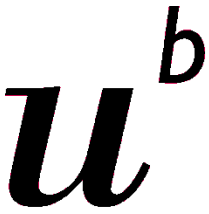
Review protocol

Systematic Review of Pneumococcal Conjugate Vaccines: Safety, Immunogenicity, Efficacy and Effectiveness

Pippa Scott, Nicola Low and Matthias Egger



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Institute of Social and Preventive Medicine

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Definitions

Booster (or Booster dose)	A pneumococcal vaccination given some time after the primary series. Where multiple doses are given in the primary series, a booster is usually a dose given after an interval longer than the interval between doses in the primary series. In schedules consisting of one dose in the primary course, a further dose might be considered a booster if given three or more months after the first.
Carriage	The colonization of the nasopharynx by *S. pneumoniae*.
Effectiveness	The extent to which a specific intervention, procedure, regimen, or service, when deployed in the field in routine circumstances, does what it is intended to do for a specified population [1]. In the context of this review it refers to clinical outcomes assessed in settings other than randomized (or quasi-randomized) controlled trials, and refers to any result, not only those which are beneficial.
Efficacy	Efficacy has been defined as "the extent to which a specific intervention, procedure, regimen, or service provides a beneficial result under ideal conditions"[1], but in this review it will be used to mean clinical outcomes assessed in randomized (or quasi-randomized) controlled trials only, and refers to any result, not only those which are beneficial. This will be estimated through the equation: $$VE = \left(1 - \frac{rate\ (or\ risk) in\ vaccinated}{rate\ (or\ risk) in\ unvaccinated}\right) \text{x } 100$$

Abbreviations

GSK	GlaxoSmithKline
PCV	Pneumococcal conjugate vaccine
PPV	Pneumococcal polysaccharide vaccine
ST	Serotype/s
VE	Vaccine efficacy
WHO	World Health Organization

1 Background

Streptococcus pneumoniae can cause a range of illnesses including pneumonia, invasive disease (septicemia and meningitis), bronchitis, otitis media and sinusitis. Death can also occur as a result of infection with *S. pneumoniae* and the WHO estimated in 2005 that 0.7-1 million children die annually from pneumococcal disease. [2]

Vaccines have been used as a preventive measure against pneumococcal disease but there is little evidence, based on high quality randomized controlled trials, that the existing 23-valent pneumococcal polysaccharide vaccine (PPV23) is effective in preventing pneumococcal pneumonia or death in adults[3]. Its efficacy against invasive pneumococcal disease remains controversial. [3, 4] Additionally PPV23, available since the early 1980s (licensed in the US in1983), is not licensed in children less than two years old. Pneumococcal conjugate vaccines (PCV), based on the conjugation of selected capsular polysaccharides to a protein carrier, have been more recently developed with the first being licensed in the US in 2000 [5]. The seven-valent conjugate vaccine (PCV7, containing serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F, Prevnar®, Wyeth) is licensed in the US for use in children up to nine years of age [6] and is currently in use around the world. A vaccine with 10 serotypes (serotypes 1, 5 and 7F in addition to the seven serotypes in Prevnar®) has recently (March 2009) received European Commission authorization for children from six weeks to two years of age (Synflorix™, GSK) [7] Other vaccines with up to 13 serotypes are in development and Wyeth recently (March 31st 2009) announced that a Biologic License Application (BLA) has been submitted to the U.S. Food and Drug Administration (FDA) for a 13-valent vaccine (Prevnar 13™) containing serotypes 1, 3, 5, 6A, 7F and 19A in addition to the serotypes in the seven-valent vaccine [8]. The World Health Organization (WHO) position paper, published in 2007, states that it should be a priority to include the seven-valent pneumococcal conjugate vaccine in national immunization programs, especially in countries where mortality among children aged less than 5 years is greater than 50 per 1000 live births, or where more than 50,000 children die annually [2].

A range of schedules have been used for pneumococcal conjugate vaccines, usually consisting of two or three doses in the primary vaccination series, and sometimes followed by a booster (of either PCV or PPV23) which is often given in the second year of life. A review by Oosterhuis-Kafeja et al. studies published before May 2006 concluded that the percentage of infants achieving the protective cut-off set by the WHO in trials using PCV7 or a nine-valent pneumococcal conjugate vaccine (PCV9) with “2+1” schedules (two doses in the primary vaccination series plus a booster) one month after the last priming dose was comparable to that found with “3+1” schedules assessed at the same time point [9]. Data are rapidly accumulating on this topic (a repeat of the search strategy used by Oosterhuis-Kafeja et al. produced 822 returned articles compared with the 511 articles retrieved in 2006) and the need for a new and systematic review is growing. In particular, the safety, immunogenicity and clinical efficacy/effectiveness need to be examined for a range of schedules (particularly differing numbers of doses and different ages at initiation) to inform discussion and recommendations on optimizing pneumococcal vaccination schedules for a variety of settings. A systematic review of evidence from all available sources will summarize the evidence available to date and identify gaps in evidence. Through this it will provide parameters for infectious disease modeling form a basis for a framework for guiding decisions on appropriate PCV vaccinations schedules and aid the targeting of primary research to fill the identified data gaps.

2 Objective

To systematically identify and synthesize data on safety, immunogenicity, clinical efficacy,

and effectiveness of pneumococcal conjugate vaccine for a variety of schedules.

3 Study questions

Study questions are listed below. In this list, the term “outcomes” refers to safety, immunogenicity, clinical efficacy, clinical effectiveness and pneumococcal carriage. Each question is applicable to both general population and high-risk subgroups (e.g. HIV-infected children). These questions are further illustrated in Table 1.

1. What is the effect of any PCV schedule on relevant outcomes?
2. What is the effect of the number of PCV doses on relevant outcomes?
3. What is the effect of the age at initiation of PCV vaccination on relevant outcomes?
4. What is the effect of the length of dosing interval on relevant outcomes?
5. What is the effect of giving a booster on relevant outcomes?
6. What is the effect of using PPV23 as a booster rather than PCV on relevant outcomes?
7. What is the effect of co-administration of other vaccines on relevant outcomes?
8. What is the effect of co-administration of other medical preparations (e.g. vitamin A) on relevant outcomes?

Table 1: Study questions

	Outcomes or measures*										
	Safety	Immuno-genicity	Clinical efficacy - RCTs only. Includes duration and degree			Clinical effectiveness - other study designs			Carriage - in RCTs and other study designs (separately)		
			All ST	Vaccine ST	Non-vaccine ST	All ST	Vaccine ST	Non-vaccine ST	All ST	Vaccine ST	Non-vaccine ST
Any PCV schedule	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Number of PCV doses	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Age at initiation of PCV vaccination	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Length of dosing interval	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
A booster dose	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
PCV as a booster rather than PPV23	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Co-administration of other vaccines	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Co-administration of other medical preparations	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔

ST sero-types
* for both general population and high-risk subgroups

4 Methods

We will identify and critically appraise the best available evidence that addresses important outcomes and provide an evidence profile that summarizes the findings for each outcome.

In this section we set out the research questions and the methods for preparing the systematic review.

Due to the complex nature of the review and the questions being investigated, the review will be described and undertaken in two parts:

1. A review of randomized controlled trials (RCTs) or quasi-randomized controlled trials ("Part A") , and
2. A review of data available from other study designs ("Part B")

PART A: Randomized and quasi-randomized controlled trials

4.1 Inclusion Criteria

We will search for reports of studies in which the population, comparison group, intervention, and outcomes fulfil the following criteria:

4.1.1 Study design

We will consider the following study designs for inclusion: Randomized controlled trials; quasi-randomized controlled trials (e.g. those with allocation strategies based on alternation, date of birth or case record number).

4.1.2 Population

All age groups will be considered in this review.

4.1.3 Intervention

A licensed pneumococcal conjugate vaccine, or alternatively a pneumococcal conjugate vaccine which has entered phase II/III testing (other than dose finding studies alone) and whose development has not been permanently or indefinitely halted. Any schedule of administration will be included.

4.1.4 Comparison

One or more of the following comparisons:

1. a comparison between pneumococcal conjugate vaccination (any schedule) and pneumococcal polysaccharide vaccine.
2. a comparison between pneumococcal conjugate vaccination (any schedule) and placebo or a non-pneumococcal vaccine.
3. a comparison between different numbers of doses of pneumococcal conjugate vaccine in the primary vaccination series.
4. a comparison between different ages at first vaccination and/or different dosing intervals where the same numbers of doses pneumococcal conjugate vaccine are

given in the primary vaccination series.

5. a comparison between a booster dose of pneumococcal conjugate vaccine given after the first year of life and the same schedule without the booster dose, or with a booster dose given at a different time point or with a different pneumococcal vaccine used as a booster.
6. a comparison between any pneumococcal conjugate vaccine schedule and the same schedule plus a co-administered childhood vaccine other than pneumococcal vaccine.
7. any other comparison encountered in the course of the review which might be relevant for optimizing schedules for pneumococcal conjugate vaccines.

4.1.5 Outcomes reported

One or more of the following:

Safety

a. Serious adverse events after vaccination
b. Mortality after vaccination
c. Wheezing after vaccination
d. Other respiratory disease after vaccination

Immunogenicity

a. seropositivity after vaccination
b. seroconversion (changing from seronegative before vaccination to seropositive after vaccination)
c. seroconversion (four-fold rise in titer/concentration or similar measure)
d. geometric mean titer/concentration (or other summary measure)
e. mean (or other summary measure) change in titer (or similar measure) in individuals (before vs. after vaccination).

Clinical efficacy

WHO definitions will be used for these outcomes.

a. pneumonia from all causes
b. presumptive pneumococcal pneumonia (any serotype, vaccine serotype, or non-vaccine serotype)
c. definitive pneumococcal pneumonia (any serotype, vaccine serotype, or non-vaccine serotype)
d. death from all causes
e. death from pneumonia, and
f. death from pneumococcal infection (any serotype, vaccine serotype, or non-vaccine serotype)
g. bacteremia or invasive pneumococcal disease (any serotype, vaccine serotype, or

non-vaccine serotype)

h. pneumococcal meningitis (any serotype, vaccine serotype, or non-vaccine serotype)
i. otitis media (all causes)
j. pneumococcal otitis media (any serotype, vaccine serotype, or non-vaccine serotype)
k. bronchitis from all causes
l. sinusitis

Nasopharyngeal carriage

a. percentage carriage of *S. pneumoniae* (any serotype) before and after vaccination
b. percentage carriage of *S. pneumoniae* (broken down by serotype) before and after vaccination

4.2 Exclusion criteria

- Uncontrolled studies, observational intervention studies, and animal and laboratory studies will be excluded.
- Studies on vaccines which have never been licensed and whose development has been permanently or indefinitely halted will be excluded.
- Dose finding studies will be excluded.

4.3 Search strategy

4.3.1 Electronic databases

The following databases will be searched from beginning of records for each database through to 2009 without language restrictions:

- Embase.com (in addition to the 12 million EMBASE records from 1974 onwards, Embase.com also includes over 7 million unique records from MEDLINE from 1966 to date, allowing both databases to be searched simultaneously). Alternatively, EMBASE and MEDLINE will be searched separately.
- The Cochrane Library (including the Cochrane Central Register of Controlled Trials (CENTRAL));
- National and international registries on clinical trials as detailed by the CochraneHandbook (Box 6.2.h)[10, 11]. These include databases covering Australia, China, India, Japan, the Netherlands, New Zealand, South Africa, the United Kingdom, the United States and well as the European Union, International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) and other international registers.
- Regulatory authority dossiers for licensure (e.g. FDA)
- African Index Medicus (AIM); Indian Medlars Centre (IndMed); Latin American and Caribbean Health Sciences Literature (LILACS), and other regional databases.

Search terms

Search terms will use Medical Subject Headings (MeSH) or terms specific to each database and will be based on search strategies defined in the Cochrane Handbook [10, 11] and will include:

- terms relating to pneumococcal vaccine/s, and
- terms relating to the word conjugate
- terms combining vaccination and pneumococcal disease

We will not specify search terms for population group, study design or outcome.

4.3.2 Additional searches

Due to much data on PCV remaining unpublished we will perform additional searches.

- We will search for potentially eligible studies in the reference lists of relevant reviews and articles identified through the electronic literature search, based on the titles of cited papers.
- We will contact experts in the field of pneumococcal conjugate vaccine to determine if they are aware of unpublished or ongoing trials which may be eligible for inclusion.
- We will contact the manufacturers of pneumococcal conjugate vaccines to obtain unpublished data on trials of such vaccines.

4.4 Selection of eligible studies

The lists of articles identified by the search strategy will be independently reviewed by at least two suitably qualified reviewers using the inclusion and exclusion criteria listed in paragraphs 4.1 and 4.2. Any study selected as being potentially eligible by either reviewer or which contains insufficient information for a decision to be made, will be retained for review of the full text.

4.4.1 Potentially eligible studies

The reviewers will read the abstract of each identified article if fewer than 500 articles are returned in total. If the searches identify 500 or more articles, the reviewers will select potentially eligible titles first and will then read the abstracts of titles that potentially fit the inclusion criteria. If no abstract is available electronically, the full text of the article will be requested. The abstracts of articles identified through additional searches will be reviewed in the same manner as for studies identified through database searches.

4.4.2 Retrieval of full-text articles

We will obtain the full text of articles or other documents reporting studies identified as being potentially eligible for inclusion. We will make every effort to locate documents through internet downloads, inter-library loans and contacting authors of reviews citing potentially eligible documents. We will request translation if necessary to confirm or refute eligibility.

4.4.3 Selection of studies for inclusion

Each full text article will be examined by at least two reviewers and lists of studies considered eligible for inclusion will be compared. Studies identified by all reviewers as being eligible for inclusion and having adequate data for extraction will be included in the review. Where there are discrepancies, the reasons for these will be discussed and a decision about inclusion reached by consensus. If there is no agreement, a further independent reviewer will adjudicate to make a final decision about eligibility.

4.5 Data extraction forms

We will develop forms for extracting consistent data about:

- exposures and outcomes (including methods or criteria for diagnosis);
- tests used to assess outcomes, any cut-off points used in the assessment of immunogenicity and the time between last vaccination and outcome assessment
- occurrence of disease which may affect immunogenicity outcomes;
- co-administration of other vaccines or pharmaceuticals;
- potential confounders if relevant;
- background data (e.g. geographic and demographic information);
- methodological and reporting quality (specific for each type of study design and based on published checklists of items likely to cause bias); and
- other potentially relevant information such as funding source.

Study designs will also be assessed to determine whether results are a measure of direct effects, indirect effects, or a combination of both.

Data extraction forms will be designed to capture any information for the outcomes listed in paragraph 4.1.5. If an outcome can be assessed by more than one diagnostic method a hierarchy of these methods will be defined as the extraction form is being developed and finalized prior to data analysis. If an outcome was assessed by more than one diagnostic method with in a study, results obtained by each method will be extracted.

We will pilot test the forms to ensure ease of use and capture of all relevant data.

The forms will be developed using Epidata (Epidata version 3.1, EpiData Association, Odense, Denmark).

4.6 Data extraction

Appropriately qualified people will extract and enter data independently and in duplicate from each included study. Articles in languages other than English will either be translated first and then duplicate data extraction conducted as above or, if there are two reviewers who understand the language of publication, they will extract the data directly.

Data entry will be into Epidata. The two files of independently extracted data will be compared using the validation function available in this program. Discrepancies in data extraction or data entry will be resolved by consensus. If there is no agreement a third independent reviewer will adjudicate to make a final decision.

Studies might be excluded at the data entry stage if it becomes apparent that inclusion criteria are not met or there is not enough information in the documents to extract the required data.

We will not contact authors for clarification about details of their studies.

4.7 Data analysis

We will produce descriptive tables summarizing information about study design, study quality and results of all included studies.

We will analyze and report available data for each outcome as defined. If an outcome can be assessed by more than one diagnostic method, analysis will be conducted using data from the highest level available in each study, using a predefined hierarchy. If there are enough studies reporting an exposure-outcome association, or the frequency of an outcome, we will present these in forest plots and consider combining the data statistically in a meta-analysis. We will examine heterogeneity of the results first using chi-square tests and I-square tests.[12] If meta-analysis is appropriate, we will calculate summary weighted effect measures and 95% confidence intervals, using random effects models [13]. If the results are too heterogeneous to combine statistically, we will explore this using stratification and/or meta-regression techniques as appropriate. Stratification will be on criteria such as quality of study, baseline intervention (e.g. placebo or non-pneumococcal vaccine), time since last vaccination, properties of all groups in each study which may have a bearing on outcomes (e.g. co-administration of other vaccines or pharmaceuticals), the randomization scheme (individual vs. cluster) and other suitable criteria. If additional intervention/s which might affect outcome measures are applied differentially over intervention groups within a study (potentially introducing confounding), comparisons between groups receiving levels of the additional interventions will either be excluded from analyses or analyzed separately from data from other studies (e.g. to examine the effects of co-administration of other vaccines on immunogenicity).

If sufficient data are available, results will also be examined for apparent bias in the reporting/publication of studies using funnel plots and the Egger test.[14]

If appropriate, vaccine efficacy will be calculated taking study design and parameters available (e.g. cumulative incidence or incidence rates) in to account (based on discussions by Halloran et al. [15, 16]). Numbers needed to treat to prevent one case of a clinical outcome (NNTs) will also be calculated if appropriate.

Data analysis will be conducted with Stata (Intercooled Stata 9.2 , StataCorp, Texas, USA)

4.8 Assessment of study quality

Due to the influence study quality can have on meta-analyses [3] , we will assess study quality using checklists of items associated with methodological and reporting quality that are specific to each study design (e.g. for RCTs, those listed in Egger et al. 2001 [14]).

4.9 Write report

Reports will be written following the appropriate guidelines (e.g. QUOROM Guidelines for reporting of meta-analyses and systematic reviews of randomized controlled trials) and will clearly present the methods used as well as findings.

PART B: Other study designs

4.10 Inclusion Criteria

We will search for reports of studies which fulfil the following criteria:

4.10.1 Study design

We will consider the following study designs for inclusion: case-control studies, cohort studies, cross-sectional studies, population surveillance data, and ecological studies.

4.10.2 Population

All age groups will be considered in this review

4.10.3 Intervention

A licensed pneumococcal conjugate vaccine or, alternatively, a pneumococcal conjugate vaccine which has entered phase II/III testing (other than dose finding studies alone) and whose development has not been permanently or indefinitely halted. Any schedule of administration will be included.

4.10.4 Comparison

We will consider

A. surveillance or other population-based data without a control group where there are both:
    1. a clearly defined point in time when the intervention occurred [17], and
    2. at least 3 data points before and 3 after the intervention [17]
B. other study designs with one or more of the following comparisons:
    1. a comparison between pneumococcal conjugate vaccination (any schedule) and pneumococcal polysaccharide vaccine.
    2. a comparison between pneumococcal conjugate vaccination (any schedule) and no pneumococcal vaccination.
    3. a comparison between different numbers of doses of pneumococcal conjugate vaccine in the primary vaccination series.
    4. a comparison between different ages at first vaccination and/or different dosing intervals where the same numbers of doses pneumococcal conjugate vaccine are given in the primary vaccination series.
    5. a comparison between a booster dose of pneumococcal conjugate vaccine given after the first year of life and the same schedule without the booster dose, or with a booster dose given at a different time point or with a different pneumococcal vaccine used as a booster.
    6. a comparison between any pneumococcal conjugate vaccine schedule and the same schedule plus a co-administered childhood vaccine other than pneumococcal vaccine.
    7. any other comparison encountered in the course of the review which might be

relevant for optimizing schedules for pneumococcal conjugate vaccines.

4.10.5 Outcomes reported

Studies must report one or more of the outcomes listed in section 4.1.5, above.

4.11 Exclusion criteria

- Animal and laboratory studies will be excluded.
- Studies on vaccines which have never been licensed and whose development has been permanently or indefinitely halted will be excluded.
- Dose finding studies will be excluded.

4.12 Search strategy

See section 4.3 for the search strategy.

4.13 Selection of eligible studies

See section 4.4 for methods of selection of eligible studies

4.14 Data extraction forms

We will develop forms (specific for study design if required) for extracting consistent data about:

- exposures and outcomes (including methods or criteria for diagnosis);
- tests used to assess outcomes, and the time between last vaccination and outcome assessment;
- co-administration of other vaccines or pharmaceuticals;
- potential confounders ;
- background data (e.g. geographic and demographic information);
- methodological and reporting quality (specific for each type of study design and based on published checklists of items likely to cause bias); and
- other potentially relevant information such as funding source.

Data extraction forms will be designed to capture any information for the outcomes listed in paragraph 4.1.5. If an outcome can be assessed by more than one diagnostic method a hierarchy of these methods will be defined as the extraction form is being developed and finalized prior to data analysis. If an outcome was assessed by more than one diagnostic method with in a study, results obtained by each method will be extracted.

We will pilot test the forms to ensure ease of use and capture of all relevant data.

The forms will be developed using Epidata (Epidata version 3.1, EpiData Association, Odense, Denmark).

4.15 Data extraction

See section 4.6 for data extraction methods.

4.16 Data analysis

We will produce descriptive tables summarizing information about study design, study quality and results of all included studies.

We will analyze and report available data for each outcome as defined. Data from different study designs will be analyzed separately. If an outcome can be assessed by more than one diagnostic method, analysis will be conducted using data from the highest level available in each study, using a predefined hierarchy. If there are enough studies reporting an exposure-outcome association, or the frequency of an outcome, we will present these in forest plots and consider combining the data statistically in a meta-analysis. We will examine heterogeneity of the results first using chi-square tests and I-square tests.[12] If meta-analysis is appropriate, we will calculate summary weighted effect measures and 95% confidence intervals, using random effects models [13]. If the results are too heterogeneous to combine statistically, we will explore this using stratification and/or meta-regression techniques as appropriate. Stratification will be on criteria such as quality of study, and population characteristics of each study which may have a bearing on outcomes and other suitable criteria. If sufficient data are available, results will also be examined for apparent bias in the reporting/publication of studies using funnel plots and the Egger test.[14]

Data analysis will be conducted with Stata (Intercooled Stata 9.2 , StataCorp, Texas, USA)

4.17 Assessment of study quality

See section 4.8 for the assessment of study quality

4.18 Write report

See section 4.9 for details on report writing.

5 References

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