 2000). Local reactions following PCV7 occur in 10% to 20% of recipients and are more common with the fourth dose than the first three doses. No severe adverse events attributable to PCV7 have been reported. The vaccine could substantially reduce the impact of pneumococcal disease in immunized children (Isaacman 2010; Pilishvili 2010); however, it does not have an effect on the morbidity and mortality of the younger infants, especially those less than three months of age. This may be due to the fact that serum IgG (immunoglobulin G) antibodies against polysaccharides increase only after the second and third vaccine doses are administered (Rennels 1998).

PCV7 given to the children has had a substantial effect on pneumococcal disease in the United States since its introduction in 2000. A large, population-based surveillance system monitoring invasive pneumococcal disease in a population of nearly 20 million persons in the United States, found that rates of invasive pneumococcal disease in children younger than two years of age were 68.6% lower in 2001 compared with rates of disease before the vaccine was introduced (Whitney 2003). Furthermore, widespread vaccination of children with PCV7 has shown a 'herd effect' in decreasing the carriage rate of *S. pneumoniae* in children, who are an important vector of *S. pneumoniae* to other children and adults (Dagan 2000; Pilishvili 2010). Data from the same surveillance indicate that unvaccinated adults are benefiting from the vaccination of children. Infection rates in adults fell 8% to 32% when compared with the average rates in 1998 and 1999 (Whitney 2003). However, invasive pneumococcal disease caused by non-PCV7 serotypes has increased and partially offset the reductions (CDC 2010; Pilishvili 2010). Overall, rates of invasive pneumococcal disease have remained stable at 22 to 25 cases per 100,000 since 2002 (CDC 2010; Pilishvili 2010). An increase in disease due to non-PCV-7 serotypes and the need for broader serotype coverage to address the global disease burden provides a rationale for a second-generation conjugate vaccine, 10-valent pneumococcal conjugated vaccine (PCV10, including serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F) and 13-valent pneumococcal conjugated vaccine (PCV13, including serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F) (Grijalva 2011; WHO 2012). The Advisory Committee on Immunization Practices in the United States has recommended the use of PCV13 for immunization of infants since 2010 (CDC 2010) and the World Health Organization has recommended to replace PCV7 by PCV10 or PCV13 for immunization of infants in 2012 (WHO 2012).

How the intervention might work

Maternal immunization could help to prevent the two to three million neonatal and early infant deaths that occur in low- to middle-income countries each year (Greenwood 2003). Maternal pneumococcal immunization may be a way of preventing pneumococcal disease during the first months of life before infant-administered pneumococcal conjugate vaccine starts to produce protection. This strategy has the potential to impact on public health, as has been seen by the prevention of tetanus neonatorum through maternal immunization (Khan 2013). An effective delivery system for maternal immunization already exists and, because of

the success of maternal tetanus immunization, this approach to the prevention of serious illness or death in young infants is widely accepted by the general population.

Why it is important to do this review

There are clinical studies on maternal pneumococcal immunization to prevent infant infection, but information regarding effectiveness of the intervention is not known.

OBJECTIVES

To assess the effectiveness of pneumococcal vaccine administered to pregnant women in preventing pneumococcal infection in the infant.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials. Quasi-randomized controlled trials were not included.

Types of participants

Healthy women with uncomplicated pregnancies.

Types of interventions

Pneumococcal vaccine (polysaccharide or conjugate) compared with placebo or doing nothing, or with another vaccine.

Types of outcome measures

Primary outcomes

(1) Neonatal pneumococcal infection:

- pneumonia (diagnosed by clinical findings and radiological or laboratory findings);
- meningitis (diagnosed by clinical findings and laboratory findings);
- bacteremia/sepsis (diagnosed by clinical findings and laboratory findings);
- neonatal death (due to pneumococcal infection);
- otitis media (diagnosed by clinical findings and laboratory findings).

(2) Neonatal pneumococcal colonization:

- at two to three months of age;
- by six to seven months of age.

Secondary outcomes

(1) Neonatal antibody levels.
(2) Adverse neonatal effects.
(3) Maternal antibody levels.
(4) Incidence of maternal pneumococcal colonization during labor.
(5) Adverse maternal effects.
(6) Neonatal pneumococcal colonization by 16 months of age.

Search methods for identification of studies

The following methods section of this review is based on a standard template used by the Cochrane Pregnancy and Childbirth Group.

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (31 July 2014).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;
3. weekly searches of Embase;
4. handsearches of 30 journals and the proceedings of major conferences;
5. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL, MEDLINE and Embase, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

We did not apply any language restrictions.

(Please see Appendix 1 for details of additional searches carried out in the initial version of the review (Chaithongwongwatthana 2006).)

Searching other resources

We searched cited references from retrieved articles for additional studies. We reviewed abstracts and letters to the editor to identify randomized controlled trials that have not been published. If we identified a randomized controlled trial, we contacted the primary investigator directly to obtain further data. We reviewed editorials, indicating expert opinion, to identify and ensure that no key studies were missed for inclusion in this review.

We did not apply any language restrictions.

Data collection and analysis

For methods used in the previous version of this review, *see* Chaithongwongwatthana 2012.

For this update, the following methods were used for assessing the two reports that were identified as a result of the updated search.

The following methods section of this review is based on a standard template used by the Cochrane Pregnancy and Childbirth Group.

Selection of studies

Two review authors independently assessed for inclusion all the potential studies identified as a result of the search strategy. We resolved any disagreement through discussion or, if required, we consulted the third review author.

Data extraction and management

We designed a form to extract data. For eligible studies, two review authors extracted the data using the agreed form. We resolved discrepancies through discussion or, if required, we consulted the third review author. Data were entered into Review Manager software (RevMan 2014) and checked for accuracy.

When information regarding any of the above was unclear, we contacted authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Any disagreement was resolved by discussion or by involving a third assessor.

(1) Random sequence generation (checking for possible selection bias)

We described for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We assessed the method as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We described for each included study the method used to conceal allocation to interventions prior to assignment and assessed whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We assessed the methods as:

- low risk of bias (e.g. telephone or central randomization; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

(3.1) Blinding of participants and personnel (checking for possible performance bias)

We described for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We considered that studies were at low risk of bias if they were blinded, or if we judged that the lack of blinding unlikely to affect results. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed the methods as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We described for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We described for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomized participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported, or could be supplied by the trial authors, we planned to re-include missing data in the analyses which we undertook.

We assessed methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomization);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

We described for each included study how we investigated the possibility of selective outcome reporting bias and what we found.

We assessed the methods as:

- low risk of bias (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)

We described for each included study any important concerns we had about other possible sources of bias.

(7) Overall risk of bias

We made explicit judgements about whether studies were at high risk of bias, according to the criteria given in the *Handbook* (Higgins 2011). With reference to (1) to (6) above, we planned to assess the likely magnitude and direction of the bias and whether we considered it is likely to impact on the findings. In future updates, we will explore the impact of the level of bias through undertaking sensitivity analyses - *see* Sensitivity analysis.

For this update, the quality of the evidence was assessed using the GRADE approach (Schunemann 2009) in order to assess the quality of the body of evidence relating to the following outcomes for the main comparisons.

1. Neonatal infection - pneumonia
2. Neonatal infection - meningitis
3. Neonatal infection - otitis media
4. Neonatal infection - all
5. Neonatal infection - neonatal death
6. Pneumococcal colonization - two to three months
7. Pneumococcal colonization - six to seven months

GRADE profiler (GRADE 2008) was used to import data from Review Manager 5.3 (RevMan 2014) in order to create a 'Summary of findings' table. A summary of the intervention effect and a measure of quality for each of the above outcomes was produced using the GRADE approach. The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome. The evidence can be downgraded from 'high quality' by one level for serious (or by two levels for very serious) limitations, depending on assessments for risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias.

The primary outcomes were included in the Summary of findings for the main comparison. For neonatal infection, none of the included trials in this review reported the outcome of neonatal death. Neonatal pneumococcal colonization by 16 months of age was reported in one trial, but it was not included as a primary outcome or in the 'Summary of findings' table because the colonization at this time point may be confounded by neonatal vaccination.

Measures of treatment effect

Dichotomous data

For dichotomous data, we presented results as summary risk ratio with 95% confidence intervals.

Continuous data

We did not identify an continuous outcomes. We planned to use the mean difference if outcomes were measured in the same way between trials. We would have used the standardized mean difference to combine trials that measured the same outcome, but used different methods.

Unit of analysis issues

Cluster-randomized trials

For this update we did not include any cluster-randomized trials in the review. If in future updates eligible cluster-randomized trials are identified, we will include these cluster-randomized trials in the analyses along with individually-randomized trials. We will adjust their sample sizes or standard errors using the methods described in the *Handbook* using an estimate of the intra-cluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomized trials and individually-randomized trials, we plan to synthesize the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomization unit is considered to be unlikely.

We will also acknowledge heterogeneity in the randomization unit and perform a sensitivity analysis to investigate the effects of the randomization unit.

Dealing with missing data

For included studies, we noted levels of attrition. In future updates, if more eligible studies are included, the impact of including studies with high levels of missing data in the overall assessment of treatment effect will be explored by using sensitivity analysis.

For all outcomes, analyses were carried out, as far as possible, on an intention-to-treat basis i.e. we attempted to include all participants randomized to each group in the analyses. The denominator for each outcome in each trial was the number randomized minus any participants whose outcomes were known to be missing.

Assessment of heterogeneity

We assessed statistical heterogeneity in each meta-analysis using the Tau^2, I^2 and Chi^2 statistics. We regarded heterogeneity as substantial if an I^2 was greater than 30% and either the Tau^2 was greater than zero, or there was a low P value (less than 0.10) in the Chi^2 test for heterogeneity. Had we identified substantial heterogeneity (above 30%), we planned to explore it by pre-specified subgroup analysis.

Assessment of reporting biases

In future updates, if there are 10 or more studies in the meta-analysis, we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually. If asymmetry is suggested by a visual assessment, we will perform exploratory analyses to investigate it.

Data synthesis

We carried out statistical analysis using the Review Manager software (RevMan 2014). We used fixed-effect meta-analysis for combining data where it was reasonable to assume that studies were estimating the same underlying treatment effect: i.e. where trials were examining the same intervention, and the trials' populations and methods were judged sufficiently similar.

Where there was clinical heterogeneity sufficient to expect that the underlying treatment effects differed between trials, or if substantial statistical heterogeneity was detected, we used random-effects meta-analysis to produce an overall summary, if an average treatment effect across trials was considered clinically meaningful. The random-effects summary was treated as the average range of possible treatment effects and discussed the clinical implications of treatment effects differing between trials. If the average treatment effect was not clinically meaningful, we did not combine trials. Where we used random-effects analyses, the results were presented as the average treatment effect with 95% confidence intervals, and the estimates of Tau^2 and I^2.

Subgroup analysis and investigation of heterogeneity

Had we identified substantial heterogeneity, we planned to investigate it using subgroup analyses and sensitivity analyses. We would have considered whether an overall summary was meaningful, and if it was, we planned to use random-effects analysis to produce it.

We planned to carry out the following subgroup analyses:

1. types of pneumococcal vaccine (polysaccharide versus conjugate);
2. countries of participants (high-income versus low- to middle-income).

The following outcomes were planned for use in subgroup analyses:

1. neonatal pneumococcal infection;
2. neonatal pneumococcal colonization.

There were too few trials included in this review to conduct meaningful subgroup analysis.

We assessed subgroup differences by interaction tests available within RevMan (RevMan 2014). We reported the results of subgroup analyses quoting the Chi^2 statistic and P value, and the interaction test I^2 value.

Sensitivity analysis

We planned to carry out sensitivity analyses to explore the effect of trial quality assessed by concealment of allocation, high attrition rates, or both, with poor quality studies being excluded from the analyses in order to assess whether this makes any difference to the overall result.

There were too few trials included in this review to conduct meaningful sensitivity analysis.

RESULTS

Description of studies

Results of the search

We identified 10 studies as potentially eligible for inclusion in this review. We included seven trials and excluded two trials, one trial is ongoing (Dunbar 2007). Seven new reports were identified in the updated search. All of them reported new information from the two included trials (Lopes 2009; Zaman 2008).

Included studies

One trial (Obaro 2004) did not contribute data toward the analyses because it did not report the outcomes of interest. A total of 919 pregnant women participated in the other six included studies comparing 23-valent pneumococcal polysaccharide vaccine with control vaccine (O' Dempsey 1996; Munoz 2001; Shahid 1995; Zaman 2008) or no vaccine (Lopes 2009; Quiambao 2003). The O' Dempsey 1996 trial included 75 women in each group. The Munoz 2001 trial used a 2:1 randomization scheme with 20 women in the vaccine group and 40 women in control group. The Shahid 1995 trial included 36 women in vaccine group and 34 women in control group. The Zaman 2008 trial included 168 women in vaccine group and 172 women in control group. Lopes 2009 was a trial with three arms. We have included data from two of the arms: 47 women in a control group (no vaccine) and 45 women who received vaccine at 30 to 34 weeks of gestation. The third arm involved 47 women who received vaccine after delivery; these data were not included from our analyses. Quiambao 2003 employed a 2:1 randomization scheme and included 106 women in vaccine group and 54 women in control group.

Participants

This review includes data from six trials with a total of 919 pregnant women. A total of 497 women were randomized to be immunized with pneumococcal polysaccharide vaccine and 422 women were randomized to control vaccines. The included trials were conducted in various settings; one in Brazil (Lopes 2009), one in the United States (Munoz 2001), two in the Gambia (O' Dempsey 1996; Obaro 2004), one in the Philippines (Quiambao 2003), and two in Bangladesh (Shahid 1995; Zaman 2008). All participants were healthy women with an uncomplicated pregnancy. Lopes 2009 and Obaro 2004 had no available data on participants' mean age but for the other included trials (Munoz 2001; O' Dempsey 1996; Quiambao 2003; Shahid 1995; Zaman 2008), the mean age of the women in each study was 30.2 (Munoz 2001), 22.0 (O' Dempsey 1996), 26.8 (Quiambao 2003), 25.6 (Shahid 1995), and 24.9 (Zaman 2008) years.

Interventions

All trials used a 23-valent pneumococcal polysaccharide vaccine compared with control vaccine or no vaccine. One trial (Munoz 2001) used *Hemophilus influenzae* conjugate vaccine as the control; two trials (O' Dempsey 1996; Shahid 1995) used meningococcal vaccine as the control; one trial (Zaman 2008) used inactivated influenza vaccine as the control while the other two trials (Lopes 2009; Quiambao 2003) had no control vaccine. All women received a single injection of pneumococcal or control vaccine (where used). The mean gestational age at the time of immunization in each study was no available data (Lopes 2009), 33.3 (Munoz 2001), 38.0 (O' Dempsey 1996), 27.3 weeks (Quiambao 2003), 32.3 (Shahid 1995), and no available data (Zaman 2008). The mean interval between immunization and delivery in each study was 43.6 (Munoz 2001), 44.1 (O' Dempsey 1996), 51.4 (Shahid 1995), 54.9 (Zaman 2008), not available data (Lopes 2009) and 76.3 days (Quiambao 2003) respectively.

Outcomes

Two studies reported the incidence of neonatal infection (Lopes 2009; O' Dempsey 1996). Two trials reported the incidence of neonatal pneumococcal colonization (Lopes 2009; Munoz 2001). Three trials (Munoz 2001; O' Dempsey 1996; Quiambao 2003)

reported neonatal antibody levels as geometric mean with 95% confidence interval. Three trials (Munoz 2001; O' Dempsey 1996; Shahid 1995) reported maternal antibody levels. One trial reported (Zaman 2008) the percentage of mothers with seroprotection. No serious adverse reactions attributable to the vaccines were observed in all studies (*see* Characteristics of included studies).

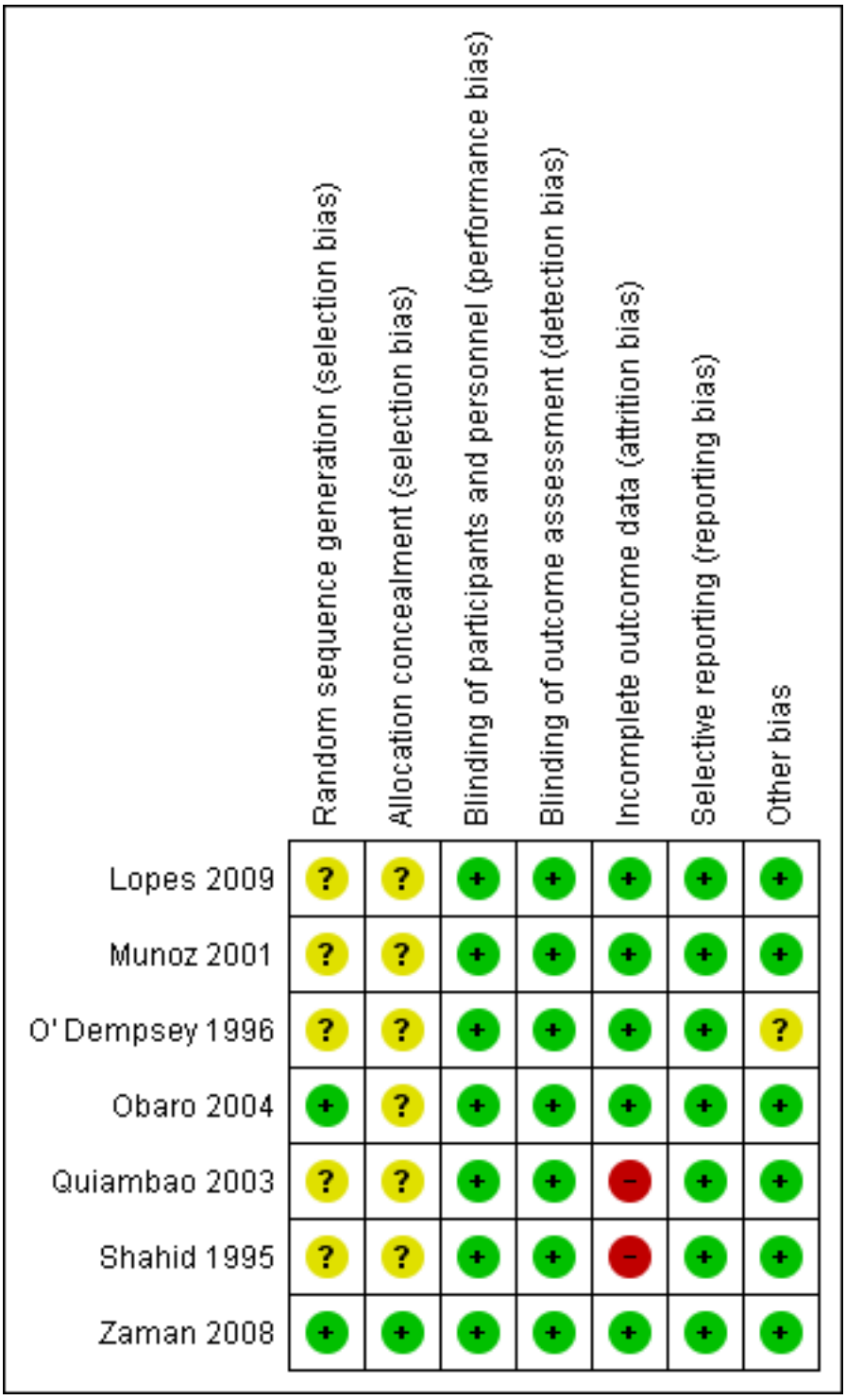
Excluded studies

We excluded two trials *(* Daly 2003; Glezen 2000). *See* Characteristics of excluded studies table.

Risk of bias in included studies

One trial was at low risk of bias (Zaman 2008). All the remaining trials were at unclear risk of selection bias. High risk for attrition bias was noted in the two trials (Quiambao 2003; Shahid 1995). The risk of bias in the included trials is summarized in the 'Risk of bias' graph (Figure 1).

Figure 1. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Only one trial (Zaman 2008) described the method of random allocation and allocation concealment. The other six trials had an unclear risk of selection bias.

Blinding

Four trials (Munoz 2001; O' Dempsey 1996; Shahid 1995; Zaman 2008) were double-blind studies. Although the other two trials were not double-blind studies, the risk of detection bias was low because the reported outcomes were objective outcomes.

Incomplete outcome data

Only one trial (Lopes 2009) had complete follow-up. There were two trials (Quiambao 2003; Shahid 1995) that had high risk for attrition bias due to high proportion of incomplete outcome data.

Selective reporting

All trials had low risk for reporting bias.

Other potential sources of bias

None.

Effects of interventions

See: **Summary of findings for the main comparison** Pneumococcal vaccine versus control vaccine for preventing infant infection

Comparison

Primary outcomes

Neonatal infections

Only two trials (Lopes 2009; O' Dempsey 1996) with 241 pregnancies reported these outcomes. There was insufficient evidence to show an effect of maternal pneumococcal vaccine during pregnancy in reduction of neonatal infections (risk ratio (RR) 0.66; 95% confidence interval (CI) 0.30 to 1.46) including pneumonia (RR 0.58; 95% CI 0.18 to 1.90), meningitis (RR 3.04; 95% CI 0.13 to 73.44), and otitis media (RR 0.14; 95% CI 0.01 to 2.75). *See* Analysis 1.1.

None of the included trials in this review reported the outcome of neonatal death due to pneumococcal infection.

Neonatal pneumococcal colonization

Two studies (Lopes 2009; Munoz 2001) with 148 pregnancies reported this outcome at several time points and according to three serotypes (6, 14 and 19). There was not enough evidence to show an effect of maternal pneumococcal vaccination in reduction of neonatal nasal carriage of pneumococci at two to three months of age (average RR 1.13; 95% CI 0.46 to 2.78) or by six to seven months of age (average RR 0.67; 95% CI 0.22 to 2.08, I^2 = 54%, Tau^2 = 0.38). Nevertheless, the results showed a statistically significant decrease in the incidence of pneumococcal colonization in infants by 16 months of age (RR 0.33; 95% CI 0.11 to 0.98; one study, 56 infants). *See* Analysis 1.2. One study with 92 women (Lopes 2009) found no group differences in pneumococcal colonization according to serotype 6, 14 or 19 (RR 0.12, 95% CI 0.01 to 2.09; not estimable; and RR 2.09, 95% CI 0.40 to 10.85, respectively).

Heterogeneity was noted for neonatal colonization at the time point six to seven months of age. This substantial heterogeneity may be from participants from different settings. Lopes 2009 conducted the trial in Brazil while Munoz 2001 conducted the trial in the United States. However, no statistical significant difference between the vaccine group and control group was found in either trial (RR 1.04; 95% CI 0.48 to 2.27 in Lopes 2009 and RR 0.32; 95% CI 0.08 to 1.29 in Munoz 2001).

Secondary outcomes

Neonatal antibody levels

Antibody levels were reported as geometric means and 95% CIs. There were inconsistent results between studies. Two studies (Munoz 2001; Quiambao 2003) showed significantly higher immunoglobulin G (IgG) levels in cord blood in the pneumococcal vaccine group when compared with the control group for all serotypes. In contrast, O' Dempsey 1996 showed no difference in neonatal antibody levels between the pneumococcal vaccine group and the control group. *See* Analysis 1.3.

Maternal antibody levels

Antibody levels were reported as geometric means and 95% CIs. One study (Munoz 2001) showed significantly higher IgG levels in maternal serum in women immunized with pneumococcal vaccine when compared with control vaccine regardless of any serotypes. The other study (O' Dempsey 1996) showed significantly higher maternal antibody levels only for serotype 14, but no evidence of an effect of the pneumococcal vaccine resulting in an increase in maternal antibody levels in the other serotypes. *See* Analysis 1.4.

Percentage of mothers with seroprotection was also reported in one trial with 340 women (Zaman 2008). This outcome was measured according to serotype (6, 14 or 19) and at two time points (delivery and 12 months post-delivery). Results favored the intervention group for serotype 6 at delivery (RR 1.49, 95% CI 1.31 to 1.69); serotype 14 at delivery (RR 1.40, 95% CI 1.25 to 1.56) and serotype 19 at delivery (RR 2.29, 95% CI 1.89 to 2.76). There were no group differences seen at 12 months post-delivery for serotypes 6 or 14 (RR 1.06, 95% CI 1.00 to 1.12 and RR 1.06, 95% CI 0.98 to 1.15, respectively). Results favored the intervention group for serotype 19 measured at 12 months post delivery (RR 1.59, 95% CI 1.37 to 1.85). See Analysis 1.5.

Adverse maternal effects

Two studies (Munoz 2001; Shahid 1995) reported tenderness at the injection site but this was not significantly different between the intervention and control groups (average RR 3.20; 95% CI 0.32 to 31.54, I^2 = 79%, Tau^2 = 2.24 (Analysis 1.6)). The substantial heterogeneity may be from the different control vaccine used in the trials. Munoz 2001 used *Hemophilus influenzae* type b conjugate vaccine as control and found significant higher rate of tenderness in the pneumococcal vaccine group (RR 12.00; 95% CI 1.55 to 93.01). Shahid 1995 used meningococcal vaccine as control and found no significant difference of tenderness between the groups (RR 1.28; 95% CI 0.77 to 2.13).

DISCUSSION

Summary of main results

There was no evidence of an effect of pneumococcal vaccination during pregnancy in preventing neonatal infections; however, there were only two trials (Lopes 2009; O' Dempsey 1996) reporting this outcome. The power to detect this effect might be too low because of a small sample size. Results of one study (Munoz 2001) suggested that maternal pneumococcal vaccination can reduce the risk of pneumococcal colonization by 16 months of age, but no effect was shown at earlier ages.

An inconsistent result between two trials (Munoz 2001; Shahid 1995) was shown regarding tenderness at the injection site. This may due to the different control vaccines used in the studies. Although there tends to be increased tenderness among women injected with pneumococcal vaccine, this symptom lasted only a few days after injection and no serious adverse events were reported in all of the trials.

Overall completeness and applicability of evidence

There are some limitations that should be considered when interpreting the results of this review. First, neonatal infection, the most significant outcome, was only reported in two trials with small numbers of participants. Neonatal death due to pneumococcal infections was not reported in any included trial. Second, the effect on neonatal pneumococcal colonization at 16 months of age with no effect demonstrated at two to seven months may not be due to the vaccine administered during pregnancy. There was no detail regarding the confounding factors or co-intervention reported in the trial. The included studies did not report on breastfeeding or antibody level in breast milk that may impact on antibody transfer to the neonates.

Quality of the evidence

Only one trial (Zaman 2008) described the precise method of random allocation and demonstrated method of allocation concealment. Four trials (Munoz 2001; O' Dempsey 1996; Shahid 1995; Zaman 2008) were double-blind studies. Only one trial (Lopes 2009) had complete follow-up.

Overall, the quality of evidence is low for all outcomes (Summary of findings for the main comparison). Outcomes had wide confidence intervals crossing the line of no effect, and included trials had small numbers of participants and few events, which led to downgrading evidence for imprecision of findings. There were no included studies that reported the primary outcome of neonatal death due to pneumococcal infection, but this important outcome is included in the GRADE table to highlight this gap in the evidence.

Potential biases in the review process

None.

Agreements and disagreements with other studies or reviews

A non-randomized study in Papua New Guinea (Lehmann 2002) compared neonatal antibody level between women who were immunized with 23-valent pneumococcal polysaccharide vaccine at 28 to 38 weeks' gestation and unimmunized women. The results were similar to the two included studies (Munoz 2001; Quiambao 2003). Geometric mean antibody titers were significantly higher in children of the immunized mothers than in those of the unimmunized group.

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient evidence from randomized controlled trials to support the use of pneumococcal vaccination during pregnancy for preventing infant infections. Pneumococcal vaccine is recommended for administration to pregnant women when they have underlying medical conditions for preventing maternal infections (ACOG 2003). None of the studies reported risk from the vaccine to fetus. Risk to a developing fetus from vaccination of the mother during pregnancy is primarily theoretical. No evidence exists of risk from vaccinating pregnant women with inactivated virus or bacterial vaccines or toxoids (CDC 2011). The benefits of vaccinating pregnant women usually outweigh potential risks when the likelihood of disease exposure is high, when infection would pose a risk to the mother or fetus, and when the vaccine is unlikely to cause harm.

One of the strategies to prevent infection in the neonatal and early infant period is neonatal vaccination. Two recent trials (Pomat 2013; Scott 2011) showed impressive results of earlier PCV7 administration to the newborn (at birth or shortly after birth). Although no clinical outcomes have yet been reported, both trials demonstrated that neonatal PCV7 vaccination was safe, immunogenic and not associated with immune tolerance. Vaccination beginning at birth may be a considerable option to minimize invasive pneumococcal disease in these young infants.

Implications for research

The review included a small number of randomized controlled trials on pneumococcal vaccination during pregnancy, therefore, they may not have enough power to detect the effectiveness on preventing infant infections. Future trials need to choose the vaccine type as well as the timing of vaccination that could maximize maternal immunogenicity and antibody transfer to the fetus. A new approach using recombinant pneumococcal surface protein A (PspA) as a protein-based vaccine has been investigated in mice (Kono 2011).

None of the included studies in this review reported the primary outcome of neonatal death due to pneumococcal infection.

As previously discussed, the future vaccine formulations containing additional serotypes and earlier administration to the newborn needs to be evaluated for its effectiveness in reducing invasive pneumococcal disease in children. If it is the case, trials of pneumococcal vaccination during pregnancy for preventing infant infection may not be needed.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Lopes 2009

Methods	Pregnant women were randomly assigned to one of three groups for the study.
Participants	Country: Brazil. Number: 47 women in the control group (no vaccine); 45 women received vaccine at 30-34 weeks of gestation; and 47 women received vaccine after delivery. Mean age: data not available. Mean gestational age: data not available.

Lopes 2009 *(Continued)*

Interventions	23-valent pneumococcal polysaccharide vaccine.
Outcomes	Incidence of neonatal infection. Incidence of infant pneumococcal colonization. Maternal antibody levels (GM).
Notes	Data from women received vaccine after delivery were excluded from analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details were not reported.
Allocation concealment (selection bias)	Unclear risk	Details were not reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Lack of blinding would be unlikely to affect results.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Lack of blinding would be unlikely to affect results.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All infants completed follow-up at 3 months old.
Selective reporting (reporting bias)	Low risk	All outcomes were predefined and reported.
Other bias	Low risk	The trial appears to be free of industry sponsorship.

Munoz 2001

Methods	The study was a prospective, double-blind, randomized, controlled trial.
Participants	Country: United States. Number: 20 women in the intervention group and 40 women in the control group. Mean age: 30.2 years. Mean gestational age: 33.3 weeks.
Interventions	23-valent pneumococcal polysaccharide vaccine vs *Hemophilus influenzae* type b conjugate vaccine.
Outcomes	Incidence of neonatal and infant pneumococcal colonization. Neonatal antibody levels (GM). Maternal antibody levels (GM). Incidence of tenderness at the injection site.

Munoz 2001 *(Continued)*

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details were not reported.
Allocation concealment (selection bias)	Unclear risk	Details were not reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: “double blind”.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: “double blind”.
Incomplete outcome data (attrition bias) All outcomes	Low risk	2/60 were lost to follow-up.
Selective reporting (reporting bias)	Low risk	All outcomes were predefined and reported.
Other bias	Low risk	The trial appears to be free of industry sponsorship.

O' Dempsey 1996

Methods	Women were randomized to receive either pneumococcal vaccine or control vaccine.
Participants	Country: The Gambia. Number: 75 women in the intervention group and 75 women in the control group. Mean age: 22.0 years. Mean gestational age: 38.0 weeks.
Interventions	23-valent pneumococcal polysaccharide vaccine vs meningococcal vaccine.
Outcomes	Incidence of neonatal pneumonia. Incidence of neonatal meningitis. Incidence of neonatal otitis media. Neonatal antibody levels (GM). Maternal antibody levels (GM).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

O' Dempsey 1996 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Details were not reported.
Allocation concealment (selection bias)	Unclear risk	Details were not reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Lack of blinding would be unlikely to affect results.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Lack of blinding would be unlikely to affect results.
Incomplete outcome data (attrition bias) All outcomes	Low risk	1/150 were lost to follow-up.
Selective reporting (reporting bias)	Low risk	All outcomes were predefined and reported.
Other bias	Unclear risk	Vaccines were provided by industry sponsorship, but none of the authors affiliated with the company.

Obaro 2004

Methods	The study was a randomized, double-blind, controlled trial.
Participants	Country: The Gambia. Number: 56 women in the intervention group and 57 women in the control group. Mean age: data not available. Mean gestational age: data not available.
Interventions	23-valent pneumococcal polysaccharide vaccine vs meningococcal vaccine.
Outcomes	Pneumococcal polysaccharide-specific s-IgA antibody concentrations in breast milk.
Notes	Did not contribute data to analysis.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Participants were vaccinated with 1 dose of either a pneumococcal vaccine or control by computer-generated random assignment.
Allocation concealment (selection bias)	Unclear risk	Details were not reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: “double blind”.

Obaro 2004 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double blind".
Incomplete outcome data (attrition bias) All outcomes	Low risk	Two mothers withdrew their consent before the completion of the study, and 6 mothers traveled out of the study area and did not return before the completion of the study.
Selective reporting (reporting bias)	Low risk	All outcomes were predefined and reported.
Other bias	Low risk	The trial appears to be free of industry sponsorship.

Quiambao 2003

Methods	The study was a randomized, controlled trial.
Participants	Country: Philippines. Number: 106 women in the intervention group and 54 women in the control group. Mean age: 26.8 years. Mean gestational age: 27.3 weeks.
Interventions	23-valent pneumococcal polysaccharide vaccine.
Outcomes	Neonatal antibody levels (GM).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details were not reported.
Allocation concealment (selection bias)	Unclear risk	Details were not reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Lack of blinding would be unlikely to affect results.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Lack of blinding would be unlikely to affect results.
Incomplete outcome data (attrition bias) All outcomes	High risk	Cord blood was obtained from 42/54 in the control group and 82/106 in the intervention group.
Selective reporting (reporting bias)	Low risk	All outcomes were predefined and reported.

Quiambao 2003 *(Continued)*

Other bias	Low risk	The trial appears to be free of industry sponsorship.

Shahid 1995

Methods	The study was a prospective double-blind controlled trial.
Participants	Country: Bangladesh. Number: 36 women in the intervention group and 34 women in the control group. Mean age: 25.6 years. Mean gestational age: 32.3 weeks.
Interventions	23-valent pneumococcal polysaccharide vaccine vs meningococcal vaccine.
Outcomes	Maternal antibody levels (GM). Incidence of tenderness at the injection site.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details were not reported.
Allocation concealment (selection bias)	Unclear risk	Details were not reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: “double blind”.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: “double blind”.
Incomplete outcome data (attrition bias) All outcomes	High risk	7/36 missing from intervention group; 10/34 missing from control group.
Selective reporting (reporting bias)	Low risk	All outcomes were predefined and reported.
Other bias	Low risk	The trial appears to be free of industry sponsorship.

Zaman 2008

Methods	The study was a prospective, controlled, blinded, randomized trial.
Participants	Country: Bangladesh. Number: 168 women in the intervention group and 172 women in the control group.

Zaman 2008 *(Continued)*

	Mean age: 24.9 years. Mean gestational age: data not available.
Interventions	23-valent pneumococcal polysaccharide vaccine vs influenza vaccine.
Outcomes	Incidence of neonatal influenza. Incidence of maternal influenza. Percentage of mothers with seroprotection.
Notes	The main purpose of the trial was to assess the effectiveness of influenza vaccine.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomization sequence was computer-generated.
Allocation concealment (selection bias)	Low risk	The randomization sequentially numbered opaque envelopes with data regarding assignments to study groups were provided to each clinic.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: “double blind”.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: “double blind”.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Of the mother–infant pairs, 316 were observed for the full 24-week period.
Selective reporting (reporting bias)	Low risk	All outcomes were predefined and reported.
Other bias	Low risk	The trial appears to be free of industry sponsorship and the conflict of interest was declared.

GM: geometric mean
vs: versus

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Daly 2003	The objective of this pilot study was to estimate enrolment rate for the phase III trial, not for the determination of the effectiveness of maternal immunization.
Glezen 2000	It was an abstract only and there was not enough information in the abstract.

Characteristics of ongoing studies *[ordered by study ID]*

Dunbar 2007

Trial name or title	PneuMum.
Methods	Randomized controlled trial.
Participants	Country: Australia. Number: 210 women aged 18–39 years who have an uncomplicated pregnancy: 70 women will receive pneumococcal vaccine in the third trimester; 70 at delivery; and 70 at 7 months after childbirth (the control group).
Interventions	23-valent pneumococcal polysaccharide vaccine.
Outcomes	Incidence of neonatal otitis media. Incidence of neonatal pneumococcal colonization. Neonatal antibody levels.
Starting date	2007.
Contact information	melissa.dunbar@menzies.edu.au.
Notes	

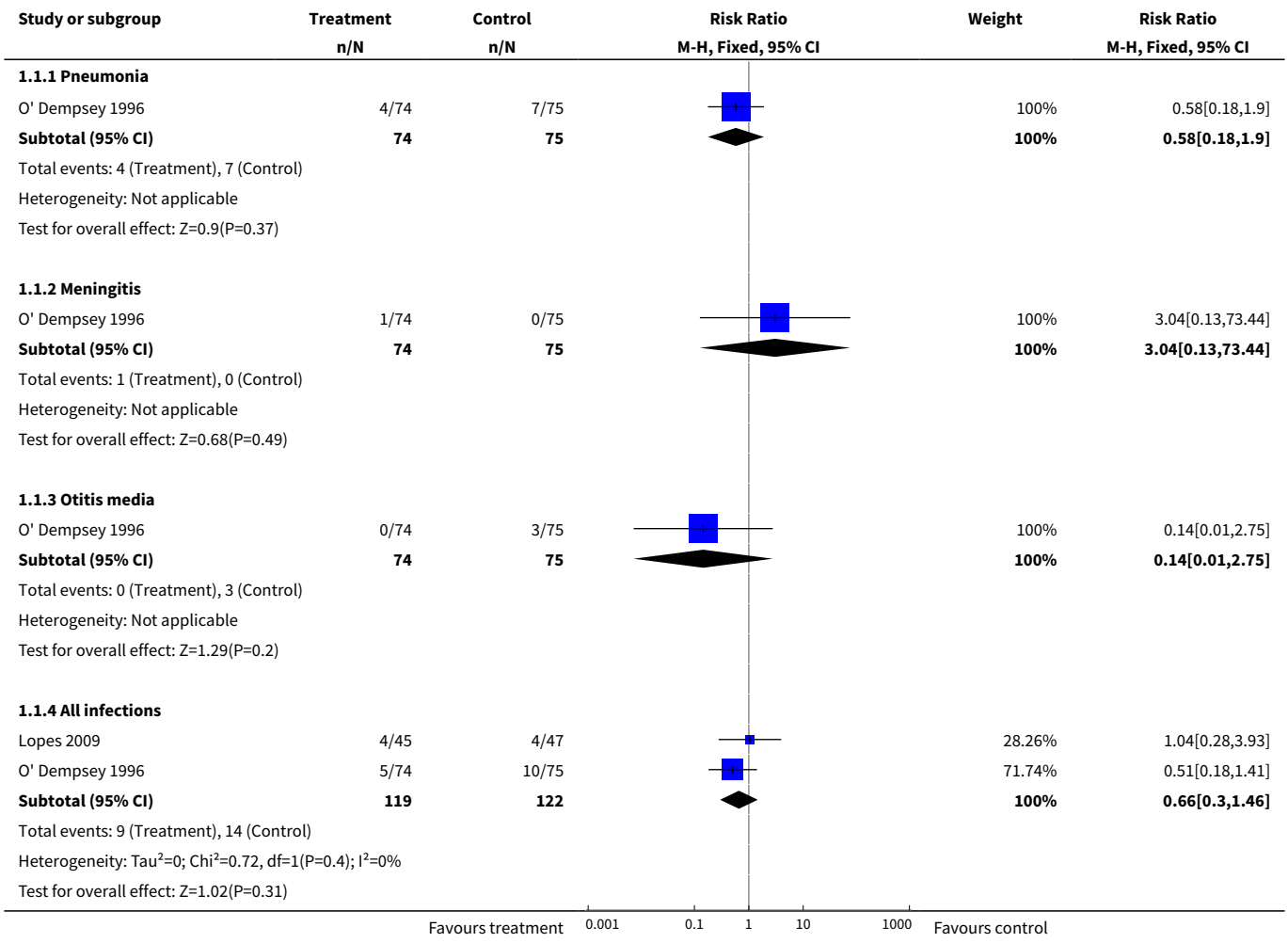
DATA AND ANALYSES

Comparison 1. Pneumococcal vaccine versus control vaccine

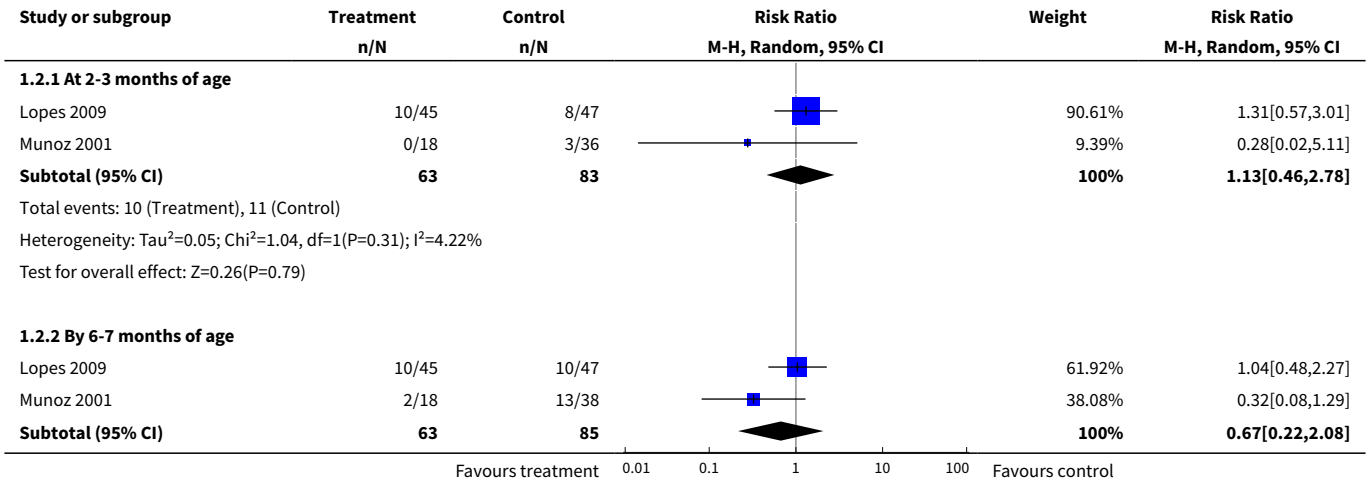
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Neonatal infection	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Pneumonia	1	149	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.18, 1.90]
1.2 Meningitis	1	149	Risk Ratio (M-H, Fixed, 95% CI)	3.04 [0.13, 73.44]
1.3 Otitis media	1	149	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 2.75]
1.4 All infections	2	241	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.30, 1.46]
2 Pneumococcal colonization	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 At 2-3 months of age	2	146	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.46, 2.78]
2.2 By 6-7 months of age	2	148	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.22, 2.08]

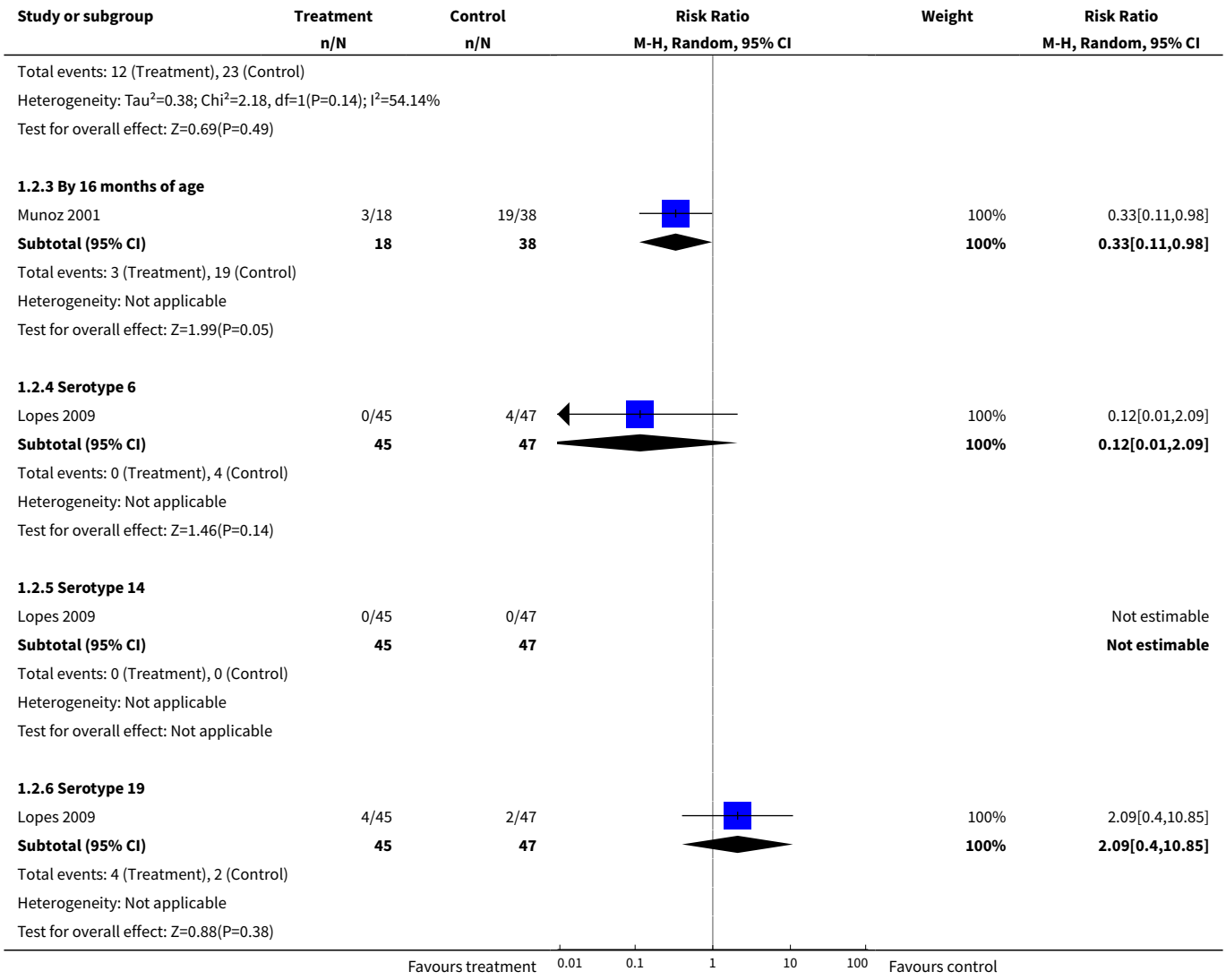
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.3 By 16 months of age	1	56	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.11, 0.98]
2.4 Serotype 6	1	92	Risk Ratio (M-H, Random, 95% CI)	0.12 [0.01, 2.09]
2.5 Serotype 14	1	92	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.6 Serotype 19	1	92	Risk Ratio (M-H, Random, 95% CI)	2.09 [0.40, 10.85]
3 Neonatal antibody levels at birth			Other data	No numeric data
3.1 Serotype 6			Other data	No numeric data
3.2 Serotype 14			Other data	No numeric data
3.3 Serotype 19			Other data	No numeric data
4 Maternal antibody levels post vaccination			Other data	No numeric data
4.1 Serotype 6			Other data	No numeric data
4.2 Serotype 14			Other data	No numeric data
4.3 Serotype 19			Other data	No numeric data
5 Percentage of mothers with seroprotection	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Serotype 6 at delivery	1	340	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [1.31, 1.69]
5.2 Serotype 14 at delivery	1	340	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [1.25, 1.56]
5.3 Serotype 19 at delivery	1	340	Risk Ratio (M-H, Fixed, 95% CI)	2.29 [1.89, 2.76]
5.4 Serotype 6 at 12 months post-delivery	1	340	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [1.00, 1.12]
5.5 Serotype 14 at 12 months post-delivery	1	340	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.98, 1.15]
5.6 Serotype 19 at 12 months post-delivery	1	340	Risk Ratio (M-H, Fixed, 95% CI)	1.59 [1.37, 1.85]
6 Adverse maternal effects	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 Tenderness at the injection site	2	130	Risk Ratio (M-H, Random, 95% CI)	3.20 [0.32, 31.54]

Analysis 1.1. Comparison 1 Pneumococcal vaccine versus control vaccine, Outcome 1 Neonatal infection.



Analysis 1.2. Comparison 1 Pneumococcal vaccine versus control vaccine, Outcome 2 Pneumococcal colonization.





Analysis 1.3. Comparison 1 Pneumococcal vaccine versus control vaccine, Outcome 3 Neonatal antibody levels at birth.

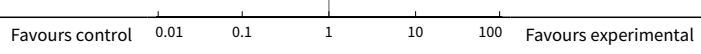
			Neonatal antibody levels at birth			
Study	**Treatment N**	**Treatment IgG GM**	**Treatment 95% CI**	**Control N**	**Control IgG GM**	**Control 95% CI**
			Serotype 6			
Munoz 2001	20	3.7	2.6 to 5.3	40	1.1	0.8 to 1.5
O' Dempsey 1996	43	2.7	1.7 to 4.4	26	5.7	2.9 to 11.3
Quiambao 2003	82	5.3	4.0 to 7.1	42	0.87	0.58 to 1.3
			Serotype 14			
Munoz 2001	19	13.4	7.3 to 25.1	39	3.0	2.2 to 3.9
O' Dempsey 1996	41	13.1	8.6 to 20.0	23	7.1	3.7 to 13.3
Quiambao 2003	82	8.1	6.1 to 10.7	42	2.4	1.6 to 3.7
			Serotype 19			
Munoz 2001	19	3.6	2.3 to 5.6	39	1.5	1.1 to 2.1
O' Dempsey 1996	43	4.1	2.7 to 5.9	24	3.6	1.8 to 7.3
Quiambao 2003	82	21.9	15.2 to 31.6	42	3.9	2.5 to 6.1

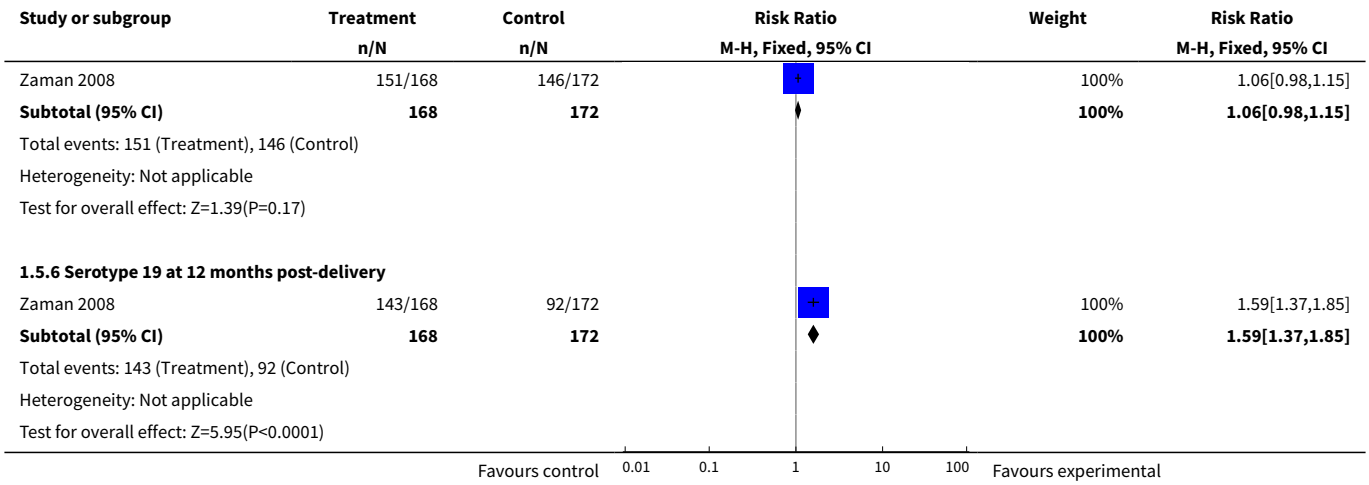
Analysis 1.4. Comparison 1 Pneumococcal vaccine versus control vaccine, Outcome 4 Maternal antibody levels post vaccination.

		Maternal antibody levels post vaccination				
Study	Treatment N	Treatment IgG GM	Treatment 95% CI	Control N	Control IgG GM	Control 95% CI
Serotype 6						
Munoz 2001	20	4.4	2.7 - 7.1	40	0.9	0.6 - 1.3
O' Dempsey 1996	49	7.3	4.4 - 12.0	26	14.4	6.4 - 32.7
Shahid 1995	29	13.8	NA	24	5.3	NA
Serotype 14						
Munoz 2001	20	16.8	8.0 - 35.5	40	3.0	2.2 - 4.0
O' Dempsey 1996	49	43.1	39.5 - 70.6	26	18.8	9.2 - 38.8
Serotype 19						
Munoz 2001	20	3.7	2.3 - 6.0	40	1.4	1.0 - 1.9
O' Dempsey 1996	49	11.8	7.7 - 18.2	26	10.3	4.3 - 25.2
Shahid 1995	29	17.4	NA	24	4.7	NA

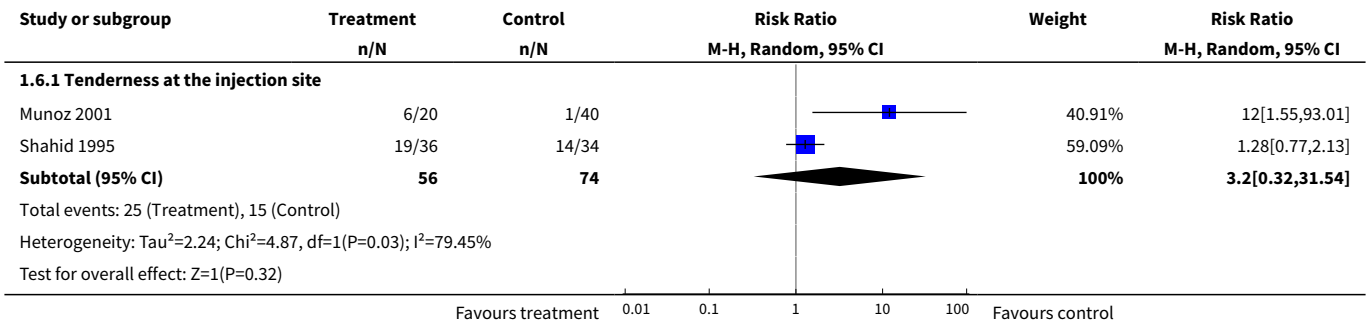
Analysis 1.5. Comparison 1 Pneumococcal vaccine versus control vaccine, Outcome 5 Percentage of mothers with seroprotection.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.5.1 Serotype 6 at delivery					
Zaman 2008	154/168	106/172		100%	1.49[1.31,1.69]
Subtotal (95% CI)	**168**	**172**		**100%**	**1.49[1.31,1.69]**
Total events: 154 (Treatment), 106 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=6.16(P<0.0001)					
1.5.2 Serotype 14 at delivery					
Zaman 2008	157/168	115/172		100%	1.4[1.25,1.56]
Subtotal (95% CI)	**168**	**172**		**100%**	**1.4[1.25,1.56]**
Total events: 157 (Treatment), 115 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=5.83(P<0.0001)					
1.5.3 Serotype 19 at delivery					
Zaman 2008	154/168	69/172		100%	2.29[1.89,2.76]
Subtotal (95% CI)	**168**	**172**		**100%**	**2.29[1.89,2.76]**
Total events: 154 (Treatment), 69 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=8.61(P<0.0001)					
1.5.4 Serotype 6 at 12 months post-delivery					
Zaman 2008	160/168	155/172		100%	1.06[1,1.12]
Subtotal (95% CI)	**168**	**172**		**100%**	**1.06[1,1.12]**
Total events: 160 (Treatment), 155 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.81(P=0.07)					
1.5.5 Serotype 14 at 12 months post-delivery					





Analysis 1.6. Comparison 1 Pneumococcal vaccine versus control vaccine, Outcome 6 Adverse maternal effects.



APPENDICES

Appendix 1. Search strategy

In the initial version of the review, we searched the Cochrane Central Register of Controlled Trials (*The Cochrane Library* 2004, Issue 2), MEDLINE (January 1966 to June 2004) and EMBASE (January 1985 to June 2004).

CENTRAL (*The Cochrane Library* 2004, Issue 2)

#1 PREGNANCY*:ME
#2 PREGNAN*
#3 MATERN*
#4 ANTEPART*
#5 PRENATAL
#6 ANTENATAL
#7 PERINATAL
#8 ((((((#1 or #2) or #3) or #4) or #5) or #6) or #7)
#9 PNEUMOCOCC*
#10 PNEUMOCOCCAL*:ME
#11 (#9 or #10)
#12 VACCIN*
#13 VACCINE*:ME
#14 IMMUNUNIZATION*:ME
#15 ((#12 or #13) or #14)

#16 (#11 and #15)
#17 (#8 and #16)

We adapted the above search strategy to search MEDLINE (January 1966 to June 2004) and EMBASE (January 1985 to June 2004) by selecting appropriate MeSH and/or keywords from their respective thesauri.

WHAT'S NEW

Date	Event	Description
30 September 2014	New citation required but conclusions have not changed	Review updated.
30 September 2014	New search has been performed	Search updated. Seven new reports were identified. All of them reported new information for two included studies (Lopes 2009; Zaman 2008). Data from the new reports were added. A 'Summary of findings' table has been incorporated.

HISTORY

Protocol first published: Issue 3, 2004
Review first published: Issue 1, 2006

Date	Event	Description
31 December 2011	New search has been performed	Search updated. One new trial identified (Zaman 2008) and included. Trial reports previously awaiting classification, have now been incorporated into the review as two new included studies (Lopes 2009; Obaro 2004) and one ongoing study (Dunbar 2007). One study, previously classified as excluded (Quiambao 2003) has now been included. This updated review is now comprised of seven included studies, two excluded studies and one ongoing study.
31 December 2011	New citation required but conclusions have not changed	For this update we have added two new included studies. The overall results and conclusions have not changed.
31 December 2011	New search has been performed	Updated search, adding two included studies.
6 July 2011	Amended	Search updated. Eight reports added to Studies awaiting classification (Deubzer 2004; Dunbar 2007a; Henkle 2010; Holmlund 2011; Lopes 2009a; Obaro 2004a; Quiambao 2007; Steinhoff 2010).
8 May 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Surasith Chaithongwongwatthana (SC) designed the review and wrote the protocol. Waralak Yamasmit (WY), Sompop Limpongsanurak (SL), Pisake Lumbiganon (PL), and Jorge Tolosa (JT) provided general advice and approved the published version. SC and WY conducted and drafted the review. SL, PL, and JT gave intellectual comments on the review and approved the final version.

For the 2014 update, SC and WY contributed to data extraction and assessment of risk of bias in studies. SC conducted data analysis and updated the main text. The final version of the updated review was approved by all review authors.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Chulalongkorn University, Thailand.
- Faculty of Medicine Vajira Hospital, Navamindradhiraj University, Thailand.
- Khon Kaen University, Thailand.
- Oregon Health Science University, USA.
- Global Network for Perinatal and Reproductive Health (GNPRH), USA.

External sources

- Thailand Research Fund (Senior Research Scholar), Thailand.
- UNDP-UNFPA-UNICEF-WHO-World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), Department of Reproductive Health and Research (RHR), World Health Organization, Switzerland.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

For the initial version of the review, we searched the Cochrane Central Register of Controlled Trials (*The Cochrane Library* 2004 Issue 2), MEDLINE (January 1966 to June 2004) and EMBASE (January 1985 to June 2004). This additional searching has not been carried out for this update.

The outcomes have been separated into 'Primary' and 'Secondary' outcomes and the methods have been updated to reflect the latest *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

INDEX TERMS

Medical Subject Headings (MeSH)

Gestational Age; Pneumococcal Infections [immunology] [*prevention & control]; Pneumococcal Vaccines [*administration & dosage]; Randomized Controlled Trials as Topic; Vaccination [*methods]

MeSH check words

Female; Humans; Infant; Infant, Newborn; Pregnancy