Pneumococcal conjugate vaccines:

A systematic review of data from randomized controlled trials and observational studies of childhood schedules using 7-, 9-, 10- and 13-valent vaccines

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Annexes

Abbreviations

b	booster (denotes the use of a pneumococcal conjugate vaccine booster or, if specified, a pneumococcal polysaccharide vaccine booster, when used in abbreviation of vaccine schedules)
CI	confidence interval
DSMB	Data and safety monitoring board
ELISA	enzyme-linked immunosorbent assay
FDA	United States Food and Drug Administration
GMC	geometric mean (antibody) concentration
I^2	I^2 statistic, a statistical measure of between-trial heterogeneity
IPD	invasive pneumococcal disease
ITT	intention-to-treat analysis
NVT	non-vaccine serotype(s)
OPA	opsonophagocytic activity
OR	odds ratio
p	Denotes the number of primary doses, when used in the abbreviation of a vaccination schedule, e.g. 3p means 3 primary doses
PCV	pneumococcal conjugate vaccine
PP	per protocol analysis
PPV	pneumococcal polysaccharide vaccine
RCT	randomized controlled trial
SAE	serious adverse event
SIDS	sudden infant death syndrome
USA	United States of America
VAT	vaccine-associated serotype(s)
VE	vaccine efficacy
v	valent
vs	versus
VT	vaccine serotype(s)
WHO	World Health Organization
95% CI	95% confidence interval

Definitions and clarifications

Adverse event (AE)	Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigation) product, whether or not related to the medicinal (investigation) product [1].
Bacteraemia	A positive *Streptococcus pneumoniae* culture from the blood.
Booster	For the purposes of this report, a booster is defined as a vaccine dose given after the last dose in a primary series, at 10 months of age or older. After catch-up schedules, a booster is defined as a dose given after an interval greater than the interval between the catch-up doses.
Catch-up dose(s)	PCV schedules started after 12 months of age, with no doses of PCV having been given in infancy.
Death from all causes	All deaths, regardless of cause.
Death from pneumonia	Death that has been classified by trial investigators as having been caused by pneumonia. Different levels of diagnostic certainty are included in this definition (e.g. clinical diagnoses of pneumonia, radiographically confirmed pneumonia and radiographically confirmed pneumonia using WHO criteria). Levels of diagnostic certainty are analysed separately, where possible.
Death from pneumococcal infection	Death that has been classified by trial investigators as having been caused by pneumococcal infection.
Definitive pneumococcal pneumonia	Pneumonia with a positive *Streptococcus pneumoniae* culture from a sample taken from the lung in conditions that minimize contamination of the sample (e.g. transthoracic lung biopsy). Different levels of diagnostic certainty are included in this definition (e.g. clinical diagnoses of pneumonia, radiographically confirmed pneumonia and radiographically confirmed pneumonia using WHO criteria). Levels of diagnostic certainty are analysed separately where possible. In this review, pneumonia with a positive *Streptococcus pneumoniae* culture from blood or another normally sterile site is considered a sub-group of invasive pneumococcal disease, not as definitive pneumococcal pneumonia.
Invasive pneumococcal disease (IPD)	A positive *Streptococcus pneumoniae* culture from a normally sterile body fluid (cerebrospinal fluid, blood, synovial fluid).
Otitis media	Otitis media as defined by trial investigators.
Pneumococcal otitis media	Otitis media as defined by trial investigators, with a positive *Streptococcus pneumoniae* culture.

Pneumonia from all causes	All cases of pneumonia, regardless or causative organism or pathogen. Different levels of diagnostic certainty are included in this definition (e.g. clinical diagnoses of pneumonia, radiographically confirmed pneumonia and radiographically confirmed pneumonia using WHO criteria). Levels of diagnostic certainty are analysed separately where possible.
Primary series	Vaccination doses given in infancy and completed before 12 months of age. Intended intervals between doses should be the same. Vaccine doses started after 12 months are referred to as catch-up doses.
Serious adverse event(s) (SAE)	Any adverse event that, at any dose, has one or more of the following attributes [1, 2]: i) Results in death. ii) Is life-threatening. iii) Requires inpatient hospitalization or prolongation of existing hospitalization. iv) Results in persistent or significant disability/incapacity. v) Results in an important medical event that may not be immediately life-threatening, nor directly result in death or hospitalization, but which may jeopardize the patient.
Seropositivity	An antibody concentration or titre above a defined threshold. A threshold of 0.35µg/ml was used to define seropositivity in the primary analysis. This level has been accepted by the World Health Organization (WHO) for the evaluation of new pneumococcal conjugate vaccines in head-to-head comparisons with the already licensed 7-valent PCV7 [1, 2].
Vaccine effectiveness	Effectiveness has been defined as a "measure of the extent to which a specific intervention, procedure, regimen, or service, when deployed in the field in the usual circumstances, does what it is intended to do for a specified population" [2]. In general, cohort and case–control studies report on effectiveness rather than efficacy. Vaccine effectiveness is estimated as: $$Vaccine\ effectiveness = \left(1 - \frac{rate\ (or\ risk)in\ vaccinated}{rate\ (or\ risk)in\ unvaccinated}\right) x\,1$$ In case–control studies it is estimated as: $$Vaccine\ effectiveness = (1 - odds\ ratio)\,x\,100$$ where the unvaccinated are the baseline in the calculated odds ratio.
Vaccine efficacy	Efficacy has been defined as "the extent to which a specific intervention, procedure, regimen or service provides a beneficial result under ideal conditions" [3]. In this review, it is used to refer to any result, not only those that are beneficial. Vaccine efficacy is estimated as: $$VE = \left(1 - \frac{rate\ (or\ risk)in\ vaccinated}{rate\ (or\ risk)in\ unvaccinated}\right) x\,100$$

Section 1. Executive summary

1.1. Objectives

The objectives of the systematic review were to collect evidence on pneumococcal conjugate vaccine (PCV) schedules, to summarize the available data and to identify gaps in evidence that might shape future research in this area.

1.2. Review methods

A search was conducted in 12 electronic databases of published articles, trial registers, industry databases and other documents from the earliest citation until August 2009. The search was updated in March 2010.

Items selected for inclusion in the search reported on randomized controlled trials (RCTs), cohort or case–control studies in children up to 18 years of age, using a 7-, 9-, 10- or 13-valent PCV schedule.

Eligible studies included comparisons between schedules with a different number of doses, different ages at the start of vaccination, a different interval between doses, or a PCV schedule compared with no PCV.

Structured piloted forms were used to extract data on: the schedule; clinical disease outcomes (invasive pneumococcal disease, IPD, pneumonia, otitis media); mortality; nasopharyngeal carriage of pneumococci; serotype specific seropositivity (%); geometric mean concentrations (GMC); study characteristics; and potential sources of bias and heterogeneity.

Where appropriate, random effects meta-analyses were used to combine results statistically. Between-trial heterogeneity was described using the I^2 statistic, where values below 25% represent low heterogeneity, up to 50% moderate heterogeneity, up to 75% equal severe heterogeneity and more than 75%, very severe heterogeneity.

Vaccine schedules are described using the following abbreviated style :

- 3p 3 doses in the primary (p) vaccination schedule with all doses given before 12 months of age;
- +1 a booster dose.

All doses are PCV unless otherwise noted. Protective effects of PCV against clinical disease are reported as vaccine efficacy (VE) in RCTs, and vaccine effectiveness in case–control studies.

1.3. Results

A total of 3217 items were identified, comprising 31 eligible RCTs, 18 eligible cohort studies and two eligible case–control studies.

Thirty-one different types of schedule comparison were examined among these RCTs, including a PCV schedule versus (vs) no vaccination; 15 schedules were examined in the cohort studies and 11 in the case–control studies.

1.3.1. Direct comparison between PCV schedules

The scarce data on clinical outcomes available from RCTs that directly compared different PCV schedules were extracted from reasons for loss to follow-up or from reports of (serious) adverse events. These were described but not used to estimate measures of the effect of PCV. Limited data were extracted on clinical disease outcomes and mortality from the case–control and cohort studies.

Three RCTs reported on carriage data for direct comparisons between schedules. Results showed that vaccination with more doses of PCV might result in less carriage of vaccine serotypes, but the evidence for this was not strong.

Immunological data were the most abundant outcome type for direct comparison between schedules. Schedules containing 2 or 3 primary doses generally resulted in high levels of seropositivity (above a threshold of 0.35µg/ml) 1 month after the last primary vaccination. Differences between these schedules after primary vaccination were generally small, with the exception of serotypes 6B and 23F. Booster doses resulted in increased proportions of seropositive individuals.

1.3.1.1 2p vs 1p schedules and 3p vs 1p schedules

There were no data about clinical disease outcomes. Limited data about mortality were collected in one RCT.

Carriage data were reported in two RCTs. At 6 months of age, 3 primary doses of vaccine might result in less carriage of vaccine serotypes than 1 primary dose but the confidence interval around the combined odds ratio was wide (2 RCTs). By 12 and 18 months of age both 2p and 3p schedules might result in less vaccine serotype carriage than 1 primary dose but confidence intervals were again wide (1 RCT). Results for non-vaccine serotype carriage were less consistent than for vaccine serotypes, although no marked differences were seen between schedules.

Immunological data were collected in 2 RCTs. Schedules containing 1 primary dose were less immunogenic than 2p and 3p schedules at 6 months of age for all serotypes for both seropositivity and GMC (2 RCTs). Differences between 1p and either 2p or 3p schedules at 12 and 17 months (1 RCT) were less marked for both outcomes.

1.3.1.2 3p vs 2p schedules

There were no data about clinical disease outcomes from RCTs or cohort studies. Limited data about mortality were collected in one RCT. One case–control study reported an odds ratio of 1.5 (95% confidence interval, CI 0.54, 4.35) for vaccine serotype IPD, adjusted for the presence of underlying conditions, comparing 3p with 2p schedules.

Carriage data were reported in two RCTs. At 6 months of age, 3p schedules might result in less carriage of vaccine serotypes than 2p schedules, but the confidence interval was wide (2 RCTs). Results for vaccine serotype carriage showed neither schedule to be consistently better at older age, but 3p doses might be slightly favoured over 2p doses (1 RCT). Results for non-vaccine serotype carriage showed no marked differences between schedules.

Immunological data were reported in five RCTs and one cohort study. Both 3p and 2p schedules resulted in high levels of seropositivity for most serotypes at 6 months of age (5 RCTs), with levels generally slightly higher in the 3p group. The biggest differences were seen for serotypes 6B

and 23F. Differences at 6 months of age appeared to persist at 12 months (2 RCTs), but with a decline in the proportion seropositive in both groups. Between-trial heterogeneity in results was often high in these analyses.

1.3.1.3 2p+1 vs 2p schedules

No data about clinical disease outcomes or mortality from RCTs or cohort studies were available. One case–control study reported an odds ratio of 0.85 (95% CI 0.08, 9.1) for vaccine serotype invasive pneumococcal disease, adjusted for the presence of underlying conditions, comparing 2p+1 to 2p schedules.

Carriage data were reported in one RCT. At 12 months of age, 1 month after the booster dose, the 2p+1 group appeared to show less vaccine serotype carriage than the 2p group. This was more marked at 18 months of age, but no advantage was apparent by 24 months of age.

No immunological data were available for this comparison.

1.3.1.4 3p vs 2p+1 schedules

No data about clinical disease outcomes or mortality from RCTs were available. One case–control study reported an odds ratio of 1.5 (95% CI 0.15, 14.6) for vaccine serotype IPD, adjusted for the presence of underlying conditions, comparing 3p to 2p+1 schedules.

No carriage data from RCTs, cohort studies or case–control studies were available as of 1 September 2011, although data relevant to this review is expected to be published soon.

Immunological data after the booster dose were reported in one RCT (results after the primary series are reported in the comparison of 3p vs 2p schedules). At 13 months, antibody concentrations were substantially higher in the 2p+1 group (1 month after the booster) than the 3p group (7 months after the last primary dose), but these differences were smaller by 19 months (1 RCT).

1.3.1.5 3p+1 vs 2p+1 schedules

Limited clinical disease outcome data were collected in two RCTs. One case–control study reported an odds ratio of 0 (95% CI 0, 10.1) for vaccine serotype IPD, adjusted for the presence of underlying conditions, comparing 3p+1 to 2p+1 schedules.

No carriage data from RCTs, cohort studies or case–control studies were available as of 1 September 2011, although data relevant to this review is expected to be published soon.

Immunological data after the booster dose were collected in three RCTs. Both schedules resulted in high levels of seropositivity after the booster dose with little between-trial heterogeneity for most serotypes (2 RCTs). The largest differences, favouring the 3p+1 schedule, were seen for serotypes 6B and 23F (2 RCTs). Results of opsonophagocytic activity were similar in both groups, except that a difference favouring the 3p+1 schedule was also seen for serotype 5 (1 RCT).

1.3.1.6 3p+1 vs 3p schedules

No clinical data from RCTs were available. One case–control study reported an odds ratio of 0 (95% CI 0, 0.87) for vaccine serotype IPD, adjusted for the presence of underlying conditions, comparing 3p+1 to 3p schedules.

No carriage data from RCTs, cohort studies or case–control studies were available as of 1 September 2011, although data relevant to this review is expected to be published soon.

Immunological data were reported in two RCTs. Antibody concentrations were substantially higher at 13 months in the 3p+1 group (1 month after the booster) than in the 3p group (7–10

months after the last primary dose) with low between-trial heterogeneity (2 RCTs). These differences were smaller at 19 months (1 RCT).

1.3.1.7 Late vs early start schedules

No clinical or carriage data from RCTs, cohort studies or case–control studies were available.

Immunological data were reported in four RCTs. A comparison of antibody concentrations in three of these favoured the early start in one RCT (2 weeks younger at first dose); the late start in one RCT (3 months older); and showed no difference in one RCT (1 month difference). Differences existed in terms of schedules and intervals between the last dose and immunological assessment, both between comparison groups and between trials.

1.3.1.8 2-month vs 1-month interval schedules

No clinical data from RCTs or case–control studies were available. Limited clinical data were reported in three cohort studies.

Immunological data were reported in three cohort studies. In one study on PCV7, a 3p schedule at 2-month intervals (2, 4, 6m) tended to result in similar or higher percentages seropositive, tested 1 month after vaccination, than a 3p, 1-month interval group (1.5, 2.5, 3.5m), although this difference was annulled by 12–18 months of age. A similar pattern was seen in a 2p, 2-month interval schedule (2, 4m) compared with a 2p, 1-month interval schedule (2, 3m) except that differences persisted to 12 months (1 cohort study). For PCV10, the 3p, 2-month interval group tended to have similar or lower percentages seropositive at 1 month after vaccination than the 3p group with a 1-month interval, and this persisted at 12–18 months of age (1 cohort study).

1.3.1.9 Long vs short interval between primary and booster schedules

Limited clinical data were reported in one RCT, but none from cohort or case–control studies. No carriage data were available.

Immunological data were reported in two RCTs. Seropositivity levels were very high (threshold 0.20µg/ml) with both booster schedules (1 RCT, 10–12 months vs 8–10 months after the last primary dose). Late booster dose groups tended to have higher antibody concentrations than early booster groups, but confidence intervals crossed 1 for all serotypes except 4 and 23F (2 RCTs, 10–12 months vs 8–10 months, and 11–12 months vs 8–9 months after last primary dose respectively).

1.3.2. Comparisons of PCV schedule vs no PCV

For IPD caused by vaccine serotypes, VE estimates for 3p+0 schedules were 71% (95% CI 52, 82%, I^2 0%, 2 RCTs) and for 3p+1 schedules 87% (95% CI 76, 95%, I^2 0%, 2 RCTs), using intention-to-treat (ITT) data in individually randomized trials. Estimates were similar in HIV-infected and -uninfected infants vaccinated with a 3p+0 schedule. Trials of 3p+1 schedules were carried out in high-income countries, whereas trials of 3p+0 schedules took place in low- or middle-income countries.

For IPD caused by any pneumococcal serotype, the estimated VE in the USA1 7v trial was higher than in other individually randomized trials and the single cluster randomized trial.

Estimated VE for radiologically confirmed pneumonia (first episode) was 14% (95% CI 9, 37%, I^2 70%, 2 RCTs) for 3p+0 schedules, and 25% (95% CI 6, 41%, 1 RCT) for 3p+1 schedules, using ITT data. There was a lack of sensitivity and specificity in the clinical and radiological diagnosis

of pneumonia, which could have biased VE for pneumonia towards no effect of PCV. Generally, few deaths were reported in RCTs.

Carriage of vaccine serotypes was generally lower in children receiving PCV, while carriage of non-vaccine serotypes was generally higher when compared to children not receiving PCV.

Immunological data for these comparisons were not analysed in this review.

1.3.2.1 1p schedules vs no PCV

No clinical data from RCTs or cohort studies were available. One case–control study reported vaccine effectiveness of 73% (95% CI 43, 87%) against vaccine serotype IPD for 1 primary dose of PCV.

Carriage data were reported in two RCTs. Children at 6, 9, 12 and 18 months of age who received 1 primary dose of PCV were less likely to be carrying vaccine serotypes than the no PCV group, but confidence intervals were wide and crossed 1 at most time points (1 RCT). The group that received PCV was more likely to be carrying non-vaccine serotypes at 6, 9 and 12 months of age than the group that did not (1 RCT).

1.3.2.2 2p schedules vs no PCV

No clinical data from RCTs or cohort studies were available. One case-control study reported vaccine effectiveness of 96% (95% CI 88, 99%) against vaccine serotype IPD for 2p schedules.

Carriage data were reported in three RCTs. Children at 6 and 9 months of age receiving 2 primary doses of PCV were less likely to be carrying vaccine serotypes than those who did not (1 RCT). At 12 months (2 RCTs), 18 months (2 RCTs) and 24 months (1 RCT) of age, the vaccinated groups were also less likely to be carrying vaccine serotypes than the unvaccinated groups. The groups that received PCV were more likely to be carrying non-vaccine serotypes at all ages (1 RCT).

1.3.2.3 3p schedules vs no PCV

Clinical disease outcomes were reported in two RCTs and one case–control study.

For IPD caused by vaccine serotypes, VE was estimated at 71% (95% CI 52, 82%, I^2 0%, 2 RCTs) using ITT data. Estimates were similar in HIV-infected and -uninfected infants. One case–control study reported vaccine effectiveness of 95% (95% CI 88, 98%) against vaccine serotype IPD for 3p schedules.

For radiologically confirmed pneumonia (first episode), estimated VE using ITT data was 14% (95% CI 9, 37%, I^2 70%, 2 RCTs) and heterogeneity was not explained by the inclusion of HIV-infected children.

Mortality was reported as an outcome in two RCTs, with limited mortality data reported in four RCTs. VE against all-cause mortality was 16% (95% CI 3, 28%) in the Gambia and 5% (95% CI -13, 21%) in South Africa.

Carriage data were reported in six RCTs. At around 6 months (3 RCTs), 9 months (3 RCTs), 12 months (2 RCTs) and 18 months (1 RCT) of age, groups receiving 3p schedules were less likely to be carrying vaccine serotypes than groups that did not, but confidence intervals often crossed 1. The groups receiving PCV were more likely to be carrying non-vaccine serotypes at 6 and 9 months of age. This pattern was less marked at 12 months of age.

1.3.2.4 2p+1 schedules vs no PCV

No clinical data from RCTs or cohort studies were available. One case–control study reported vaccine effectiveness of 98% (95% CI 75, 100%) against vaccine serotype IPD for 2p+1 schedules.

Carriage data were reported in one RCT. At 12, 18 and 24 months of age, the vaccinated group was less likely to be carrying vaccine serotypes and more likely to be carrying non-vaccine serotypes than the unvaccinated group.

1.3.2.5 3p+1 schedules vs no PCV

Clinical disease outcomes were reported in three RCTs and one case–control study.

For IPD caused by vaccine serotypes, VE was 87% (95% CI 76, 95%, I^2 0%) using ITT data in individually randomized trials (2 RCTs) and 86% (95% CI 40, 97%) in the cluster-randomized trial (1 RCT). One case–control study reported vaccine effectiveness of 100% (95% CI 94, 100%) against vaccine serotype IPD for 3p+1 schedules.

For radiologically confirmed pneumonia (first episode), estimated VE using ITT data was 25% (95% CI 6, 41%) (1 RCT).

For otitis media, 3p+1 schedules protected against pneumococcal (VE 46%, 95% CI 10, 55%, I^2 17%, 2 RCTs) but not all-cause otitis media (VE 6%, 95% CI 4, 9%, I^2 0%, 2 RCTs) in healthy children, using ITT data.

Mortality data could be extracted from three RCTs. There were too few deaths to estimate VE against this outcome.

Carriage data were reported in two RCTs. At 18 months of age, point estimates suggested that vaccinated groups were less likely to be carrying vaccine serotypes (2 RCTs) and more likely to be carrying non-vaccine serotypes (1 RCT).

1.3.2.6 Catch-up schedules vs no PCV

Data from RCTs and cohort studies about IPD and pneumonia were not available. One case–control study reported vaccine effectiveness against vaccine serotype IPD of 93% (95% CI 68, 98%) for 1 dose at 12–23 months of age, and 96% (95% CI 81, 99%) for 2 doses at the same age.

Four RCTs reported on otitis media. Between-trial heterogeneity was high, but was reduced when populations were stratified by baseline disease status. Catch-up doses did not protect against all-cause otitis media in children with a history of ear infections using per protocol data (VE -27%, 95% CI -57, -3%, I^2 0%, 2 RCTs). In healthy children, per protocol VE was 17% (95% CI -2, 33%, 1 RCT).

Carriage data could be analysed in two RCTs. At 7, 14, 20 and 26 months after the first dose of vaccine, the vaccinated group was less likely to be carrying vaccine serotypes than the unvaccinated group (1 RCT). Point estimates suggested that the group that received PCV was more likely to be carrying non-vaccine serotypes at 14, 20 and 26 months after the first dose of vaccine, with the difference becoming more marked over time.

1.4 Discussion

1.4.1 Strengths and limitations

The main strengths of this review were the wide and comprehensive search strategy and rigorous methods for selecting studies and extracting data. Key data are unlikely to have been missed.

A further strength was the extent of analyses conducted for clinical, carriage and immunological outcomes.

The limited data available for this review meant that there were insufficient RCTs to allow a formal examination of the potential causes of between-trial heterogeneity in results using tools such as meta-regression. Potential reasons for heterogeneity, such as interval between last dose and blood sampling, have been suggested.

Varying standards of reporting of methods and data in RCT reports were a major limitation to the systematic synthesis of evidence in this review.

1.4.2 Main findings and interpretation

This review found no definitive evidence from RCTs that any specific PCV schedule is superior to another for clinical disease outcomes or mortality. This is because no RCT reporting clinical disease outcomes directly compared PCV schedules.

There was RCT evidence that both 3p+0 and 3p+1 schedules protect against IPD and pneumonia for the follow-up periods studied when compared with no PCV. Protection against IPD caused by vaccine serotypes was stronger than for all serotypes combined. There was no evidence of an increase in disease caused by non-vaccine serotypes, but this was limited to the follow-up periods of the RCTs.

No RCT compared 2p+0 or 2p+1 schedules with no PCV and reported IPD or pneumonia.

Evidence from nasopharyngeal carriage data did not definitively show that any specific PCV schedule is superior to another. For 2p, 3p, 2p+1 and catch-up schedules, there was evidence that PCV reduces carriage of vaccine serotypes and increases carriage of non-vaccine serotypes when compared with no PCV. However, the precise relationship between changes in pneumococcal carriage and clinical disease outcomes remains to be established.

Some differences were identified in immunological outcomes following vaccination with different PCV schedules. Schedules with a higher number of primary doses tended to result in higher levels of seropositivity for all analysed serotypes shortly after completion of the primary schedule. Differences favouring the schedule with more doses were more marked for serotypes 6B and 23F in most of these comparisons. There were high levels of between-trial heterogeneity for many comparisons, but these did not alter the main findings.

Both 3p and 2p schedules resulted in high levels of seropositivity for most serotypes. Differences between groups were generally small and mostly favoured the 3p schedule at 6 and 12 months (5 RCTs). Differences in seropositivity between groups receiving 3p or 2p schedules were somewhat smaller after a booster dose of PCV. Both 3p+1 and 2p+1 schedules resulted in high levels of seropositivity for most serotypes shortly after the booster dose (2 RCTs).

The clinical relevance of differences in immunological outcomes observed between groups in this review is not known. The levels of antibodies that provide protection against clinical disease are not known either, and might differ between serotypes, for different clinical outcomes and in different populations.

The immunological data contained in this review stem primarily from healthy populations. The immunological findings might not be generalizable to high-risk groups.

1.4.3 Implications for future research

It is important to conduct RCTs that directly compare the effects of different vaccine schedules so that differences in the outcomes observed are likely to be due to the biological effects of the vaccine. Randomization is needed to minimize the biases and confounding that affect the interpretation of data from non-randomized study designs. Indirect comparisons of outcomes between RCTs that have investigated different schedules are also susceptible to bias, unless

statistical methods that respect the original randomization, such as network meta-analysis, are used.

In the absence of evidence about the superiority of any particular PCV schedule, future RCTs will need to determine whether different vaccination schedules are equivalent in their effects on carriage and clinical outcomes. Sample size calculations should therefore be based on the demonstration of non-inferiority, even though the sample size required is greater than for the demonstration of superiority.

The timing of vaccination and immunological assessments should be taken into consideration in the design of RCTs comparing different vaccination schedules. The design should allow the comparison of schedules with the same interval between the last vaccination and the assessment, as well as comparisons when children are the same age. Longer follow-up in RCTs of immunological responses to PCV would also be useful.

Additional information about the effects of different intervals between doses in a primary schedule would be valuable, particularly for 2-dose primary schedules.

The long-term effects of vaccination schedules on clinical outcomes cannot be studied in RCTs. Different vaccination schedules might have long-term effects on control of disease, herd effects and serotype replacement by non-vaccine serotypes. Post-introduction surveillance is therefore essential for monitoring these outcomes.

Systematic reviews investigating vaccination schedules that include case–control and cohort studies can contribute additional clinical data that are not available from RCTs. The added value of including these study designs in literature searches needs to be weighed against the much larger number of items retrieved from less specific search strategies.

1.5 Conclusions

This comprehensive systematic review of RCTs of PCV vaccination schedules found no definitive evidence that any particular schedule is superior to another in its effect on clinical disease, mortality, or carriage outcomes. The review found some evidence that schedules containing 2 or 3 doses in the primary series provide better seropositivity and GMC outcomes than schedules with only 1 dose. Differences between other schedules were less marked. The interpretation of differences in immunological outcomes was limited because of uncertainty about their clinical relevance. At present, the choice of PCV schedule is likely to be informed by knowledge of the local epidemiology of pneumococcal disease and about health service delivery of other vaccinations in the National Immunization Programme. Additional direct evidence about the relative benefits of different PCV schedules is needed to help guide public health decision-making.

Section 2. Pneumococcal conjugate vaccines

A systematic review of clinical and carriage data from randomized controlled trials of childhood schedules using 7-, 9-, 10- and 13-valent vaccines

2.1 Overview

2.1.1 Objective

The objective of this section of the report is to present the results of clinical outcomes and nasopharyngeal carriage of pneumococcal serotypes studied in randomized controlled trials (RCTs).

2.1.2 Review methods

The search covered 12 electronic databases of published articles, trial registers, industry databases and other documents from the earliest citation until August 2009. The search was updated in March 2010.

Studies that reported on RCTs or quasi-RCTs in children up to 18 years were selected. Interventions could cover any vaccination schedule using 7-, 9-, 10- or 13-valent pneumococcal conjugate vaccine (PCV).

Comparisons comprised schedules with different ages at the start of vaccination, different intervals between doses, different numbers of doses, or any PCV schedule compared with no PCV.

The following data were extracted onto structured piloted forms: schedule, numbers of events, ratio measures of effect, vaccine efficacy (VE), as well as study characteristics, and potential sources of bias and heterogeneity.

Outcomes reported are invasive pneumococcal disease (IPD), pneumonia, otitis media, mortality, and nasopharyngeal carriage of pneumococci for: all serotypes, serotypes included in the vaccine, non-vaccine serotypes and, where reported, vaccine-associated serotypes, and non-vaccine serotypes excluding vaccine-associated serotypes.

Random effects meta-analysis was used to combine results statistically, where appropriate. To compare clinical data between groups of children receiving or not receiving PCV, rate or risk ratios (and 95% confidence intervals, CI) were calculated from reported vaccine efficacy (VE) data. To compare carriage between groups of children receiving different schedules (including no PCV), prevalence odds ratios (with 95% CI) were calculated. Between-trial heterogeneity is described using the I^2 statistic where values below 25% represent low levels of heterogeneity, up to 50% moderate, up to 75% high levels and more than 75% very high levels of heterogeneity.

Vaccine schedules were abbreviated as follows: 3p – 3 doses in the primary (p) vaccination schedule with all doses given before 12 months of age; +1 – a booster dose. If the booster was pneumococcal polysaccharide vaccine (PPV), this is noted explicitly. In this summary, protective

effects of PCV against clinical disease are reported as VE in RCTs and vaccine effectiveness in case–control studies.

2.1.3 Results

Of the 3217 relevant search items, 31 eligible RCTs were identified, of which 23 reported extractable data on clinical outcomes and/or nasopharyngeal carriage. There were 28 different comparison types in these 23 RCTs.

2.1.3.1 Clinical outcomes

Direct comparison between PCV schedules

Few data existed on clinical outcomes in RCTs that directly compared different PCV schedules. Clinical data were extracted from reasons for loss to follow-up or reports of (serious) adverse events, meaning that observation periods were relatively short, often not continuous and mainly covered time periods where the vaccination course had not been completed and the full protective potential was unlikely to have been reached. These data are described in this review but not used to estimate measures of the effect of PCV.

a) Comparisons of PCV vs no PCV schedules

Ten RCTs using either 3p+1 or 3p+0 PCV schedules reported at least one eligible clinical outcome. Five of these RCTs reported on IPD, three on pneumonia, three on otitis media and 10 on mortality. In general, analyses that combined results across schedules were consistent with those stratified by schedule.

RCTs of 3p+1 schedules were carried out in high-income countries (Finland, United States of America (USA)), while RCTs of 3p+0 schedules were performed in low- or middle-income countries (the Gambia, South Africa).

A further five RCTs compared catch-up (toddler) schedules to no PCV. Otitis media was the only clinical outcome reported for most of these RCTs.

For IPD caused by any pneumococcal serotype, the estimated VE in the USA1 7v trial was higher than in other individually randomized trials and the single cluster-randomized trial. The detection of less clinically severe invasive disease in this trial and the distribution of serotypes in the USA1 7v population are among potential explanations for this result.

For IPD caused by vaccine serotypes, VE estimates for 3p+0 schedules were 71% (95% CI 52, 82%, I^2 0%, 2 RCTs) and for 3p+1 schedules 87% (95% CI 76, 95%, I^2 0%, 2 RCTs) using intention-to-treat (ITT) data in individually randomized trials, and 86% (95% CI 40, 97%) in the cluster-randomized trial (3p+1). Estimates were similar in HIV-infected and -uninfected infants vaccinated with a 3p+0 schedule.

For radiologically confirmed pneumonia (first episode), estimated VE for 3p+0 schedules using ITT data was 14% (95% CI 9, 37%, I^2 70%, 2 RCTs) and heterogeneity was not explained by the inclusion of HIV-infected children. For 3p+1 using ITT data, VE was 25% (95% CI 6, 41%, 1 trial).

For otitis media, only 3p+1 and catch-up schedules were investigated. 3p+1 schedules protected against pneumococcal (VE 46%, 95% CI 10, 55%, I^2 17%, 2 RCTs) but not all-cause otitis media (VE 6%, 95% CI 4, 9%, I^2 0%) in healthy children, using ITT data. Catch-up doses did not protect

against all-cause otitis media in children with a history of ear infections, using available per protocol data (VE -27%, 95% CI -57, -3%, I^2 0%, 2 RCTs). In healthy children, per protocol VE was 17%, 95% CI -2, 33%, 1 trial).

Generally, few deaths were reported in RCTs, with only two reporting more than 25 deaths. In both RCTs, fewer deaths occurred in the vaccinated group.

b) 1p or 2p vs no PCV schedules

No clinical data from RCTs were available on either of these comparisons.

c) 3p schedules vs no PCV

Clinical disease outcomes were reported in two RCTs. For IPD caused by vaccine serotypes, the VE estimate was 71% (95% CI 52, 82%, I^2 0%, 2 RCTs) using ITT data. Estimates were similar in HIV-infected and -uninfected infants.

For radiologically confirmed pneumonia (first episode), estimated VE using ITT data was 14% (95% CI 9, 37%, I^2 70%, 2 RCTs) and heterogeneity was not explained by the inclusion of HIV-infected children.

Mortality was reported as an outcome in two RCTs, with limited mortality data reported in four RCTs. VE against all-cause mortality was 16% (95% CI 3, 28%) in the Gambia and 5% (95% CI -13, 21%) in South Africa.

d) 2p+1 vs no PCV schedules

No clinical data from RCTs were available.

e) 3p+1 vs no PCV schedules

Clinical disease outcomes were reported in three RCTs. For IPD caused by vaccine serotypes, VE was 87% (95% CI 76, 95%, I^2 0%) using ITT data in individually randomized trials (2 RCTs) and 86% (95% CI 40, 97%) in the cluster-randomized trial (1 RCT).

For radiologically confirmed pneumonia (first episode), estimated VE using ITT data was 25% (95% CI 6, 41%) (1 RCT).

For otitis media, 3p+1 schedules protected against pneumococcal (VE 46%, 95% CI 10, 55%, I^2 17%, 2 RCTs) but not all-cause otitis media (VE 6%, 95% CI 4, 9%, I^2 0%) in healthy children using ITT data.

Mortality data could be extracted from three RCTs. There were too few deaths to estimate VE against this outcome.

f) Catch-up vs no PCV schedules

Data on IPD and pneumonia were not available from RCTs, although four reported on otitis media. Between-trial heterogeneity was high, but was reduced when populations were stratified by baseline disease status. Catch-up doses did not protect against all-cause otitis media in children with a history of ear infections using per protocol data (VE -27%, 95% CI -57, -3%, I^2 0%, 2 RCTs). In healthy children, per protocol VE was 17%, 95% CI -2, 33% (1 RCT).

2.1.3.2 Nasopharyngeal pneumococcal carriage

Direct comparison between PCV schedules

Three RCTs compared carriage of pneumococcal serotypes with different PCV schedules. Results showed that vaccination with more doses of PCV might result in less carriage of vaccine serotypes than fewer doses, but the evidence for this was not strong.

Results for non-vaccine serotype carriage were less consistent than results for vaccine serotypes.

a) 2p vs 1p schedules and 3p vs 1p schedules

Carriage data were reported in two RCTs. At 6 months of age, 3p doses of vaccine might result in less carriage of vaccine serotypes than 1p dose, but the confidence interval around the combined odds ratio was wide (2 RCTs). By 12 and 18 months of age, both 2p and 3p schedules might result in less vaccine serotype carriage than 1 primary dose, but again confidence intervals were wide (1 RCT). Results for non-vaccine serotype carriage were less consistent than for vaccine serotypes, but did not show marked differences between schedules.

b) 3p vs 2p schedules

Carriage data were reported in two RCTs. At 6 months of age, 3p schedules of vaccine might result in less carriage of vaccine serotypes than 2p schedules, but the confidence interval was wide (2 RCTs). Results for vaccine serotype carriage did not consistently show either schedule to be better at an older age, but 3p doses might be slightly favoured (1 RCT). Results for non-vaccine serotype carriage did not show marked differences between schedules.

c) 2p+1 vs 2p schedules

Carriage data were reported in one RCT. At 12 months of age (1 month after the 2p+1 group received the booster dose), there might be less vaccine serotype carriage with a booster dose than without. This was more marked at 18 months, but no advantage was apparent by 24 months of age.

d) 3p vs 2p+1; 3p+1 vs 2p+1; 3p+1 vs 3p schedules

No carriage data from RCTs were available on these three schedules as of 1 September 2011.

e) Later vs earlier start schedules

No carriage data from RCTs were available as of 1 September 2011.

f) 2-month vs 1-month intervals

No carriage data from RCTs were available as of 1 September 2011.

g) Longer vs shorter interval between primary and booster

No carriage data from RCTs were available as of 1 September 2011.

Comparisons of PCV schedules with no PCV

Nasopharyngeal carriage of pneumococci was reported in 10 RCTs that compared a PCV schedule with no PVC (comparisons U–Y).

Carriage of vaccine serotypes was generally lower in children receiving PCV, and carriage of non-vaccine serotypes was generally higher in children receiving PCV compared with those not receiving PCV.

a) 1p vs no PCV schedules

Carriage data were reported in two RCTs. At 6, 9, 12 and 18 months of age, the group receiving 1p dose of PCV was less likely to be carrying vaccine serotypes than the group that did not, but confidence intervals were wide and crossed 1 at most time points (1 RCT). The group that received PCV was more likely to be carrying non-vaccine serotypes at 6, 9 and 12 months of age than the group that did not (1 RCT).

b) 2p vs no PCV schedules

Carriage data were reported in three RCTs. At 6 and 9 months of age, the group receiving 2p doses of PCV was less likely to be carrying vaccine serotypes than the group that did not (1 RCT). At 12

months (2 RCTs), 18 months (2 RCTs) and 24 months (1 RCT) of age, the vaccinated groups were less likely to be carrying vaccine serotypes than the unvaccinated groups. Individuals that received PCV were more likely to be carrying non-vaccine serotypes at all ages (1 RCT).

c) 3p vs no PCV schedules

Carriage data were reported in six RCTs. Data from the five individually randomized trials at around 6 months (3 RCTs), 9 months (3 RCTs), 12 months (2 RCTs) and 18 months (1 RCT) of age showed that groups receiving 3p schedules were less likely to be carrying vaccine serotypes than groups that did not receive PCV, but confidence intervals often crossed 1. The groups receiving PCV were more likely to be carrying non-vaccine serotypes at 6 and 9 months of age. This pattern was less marked at 12 months of age.

d) 2p+1 vs no PCV schedules

Carriage data were reported in one RCT. At 12, 18 and 24 months of age, the vaccinated group was less likely to be carrying vaccine serotypes and more likely to be carrying non-vaccine serotypes than the unvaccinated group.

e) 3p+1 vs no PCV schedules

Scarce carriage data were reported in two RCTs. Data from the sole individually randomized trial were only available for vaccine serotypes and at 18 months of age. These data showed that vaccinated groups were less likely to be carrying vaccine serotypes (1 RCT).

f) Catch-up vs no PCV schedules

Carriage data could be analysed for two RCTs. At 7, 14, 20 and 26 months after the first dose of vaccine, the vaccinated group was less likely to be carrying vaccine serotypes than the unvaccinated group (1 RCT). Point estimates suggest that the group that received PCV were more likely to be carrying non-vaccine serotypes at 14, 20 and 26 months after the first dose of vaccine, with the difference becoming more marked over time (1 RCT).

2.1.4 Discussion

2.1.4.1 Strengths and limitations

The main strengths of this review were the wide and comprehensive search strategy and rigorous methods for selecting studies and extracting data.

A further strength was the extent of analyses conducted. For clinical data, multiple clinical disease outcomes were analysed using both ITT and per protocol data. These analyses were also conducted for healthy and high-risk groups separately, and were stratified by study design (individually or cluster randomized), unlike previous reviews. The authors believe that carriage data have not previously been synthesized in meta-analyses. Carriage data were analysed for a large number of comparisons at multiple time points for each comparison.

A limitation of the data available for this review is that there were insufficient RCTs to allow a formal examination of the potential causes of between-trial heterogeneity in results using tools such as meta-regression.

Differing levels of reporting of data from RCTs is a major limitation to the systematic synthesis of evidence in this review.

2.1.4.2 Main findings and interpretation

The review found no definitive evidence from RCTs that any specific PCV schedule is superior to another for clinical disease outcomes or mortality, since no RCTs directly compare schedules for these outcomes.

RCT evidence did show that 3p+0 and 3p+1 schedules protect against IPD and pneumonia for the follow-up periods studied. Protection against IPD caused by vaccine serotypes was stronger than for all serotypes combined. There was no evidence of an increase in disease caused by non-vaccine serotypes, but this was limited to the follow-up periods of the RCTs. However, no RCTs compared 2p+0 or 2p+1 schedules with no PCV and reported IPD or pneumonia.

Interpretation of pneumonia data is further complicated by the lack of sensitivity and specificity in the clinical and radiological diagnosis of pneumonia. This could have biased VE for pneumonia towards the null value of no effect of PCV.

No definitive evidence was found from three identified RCTs measuring nasopharyngeal carriage of pneumococci that any specific PCV schedule is superior to another. For 2p, 3p, 2p+1 and catch-up schedules, there was evidence that PCV reduces carriage of vaccine serotypes and increases carriage of non-vaccine serotypes when compared with no PCV. However, the precise relationship between changes in pneumococcal carriage and clinical disease outcomes remains to be established.

2.1.4.3 Implications for future research

In the absence of evidence about the superiority of any particular PCV schedule, future RCTs will need to determine whether different vaccination schedules are equivalent in their effects on carriage and clinical outcomes. Sample size calculations should therefore be based on the demonstration of non-inferiority, even though the sample size required is greater than for the demonstration of superiority.

The long-term effects of vaccination schedules cannot be studied in RCTs. Different vaccination schedules might have long-term effects on control of disease, herd effects and serotype replacement by non-vaccine serotypes. Post-introduction surveillance is therefore essential to monitor these outcomes.

2.1.5 Conclusions

The comprehensive systematic review of RCTs of PCV vaccination schedules found no definitive evidence that any particular PCV schedule is superior to another in its effect on clinical disease, mortality, or carriage outcomes. At present, the choice of PCV schedule is likely to be informed by knowledge of the local epidemiology of pneumococcal disease and about health service delivery of other vaccinations in the National Immunization Programme. Additional evidence about the relative benefits of different PCV schedules is needed to help guide public health decision-making.

2.2 Introduction

Streptococcus pneumoniae can cause a range of illnesses, including pneumonia, IPD (septicaemia and meningitis), bronchitis, otitis media and sinusitis. WHO estimated in 2005 that between 0.7–1 million children die annually from pneumococcal disease [4].

Vaccines have long been used to prevent pneumococcal disease. A PPV23 has been available since the early 1980s (licensed in the USA in 1983). However, a systematic review found little evidence that it was effective in preventing pneumococcal pneumonia or death in adults, based on the results of RCTs with a low risk of bias [5]. The efficacy of PPV against IPD remains controversial [5, 6] and it is not licensed for children under 2 years of age.

PCVs, based on the conjugation of selected capsular polysaccharides to a protein carrier, have been developed more recently, the first being licensed in the USA in 2000 [7]. PCV7 (containing serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F, Prevnar®, Wyeth), is licensed in the USA for use in children up to 9 years of age [8] and, as of January 2007, was licensed in 70 countries [4]. A vaccine with 10 serotypes (serotypes 1, 5 and 7F in addition to the 7 serotypes in Prevnar®) received European Commission authorization in March 2009 for children from 6 weeks to 2 years of age (Synflorix™, Glaxo Smith Kline, GSK) [9]. The 13v vaccine (Prevnar 13™, Wyeth, containing serotypes 1, 3, 5, 6A, 7F and 19A in addition to the serotypes in PCV7) was licensed for children aged 6 weeks to 5 years by the European Commission in December 2009 and by the US Food and Drug Administration (FDA) in February 2010. Large clinical trials of 9v and 11v vaccines have also been conducted, but the vaccines have never been licensed.

The capsular polysaccharides in the 7v, 9v and 13v vaccines are, or were conjugated to CRM_{197} (a non-toxic mutant of diphtheria toxoid), and each polysaccharide in the 10v and 11v vaccines is or was conjugated to either protein D (derived from non-typeable *Haemophilus influenzae*) carrier protein, a tetanus toxoid carrier protein or a diphtheria toxoid carrier protein.

The WHO position paper on PCV, published in 2007, states that the 7v vaccine should be included as a priority in national immunization programmes, especially in countries where mortality among children aged under 5 years is greater than 50 per 1000 live births, or where more than 50 000 children die annually [4]. Current schedules vary, but usually consist of 3p schedules, or 2p followed by a booster in the second year of life [4].

Data are rapidly accumulating on the effects of PCV, particularly on immunological outcomes, as vaccines incorporating increasing numbers of pneumococcal serotypes, or different carrier proteins, become available. Clinical efficacy, effectiveness and immunogenicity need to be examined for a range of schedules (relating to different numbers of doses, intervals between doses, and ages at initiation) to inform discussion and recommendations on optimizing pneumococcal vaccination schedules in different settings.

Within the overall aim of the systematic review, this section of the report presents the methods and results for clinical and pneumococcal carriage outcomes.

2.3 Methods

A study protocol was written and finalized before the start of the review[1]. The methods of the review are summarized here, with deviations from the protocol described, where they occurred.

[1] available on request from the authors.

2.3.1 Search strategy

The following databases were searched:

- Medline and Embase (in Embase.com);
- the Cochrane Library;
- African Index Medicus (AIM);
- the Indian Medlars Centre (IndMed);
- Latin American and Caribbean Health Sciences (LILACs);
- Current Controlled Trials metaRegister of Controlled Trials (mRCT, active and archived registers);
- UK Clinical Trials Gateway (UKCTG);
- US Food and Drug Administration (FDA);
- European Public Assessment Report (EPAR) listings of the European Medicines Agency (EMEA);
- WHO International Clinical Trials Registry Platform Search Portal, including
    - ClinicalTrials.gov
    - International Standard Randomised Controlled Trial Number Register (ISRCTN)
    - clinical trial registries of Australia, the People's Republic of China, Germany, India, the Islamic Republic of Iran, the Netherlands, New Zealand and Sri Lanka);
- GSK Clinical Study Register; and
- Clinicalstudyresults.org (includes Wyeth trial listings).

Search strings were developed by combining thesaurus and free text search terms relating to pneumococcus, streptococcus, conjugated vaccine, immunisation, or names of licensed PCVs. There were no restrictions on language, study design, or date of publication or listing. Search terms were adapted as required for each database. Full details of search strategies are listed in Annex 2.1. In addition, bibliographies of selected review articles were screened for relevant studies and meta-analyses, and experts in the field were contacted to ask for other publications or studies that might fit the selection criteria. The first searches were conducted on 28 August 2009 and the Embase.com search was repeated on 17 March 2010.

2.3.2 Selection of studies

Two pairs of reviewers independently evaluated articles retrieved in the August 2009 searches for eligibility for inclusion in the review. The selection criteria for these studies are described below.

2.3.2.1 Inclusion criteria

a) Study design

The following study designs were considered for inclusion: RCTs or quasi-RCTs, where individuals or groups were randomized to any of the following comparison groups.

a) Population

Studies containing data relating to the vaccination of children aged up to 18 years.

b) Intervention

Studies relating to vaccination with licensed formulations of PCV (7v, 10v or 13v) were included. The protocol specified that only data from studies using licensed vaccines could be included. However, studies using 9v vaccines were subsequently included owing to the limited clinical data, and the fact that formulations of 7v and 9v vaccine were similar

(except for the two additional serotypes). The 11v vaccine was not included as the formulation changed substantially prior to licensure of the 10v product. The pneumococcal serotypes included in each vaccine are shown in Table 2.1.

Table 2.1 Pneumococcal serotypes contained in different vaccines

Vaccine	Pneumococcal serotype												
	1	3	4	5	6A	6B	7F	9V	14	18C	19A	19F	23F
7-valent			✓			✓		✓	✓	✓		✓	✓
9-valent	✓		✓	✓		✓		✓	✓	✓		✓	✓
10-valent	✓		✓	✓		✓	✓	✓	✓	✓		✓	✓
13-valent	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

c) Comparison groups

Studies with the following comparison groups were considered for inclusion:

- different number of doses;
- different intervals between doses;
- different ages at the start of a vaccination schedule;
- placebo injection, another vaccine, or nothing.

d) Clinical and carriage outcomes

Studies reporting any of the following outcomes, or stating that such data would be collected, were eligible for inclusion:

Clinical efficacy or effectiveness

These outcomes included different clinical conditions and, for pneumonia, different levels of diagnostic certainty (e.g. all-cause pneumonia can include clinical diagnoses of pneumonia, radiologically confirmed pneumonia using – or not using – WHO criteria). Different levels of diagnostic certainty are analysed separately where possible.

Eligible clinical outcomes:

i) Pneumonia from all causes (ideally radiologically confirmed);

ii) Presumptive pneumococcal pneumonia (any serotype, vaccine serotype, or non-vaccine serotype). Presumptive diagnosis was defined as pneumonia (ideally radiologically confirmed) combined with either a positive *S. pneumoniae* culture from nasopharyngeal or sputum samples, or antigen testing or other confirmatory test (e.g. circulating pneumolysin-specific immune complexes);

iii) Definitive pneumococcal pneumonia (any serotype, vaccine serotype, or non-vaccine serotype). Definitive diagnosis was defined as pneumonia (ideally radiologically confirmed), with a positive *S. pneumoniae* culture from a sample taken from the lung in conditions that minimize contamination of the sample (e.g. transthoracic lung biopsy). This definition was added to the protocol after the review commenced and, as such, constitutes a protocol amendment. Pneumonia with a positive *S. pneumoniae* culture from blood or another normally sterile site is now considered to be a sub-group of IPD.

iv) Death from all causes;

v) Death from pneumonia (ideally radiologically confirmed);

vi) Death from pneumococcal infection (any serotype, vaccine serotype, or non-vaccine serotype);

vii) Bacteraemia or IPD (any serotype, vaccine serotype, or non-vaccine serotype);

viii) Pneumococcal meningitis (any serotype, vaccine serotype, or non-vaccine serotype);

ix) Otitis media (all causes);

x) Pneumococcal otitis media (any serotype, vaccine serotype, or non-vaccine serotype).

Nasopharyngeal carriage of pneumococci

Eligible carriage outcomes:

i) Percentage of study participants carrying *S. pneumoniae* (any serotype) before and after vaccination;

ii) Percentage of study participants carrying *S. pneumoniae* (by serotype) before and after vaccination;

iii) Percentage of study participants carrying *S. pneumoniae* (vaccine serotype and non-vaccine serotype) before and after vaccination.

2.3.2.2 Exclusion criteria

Uncontrolled studies, observational intervention studies, dose-finding studies, and animal or laboratory studies were excluded from this section of the review.

Studies that did not contribute data to the analyses were not included, e.g. where mortality was the only clinical or carriage outcome, and no deaths were reported or mortality data could not be extracted. For completeness, references for these studies are given in the footnotes of relevant tables and figures.

2.3.3 Data extraction

Data for each study were extracted on to a structured piloted data extraction form (Epidata, Odense, Denmark). Items relating to vaccination schedule and populations, as well as outcome data were extracted. For most studies, data were extracted by one reviewer and checked for accuracy and completeness by the principal reviewer. Potential for bias within a study was also assessed by the principal reviewer.

2.3.4 Statistical analysis

2.3.4.1 Descriptive and comparative analyses of clinical and carriage outcomes

Features of included studies were summarized in tables and figures. Vaccine schedules were either described in full; by stating the intended ages at vaccination (in months); or by listing the number of doses in the primary series and whether or not a booster dose was part of the schedule (see 2.3.5.1).

For clinical outcomes, ratio measures of effect were calculated from reported VE (ratio = (1-VE)). Standard errors were calculated from confidence intervals around these ratio measures, assuming that the confidence intervals were log symmetrical around the log point estimate. If they were not, the calculation of confidence intervals might differ from that published. If VE or a ratio measure were not reported, risk ratios were calculated based on the number of individuals experiencing the outcome in each group. If this was not possible, data were summarized descriptively. In the text, percentages are reported as rounded numbers, ratio measures are reported to 2 decimal places.

For carriage outcomes, prevalence risk ratios, prevalence odds ratios and prevalence differences were used to compare groups. Prevalence odds ratios are reported unless otherwise stated because these are considered to be the most appropriate effect measure to estimate VE against pneumococcal acquisition from cross-sectional data [11].

2.3.4.2 Meta-analysis

Data were combined statistically, where appropriate, using DerSimonian and Laird random-effects meta-analyses [12], and using STATA 10 (StataCorp LP, College Station, Texas, USA) for statistical tests to examine heterogeneity of results between trials. Stratum-specific outcomes were examined, and between-trial heterogeneity quantified using the I^2 statistic. This can be interpreted as the proportion of total variation in estimated risk ratios due to between-trial heterogeneity rather than to chance [13]. Low, moderate and high levels of heterogeneity correspond to I^2 values of 25%, 50% and 75%, respectively. The level of heterogeneity was taken into account when interpreting results. Data from a single study that contributed to two or more estimates within strata were not combined statistically. Unless otherwise specified, p values relate to tests of heterogeneity.

2.3.5 Presentation of results

2.3.5.1 Description of schedules

Vaccine schedules were abbreviated using the following convention:

- 3p – 3 doses in the primary vaccination schedule with all doses given before 12 months of age;
- +1 – a booster dose. If the booster was PPV, this is noted explicitly;
- (2, 3, 4) – the intended ages at vaccination, in months;
- (+ b15) – the age at which the booster dose was intended, in months.

2.3.5.2 Description of study names

A study name was assigned to each RCT, based on the country or countries in which the trial was conducted and the number of serotypes in the PCV. Citations to individual publications are not used because data might have been collated from several publications. The citations for all publications linked to each study name are listed in Annex 2.2. For descriptive purposes, the basic details of included studies are presented in alphabetical order. The following convention was used to identify individual RCTs:

- Netherlands1 – the country in which the trial was conducted, followed by a number if more than one trial had been conducted in the same country, or a population group, e.g. Ghana infants;
- 7v – the valency of the vaccine used.

2.3.5.3 Order of presentation of comparisons between schedules

Annex 2.1 presents the clinical and carriage data in figures and tables. The basic characteristics of included studies are presented in alphabetical order (Table 2.2 and 2.3). The citations for all publications related to each study are included in Annex 2.2. Selected tables and figures from the annexes are presented in the text for ease of reference, while retaining their original chronology.

RCTs and their findings are then reported, where possible, according to the following hierarchy:

- number of doses in the schedule: the first comparisons are with 1-dose schedules; schedules with only a primary vaccination series are reported before those including booster doses (see section 2.4.2.1 for further details on schedule classification);
- type of booster: schedules involving a comparison with no booster are reported first, followed by PPV booster and PCV booster doses;
- valency, starting with PCV7;
- country, population or study name, in alphabetical order;
- serotypes, in the following order, where reported
    - Any serotype,
    - Vaccine serotype,
    - Non-vaccine serotypes,
    - Vaccine-associated serotypes (includes serotypes that are not in the vaccine but are in the same serogroup as one of the vaccine serotypes),
    - Non-vaccine, excluding vaccine-associated, serotypes (includes serotypes that are not in the vaccine and are not vaccine associated serotypes),
    - Vaccine serotypes plus serotype 6A,
    - Vaccine serotypes plus vaccine-associated serotypes.

2.3.5.4 Forest plots

Forest plots are used to display the results of meta-analyses. Each plot summarizes the available data for a comparison between two different schedules, e.g. 3p vs 2p schedules.

The forest plots present the ratio measures of effect (with 95% CI), according to study and outcome. For pneumococcal carriage, the odds ratio is presented. Where data could be pooled statistically, the combined estimate of the risk difference is presented as a diamond. The plots also include the raw data, with numbers and percentages for each comparison. Forest plots for key comparisons are included in the main text, with supplementary data in Annex 2.1.

2.3.5.5 Tables

The full results of meta-analyses comparing carriage are presented in tables. Tables display prevalence risk ratios, prevalence odds ratios and prevalence differences.

2.4 Results

2.4.1 Literature search

Initial database searches yielded 3121 items. A further 96 items were included from reference lists, expert referral or repeat database, yielding a total of 3217 unique items (Figure 2.1). Of these, 161

– relating to 31 RCTs – were eligible for inclusion. Twenty contained data on clinical outcomes or nasopharyngeal carriage and are reported in this document. As of 1 September 2011, 41 items related to studies in progress or not yet published. Reports from the completed RCTs have been published in part or in full [10].

2.4.2 Description of eligible studies

The 23 RCTs that contained data on clinical outcomes or nasopharyngeal carriage are summarized in Table 2.2. Eleven of these trials reported clinical disease outcomes and 12 reported carriage. A further seven trials reported only mortality data, or clinical data reported as (serious) adverse events (SAE). Seventeen trials had a control group that received no doses of PCV, in 13 of which this was the only comparison group. A total of eight trials had direct comparisons between schedules.

Of the 57 787 children randomized to receive PCV in these RCTs, 3341 were in studies comparing PCV schedules: 2321 in 7v studies, 218 in 9v studies and 802 in 10v studies.

2.4.2.1 Description of comparisons available for analysis

In the 23 eligible RCTs, there were 28 comparisons available for analysis (Table 2.3, Figures 2.2 and 2.3). Sixteen of these were comparisons between groups receiving different PCV schedules and 12 compared a group that received a PCV schedule with a group that did not. Not all studies reported data that could be used in relevant comparisons.

The schedule comparisons available for analysis are multi-dimensional. There is interplay between the number of doses administered and the intervals between them. For example, when 3p schedules are compared with 2p schedules, the interval between doses might be twice as long in the 2p group if the second dose is removed from the 3p schedule to create the 2p schedule. The interval between doses might be kept the same by removing either the first or the third dose from the 3p schedule. A further type of comparison could have the same number of primary doses in each group but a longer interval in one group.

Comparisons are classified primarily by the number of doses in the primary and booster schedules in each schedule (Table 2.3). Within each comparison, sub-analyses were then conducted, separating schedules with differing intervals from those where intervals are kept constant between groups.

Examples:

i) In comparison C (Table 2.3), five studies compare a 3p with a 2p schedule. These are considered together in the initial analysis. However, dosing intervals differ between studies and between groups in studies. In sub-analyses, studies are grouped to make comparisons only between studies with both the same number of doses and dosing intervals.

ii) In comparison Q, two 3p+1 schedules are compared in each study. There is no difference in the number of doses, and the principal comparison is the difference in dosing interval between groups.

Figures 2.2 and 2.3 show included studies that report any clinical outcome, and nasopharyngeal carriage, respectively. Arrows between schedules show where direct comparisons have been made for at least one outcome. In general, 3p schedules are on the left of the figure, 2p schedules are on the right.

Table 2.2 Summary of included studies

Study name and PCV valency[1]	Country	Schedules, age at dose in months		Intervention in no-dose group	Number of participants randomized	Outcomes reported
		Intended	Actual age at administration			
Individual randomization						
Belgium 7v [14]	Belgium	2 doses + PPV(12–24)/ 1 dose + PPV(25–84)	Median 24 (12–76)[2]		38	Otitis media
						Carriage
		No doses		HepB/ HepA	36	
Chile 10v [15]	Chile	2, 4, 6, + b>18	NR		119[3]	Adverse events[4]
		2 catch-up >18			121[3]	Mortality
China 7v [16]	China	3, 4, 5 (DTaP coad)	median 3.5 (3.0–4.0)[2]		296	Adverse events[4]
		3, 4, 5 (DTaP not coad)	median 3.5 (3.0–4.0)[2]		300	Mortality
		No doses	median 3.5 (3.0–4.7)[2]	No additional intervention	204	
Europe 10v [17]	Denmark, Norway, Slovakia, Sweden	2, 3, 4, +b11	1st: mean 2.8 2nd: mean 3.9 3rd: mean 5.0 Booster: mean 11.2		176	Adverse events[4]
						Mortality
		2, 4, + b11	1st: mean 2.8 2nd: mean 4.9 Booster: mean 11.1		175	
Fiji 7v [18]	Fiji	1.5, 2.5, 3.5 +/- b12(PPV)	NR		136	Carriage
		1.5, 3.5 +/- b12(PPV)			156	
		3.5 +/- b12(PPV)			128	
		No doses +/- b12(PPV)		No additional intervention	132	
Finland 7v [19]	Finland	2, 4, 6, +b12	NR		831	IPD
				Hep B		Meningitis
		No doses			831	Otitis media
						Adverse events[4]
						Mortality
						Carriage

Study name and PCV valency[1]	Country	Schedules, age at dose in months		Intervention in no-dose group	Number of participants randomized	Outcomes reported
		Intended	Actual age at administration			
Finland 10v [20]	Finland	2, 3, 4, + b14–16	NR		101	Adverse events[4]
		2, 3, 4, + b12–14			110	Mortality
Gambia 7v [21]	the Gambia	2, 3, 4 + b10(PPV)	median 1.7, 3.0, 4.2, 10.5		228	Mortality
		2, 3 + b10(PPV)	median 1.8, 3.0, 10.5		228	Carriage
		2 + b10(PPV)	median 1.8, 10.4		228	
Gambia 9v [22]	the Gambia	3p[5]	Among those in per protocol analysis:		8718	IPD
			1st: median 2.5 (2.0–3.6)			Meningitis[6]
			2nd: median 4.1 (3.2–5.5)			Pneumonia
			3rd: median 5.6 (4.5–7.5)			Mortality
		No doses		Placebo	8719	
Gambia 9v pilot a [23]	the Gambia	2, 3, 4	NR		103	Mortality[7]
		No doses		IPV	104	Carriage
Gambia 9v pilot b [24]	the Gambia	2, 3, 4 (DTwPHib mixed)	NR		197	Mortality
		2, 3 ,4 (DTwPHib sep)			196	
		No doses		Placebo	197	
Ghana infants 9v [25]	Ghana	1.5, 2.5, 3.5 + b12 (PCV/PPV/Hib)	1st: mean 2.5		62	Mortality
			2nd: mean 3.8			
			3rd: mean 5.0			
		No doses		Hib conjugate	21	
Iceland 9v [26]	Iceland	3, 4, 5 + b12	NR		111[8]	Adverse events[4]
		3, 4, 5 + b12(PPV)				
		3, 5 + b12			112[8]	
		3, 5 + b12(PPV)				
Israel 7v [27]	Israel	2, 4, 6 + b12	NR		178	Carriage[9]
		2, 4, 6			178	
		4, 6 + b12			189	

Study name and PCV valency[1]	Country	Schedules, age at dose in months		Intervention in no-dose group	Number of participants randomized	Outcomes reported
		Intended	Actual age at administration			
Israel 9v [28]	Israel	2 doses (12–17)/ 1dose (18–35)	27.9 (IQR 21.6–31.8)[2]		132	Otitis media Carriage
		No doses		MenC	130	
Netherlands1 7v [29]	Netherlands	2 doses + PPV(12–24)/ 1dose + PPV(25–84)	Median 25.1 (12–82.3)[2]		190 193	Otitis media Carriage
		No doses		HepB/HepA		
Netherlands2 7v [30]	Netherlands	1 dose + PPV(>24)	Mean 64.8[10]		80	Otitis media Mortality
		No doses		No additional intervention	81	
Netherlands3 7v [31]	Netherlands	2 doses >18	Mean 36[2]		197	Otitis media[11]
		No doses		Placebo	187	
Netherlands4 7v [32]	Netherlands	2, 4, + b11	1st: mean 2.0 (SD 0.26) 2nd: mean 4.3 (SD 0.40) 3rd: mean 11.3 (SD 0.47)		336	Carriage
		2, 4	1st: mean 2.1 (SD 0.35) 2nd: mean 4.3 (SD 0.58)		336	
		No doses		No additional intervention	333	
South Africa 9v [33]	South Africa	1.5, 2.5, 3.5	1st: mean 1.5 (SD 0.28) 2nd: mean 2.6 (SD 0.61) 3rd: mean 3.7 (SD 0.93)		19922	IPD Meningitis Pneumonia Mortality Carriage
		No doses		Placebo	19914	
South Africa 9v pilot [34]	South Africa	1.5, 2.5, 3.5	1st:mean 1.5 (SD 0.14)[12] 2nd: mean 2.5 (SD 0.32)[12] 3rd: mean 3.5 (SD 0.43)[12]		250	Pneumonia[13] Mortality Carriage
		No doses		Placebo	250	

Study name and PCV valency[1]	Country	Schedules, age at dose in months		Intervention in no-dose group	Number of participants randomized	Outcomes reported
		Intended	Actual age at administration			
USA1 7v [35]	USA	2, 4, 6, + b12	NR		18927	IPD
		No doses		MenC	18941	Pneumonia
						Otitis media
						Mortality
Cluster randomization						
USA2 7v [36]	USA	3p+1 / 2p+1 / 2doses[14]	1st (3p+1 group): mean 2.7 (SD 1.5)		2971/ 315/ 876	IPD
						Meningitis
						Otitis media
						Mortality
				MenC	2818/ 295/ 813	Carriage
		No doses				

Legend:

b – booster; coad – coadministered (vaccines given at same time); DTaP – diphtheria, tetanus, acellular pertussis vaccine; DTwP – diphtheria, tetanus, whole cell pertussis vaccine; HepA – Hepatitis A vaccine; HepB – Hepatitis B vaccine; Hib – *Haemophilus influenzae* type b vaccine; IPD – invasive pneumococcal disease; IPV - inactivated poliovirus vaccine; IQR – interquartile range; MenC – meningococcus group C conjugate vaccine; mixed – vaccines given at same time in same syringe; NR – not reported; PCV – pneumococcal conjugate vaccine; PPV – pneumococcal polysaccharide vaccine; SD – standard deviation; sep – vaccines given at same time but at separate sites; 3p – 3 dose primary schedule, etc.; +1 – booster dose.

Studies are not included in this report if mortality was the only clinical or carriage outcome, and no deaths were reported or mortality data could not be extracted. There are four studies in this category: three report no deaths [37–39] and for one, mortality data were not extractable [40].

1 A single primary reference is cited for each study (further references are available in Annex 2.2). Study names were assigned for this review, although several studies use alternative names elsewhere in the literature: Finland 7v, "Finnish Acute Otitis Media"; Belgium 7v, Netherlands1 7v, "Omavax"; Netherlands3 7v, "Primakid"; Netherlands4 7v, "MNOES" or "MINOES"; USA1 7v, "Northern California Kaiser Permanente"; USA2 7v, "Native American" or "American Indian".

2 Age at baseline – not clear if age at first vaccination.

3 As stated in 2366 [41], numbers in 2379 [15] differ.

4 Adverse events include eligible clinical outcomes. Not analysed because data were not specifically collected as outcomes, no case definitions were applied and data were only collected for periods immediately after vaccination.

5 No set age for doses, children 6–51 weeks given 3 doses at least 25 days apart.

6 Reported together with sepsis and therefore cannot be analysed separately.

7 Mortality data not reported clearly for each intervention group, and therefore not reported in this review.

8 Number undergoing randomization, numbers in each group unclear.

9 No extractable carriage data as of 1 September 2011; included here as immunogenicity data are available and carriage data will become available.

10 Described as "age" in published article; unclear if at baseline, first vaccination, or another time point.

11 Insufficient data reported to calculate ratios with confidence interval in relevant groups.

12 Reported as age "at recruitment", "at second visit", and "at the third vaccination", and is for all participants (PCV group and control group combined).

13 Insufficient data reported to extract separately for each group.

14 Number of doses given to children in vaccinated group age-dependent. No set age for doses: infants enrolled between age 6 weeks and 7 months – 3 doses of vaccine 2 months apart + b12–15 months of age; infants enrolled between 7 and 11 months of age – 2 doses of vaccine 2 months apart + b12–15 months; infants enrolled between 12 and 23 months of age received 2 doses of vaccine at least 2 months apart.

Table 2.3 Order of description and presentation of comparisons of vaccination schedules

Comparison	Study	Schedules, months	Time at which outcomes measured[1]			
			Clinical	Carriage in all trial participants, months	Carriage in sub-groups, months	Carriage in the community, months
Schedule vs schedule (comparisons A–T)						
Comparison A 2p vs 1p	Fiji 7v	1.5, 3.5 3.5	NA	6, 9, 12, 17	NA	NA
	Gambia 7v[2]	2, 3 2	Between enrolment and approx. 15 months of age[3]	5	NA	NA
Comparison B 3p vs 1p	Fiji 7v	1.5, 2.5, 3.5 3.5	NA	6, 9, 12, 17	NA	NA
	Gambia 7v[2]	2, 3, 4 2	Between enrolment and approx. 15 months of age[3]	5	NA	NA
Comparison C 3p vs 2p	Fiji 7v	1.5, 2.5, 3.5 1.5, 3.5	NA	6, 9, 12, 17	NA	NA
	Gambia 7v[2]	2, 3, 4 2, 3	Between enrolment and approx. 15 months of age[3]	**5**	NA	NA
	Israel 7v[2]	2, 4, 6 4, 6	NA	NA[5]	NA	NA
	Iceland 9v[2]	3, 4, 5 3, 5	For 28 days after the primary series[4]	NA	NA	NA
	Europe 10v[2]	2, 3, 4 2, 4	During "whole study period", enrolment until 1 month after last primary dose (possibly longer)	NA	NA	NA
Comparison D 2p + PPV vs 1p +PPV	Fiji 7v	1.5, 3.5 + b12(PPV) 3.5 + b12(PPV)	NA	17	NA	NA
	Gambia 7v	2, 3, 4 + b10(PPV) 2, 3 + b10(PPV)	Between enrolment and approx. 15 months of age[3]	11, 15	NA	NA
Comparison E 2p + 1 vs 2p	Netherlands4 7v	2, 4, + b11 2, 4	NA	12, 18, 24	NA	Parents of children sampled at same time as children
Comparison F 2p + 1 vs 2p + PPV	Iceland 9v	3, 5 + b12 3, 4, 5 + b12(PPV)	For 28 days after the booster dose[4]	NA	NA	NA
Comparison G 3p vs 2p + 1	Israel 7v	2, 4, 6 4, 6 + b12	NA	NA[5]	NA	NA
Comparison H 3p + PPV vs 1p+ PPV	Fiji 7v	1.5, 2.5, 3.5 + b12(PPV) 3.5 + b12(PPV)	NA	17	NA	NA

Comparison	Study	Schedules, months	Time at which outcomes measured[1]			
			Clinical	Carriage in all trial participants, months	Carriage in sub-groups, months	Carriage in the community, months
	Gambia 7v	2, 3, 4 + b10(PPV) 2 + b10(PPV)	Between enrolment and approx. 15 months of age[3]	11, 15	NA	NA
Comparison I 3p + PPV vs 2p +PPV	Fiji 7v	1.5, 2.5, 3.5 + b12(PPV) 1.5, 3.5 + b12(PPV)	NA	17	NA	NA
	Gambia 7v	2, 3, 4 + b10(PPV) 2 , 3 + b10(PPV)	Between enrolment and approx. 15 months of age[3]	11, 15	NA	NA
	Iceland 9v	3, 4, 5 + b12(PPV) 3, 5 + b12 (PPV)	For 28 days after the booster dose[4]	NA	NA	NA
Comparison J 3p + PPV vs 2p + 1	Iceland 9v	3, 4, 5 + b12(PPV) 3, 5 + b12	For 28 days after the booster dose[4]	NA	NA	NA
Comparison K 3p + 1 vs 2p +PPV	Iceland 9v	3, 4, 5 + b12 3, 5 + b12(PPV)	For 28 days after the booster dose[4]	NA	NA	NA
Comparison L 3p + 1 vs 2p +1	Israel 7v	2, 4, 6 + b12 4, 6 + b12	NA	NA[5]	NA	NA
	Iceland 9v	3, 5 + b12 3, 4, 5 + b12	For 28 days after booster dose[4]	NA	NA	NA
	Europe 10v	2, 3, 4 + b11 2, 4 + b11	"whole study period", for 1 month after booster received?[4]	NA	NA	NA
Comparison M 3p + 1 vs 3p	Israel 7v	2, 4, 6 + b12 2, 4, 6	NA	NA[5]	NA	NA
Comparison N 3p + 1 vs 3p + PPV	Iceland 9v	3, 4, 5 + b12 3, 4, 5 + b12(PPV)	For 28 days after booster dose[4]	NA	NA	NA
Comparison Q longer interval between primary and booster vs shorter interval between primary and booster	Finland 10v	2, 3, 4 + b14–16 2, 3, 4 + b12–14	"extended safety follow-up" period[4]	NA	NA	NA
Comparison T Primary (+/- booster) vs catch-up	Chile 10v	2, 4, 6 + b>18 2 catch-up >18	From booster dose until end of extended safety follow-up[4]	NA	NA	NA
Schedule vs no PCV (comparisons U–Z)						
Comparison U1 1p vs 0	Fiji 7v	3.5 no PCV and no PPV	NA	6, 9, 12, 17	NA	NA
	South Africa 9v pilot	1.5, 2.5, 3.5 no PCV and no PPV	NA	2.5	NA	NA
Comparison U2 2p vs 0	Fiji 7v	1.5, 3.5 no PCV and no PPV	NA	6, 9, 12, 17	NA	NA

Comparison	Study	Schedules, months	Time at which outcomes measured[1]			
			Clinical	**Carriage in all trial participants, months**	**Carriage in sub-groups, months**	**Carriage in the community, months**
	Netherlands4 7v	2, 4 no PCV and no PPV	NA	12, 18, 24	NA	Parents of children sampled at same time as children
	South Africa 9v pilot	1.5, 2.5, 3.5 no PCV and no PPV	NA	3.5	NA	NA
Comparison U3 3p vs 0	China 7v	3, 4, 5 (DTaP coad) 3, 4, 5 (DTaP not coad) no PCV and no PPV	Until maximum 30–50d after 3rd dose	NA	NA	NA
	Fiji 7v	1.5, 2.5, 3.5 no PCV and no PPV	NA	6, 9, 12, 17	NA	NA
	Finland 7v	2, 4, 6 No doses	Otitis outcomes only. Starting time varies between ITT (at randomization) and PP (at 14d after 3rd dose) analyses	12	NA	NA
	USA2 7v	3p[6] no PCV and no PPV	NA	NA	1 month after 3rd dose, before booster	Household members also sampled at same time as subgroup
	Gambia 9v	3p[7] no PCV and no PPV	Until end study (2 years follow-up). Start time varies between ITT (at randomization) and PP (at 14d after 3rd dose) analyses	NA	NA	NA
	Gambia 9v pilot a	2, 3, 4 no PCV and no PPV	Until 1 month after 3rd dose[8]	5, 9	NA	NA
	Gambia 9v pilot b	2, 3, 4 (DTwPHib mixed) 2, 3 ,4 (DTwPHib sep) no PCV and no PPV	"during the surveillance period", until 1 month after dose 3?	NA	NA	NA
	Ghana infants 9v	1.5, 2.5, 3.5 + b12 (PCV/PPV/Hib) No doses	Between enrolment and approx. 13 months	NA	NA	NA
	South Africa 9v	1.5, 2.5, 3.5 no PCV and no PPV	Until target number of cases reached. Maximum 3.7 years.). Start time varies between ITT (at randomization?) and PP (at 14d after 3rd dose)	NA	Mean 5.35 years after 3rd dose	NA
	South Africa 9v pilot	1.5, 2.5, 3.5 no PCV and no PPV	From enrolment until 9 months	2.5, 3.5, 9	NA	NA
	Chile 10v	2, 4, 6 no PCV and no PPV	"whole study period", enrolment until 1 month after last primary	NA	NA	NA

Comparison	Study	Schedules, months	Time at which outcomes measured[1]			
			Clinical	Carriage in all trial participants, months	Carriage in sub-groups, months	Carriage in the community, months
			dose (possibly longer)[4]			
Comparison V1 1p + PPV vs 0	Fiji 7v	3.5 + b12(PPV) no PCV (+/- 12(PPV))	NA	17	NA	NA
Comparison V2 2p + PPV vs 0	Fiji 7v	1.5, 3.5 + b12(PPV) no PCV (+/- 12(PPV))	NA	17	NA	NA
Comparison V3 3p + PPV vs 0	Fiji 7v	1.5, 2.5, 3.5 + b12(PPV) no PCV (+/- 12(PPV))	NA	17	NA	NA
Comparison W2 2p + 1 vs 0	Netherlands4 7v	2, 4, + b11 no PCV and no PPV	NA	12, 18, 24	NA	Parents of children sampled at same time as children
Comparison W3 3p + 1 vs 0	Finland 7v	2, 4, 6, + b12 no PCV and no PPV	Until 24 months of age. Starting time varies between ITT (at randomization) and PP (at 14d after 3rd dose) analyses	18	NA	NA
	USA1 7v	2, 4, 6, + b12 no PCV and no PPV	Until April 1999	NA	NA	NA
	USA2 7v	3p+1[6] no PCV and no PPV	April 1997 to May 2000	NA	18–24. Also after trial unblinded, cross-sectional study conducted	Household members sampled at same time as subgroup before unblinding
	Ghana infants 9v	1.5, 2.5, 3.5 + b12 (PCV/PPV/Hib) no PCV and no PPV	Enrolment until end of follow-up, unclear age at which follow-up ended	NA	NA	NA
Comparison W4 1, 2, 3 or 4 doses vs 0	USA2 7v	3p+1 / 2p+1 / 2doses[6] no PCV and no PPV	April 1997 to May 2000	NA		Community study after trial completion
Comparison X1 1 catch-up dose vs 0	Netherlands1 7v	1 dose (25–84m) + PPV 7 months later no PCV and no PPV	NA	7, 14, 20, 26 months after 1st dose[9]	NA	NA
	Netherlands2 7v	1 dose + PPV (>24m) no PCV and no PPV	For 6 months after spontaneous extrusion of the TTs	NA	NA	NA
Comparison X2 2 catch up doses vs 0	Netherlands1 7v	2 doses with 1 month interval (12–24m) + PPV 6 months later no PCV and no PPV	NA	7, 14, 20, 26 months after 1st dose[9]	NA	NA
	Netherlands3 7v	2 doses >18m no PCV and no PPV	From 14 days after 2nd set of vaccinations, for 18 or 6 months, depending on year of inclusion	NA	NA	NA

Comparison	Study	Schedules, months	Time at which outcomes measured[1]			
			Clinical	Carriage in all trial participants, months	Carriage in sub-groups, months	Carriage in the community, months
Comparison Y 1 or 2 catch-up doses vs 0	Belgium 7v	2 doses with 1 month interval (12–24m) + PPV 6 months later/ 1 dose (25–84m) + PPV 7 months later no PCV and no PPV	1 month after complete vaccination until 26 months after vaccination	7, 14, 20, 26 months after 1st dose[9]	NA	NA
	Netherlands1 7v	2 doses with 1 month interval (12–24m) + PPV 6 months later/ 1 dose (25–84m) + PPV 7 months later no PCV and no PPV	1 month after complete vaccination until 26 months after vaccination	7, 14, 20, 26 months after 1st dose	NA	NA
	Israel 9v	2 doses (12–17m)/ 1dose (18–35m) no PCV and no PPV	2 years, starting 1 month after complete vaccination	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 18[9]	NA	NA

Legend:

b – booster; coad – coadministered (vaccines given at same time); DTaP – diphtheria, tetanus, acellular pertussis vaccine; DTwP – diphtheria, tetanus, whole cell pertussis vaccine; HepA – Hepatitis A vaccine; HepB – Hepatitis B vaccine; Hib – *Haemophilus influenzae* type b vaccine; IPD – invasive pneumococcal disease; IPV – inactivated poliovirus vaccine; IQR – interquartile range; ITT – intention-to-treat analysis; m – month(s); MenC – meningococcus group C conjugate vaccine; mixed – vaccines given at same time in same syringe; NA – not assessed; PCV – pneumococcal conjugate vaccine; PPV – pneumococcal polysaccharide vaccine; PP – per protocol analysis; SD – standard deviation; sep – vaccines given at same time but at separate sites; TT – tympanic tube; 3p – 3 dose primary schedule, etc.; +1 – booster dose.

Shaded grey rows are comparisons that are reported in main text.

1 All times are in months of age unless otherwise stated. Carriage in all trial participants is carriage data where attempts were made to sample all those randomized and enrolled in the RCT. Carriage in sub-groups is carriage data where a sub-set of those randomized and enrolled in the RCT was selected for sampling. Carriage in the community is carriage data where people such as parents or siblings of trial participants were sampled to assess indirect effects of vaccination.

2 Samples taken before booster dose, so comparison of primary schedule also possible.

3 Not possible to distinguish between pre- and post-PPV periods.

4 Adverse events include eligible clinical outcomes. Not analysed because data were not specifically collected as outcomes, no case definitions were applied and data were only collected for periods immediately after vaccination.

5 No extractable data as of 1 September 2011.

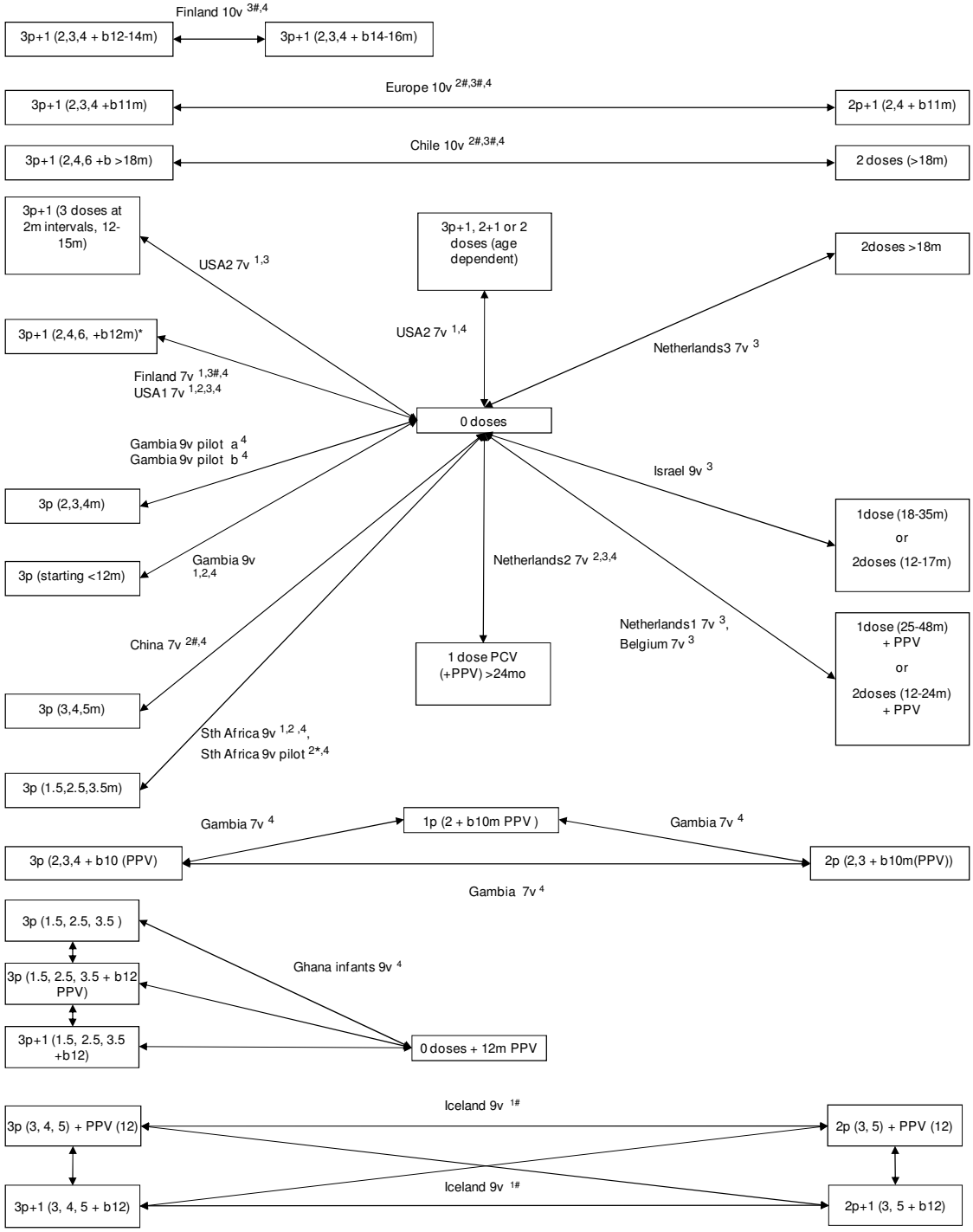
6 Number of dose given to children in vaccinated group age-dependent. No set age for doses: infants enrolled between age 6 weeks and 7 months – 3 doses of vaccine 2 months apart plus booster at 12–15 months of age; infants enrolled between 7 and 11 months of age – 2 doses of vaccine 2 months apart plus booster at b12–15 months; infants enrolled between 12 and 23 months of age received 2 doses of vaccine at least 2 months apart.

7 No set age for doses, children 6–51 weeks given 3 doses at least 25 days apart.

8 Data not reported clearly for each intervention group, and therefore not reported in this review.

9 Denominators not reported and not possible to calculate; results not included in meta-analyses.

Figure 2.2 Clinical outcomes following PCV vaccination: comparisons available in included trials



Legend:

b – booster (PCV unless explicitly stated as PPV); m – month(s); PCV – pneumococcal conjugate vaccine; PPV – pneumococcal polysaccharide vaccine.

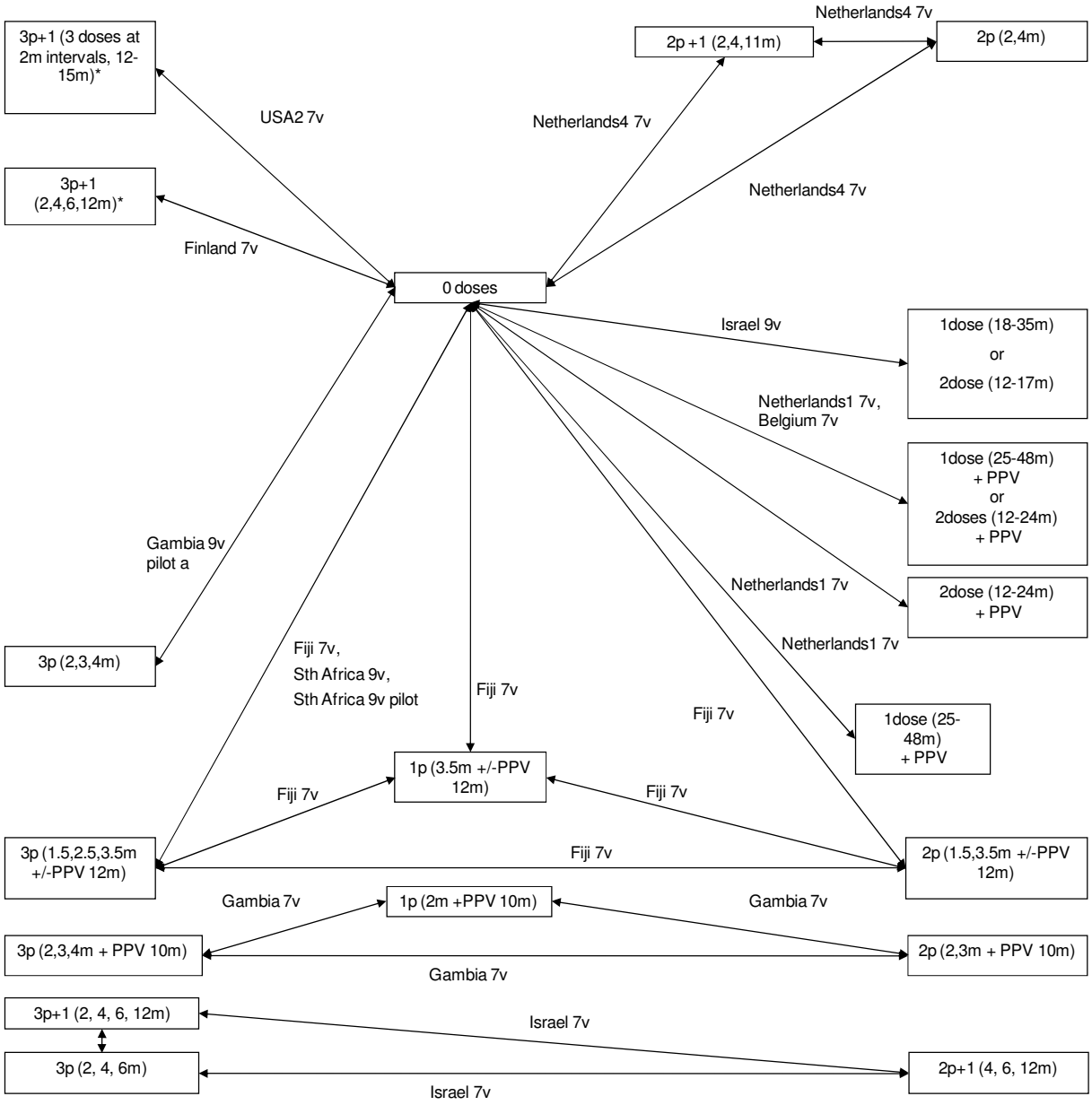
Studies not included in this report if mortality was the only clinical or carriage outcome, and no deaths were reported or mortality data could not be extracted. There are four studies in this category: three report no deaths [37–39], and for the fourth, mortality data were not extractable [40].

3p + 1 (2,3,4,11m)	Schedule described as, e.g. 3p – number of doses in primary schedule; +1 – booster dose; (2,3,4,11m) – ages when vaccine doses intended to be given.

Study names for each comparison are along the lines connecting each schedule.

Superscript numbers refer to outcomes described: 1 – IPD; 2 – pneumonia; 3 – otitis media; 4 – mortality; # – outcome extracted from reports of (serious) adverse events only; * – not reported separately for each intervention group.

Figure 2.3 Carriage of pneumococcal serotypes following PCV vaccination: comparisons available in included trials



Legend:

b – booster (PCV unless explicitly stated as PPV); PCV – pneumococcal conjugate vaccine; PPV – pneumococcal polysaccharide vaccine.

3p + 1 (2,3,4,11m)	Schedule described as, e.g. 3p – number of doses in primary schedule; +1 – booster dose; (2,3,4,11m) – ages when vaccine doses intended to be given.

Study names for each comparison are along the lines connecting each schedule.

Superscript numbers refer to outcomes described: 1 – IPD; 2 – pneumonia; 3 – otitis media; 4 – mortality; * – sample/s also taken before booster dose.

2.4.3 Clinical outcomes, schedule vs schedule comparisons

Summary

- *Very few data on clinical outcomes could be extracted from RCTs that directly compared different PCV schedules.*
- *Clinical data were extracted from reasons for loss to follow-up or reports of SAE as observation periods were relatively short, often not continuous and mainly covered time periods before the vaccination course had been completed, and thus the full protective potential was unlikely to have been reached.*

2.4.3.1 Summary according to outcome, all comparisons

Overall, there were few data from RCTs directly comparing PCV schedules.

The available clinical disease outcome data were collected as SAEs. These data are unsuitable for the estimation of relative efficacy of different PCV vaccine schedules for the following reasons: first, observation periods were relatively short and often not continuous; second, the period of observation mainly covered time periods before completion of the vaccination course, and the full protective potential was unlikely to have been reached; and third, case definitions for clinical disease outcomes were usually not defined, and detection and reporting might not have been complete (e.g. invasive disease might only be reported as a cause of death and non-fatal cases might not be reported).

Indirect comparisons between intervention groups that received differing schedules as part of separate RCTs have not been made. The number of studies that could be compared for IPD and pneumonia is limited (see Discussion, section 2.5).

2.4.3.2 Methodological issues affecting results, schedule vs schedule comparisons

There were too few data from RCTs directly comparing PCV schedules to examine reasons for heterogeneity.

2.4.3.3 Comparison A: 2p vs1p

One RCT reported on any clinical outcome for this comparison (Gambia 7v).

a) Invasive pneumococcal disease, pneumonia, otitis media

No data available.

b) Mortality

In Gambia 7v, mortality data were reported as reasons for loss to follow-up and no causes of death were given. There were 8 deaths reported among the 228 infants randomized to the 2-dose group (4% 95% CI 2, 7%) and 2 deaths among the 228 infants randomized to the 1-dose group (1% 95% CI 0.1, 3%).

2.4.3.4 Comparison B: 3p vs 1p

One RCT reported on any clinical outcome for this comparison (Gambia 7v).

a) Invasive pneumococcal disease, pneumonia, otitis media

No data available.

b) Mortality

In Gambia 7v, mortality data were reported as reasons for loss to follow-up and no causes of death were given. There were 5 deaths reported among 228 infants randomized to the 3-dose group (2% 95% CI 1, 5%) and 2 deaths among the 228 infants randomized to the 1-dose group (1% 95% CI 0.1, 3%).

2.4.3.5 Comparison C: 3p vs 2p

Three RCTs reported clinical data for this comparison (Gambia 7v, Iceland 9v, Europe 10v). The data from Iceland 9v and Europe 10v were collected as adverse events, so relative efficacy was not estimated. Mortality data were reported in Gambia 7v as a reason for loss to follow-up; no causes of death were supplied.

a) Invasive pneumococcal disease

In Iceland 9v, one child in the 2p group had septicaemia 7 days after the second dose, caused by *S. pneumoniae* serotype 7F. No further cases were reported within this study. No cases of IPD were reported in Gambia 7v or Europe 10v, but neither study explicitly stated that no cases occurred.

b) Pneumonia

One case of bronchopneumonia occurred in Europe 10v in the 3p group, in the period between starting the primary course and 30 days after the last dose of the primary course. No further details were given. No cases of pneumonia were reported in Gambia 7v or Iceland 9v for this comparison, but neither study explicitly stated that no cases occurred.

c) Otitis media

Iceland 9v reported that the child with septicaemia (section 2.4.3.5.a) also later developed otitis media. No further information was given on this case and no further cases of otitis media were reported. In Europe 10v, no report was made about otitis media after primary vaccination.

d) Mortality

In Gambia 7v, there were 5 deaths among the 228 infants randomized to the 3-dose group (2% 95% CI 1, 5%) and 8 deaths among the 228 infants randomized to the 2-dose group (4% 95% CI 2, 7%). No deaths were reported in Iceland 9v and Europe 10v. In Europe 10v, it was explicitly stated that there were no deaths.

2.4.3.6 Comparison E: 2p+1 vs 2p

No data were available on clinical disease outcomes or mortality.

2.4.3.7 Comparison G: 3p vs 2p+1

No data were available on clinical disease outcomes or mortality.

2.4.3.8 Comparison L: 3p+1 vs 2p+1

Two RCTs reported clinical data for this comparison (Iceland 9v, Europe 10v). The data from these studies were collected as adverse events, and thus relative efficacy of different PCV vaccine schedules was not calculated.

a) Invasive pneumococcal disease

No cases of IPD were reported for this comparison in Europe 10v. In Iceland 9v, no cases were reported to have occurred after the booster dose. Neither study explicitly stated that no cases occurred.

b) Pneumonia

The one reported case of pneumonia occurred in the 2p+1 group of Europe 10v within 30 days of the booster dose of vaccine. In Iceland 9v, no cases of pneumonia were reported, but it was not explicitly stated that no cases occurred.

c) Otitis media

In Europe 10v, 7 of 171 (4.1%) in the 3p+1 group and 9 of 174 (5.2%) in the 2p+1 group experienced otitis media within 30 days of the booster dose. One of the cases in the 3p+1 group was classed as an SAE. Another individual in the 3p+1 group and four individuals in the 2p+1 group were recorded as having ear infections, but no further information was given.

d) Mortality

No deaths were reported in Iceland 9v and Europe 10v. In Europe 10v, it was explicitly stated that there were no deaths.

2.4.3.9 Comparison M: 3p+1 vs 3p

No data available on clinical disease outcomes or mortality.

2.4.3.10 Comparison O: Late vs early start

No data were available on clinical disease outcomes or mortality.

2.4.3.11 Comparison P: 2-month vs 1-month interval

No data were available on clinical disease outcomes or mortality.

2.4.3.12 Comparison Q: Longer vs shorter interval between primary and booster

One RCT reported clinical data for this comparison (Finland 10v). The data were collected as adverse events, and thus relative efficacy was not calculated.

a) Invasive pneumococcal disease

No cases of IPD were reported in Finland 10v, although it was not explicitly stated that no cases occurred.

b) Pneumonia

No cases of pneumonia were reported in Finland 10v, although it was not explicitly stated that no cases occurred.

c) Otitis media

In Finland 10v, 26 of 110 (24%) individuals in the 12–14 month booster group experienced otitis media within 42 days of vaccines given at 12–14 months and 14–16 months (non-PCV vaccines were given to this group at 14–16 months of age). In the 14–16 month booster group, 28 of 101 (28%) experienced otitis media within 42 days of vaccines given at 12–14 months and 14–16 months (non-PCV vaccines were given to this group at 12–14 months of age).

d) Mortality

It was explicitly stated that there were no deaths in Finland 10v.

2.4.3.13 Comparison R: Catch-up (toddler) vs catch-up schedules

No data were available on clinical disease outcomes or mortality.

2.4.3.14 Comparison T: infant vs catch-up schedules

One RCT reported clinical data for this comparison (Chile 10v). The data were collected as adverse events, and thus relative efficacy of different PCV vaccine schedules was not estimated.

a) Invasive pneumococcal disease

No cases of IPD were reported in Chile 10v, although it was not explicitly stated that no cases occurred.

b) Pneumonia

In Chile 10v, 2 of 79 individuals (3%) in the 2-catch-up dose group experienced bronchopneumonia within 30 days of one or other of the catch-up doses. It was not reported how many of the 84 children in the 3p+1 group experienced otitis media in the same period.

c) Otitis media

In Chile 10v, 2 of 84 individuals (2%) in the 3p+1 group experienced otitis media in the booster observation period (which appears to include a period after non-PCV vaccines were given after 18 months of age and before the booster dose of PCV). It was not reported how many of the 79 children in the catch-up group experienced otitis media in the same period.

d) Mortality

In Chile10v, it was explicitly stated that there were no deaths.

2.4.4 Clinical outcomes, PCV schedules vs no PCV

Summary

- *Ten RCTs using either 3p+1 or 3p+0 PCV schedules reported at least one eligible clinical outcome. Five of these RCTs reported on IPD, three on pneumonia, three on otitis media and ten on mortality. In general, analyses that combined results across schedules were consistent with those stratified by schedule.*
- *RCTs of 3p+1 schedules were conducted in high-income countries (Finland, USA), whereas RCTs of 3p+0 schedules were carried out in low- or middle-income countries (the Gambia, South Africa).*
- *A further five RCTs compared catch-up (toddler) schedules to no PCV. Otitis media was the only clinical outcome reported for most of these RCTs.*
- *For IPD caused by any pneumococcal serotype, the estimated VE in the USA1 7v trial was higher than in other individually randomized RCTs and the single cluster-randomized trials. The detection of less clinically severe invasive disease in this trial and the distribution of serotypes in the USA1 7v population are among the potential explanations for this result.*
- *For IPD caused by vaccine serotypes, VE estimates for 3p+0 schedules were 71% (95% CI 52, 82%, I^2 0%, 2 RCTs) and for 3p+1 schedules 87% (95% CI 76, 95%, I^2 0%, 2 RCTs) using intention-to-treat (ITT) data in individually randomized trials and 86% (95% CI 40, 97%) in the cluster-randomized trial (3p+1). Estimates were similar in HIV-infected and -uninfected infants vaccinated with a 3p+0 schedule.*
- *For radiologically confirmed pneumonia (first episode), estimated VE for 3p+0 schedules using ITT data was 14% (95% CI 9, 37%, I^2 70%, 2 RCTs) and heterogeneity was not explained by the inclusion of HIV-infected children. For 3p+1 using ITT data, VE was 25% (95% CI 6, 41%, 1 trial).*
- *For otitis media, only 3p+1 and catch-up schedules were investigated. 3p+1 schedules protected against pneumococcal (VE 46%, 95% CI 10, 55%, I^2 17%, 2 RCTs) but not all-cause otitis media (VE 6%, 95% CI 4, 9%, I^2 0%) in healthy children, using ITT data. Catch-up doses did not protect against all-cause otitis media in children with a history of ear infections, using more readily available per protocol data (VE -27%, 95% CI -57, -3%, I^2 0%, 2 RCTs). In healthy children, per protocol VE was 17%, (95% CI -2, 33%, 1 trial).*
- *Generally few deaths were reported in RCTs, with only two reporting more than 25 deaths. In both these RCTs, fewer deaths occurred in the vaccinated group.*

2.4.4.1 Summary of clinical data according to outcome, all schedules

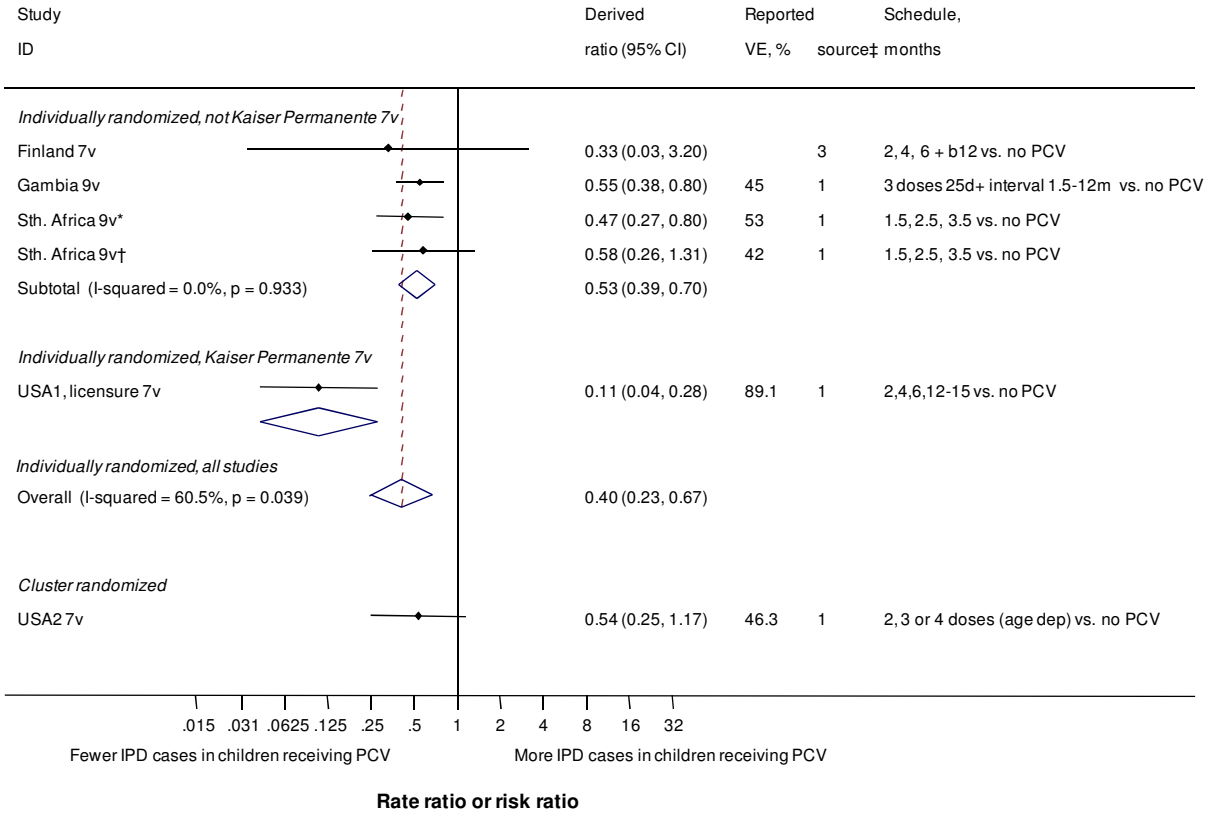
The results of meta-analyses that include all available RCTs, irrespective of schedule, were consistent with analyses that are stratified by schedule and are summarized here.

a) Invasive pneumococcal disease

Five studies reported on IPD in children receiving PCV vs no PCV (Finland 7v, Gambia 9v, South Africa 9v, USA1 7v, USA2 7v). Finland 7v, USA1 7v, USA2 7v used 3p+1 schedules and Gambia 9v and South Africa 9v used 3p schedules. South Africa 9v included both HIV-infected and -uninfected participants and data for these groups are analysed separately throughout. Data from the USA2 7v cluster-randomized trial are reported separately as they

represent direct and indirect effects, whereas in the individually randomized trials, data represent direct effects only.

Figure 2.4 Invasive pneumococcal disease, any serotype, intention-to-treat analysis, any schedule



Legend:

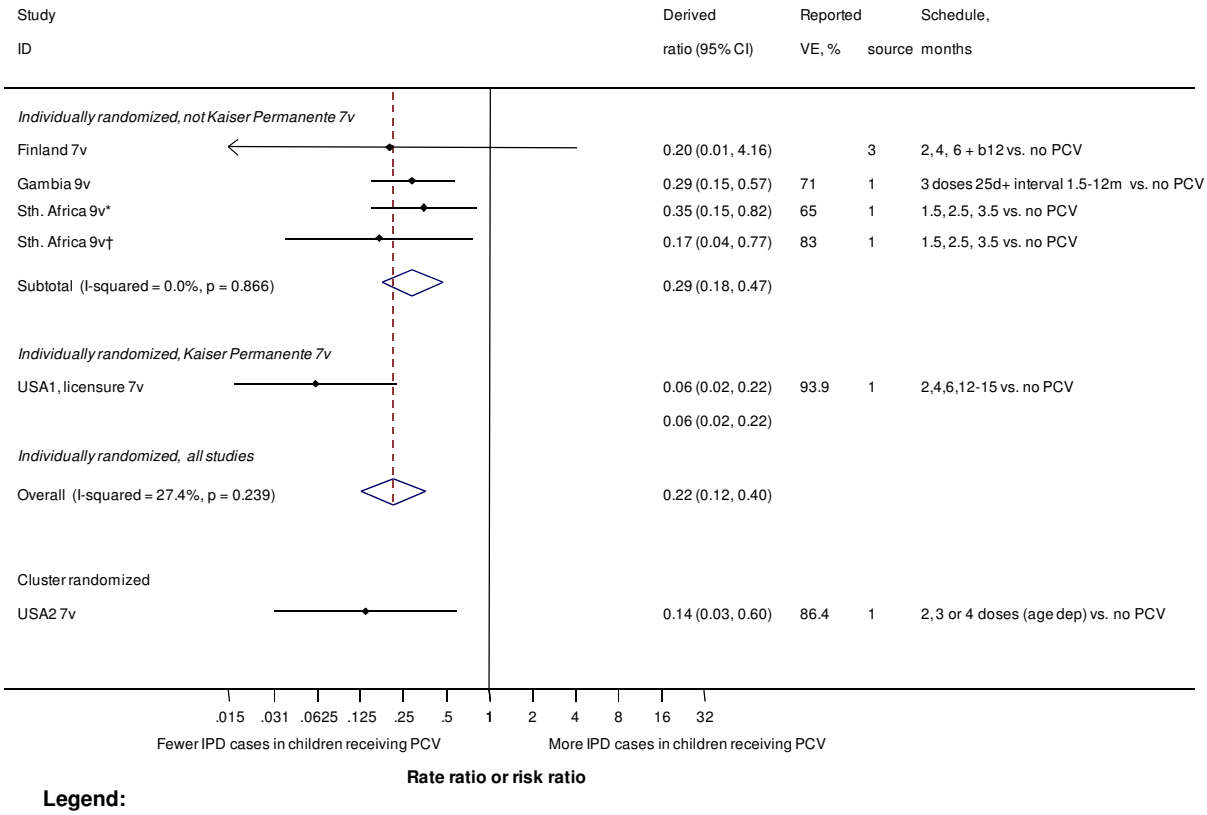
IPD – invasive pneumococcal disease; * HIV-infected; † HIV-uninfected; ‡ Source of derived ratio (1, from a reported VE based on a rate ratio; 2, reported rate ratio; 3, risk ratio calculated from reported cases/events and denominator data).

Horizontal axis represents effect estimate on logarithmic scale, comparing IPD in groups of children receiving PCV vs no PCV; vertical line through 1 shows no difference in IPD incidence between groups; effect estimate might differ between studies, depending on data provided in trial report. Solid black diamonds represent point estimate of effect estimate ratio; horizontal black line represents 95% confidence interval; points to the left of the vertical black line show a beneficial effect of PCV (fewer cases of IPD in PCV group), points to the right of the line show a detrimental effect of PCV (more cases of IPD in PCV group); blue diamond represents the pooled estimate, combined using random effects meta-analysis; vertical points of diamond represent point estimate and horizontal points represent 95% CI; red dashed vertical line represents combined effect among individually randomized studies; I^2 value is the level of statistical heterogeneity between trials (<25% low heterogeneity).

Any serotype: The results of the four individually randomized trials were heterogeneous in both ITT and per protocol (PP) analyses (I^2 >50%, Figures 2.4 and 2.5). The USA1 7v trial showed a stronger effect of PCV than all other studies. The results of the other three individually randomized trials were consistent in ITT analysis (VE 47%, 95% CI 30, 61%, I^2 0%). Estimated VE was similar in HIV-infected and -uninfected children in South Africa 9v.

Results from the cluster-randomized trial USA2 7v (VE 46%, 95% CI -17, 75%) were similar to the individually randomized trials with the exception of USA1 7v. Results of PP analyses were qualitatively similar to those of ITT analyses.

Figure 2.6 Invasive pneumococcal disease, vaccine serotypes, intention-to-treat analysis, any schedule



Legend:

IPD – invasive pneumococcal disease; * HIV-infected; † HIV-uninfected; ‡ Source of derived ratio (1, from a reported VE based on a rate ratio; 2, reported rate ratio; 3, risk ratio calculated from reported cases/events and denominator data).

Horizontal axis represents effect estimate on logarithmic scale, comparing IPD in groups of children receiving PCV vs no PCV; vertical line through 1 shows no difference in IPD incidence between groups; effect estimate might differ between studies, depending on data provided in trial report. Solid black diamonds represent point estimate of effect estimate ratio; horizontal black line represents 95% confidence interval; points to the left of the vertical black line show a beneficial effect of PCV (fewer cases of IPD in PCV group), points to the right of the line show a detrimental effect of PCV (more cases of IPD in PCV group); blue diamond represents the pooled estimate, combined using random effects meta-analysis; vertical points of diamond represent point estimate and horizontal points represent 95% CI; red dashed vertical line represents combined effect among individually randomized studies; I^2 value is the level of statistical heterogeneity between trials (<25% low heterogeneity).

Vaccine serotypes: IPD caused by vaccine serotypes was the primary efficacy outcome specified in the USA1 7v and South Africa 9v trials. Estimates of VE were greater than those for any serotype in all studies (Figures 2.6 and 2.7).

Among individually randomized trials, there was a low level of heterogeneity (I^2 27.4%, pooled VE 78%, 95% CI 60, 88%). There was no heterogeneity if USA1 7v was excluded (I^2 0%, VE 71%, 95% CI 53, 82%).

VE was somewhat higher in HIV-uninfected (83%) than -infected (65%) children, but CI overlapped. In ITT analysis without the HIV-infected group, the combined effect was 0.26 (95% CI 0.14, 0.48, VE 74%, 95% CI 52, 86%, I^2 0%).

Non-vaccine serotypes, excluding vaccine-associated serotypes: All five studies reported on the incidence of IPD caused by non-vaccine, excluding vaccine-associated, serotypes (Figures 2.10 and 2.11). The definitions of vaccine-associated serotypes were those described by the trial investigators and differed between trials.

Four RCTs reported ITT analyses (Finland 7v, USA1 7v, USA2 7v, South Africa 9v) and two reported PP analyses (Gambia 9v, USA2 7v). The combined estimate of VE for

individually randomized trials was -9% (-155, 53%) with no evidence of between-study heterogeneity (I^2 0%). Results were very similar when HIV-infected children were excluded.

b) Pneumonia

Three RCTs reported on pneumonia outcomes (Gambia 9v, South Africa 9v, USA1 7v). USA1 7v used 3p+1 schedules while Gambia 9v and South Africa 9v used 3p+0 schedules. Clinical pneumonia and radiologically confirmed pneumonia (by WHO criteria, if available) were analysed in this review. Results for all-cause pneumonia are shown in forest plots in Figures 2.12 and 2.13. Heterogeneity was moderate for both outcomes, in both ITT and PP analyses (I^2 55-62%). VE was somewhat lower for clinical pneumonia (12%, 95% CI 4, 19%) than radiologically confirmed pneumonia (25%, 95% CI 14, 35%) in intention to treat analyses but CI overlapped. Results were similar when restricted to HIV-uninfected groups and in PP analyses.

Definitive pneumococcal pneumonia was examined in one trial (Gambia 9v) using lung aspirates from a subset of infants with pneumonia, who were inpatients at a hospital and had right-sided peripheral consolidation on their radiograph. Reported VE was 73% (95% CI -2, 95%) for vaccine serotypes and 68% (95% CI 18, 89 %) for any serotype pneumonia.

c) Otitis media

Seven RCTs reported otitis media outcomes (Belgium 7v, Finland 7v, Israel 9v, Netherlands1 7v, Netherlands2 7v, USA1 7v, USA2 7v). Finland 7v, USA1 7v and USA2 7v used 3p+1 schedules while Belgium 7v, Israel 9v, Netherlands1 7v and Netherlands2 7v examined catch-up (toddler) schedules. Results are reported in detail according to schedule (Figures 14–17). One additional study in children with a history of respiratory tract infections reported this outcome, but not in enough detail for this review (Netherlands3 7v).

d) Mortality

Mortality could be extracted as an outcome in 10 included studies (China 7v, Gambia 9v, Gambia 9v pilot b, Ghana infants 9v, Finland 7v, Netherlands2 7v, South Africa 9v, South Africa 9v pilot, USA1 7v, USA2 7v). One additional study reported two deaths but did not report in which trial arm these occurred (Gambia 9v pilot a).

Finland 7v and USA1 7v used 3p+1 schedules while China 7v, Gambia 9v, Gambia 9v pilot b, Ghana infants 9v, South Africa 9v and South Africa 9v pilot examined 3p schedules. USA2 7v used a variety of schedules dependent on age. Netherlands2 7v examined a catch-up (toddler) schedule. Data are shown in Figure 2.18 and described according to schedules below.

2.4.4.2 Methodological issues affecting results, PCV schedules vs no PCV

a) Invasive pneumococcal disease

Important differences between the studies reporting clinical outcomes are presented in Table 2.4. Meta-regression analyses to investigate heterogeneity were not carried out because of the small number of RCTs. The 3p+1 RCTs differ systematically from the 3p+0 RCTs in the location of trials (3p+1 trials were conducted in the USA and Europe, 3p+0 trials were conducted in Africa). In addition, there were differences between 3p+1 trials in study population (USA2 7v was in a population at higher risk of pneumococcal disease than USA1 7v and Finland 7v) and trial design (USA1 7v and Finland 7v were individually

randomized, USA2 7v was cluster randomized). The cluster-randomized USA2 7v trial was designed to capture both direct and indirect effects of vaccination, but showed a smaller effect than the individually randomized USA1 7v trial. There were only three cases of IPD in Finland 7v, so this trial does not contribute statistically to combined VE estimates.

It has been postulated that the differences in efficacy against vaccine-type IPD might be due to lower VE against severe than mild disease [42, 43]. No trial in this review clearly stated the clinical criteria used to determine when blood or other biological samples would be taken to investigate potential IPD. Nevertheless, invasive disease measured in the USA1 7v appeared less severe (often without hospital admission) than in other trials, where most cases of IPD were among children admitted to hospital with pneumonia or meningitis.

Additionally, the fact that heterogeneity was more marked when the analysis was broadened to any serotype, suggests that serotype distribution in the population prior to vaccination might also have influenced VE. The USA1 7v trial had a high percentage of IPD caused by vaccine serotype before the trial (91%). The South Africa 9v study had a similar percentage of IPD caused by VAT in HIV-infected children. The lower estimate of VE caused by vaccine serotype might be explained if the disease causing serotypes did not match those in the vaccine, or by impaired immunity. It is also possible that serotype specific VE varies. However, there are alternative explanations such as the duration of follow-up, or a bias that could not be assessed (e.g. loss to follow-up).

b) Pneumonia

Important differences between the studies reporting clinical outcomes are presented in Table 2.4. The numbers of cases of pneumonia were much larger than the numbers of cases of IPD, indicating that more precise estimates are obtained for these outcomes than for less common ones. This might result in statistical evidence of heterogeneity even if smaller absolute differences between studies were observed for pneumonia than for rarer outcomes.

There were also differences between studies. For example, in South Africa 9v, the case definition included hospitalization whereas in USA1 7v, only about 50% of children with clinical pneumonia were assessed for WHO-defined radiological pneumonia. The specificity of diagnosis might have differed between studies, depending on background levels of pneumococcal pneumonia. For example, if *S. pneumoniae* causes the majority of pneumonia in a population, PCV efficacy against pneumonia would appear higher than in populations where *S. pneumoniae* accounts for a small proportion of disease. The reverse might be true if antibiotic use is high and pneumococcal pneumonia is less frequent. Studies are also likely to differ somewhat in the assessment of outcomes.

Additionally, the potential for bias caused by factors such as concealment of allocation during randomization and blinding of outcome assessors was difficult to assess in some studies.

2.4.4.3 Comparisons U1 and U2: 1p vs no PCV and 2p vs no PCV, respectively

No data were available on clinical disease outcomes or mortality from these studies.

2.4.4.4 Comparison U3: 3p+0 vs no PCV

a) Invasive pneumococcal disease

Two studies reported IPD (Gambia 9v, South Africa 9v). Results were very similar to those reported for analyses that combined 3p+1 and 3p+0 schedules (2.4.4.1.a).

Any serotype: Two studies reported any serotype IPD using ITT analysis (Gambia 9v, South Africa 9v, Figure 2.4). When HIV-infected individuals in South Africa 9v were included, heterogeneity was low (VE 47%, 95% CI 29, 60%, I^2 0%), and remained low even when HIV-infected individuals were excluded (VE 44%, 95% CI 22, 61%, I^2 0%).

These two studies also reported results of PP analyses (Gambia 9v, South Africa 9v, Figure 2.5, Annex 2.1). South Africa 9v reported data only for HIV-uninfected individuals. Heterogeneity between studies was moderate and the combined VE was 63% (95% CI -3, 86%, I^2 40%).

Vaccine serotypes: Both Gambia 9v and South Africa 9v studies reported vaccine serotype IPD (Figure 2.6). In ITT analysis, when HIV-infected infants in South Africa 9v were included, heterogeneity between studies was low and the combined VE was 71% (95% CI 52, 82%, I^2 0%). When HIV-infected individuals were excluded, heterogeneity between studies remained low and the combined VE was 73% (95% CI 51, 86%, I^2 0%). Gambia 9v also reported results of PP analysis (VE 77%, 95% CI 49, 90%, Figure 2.7).

Vaccine-associated serotypes: One study (South Africa 9v) reported vaccine-associated serotype IPD using ITT analysis (Figure 2.8, Annex 2.1). For HIV-uninfected children, VE reported in the manuscript was -300% (95% CI -19599, 60%) and for HIV-infected children 63% (95% CI -1, 88%). Gambia 9v reported results using per PP analysis (Figure 2.9). VE against vaccine-associated serotypes was 46% (95% CI -70, 83%).

Non-vaccine serotypes, excluding vaccine-associated serotypes: South Africa 9v reported this comparison using IIT analysis (Figure 2.10). Data were reported separately for HIV-infected (VE -30%, 95% CI -262, 54%, I^2 0%) and -uninfected infants (VE -300%, 95% CI -19599, 60%). Gambia 9v reported these data using PP analysis (Figure 2.11). VE was reported to be -65% (95% CI -327, 32%).

b) Pneumonia

Two studies (Gambia 9v, South Africa 9v) reported on pneumonia for this comparison.

Clinical pneumonia: South Africa 9v reported on clinically diagnosed pneumonia (first episode) using ITT analysis (Figure 2.12). VE was reported separately for HIV-uninfected children (17%, 95% CI 7, 26%) and -infected children (15%, 95% CI 5, 24%). The combined estimated of VE was 16% (95% CI 9, 22%, I^2 0%).

Both studies reported PP analyses for clinically diagnosed pneumonia (first episode) (Figure 2.13). The estimated VE was similar to the results of ITT analyses in South Africa 9v, but there was a high level of heterogeneity. Heterogeneity was present in analyses including and excluding HIV-infected infants (VE 14%, 95% CI 2, 24%, I^2 67%; and VE 14%, 95% CI -3, 29%, I^2 83%, respectively).

Radiologically confirmed pneumonia: Both studies reported radiologically confirmed pneumonia (first episode) using IIT analysis (Figure 2.12). There was moderate to high between-trial heterogeneity, both when HIV-infected individuals were included (VE 14%, 95% CI 9, 37%, I^2 70%) and excluded (VE 29%, 95% CI 13, 42%, I^2 64%). Gambia 9v also reported results for all episodes of radiologically confirmed pneumonia using ITT analysis (VE 36%, 95% CI 28, 43%, Figure 2.12).

Both studies reported PP analyses for radiologically confirmed pneumonia (first episode) (Figure 2.13). In South Africa, when HIV-infected individuals were included in the analysis, heterogeneity between studies was high (VE 25%, 95% CI 6, 41%, I^2 75%), but fell when they were excluded (VE 33%, 95% CI 22, 43%, I^2 32%). Gambia 9v reported the results of PP analysis for all episodes of radiologically confirmed pneumonia (VE 37%, 95% CI 27, 45%, Figure 2.13).

Definitive pneumococcal pneumonia: In Gambia 9v, which reported on definitive pneumococcal pneumonia using lung aspirates from a subset of children (0, VE was 73% (95% CI –2, 95%) for vaccine serotype pneumonia and 68% (95% CI 18, 89 %) for any pneumococcal serotype pneumonia.

c) Otitis media

No clinical data were reported for this comparison and outcome.

d) Mortality

Six studies had data about mortality that could be extracted for this comparison (China 7v, Gambia 9v, Gambia 9v pilot b, Ghana infants 9v, South Africa 9v, South Africa 9v pilot). Another study reported two deaths but did not report in which trial arm these occurred (Gambia 9v pilot a). Data are shown in Figure 2.18, except for China 7v because no SAEs were reported and therefore no deaths.

A total of 1004 deaths were reported in the remaining studies, most of which occurred in Gambia 9v and South Africa 9v. Gambia 9v reported deaths by intervention group only for the PP analysis, and only these deaths are included in the total. Gambia 9v showed strong statistical evidence of a protective effect of vaccine (VE 16%, 95% CI 3, 28%) than South Africa 9v (VE 5%, 95% CI -13, 21%). The remaining three studies experienced more deaths in the vaccinated groups, but there were only 14 deaths in total.

2.4.4.5 Comparison W2: 2p+1 vs no PCV

No data were available on clinical disease outcomes or mortality.

2.4.4.6 Comparison W3: 3p+1 vs no PCV

a) Invasive pneumococcal disease

Three studies reported this outcome within this comparison (Finland 7v, USA1 7v, USA2 7v, Figure 2.4).

Any serotype: Two individually randomized trials reported this comparison using ITT analysis (Finland 7v, USA1 7v). Heterogeneity between studies was low (VE 87%, 95% CI 69, 95%, I^2 0%). USA1 7v also reported results of PP analysis (VE 93%, 95% CI 72, 98%, Figure 2.5).

One cluster-randomized trial (USA2 7v) reported this comparison using ITT (VE 46%, 95% CI -17, 75%) and PP analysis (VE 54%, 95% CI -14, 81%, Figure 2.5).

Vaccine serotypes: Both individually randomized trials (Finland 7v, USA1 7v) reported on IPD for this comparison using ITT analysis (Figure 2.6). Heterogeneity between studies was low (VE 87%, 95% CI 76, 95%, I^2 0%). USA1 7v also reported PP analysis for this comparison (VE 97%, 95% CI 83, 100%, Figure 2.7). One cluster-randomized trial (USA2 7v) reported results of both ITT (VE 86%, 95% CI 40, 97%, Figure 2.6) and PP analysis (VE 82%, 95% CI 16, 96%, Figure 2.7).

Vaccine-associated serotypes: One individually randomized trial (USA1 7v) reported this comparison using ITT analysis (VE 67%, 95% CI -221, 97%, Figure 2.8). The cluster-randomized trial (USA2 7v) reported results for this comparison using ITT (VE -90%, 95% CI -1989, 83%, Figure 2.8) and PP analysis (VE 8%, 95% CI -1376, 94%, Figure 2.9).

Non-vaccine serotypes, excluding vaccine-associated serotypes: Two individually randomized trials reported this comparison using ITT analysis (Finland 7v, USA1 7v, Figure 2.10). Heterogeneity between studies was low and the combined VE was 25%

(95% CI -238, 83%, I^2 0%). The cluster-randomized trial (USA2 7v) reported on this comparison using ITT analysis (VE 5%, 95% CI -227, 73%, Figure 2.10) and per PP analysis (VE 8%, 95% CI -556, 87%, Figure 2.11).

b) Pneumonia

One study reported on pneumonia for this comparison (USA1 7v). For clinical pneumonia (first episode) by ITT analysis, VE was 6% (95% CI 0, 12%) and by PP analysis, 4% (95% CI -3, 12%) (Figures 2.12 and 2.13). For radiologically confirmed pneumonia (first episode), VE was 25% (95% CI 6, 41%) by ITT and 30% (95% CI 11, 46%) by PP analysis, respectively (Figures 2.12 and 2.13). This study did not report definitive pneumococcal pneumonia.

c) Otitis media

Three studies reported this outcome for this comparison (Finland 7v, USA1 7v and USA2 7v).

All-cause otitis media: Finland 7v and USA1 7v reported all-cause otitis media for individually randomized trials. Both trials were in healthy infants not selected because of prior ear infections. The combined estimates of VE were 6% (95% CI 4, 9%, I^2 0%) using ITT analysis (Figure 2.14) and 7% (95% CI 4, 10%, I^2 0%) in PP analysis (Figure 2.15). One cluster-randomized trial (USA2 7v) reported results of ITT (VE -3%, 95% CI -21, 12%) and PP analysis (VE 0%, 95% CI -19, 16%).

Pneumococcal otitis media: Finland 7v and USA1 7v trials reported pneumococcal otitis media. The combined estimates of VE were 46% (95% CI 10, 55%, I^2 17%) in ITT analysis (Figure 2.16) and 35% (95% CI 22, 45%, I^2 0%) in PP analysis (Figure 2.17).

d) Mortality

Three studies reported a total of 35 deaths for this comparison (Finland 7v, USA1 7v, USA2 7v, Figure 2.18). No individual study showed strong evidence of a reduction or increase in deaths with vaccination. In Finland 7v, only one death (in the vaccinated group) occurred in a study population of 1662 infants. In USA1 7v, reporting was limited to deaths from sudden infant death syndrome (SIDS). More deaths occurred in the unvaccinated group (8 of 18 941 individuals compared to 4 of 18 927 in the vaccinated group). In USA2 7v, more children died in the vaccinated group but 11 of the 22 deaths in both groups resulted from accidents. In USA2 7v, 3 of 4165 children died of SIDS in the vaccinated group and 2 of 3926 in the unvaccinated group. One child died of pneumococcal sepsis (serotype 5) in the vaccinated group.

2.4.4.7 Comparison X: Catch-up vs no PCV

a) Invasive pneumococcal disease

No data were available on clinical disease outcomes or mortality.

b) Pneumonia

No data were available on clinical disease outcomes or mortality.

c) Otitis media

Four studies reported on otitis media for this comparison (Belgium 7v, Israel 9v, Netherlands1 7v, Netherlands2 7v).

All-cause otitis media: Two RCTs reported all-cause otitis media using ITT analysis (Netherlands1 7v, Nethelands2 7v, Figure 2.14). Both RCTs enrolled participants with a history of ear infections. Between-trial heterogeneity was high and the combined estimate of VE was -6% (95% CI -44, 22%, I^2 75%).

Three RCTs reported all-cause otitis media using PP analysis (Belgium 7v, Israel 9v, Netherlands1 7v, Figure 2.15). Between-trial heterogeneity was high and the combined estimate of VE was -6% (95% CI -47, 24%, I^2 75%). Heterogeneity was reduced when studies were stratified by baseline clinical characteristics. Belgium 7v and Netherlands1 7v enrolled participants with a history of ear infections (VE -27%, 95% CI -57, -3%, I^2 0%). Israel 9v was conducted in a healthy population which was not selected because of prior ear infections (VE 17%, 95% CI -2, 33%).

Pneumococcal otitis media: One study (Netherlands1 7v) reported on this outcome in PP analysis only (VE 33%, 95% CI -31, 66%, Figure 2.17).

d) Mortality

One study reported on mortality as an SAE (Netherlands2 7v, Figure 2.18). In this study, the intervention group received PCV before tympanostomy and PPV afterwards, while the control group received tympanostomy only. None of the SAEs reported in the trial were deaths.

2.4.5 Nasopharyngeal carriage of S. pneumoniae*, schedule vs schedule comparisons*

Summary

- *Three RCTs (Fiji 7v, Gambia 7v, Netherlands4 7v) compared carriage of pneumococcal serotypes with different PCV schedules.*
- *By 6 months of age, 3 doses of vaccine (starting at 1.5–2 months of age, with 1-month intervals between doses) might result in less carriage of vaccine serotypes than 1 or 2 doses (comparisons B and C respectively), but confidence intervals are wide (2 RCTs).*
- *By 12 months of age, both 2 and 3 primary doses might result in less vaccine serotype carriage than 1 dose, but confidence intervals are wide (1 RCT).*
- *At 18 months, there tended to be less vaccine serotype carriage in individuals who received more doses of PCV in primary schedules than in those who received fewer doses (1 RCT).*
- *Results for non-vaccine serotype carriage were less consistent than results for vaccine serotypes.*

Three studies compared PCV schedules and reported carriage outcomes (Fiji 7v, Netherlands4 7v, Gambia 7v). Results are grouped by the following serotypes as they have been reported by trial investigators

i) Any serotype: all *S. pneumoniae* serotypes;

ii) Vaccine serotypes: including serotypes in the vaccine;

iii) Non-vaccine serotypes: including all serotypes not in the vaccine;

iv) Vaccine-associated serotypes: including all serotypes not in the vaccine but in the same serogroup as one of the vaccine serotypes;

v) Vaccine serotypes plus vaccine-associated serotypes;

vi) Vaccine serotypes plus serotype 6A;

vii) Non-vaccine serotypes excluding vaccine-associated serotypes.

The three studies that compared PCV schedules and measured carriage outcomes reported results for any serotype, vaccine serotypes and non-vaccine serotypes.

Results were reported at age 6 months (Fiji 7v, Gambia 7v), 9 months (Fiji 7v), 12 months (Fiji 7v, Gambia 7v, Netherlands4 7v), 18 months (Fiji 7v, Gambia 7v, Netherlands4 7v), and 24 months (Netherlands4 7v). The schedules examined by each study varied with time point. This is due to additional doses of vaccine being administered, such as PPV at 10 months of age in Gambia 7v.

The interval between last dose and nasopharyngeal sampling varied between groups for Gambia 7v. For example, at 6 months of age this interval was around 4 months in the 1p group, 3 months in the 2p group, and 2 months in the 3p group.

Full results for all comparisons are available in Tables 2.6–2.13. Unless otherwise stated, odds ratios are used as they are considered to be the most appropriate effect measure for carriage outcomes [11].

2.4.5.1 Comparison A: 2p vs1p

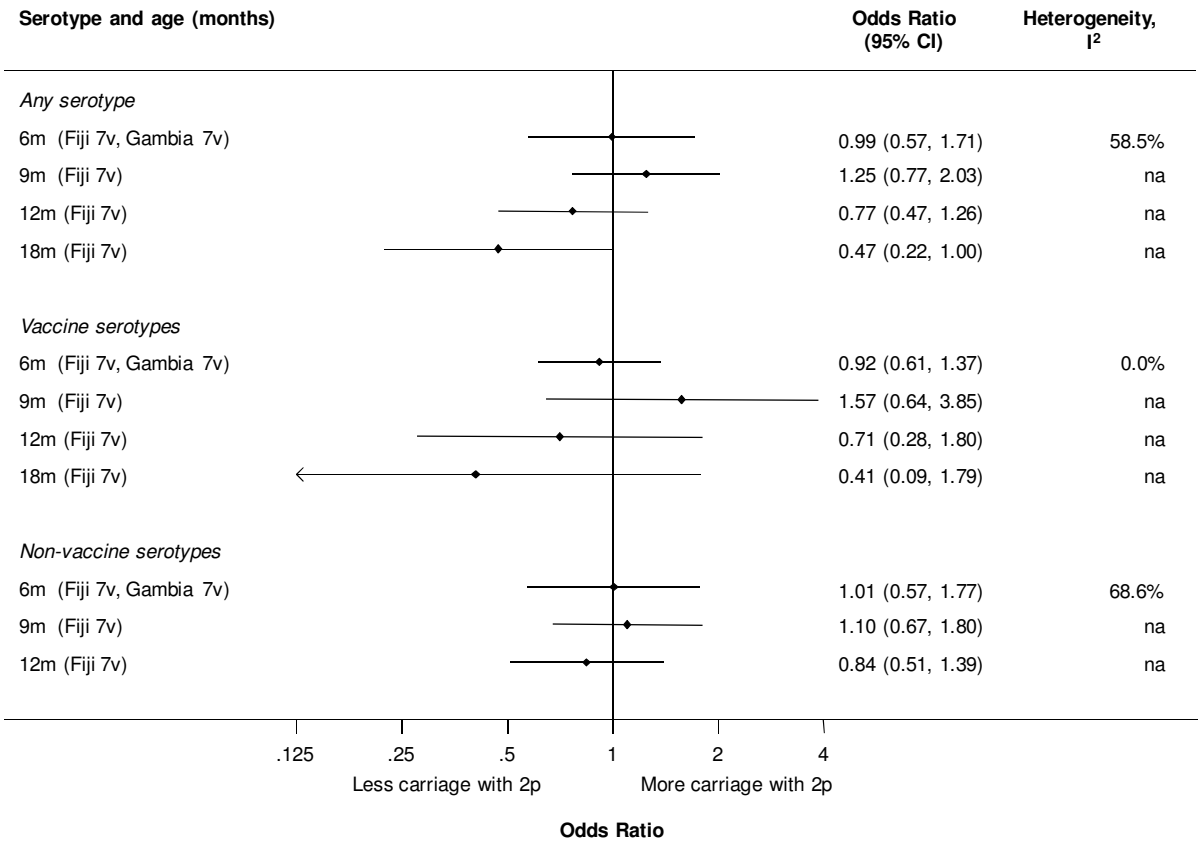
Two RCTs reported carriage data for this comparison (Fiji 7v, Gambia 7v). Fiji 7v reported carriage outcomes at around 6, 9, 12 and 18 months of age, and Gambia 7v reported carriage outcomes only at around 6 months of age for this comparison. Full results are given in Table 2.5, while Figure 2.19 shows the combined odds ratios from meta-analysis for each serotype group at different time points.

Results for carriage of any serotype showed that neither schedule was superior. Point estimates of odds ratios did not consistently favour either schedule, and confidence intervals were wide. Some evidence showed that at 18 months of age, the 2p schedule was favoured.

Results for vaccine serotype carriage showed that neither schedule was superior. Point estimates of odds ratios did not consistently favour either schedule and confidence intervals were wide. At 12 and 18 months of age, the 2p schedule might be favoured, but without strong statistical evidence.

There was little evidence of a difference in non-vaccine serotype carriage between 1p and 2p schedules. No data were reported for non-vaccine serotypes at around 17 months of age.

Figure 2.19 Nasopharyngeal carriage, Comparison A, 2p vs 1p, by serotype and age tested



Legend:

NA – not applicable as only one trial in analysis.

Ages stated are approximate. For ages at testing for individual studies, see Table 2.3

Horizontal axis represents the combined odds ratios from meta-analysis a on logarithmic scale, comparing carriage in groups of children receiving 2p vs 1p schedules; vertical line through combined odds ratio of 1 shows no difference in levels of carriage between groups.

Solid black diamonds represent point estimate of combined odds ratio; horizontal black line represents 95% confidence interval

The I^2 statistic can be interpreted as the proportion of the total variation in estimated risk ratios due to between-trial heterogeneity rather than to chance [13]. Low, moderate and high levels of heterogeneity correspond to I^2 values of 25%, 50% and 75% respectively.

2.4.5.2 Comparison B: 3p vs1p

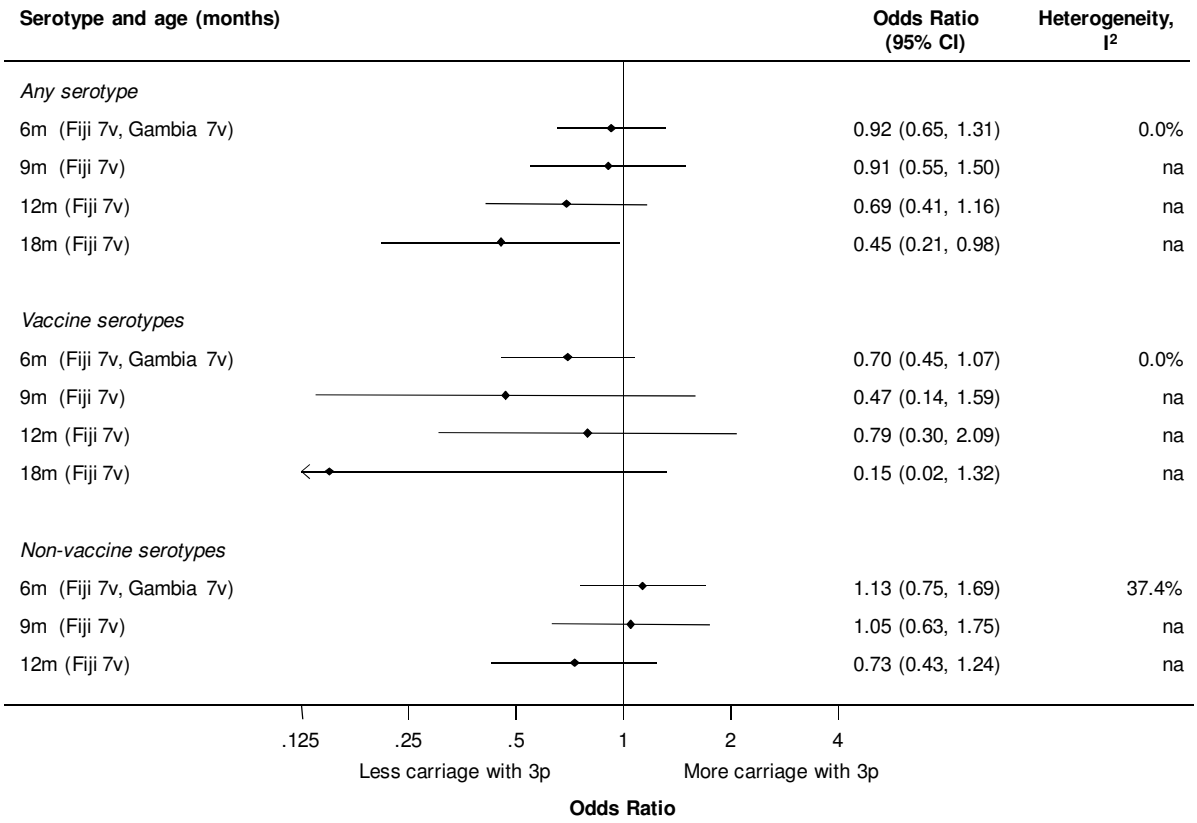
Two RCTs reported carriage data for this comparison (Fiji 7v, Gambia 7v). Fiji 7v reported carriage outcomes at around 6, 9, 12 and 18 months of age, and Gambia 7v reported carriage outcomes only at around 6 months of age. Full results for this comparison are given in Table 2.6, while Figure 2.20 shows the combined odds ratios from meta-analysis for each serotype group at different time points.

Results for carriage of any serotype tended to show less carriage with the 3p schedule than with the 1p schedule. Point estimates of odds ratios consistently favoured the 3p schedule, but confidence intervals were wide. There was some statistical evidence that at 18 months of age the 3p schedule might be favoured.

Results for vaccine serotype carriage tended to show less carriage with the 3p schedule than with the 1p schedule. Point estimates of odds ratios consistently favoured the 3p schedule, but statistical evidence for a difference was not strong.

There was little evidence of a difference in non-vaccine serotype carriage between 1p and 3p schedules. No data were reported for non-vaccine serotypes at around 17 months of age.

Figure 2.20 Nasopharyngeal carriage, Comparison B, 3p vs 1p, by serotype and age tested



Legend:

NA – not applicable as only one trial in analysis.

Ages stated are approximate. For ages at testing for individual studies, see Table 2.3.

Horizontal axis represents the combined odds ratios from meta-analysis on logarithmic scale, comparing carriage in groups of children receiving 3p vs 1p schedules; vertical line through combined odds ratio of 1 shows no difference in levels of carriage between groups.

Solid black diamonds represent point estimate of combined odds ratio; horizontal black line represents 95% confidence interval.

The I^2 statistic can be interpreted as the proportion of the total variation in estimated risk ratios due to between-trial heterogeneity rather than to chance [13]. Low, moderate and high levels of heterogeneity correspond to I^2 values of 25%, 50% and 75%, respectively.

2.4.5.3 Comparison C: 3p vs 2p

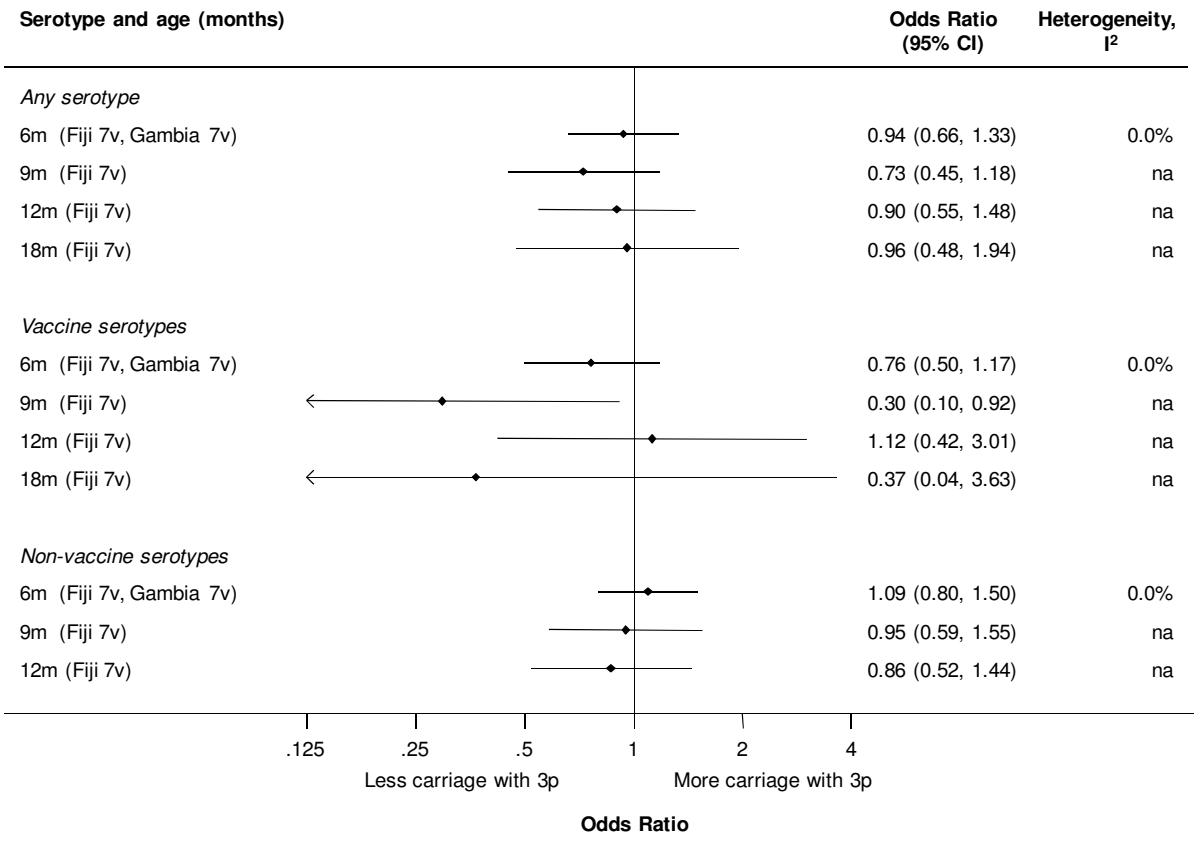
Two RCTs reported carriage data for this comparison (Fiji 7v, Gambia 7v). Fiji 7v reported carriage outcomes at around 6, 9, 12 and 18 months of age, and Gambia 7v reported these outcomes only at around 6 months of age. Full results for this comparison are given in Table 2.7. Figure 2.21 shows the combined odds ratios from meta-analysis for each serotype group at different time points for this comparison.

Results for carriage of any serotype showed neither schedule to be superior. Point estimates of odds ratios favoured the 3p schedule but were often close to 1, and the confidence intervals were wide.

Results for vaccine serotype carriage tended to show less carriage with the 3p schedule than with the 2p schedule, but this was not consistent and the statistical evidence was not strong. At 9 months of age, there was some statistical evidence of lower carriage in the 3p group than in the 2p group in the RCT that reported carriage at this time point. At other time points there was no strong evidence that either schedule was superior.

There was little evidence of a difference in non-vaccine serotype carriage between 2p and 3p schedules. No data were reported for non-vaccine serotypes at around 17 months of age.

Figure 2.21 Nasopharyngeal carriage, Comparison C, 3p vs 2p, by serotype and age tested



Legend:

NA – not applicable as only one trial in analysis.

Ages stated are approximate. For ages at testing for individual studies, see Table 2.3. Horizontal axis represents the combined odds ratios from meta-analysis a on logarithmic scale, comparing carriage in groups of children receiving 3p vs 2p schedules; vertical line through combined odds ratio of 1 shows no difference in levels of carriage between groups. Solid black diamonds represent point estimate of combined odds ratio; horizontal black line represents 95% confidence interval. The I^2 statistic can be interpreted as the proportion of the total variation in estimated risk ratios due to between-trial heterogeneity rather than to chance [13]. Low, moderate and high levels of heterogeneity correspond to I^2 values of 25%, 50% and 75%, respectively.

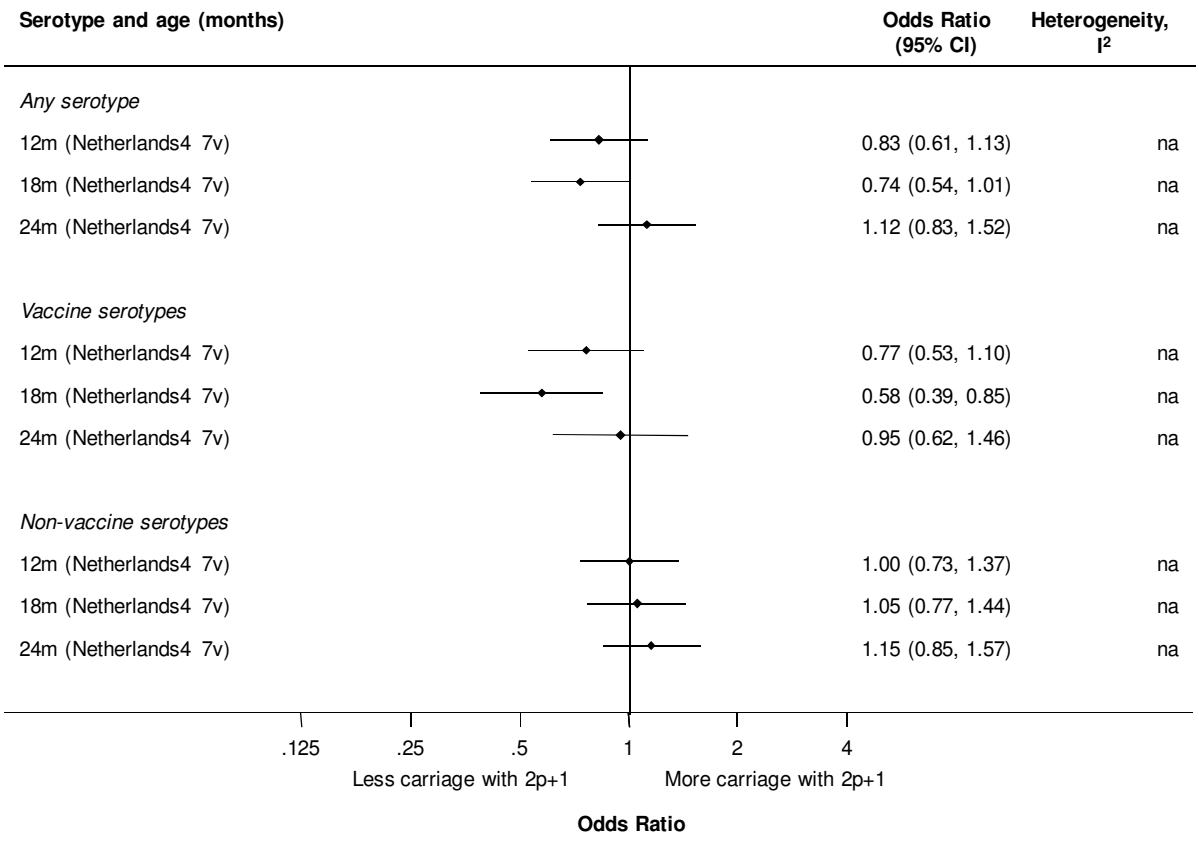
2.4.5.4 Comparison D: 2p+PPV vs 1p+PPV

Full results for this comparison are presented in Table 2.8.

2.4.5.5 Comparison E: 2p+1 vs 2p

One RCT (Netherlands4 7v) reported carriage at around 12 months of age (1 month after the 2p+1 group received the booster dose), 18 and 24 months of age. Full results for this comparison are given in Table 2.9. Figure 2.22 shows the combined odds ratios from meta-analysis for each serotype group at different time points for this comparison.

Figure 2.22 Nasopharyngeal carriage, Comparison E, 2p+1 vs 2p, by serotype and age tested



Legend:

NA – not applicable as only one trial in analysis.

Ages stated are approximate. For ages at testing for individual studies, see Table 2.3.

Horizontal axis represents the combined odds ratios from meta-analysis on logarithmic scale, comparing carriage in groups of children receiving 2p+1 vs 2p schedules; vertical line through combined odds ratio of 1 shows no difference in levels of carriage between groups. Solid black diamonds represent point estimate of combined odds ratio; horizontal black line represents 95% confidence interval The I^2 statistic can be interpreted as the proportion of the total variation in estimated risk ratios due to between-trial heterogeneity rather than to chance [13]. Low, moderate and high levels of heterogeneity correspond to I^2 values of 25%, 50% and 75%, respectively.

Results for carriage of any serotype did not consistently favour either schedule and the confidence intervals were wide.

Results for vaccine serotype carriage tended to show less carriage with the 2p+1 schedule than with the 2p schedule. At 18 months of age, there was some statistical evidence of lower carriage in the 2p+1 group than in the 2p group. At other time points there was no strong statistical evidence that the 2p+1 schedule was superior.

There was little evidence of a difference in non-vaccine serotype carriage between 2p and 2p+1 schedules.

2.4.5.6 Comparison G: 3p vs 2p + 1

No carriage data were available as of 1 September 2011. Results from one completed RCT (Israel 7v) should become available shortly.

2.4.5.7 Comparison H: 3p+PPV vs 1p+PPV

Full results for this comparison are presented in Table 2.10.

2.4.5.8 Comparison I: 3p+PPV vs 2p+PPV

Full results for this comparison are presented in Table 2.11.

2.4.5.9 Comparison L: 3p+1 vs 2p+1

No carriage data were available as of 1 September 2011. Results from one completed RCT (Israel 7v) should become available shortly.

2.4.5.10 Comparison M: 3p+1 vs 3p

No carriage data were available as of 1 September 2011. Results from one completed RCT (Israel 7v) should become available shortly.

2.4.5.11 Comparison O: Late vs early start

No carriage data were available.

2.4.5.12 Comparison P: 2-month vs 1-month interval

No carriage data were available.

2.4.5.13 Comparison Q: Long interval between primary and booster vs short interval between primary and booster

No carriage data were available.

2.4.5.14 Comparisons R and T: Catch-up (toddler) vs catch-up schedules, and infant vs catch-up schedules

No carriage data were available.

2.4.5.15 Methodological issues affecting carriage results, schedule vs schedule comparisons

Differences between studies and potential sources of bias are summarised in Table 2.12. Pre-vaccination levels of nasopharyngeal carriage differed between countries, with almost four times the level of vaccine serotype in Gambian children than in the Netherlands (Netherlands4 7v). Carriage of any serotype in the Gambian study was more than four times that in Netherlands4 7v. There appears to have been some variation in potential for detecting the carriage of multiple serotypes. In Netherlands4 7v, only one colony per sample was selected for serotyping, meaning that multiple serotype carriage could not be detected. This might lead to a biased result. In Gambia 7v, multiple serotype carriage might have been detected, based on differences in numbers of participants in tables of PPV and non-PPV serotypes. In each study, more than 85% of those randomized were sampled at both 6 and 12 months. Importantly, allocation concealment was not well enough described to determine whether this had an impact on results.

Additionally, in the Gambia 7v study, groups with more doses of PCV had been vaccinated more recently than those with fewer doses. If the degree of protection against carriage changes over time, this might have affected the results of this study.

2.4.5.16 Potentially eligible studies with comparisons of different PCV schedules, for which data may become available

Several RCTs were identified that were potentially eligible for this review, but which had no data available when studies were screened for inclusion [44–58].

2.4.6 Nasopharyngeal carriage of S. pneumoniae, PCV schedules vs no PCV

Summary

- *Nasopharyngeal carriage of pneumococci was reported in 10 studies that compare a PCV schedule with no PCV.*
- *Data show that carriage of vaccine type was generally lower in children receiving PCV, and carriage of NVT generally higher in children receiving PCV, when compared with those not receiving PCV.*

Ten studies compared a PCV schedule to no PCV vaccination and reported carriage outcomes (Belgium 7v, Fiji 7v, Finland 7v, Israel 9v, Gambia pilot a 9v, Netherlands1 7v, Netherlands4 7v, South Africa 9v, South Africa pilot 9v, USA2 7v).

Results are reported using the serotype groups in section 2.3.2.

Five studies reported any serotype, vaccine serotype (VT) and non-vaccine serotype (NVT) only (Fiji 7v, Netherlands4 7v, Gambia pilot a 9v, South Africa 9v, South Africa pilot 9v) and one further study probably reported these groups but did not explicitly state this (Netherlands1 7v). One study reported VT only (Finland 7v). One study reported any serotype, VT, NVT, VT+6A, vaccine-associated serotypes (VAT) and NVT-VAT (USA2 7v). One study probably reported any serotype, NVT-VAT, and VT+VAT, but groups were not clearly defined. Israel 9v reported results in a different manner to other studies (number of positive sample rather than number of positive individuals and thus is not reported here.

Results were reported at age 2.5 and 3.5 months (South Africa pilot 9v), 6 months (Fiji 7v, Gambia pilot a 9v, USA2 7v), 9 months (Fiji 7v, Gambia pilot a 9v, South Africa pilot 9v), 12 months (Fiji 7v, Netherlands4 7v, USA2 7v, Finland 7v), 18 months of age (Fiji 7v, Netherlands4 7v, USA2 7v, Finland 7v), 24 months (Netherlands4 7v), and approximately 5 years after vaccination (South Africa 9v). One cross sectional study also sampled children at a range of ages and times since vaccination (USA2 7v). Two RCTs examined catch-up doses of PCV at older than 12 months of age and results for these studies were reported at 7, 14, 20 and 26 months after the first vaccination (Netherlands1 7v, Belgium 7v). Denominators were not available for Belgium 7v at 14, 20 and 26 months after vaccination, and these results are not reported here.

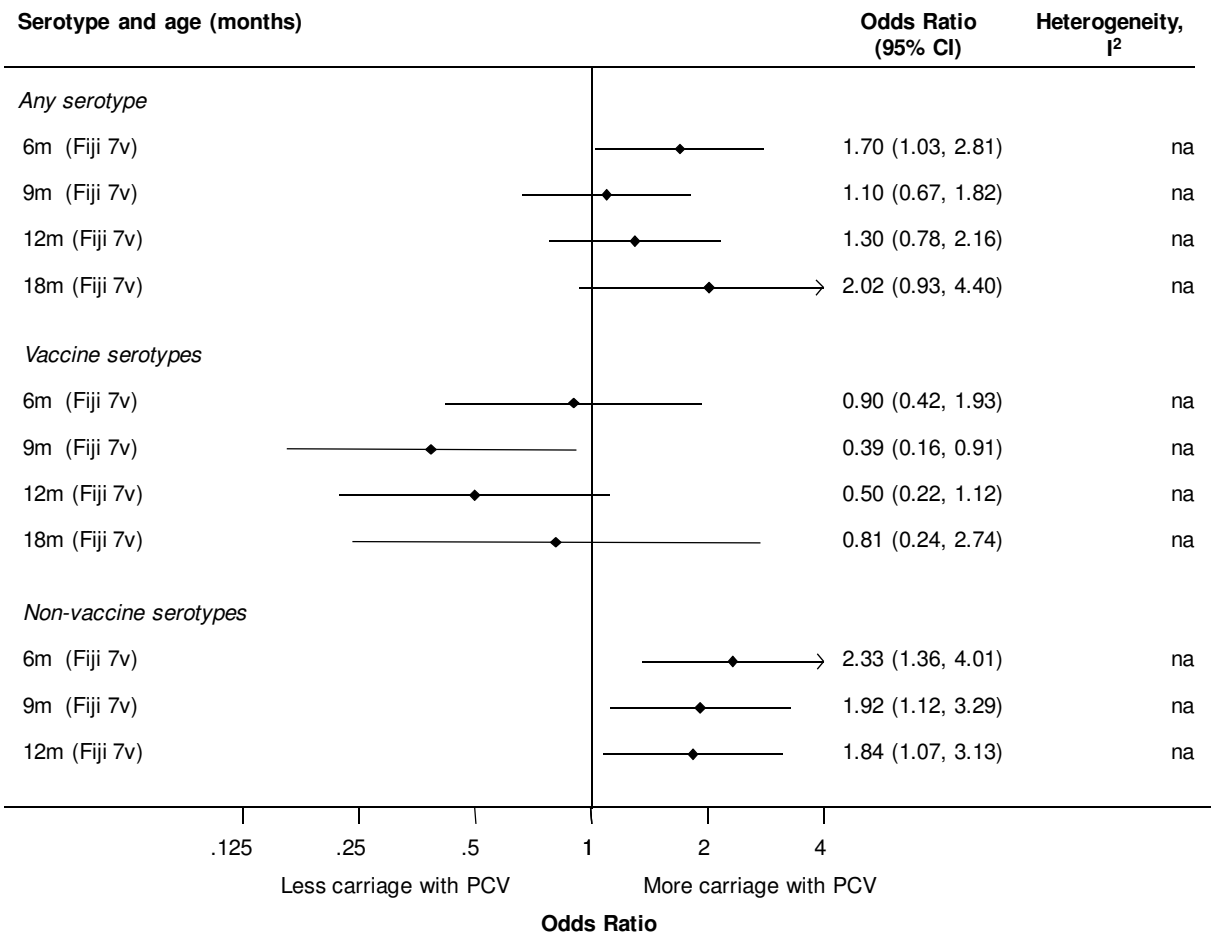
In all but two studies, a nasopharyngeal sample was to be obtained at each time point from the entire population enrolled in the RCT. In these two studies, a sub-group was sampled, which was randomly selected in one study (South Africa 9v) and non-randomly selected in the other (USA2 7v).

Full results for all comparisons are available in Tables 2.14–2.19. Unless otherwise stated, odds ratios are reported as these are considered to be the most appropriate effect measure for carriage outcomes [11].

2.4.6.1 Comparison U1: 1p vs no PCV

Full results for this comparison are given in Table 2.13. Two RCTs reported carriage data (Fiji 7v, South Africa 9v pilot, the latter only for any serotype at 2.5 months of age, after a first dose at 1.5 months). Fiji 7v did not report NVT data at 17 months of age. Figure 2.23 shows the combined odds ratios from meta-analysis for each serotype group at different time points for this comparison.

Figure 2.23 Nasopharyngeal carriage, Comparison U1, 1p vs no PCV, by serotype and age tested



Legend:

NA – not applicable as only one trial in analysis.

Ages stated are approximate. For ages at testing for individual studies, see Table 2.3.

Horizontal axis represents the combined odds ratios from meta-analysis on logarithmic scale, comparing carriage in groups of children receiving 1p vs no PCV schedules; vertical line through combined odds ratio of 1 shows no difference in levels of carriage between groups. Solid black diamonds represent point estimate of combined odds ratio; horizontal black line represents 95% confidence interval .The I^2 statistic can be interpreted as the proportion of the total variation in estimated risk ratios due to between-trial heterogeneity rather than to chance [13]. Low, moderate and high levels of heterogeneity correspond to I^2 values of 25%, 50% and 75% respectively.

Results for carriage of any serotype suggested there was more carriage in those vaccinated with PCV than those who were not. There was only strong statistical evidence of this at around 6 months of age.

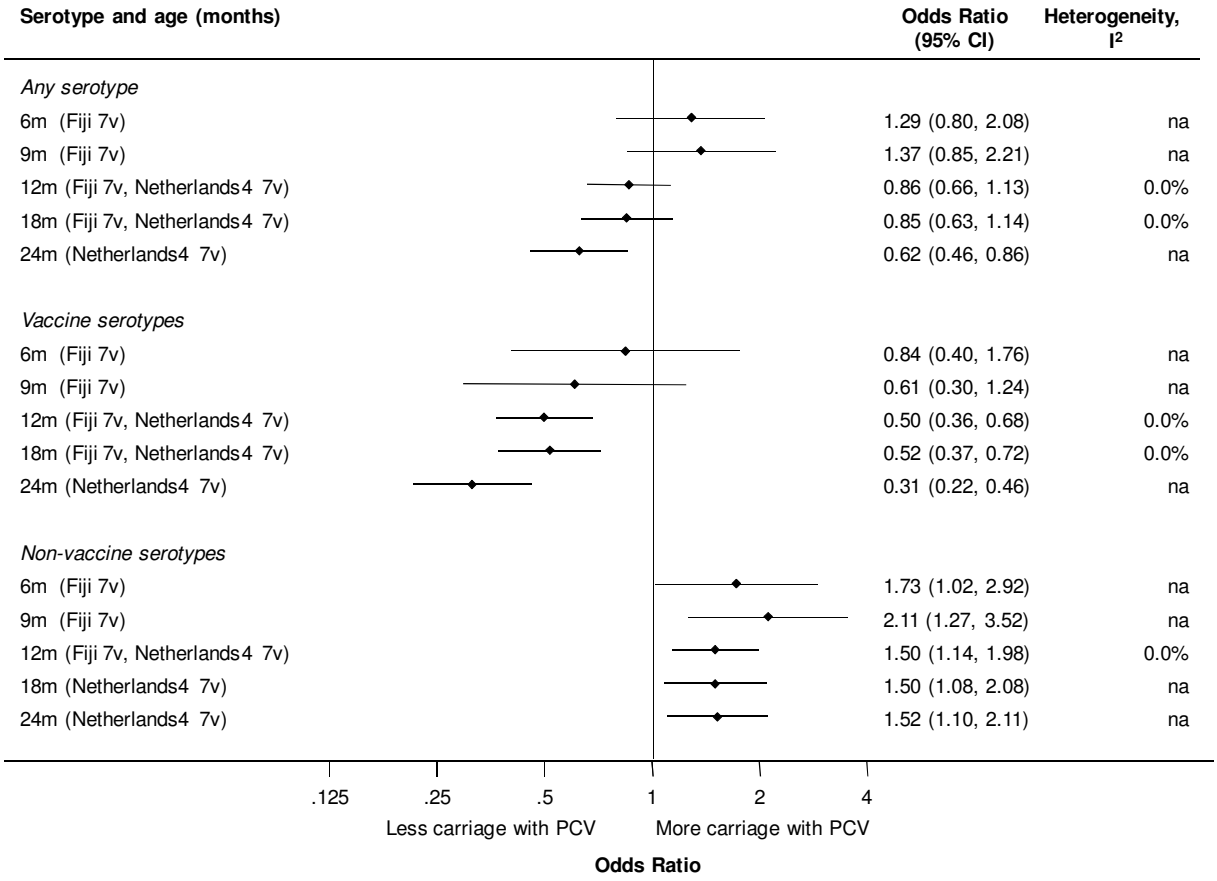
Results for vaccine serotype carriage tended to show less carriage after vaccination with the 1p schedule when compared with no vaccination. At 9 months of age, there was statistical evidence of this. At other time points, there was no strong statistical evidence that the 1p schedule reduced vaccine serotype carriage.

There was statistical evidence of more non-vaccine serotype carriage with a 1p schedule when compared with no PCV vaccination.

2.4.6.2 Comparison U2: 2p vs no PCV

Three RCTs reported carriage data for this comparison (Fiji 7v, Netherlands4 7v, South Africa 9v pilot). South Africa 9v pilot reported data only for any serotype at 3.5 months of age, after a second dose at 2.5 months of age. Fiji 7v did not report NVT data at 17 months of age. Full results for this comparison are given in Table 2.14. Figure 2.24 shows the combined odds ratios from meta-analysis for each serotype group at different time points for this comparison.

Figure 2.24 Nasopharyngeal carriage, Comparison U2, 2p vs no PCV, by serotype and age tested



Legend:

NA– not applicable as only one trial in analysis.

Ages stated are approximate. For ages at testing for individual studies, see Table 2.3.

Horizontal axis represents the combined odds ratios from meta-analysis on logarithmic scale, comparing carriage in groups of children receiving 2p vs no PCV; vertical line through combined odds ratio of 1 shows no difference in levels of carriage between groups. Solid black diamonds represent point estimate of combined odds ratio; horizontal black line represents 95% confidence interval. The I^2 statistic can be interpreted as the proportion of the total variation in estimated risk ratios due to between-trial heterogeneity rather than to chance [13]. Low, moderate and high levels of heterogeneity correspond to I^2 values of 25%, 50% and 75%, respectively.

Results for carriage of any serotype did not consistently favour either 2 primary doses of PCV or no PCV. However, at 24 months of age there was statistical evidence of less carriage in those receiving PCV (Netherlands4 7v).

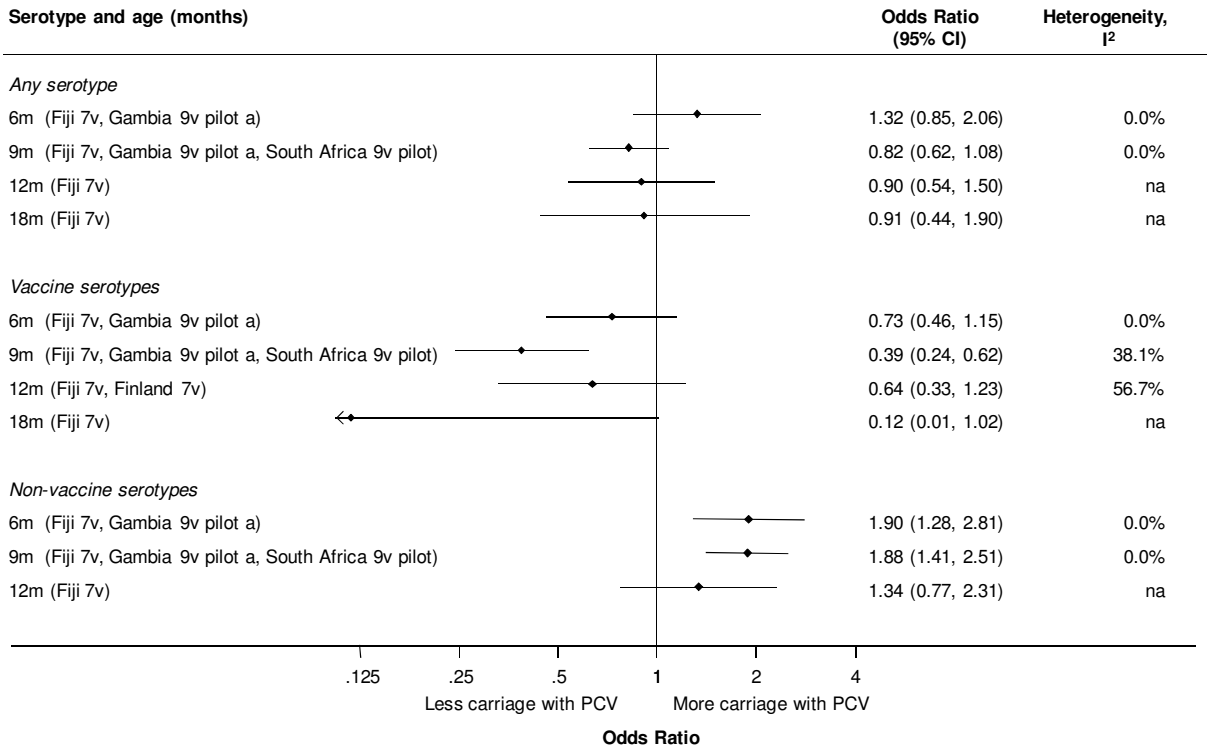
Results for vaccine serotype carriage showed less carriage after vaccination with the 2p schedule when compared to no vaccination. Confidence intervals were wide and crossed 1 at 6 and 9 months of age. At 12 months (Fiji 7v, Netherlands4 7v), 18 months (Netherlands4 7v) and 24 months of age (Netherlands4 7v), there was statistical evidence of less carriage in those receiving PCV.

There was statistical evidence of more non-vaccine serotype carriage with a 2p schedule when compared with no PCV vaccination at all time points between 6 and 24 months of age for which data were available.

2.4.6.3 Comparison U3: 3p vs no PCV

Six RCTs reported carriage data for this comparison (Fiji 7v, Finland 7v, Gambia 9v pilot a, South Africa 9v pilot, South Africa 9v, USA2 7v). Fiji 7v did not report NVT data at 17 months of age. USA2 7v was cluster randomized and a non-randomly selected sub-set were selected to participate in the carriage study. As the interpretation of data from this study differs from other studies, results from USA2 7v were not combined with other carriage data in Figure 2.25 and are reported in Table 2.15. Full results for all studies in this comparison, including stratifications by interval between doses, HIV-status and study design, are also given in Table 2.15. Figure 2.25 shows the combined odds ratios from meta-analysis (excluding USA2 7v) for each serotype group at different time points for this comparison.

Figure 2.25: Nasopharyngeal carriage, Comparison U3, 3p vs no PCV, by serotype and age tested



Legend:

NA – not applicable as only one trial in analysis.

Ages stated are approximate. For ages at testing for individual studies, see Table 2.3.

USA2 7v is not included in this analysis as it is a cluster-randomized trial and from a non-randomly selected sub-group.

Horizontal axis represents the combined odds ratios from meta-analysis on logarithmic scale, comparing carriage in groups of children receiving 3p vs no PCV; vertical line through combined odds ratio of 1 shows no difference in levels of carriage between groups. Solid black diamonds represent point estimate of combined odds ratio; horizontal black line represents 95% confidence interval. The I^2 statistic can be interpreted as the proportion of the total variation in estimated risk ratios due to between-trial heterogeneity rather than to chance [13]. Low, moderate and high levels of heterogeneity correspond to I^2 values of 25%, 50% and 75%, respectively.

Results for carriage of any serotype showed little difference between 3 primary doses of PCV and no PCV.

Results for vaccine serotype carriage showed less carriage after vaccination with the 3p schedule when compared to no vaccination. Confidence intervals were wide and crossed 1 for most time points, but there was statistical evidence of less carriage in those receiving PCV at 9 months of age.

There was statistical evidence of more non-vaccine serotype carriage with a 3p schedule when compared to no PCV vaccination, at 6 and 9 months of age. At 12 months of age, the confidence interval was wide and crossed 1, but the point estimate showed more carriage in the vaccinated group.

Results from USA2 7v showed patterns similar to those seen in the individually randomized studies.

2.4.6.4 Long-term follow up, and high-risk groups

a) Any serotype, other time points

One trial (South Africa 9v) assessed carriage an average of five years after primary vaccination. This study reported data for HIV-infected and -uninfected sub-groups.

For carriage of any serotype, the combined estimate for HIV-infected and -uninfected sub-groups showed little statistical evidence that individuals in the unvaccinated group were more likely to be carrying than the 3p group. There was little between-trial heterogeneity in results, and the confidence interval for the combined estimate crossed 1 (odds ratio, OR 0.88, 95% CI 0.57-1.36, I^2 0.0%). Results for HIV-infected and -uninfected populations are shown in Table 2.15.

For VT carriage, there was moderate heterogeneity between HIV-infected and -uninfected sub-groups (I^2 52.3%). In HIV-uninfected individuals, the unvaccinated group was more likely to carry VT than the 3p group (OR 0.64, 95% CI 0.33-1.24) and the reverse was true for the HIV-infected group (OR 1.45, 95% CI 0.59-3.56); however for both groups confidence intervals were wide and crossed 1.

For NVT carriage, the combined estimate showed no evidence of a difference between the vaccinated and unvaccinated groups, and there was little heterogeneity in results between HIV-infected and -uninfected sub-groups (OR 0.99, 95% CI 0.63-1.56, I^2 0.0%). Results for HIV-infected and -uninfected populations are shown in Table 2.15.

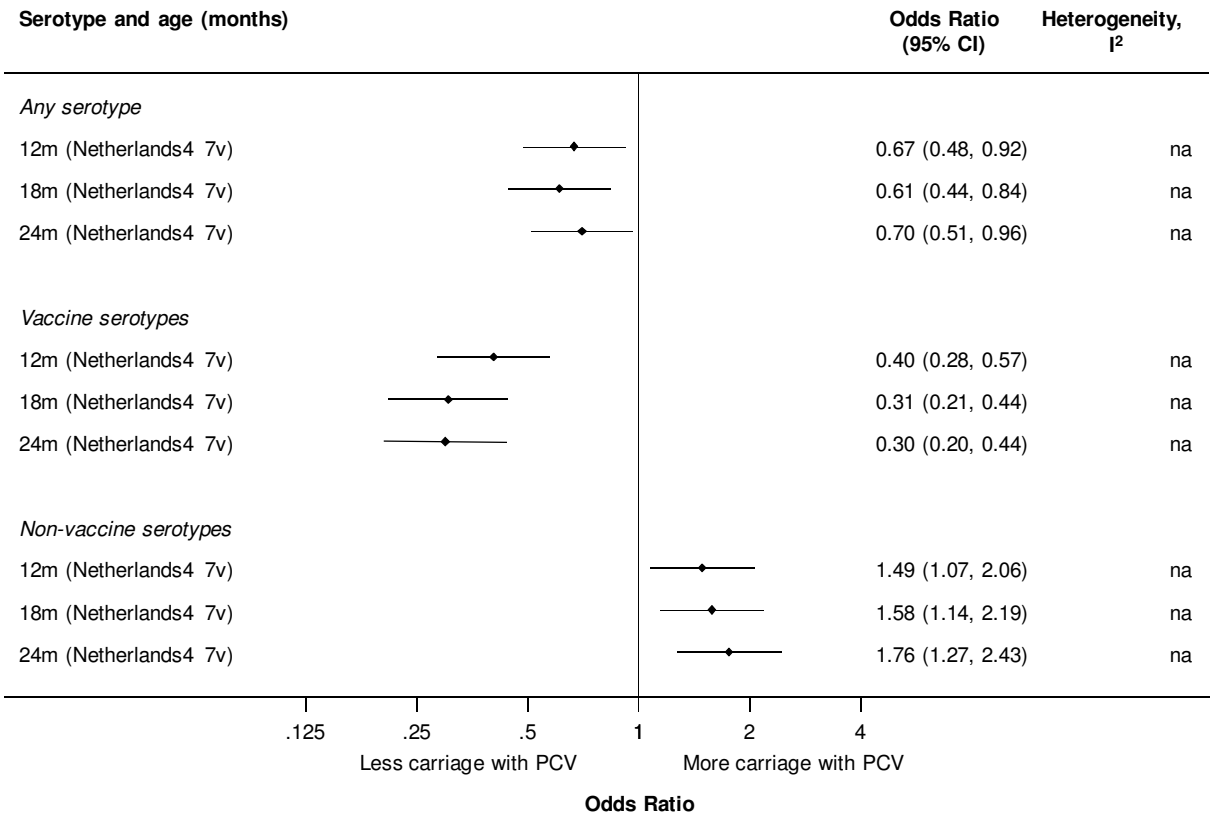
b) Other serotypes

Results for VT (plus 6A), VAT and NVT (excluding vaccine-associated types) are reported in Table 2.15.

2.4.6.5 Comparison W2: 2p+1 vs no PCV

One RCT reported carriage data for this comparison (Netherlands4 7v). Full results for this comparison are given in Table 2.16. Figure 2.26 below shows the combined odds ratios from meta-analysis for each serotype group at different time points.

Figure 2.26 Nasopharyngeal carriage, Comparison W2, 2p+1 vs no PCV, by serotype and age tested



Legend:

NA – not applicable as only one trial in analysis.

Ages stated are approximate. For ages at testing for individual studies, see Table 2.3.

Horizontal axis represents the combined odds ratios from meta-analysis a on logarithmic scale, comparing carriage in groups of children receiving 2p+1 vs no PCV; vertical line through combined odds ratio of 1 shows no difference in levels of carriage between groups. Solid black diamonds represent point estimate of combined odds ratio; horizontal black line represents 95% confidence interval. The I^2 statistic can be interpreted as the proportion of the total variation in estimated risk ratios due to between-trial heterogeneity rather than to chance [13]. Low, moderate and high levels of heterogeneity correspond to I^2 values of 25%, 50% and 75% respectively.

Results for carriage of any serotype and VT carriage showed statistical evidence of less carriage after a 2p+1 schedule than with no PCV at all time points for which data were available.

There was statistical evidence of more NVT carriage with a 2p+1 schedule when compared to no PCV vaccination at all time points for which data were available.

2.4.6.6 Comparison W3: 3p+1 vs no PCV

Two RCTs reported carriage data for this comparison (Finland 7v, USA2 7v), although data were sparse (Table 2.17). USA2 7v was cluster randomized and a non-randomly selected sub-set was chosen to participate in the carriage study. The interpretation of data from this study, therefore, differs from other studies. The only data available from Finland 7v showed that the unvaccinated group was more likely to be carrying VT than the 3p+1 group at 18 months of age (OR 0.55, 95% CI 0.43-0.71). Data from the cluster-randomized trial (USA2 7v) also favoured vaccination at 18–24 months of age for VT, but the statistical evidence was not strong. Data on NVT were only available from USA2 7v, and showed statistical evidence of more carriage at 18–24 months of age in individuals who had received a 3p+1 schedule than those who were not vaccinated.

2.4.6.7 Comparisons X1: 1 or 2 catch-up doses vs no PCV

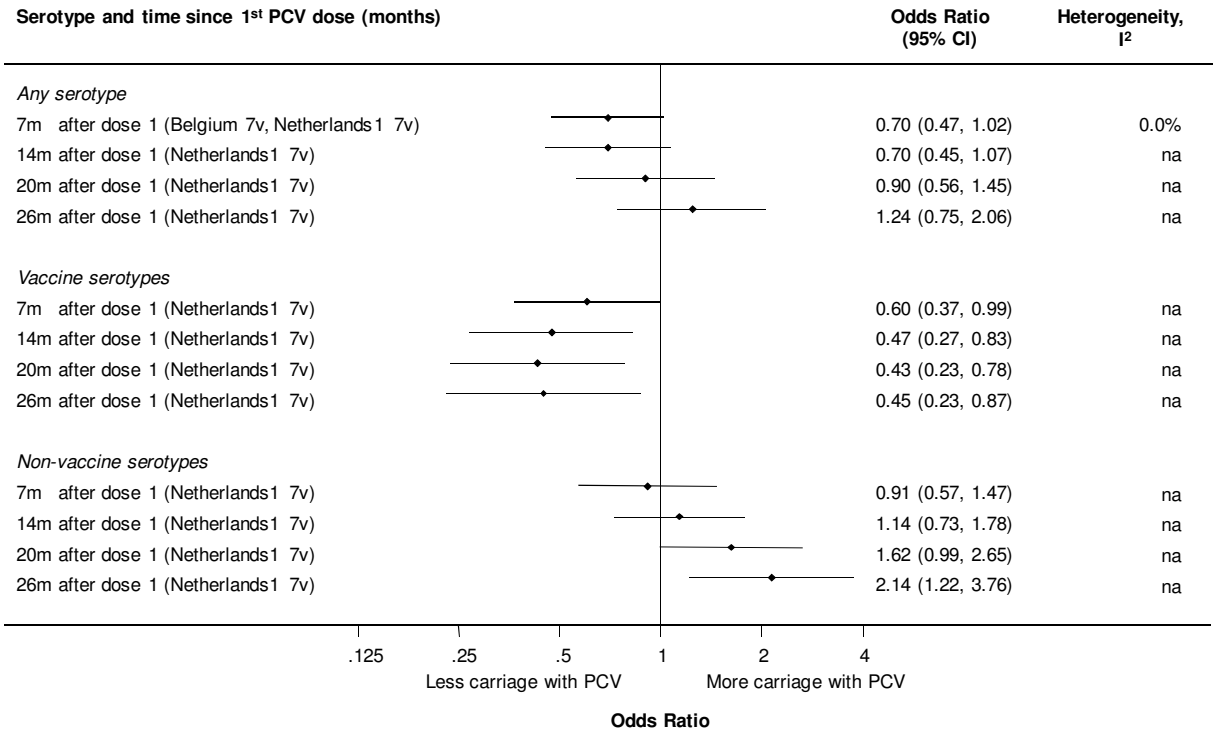
One RCT reported on these comparisons (Netherlands1 7v), although since denominators were not reported, odds ratios could not be calculated. See comparison Y for further data from these studies.

2.4.6.8 Comparison Y: 1 or 2 catch-up doses (with or without PPV) vs no PCV

Three RCTs reported carriage data for this comparison (Belgium 7v, Israel 9v, Netherlands1 7v). Netherlands1 7v reported denominator data at all time points, Belgium 7v reported denominator data for the first sample (7 months after the first dose), Israel 9v did not report denominator data.

Belgium 7v and Netherlands1 7v used the same schedule. At the time of the first sample, individuals in the intervention group had received either 1 or 2 doses of PCV (depending on age at enrolment). They also received a dose of PPV at this time point. Subsequent time points therefore compare schedules with 1 or 2 doses of PCV and 1 dose of PPV to a control group with no doses of PCV or PPV. Results are shown in Table 2.18. Figure 2.27 shows the combined odds ratios from meta-analysis.

Figure 2.27 Nasopharyngeal carriage, Comparison Y, 1 or 2 catch-up doses (with or without PPV) vs no PCV, by serotype and time since first PCV dose



Legend:

NA – not applicable, as only one trial in analysis.

Horizontal axis represents the combined odds ratios from meta-analysis on logarithmic scale, comparing carriage in groups of children receiving 1 or 2 catch-up doses vs no PCV or PPV; vertical line through combined odds ratio of 1 shows no difference in levels of carriage between groups. Solid black diamonds represent point estimate of combined odds ratio; horizontal black line represents 95% confidence interval The I^2 statistic can be interpreted as the proportion of the total variation in estimated risk ratios due to between-trial heterogeneity rather than to chance [13]. Low, moderate and high levels of heterogeneity correspond to I^2 values of 25%, 50% and 75%, respectively.

Results for carriage of any serotype did not consistently favour either catch-up schedules or no PCV.

Results for VT carriage showed statistical evidence of less carriage after vaccination with catch-up schedules when compared with no vaccination.

Results for NVT did not consistently favour either catch-up schedules or no PCV. There was statistical evidence of more NVT carriage after catch-up schedules when compared to no PCV vaccination at 26 months after the first dose of PCV.

Results reported in Israel 9v were consistent with these findings.

Other serotypes

Results for NVT (excluding VAT) and VT (plusVAT) are reported in full in Table 2.18.

2.4.6.9 Methodological issues affecting carriage results, PCV vs no PCV

Differences between studies and potential sources of bias are summarised in Table 12.

All studies were individually randomized except for USA2 7v. Therefore, all other studies estimated direct effects while USA2 7v estimated direct and indirect effects combined.

Subsets of enrolled participant were examined in two studies: USA2 7v and South Africa 9v. The former used a non-random sub-group while in the latter the sub-group was randomly selected. The carriage results from USA2 7v are more at risk of bias and confounding than results from other studies for this reason. Other factors that might put studies at risk of bias, such as allocation concealment, were not well enough described by most studies to assess their potential effect on results.

Pre-vaccination levels of nasopharyngeal carriage differed between studies, with almost four times the level of VT in infants in Netherlands4 7v than in children in Netherlands1 7v. There appears to have been some variation in potential for detecting the carriage of multiple serotypes. In Netherlands4 7v, only one colony per sample was selected for serotyping, meaning that multiple-serotype carriage could not be detected. This might lead to a biased result.

Indirect effects of PCV on nasopharyngeal carriage of pneumococcal serotypes

In the Netherlands4 7v and USA2 7v studies, nasopharyngeal carriage of pneumococci was also assessed in adults or non-vaccinated children, and adults in the same households or communities as children participating in the trials. These data are not presented here.

2.5 Discussion

The systematic review identified 23 RCTs that contained data about clinical outcomes or nasopharyngeal carriage. Eleven of these RCTs reported clinical disease outcomes and 12 reported carriage. A further seven reported only mortality data or clinical data reported as SAEs.

2.5.1 Strengths and limitations

The main strengths of this review were the wide and comprehensive search strategy and rigorous methods for selecting studies and extracting data. The inclusion criteria that specify the design features of studies and interventions and comparison groups in advance make it more likely that comparable studies can be examined.

A further strength of this review was the extent of analyses conducted. For clinical data, multiple clinical disease outcomes were analysed using both ITT and PP data. These analyses were also conducted for healthy and high-risk groups separately, and were stratified by study design (individually or cluster randomized), unlike previous reviews. The authors believe that carriage data have not been synthesized in meta-analyses before. Carriage data were analysed for a large number of comparisons at multiple time points for each comparison. Prevalence odds ratios for

carriage data are reported as the primary analysis as this has been proposed as a method to estimate vaccine efficacy against pneumococcal acquisition from cross-sectional data [11]. However, carriage prevalence ratios and prevalence differences are also reported, for completeness.

A limitation of the data available for this review was the insufficient number of trials to allow a formal examination of the potential causes of between-trial heterogeneity in results using tools such as meta-regression. Statistical analyses of the available data, however, would lack the power to show associations between these factors and trial results.

Different standards in the data from RCT reports is a major limitation to the systematic synthesis of evidence in this review. The CONSORT statement, first published in 1996 and updated in 2010 [59, 60], aims to improve the transparency of reporting of RCTs. Several journals publish RCTs of vaccination that do not endorse the CONSORT statement, such as the Pediatric Infectious Diseases Journal and Clinical Infectious Diseases. Specific items required for the appraisal and synthesis of RCTs were often omitted from published reports. For example, procedures for randomization sequence generation, allocation concealment and implementation were often not reported in adequate detail to assess the risk of bias. Furthermore, meta-analysis cannot be performed without an estimate of the precision of the effect measure [61]. However, denominator data and/or confidence intervals that were needed to estimate standard errors were often not reported.

One of the limitations of the meta-analyses based on estimates of VE in this review is that not all log confidence intervals are symmetrical around the log point estimate. This might slightly underweight studies where exact methods were used by trial investigators to calculate confidence intervals. However, in these analyses, there was often insufficient detailed information to calculate standard errors using other methods. The method used is consistent with that used in the most recent Cochrane review of clinical disease outcomes following PCV vaccination [62].

2.5.2 Main findings and interpretation

This review found no definitive evidence from RCTs that any specific PCV schedule is superior to another for clinical disease outcomes or mortality. This is because no RCTs reported clinical disease outcomes or mortality that directly compared PCV schedules. All the available data on clinical disease outcomes from direct comparisons are reported in the review of cohort and case–control studies.

There was RCT evidence that 3p+0 and 3p+1 schedules protect against IPD and pneumonia for the follow-up periods studied. Protection against IPD caused by vaccine serotypes was stronger than for all serotypes combined. There was no evidence of an increase in disease caused by non-vaccine serotypes, but this was limited to the follow-up periods of the RCTs. There were, however, no RCTs that compared 2p+0 or 2p+1 schedules to no PCV and reported IPD or pneumonia. Statistical methods can make indirect comparisons while respecting randomization [63, 64], i.e. RCTs comparing 3p vs 0 or 2p vs 0 could be used to make an indirect comparison of 3p vs 2p. In this respect, the only possible comparison in this review would be 3p vs 3p+1. However, differences within the only four eligible RCTs, would make interpretation of findings difficult. Such analyses are therefore unlikely to lead to robust findings that would change the conclusions of this review.

Interpretation of pneumonia data is further complicated by the lack of sensitivity and specificity in the clinical and radiological diagnosis of pneumonia [65]. This could have biased VE for pneumonia towards the null value of no effect of PCV.

No definitive evidence was found from the three RCTs that measured nasopharyngeal carriage of pneumococci that any specific PCV schedule is superior to another. For 2p, 3p, 2p+1 and catch-up schedules, there was evidence that PCV reduces carriage of vaccine serotypes and increases

carriage of non-vaccine serotypes when compared to no PCV for a maximum of 26 months after the last PCV dose.

Pneumococcal carriage is a promising primary outcome when investigating the effects of different PCV schedules because it is more common than severe disease outcomes or mortality. Pneumococcal carriage in the nasopharynx is the precursor of clinical disease and the reservoir for spread between individuals [66]. However, the precise relationship between changes in pneumococcal carriage and clinical disease outcomes remains to be established. The PneumoCarr project aims to establish this relationship so that VE against carriage can be used for the licensure of future vaccines [66].

2.5.3 Implications for future research and practice

At present, the choice of PCV schedule is likely to be informed by knowledge of the local epidemiology of pneumococcal disease and on health-service delivery of other vaccinations in the National Immunization Programme. Additional evidence about the relative benefits of different PCV schedules is needed to help guide public health decision-making.

In the absence of evidence on the superiority of any particular PCV schedule, future RCTs should determine whether different vaccination schedules are equivalent in their effects on carriage and clinical outcomes. Sample size calculations should therefore be based on the demonstration of non-inferiority [67], even though the sample size required is greater than for the demonstration of superiority.

The long-term effects of vaccination schedules cannot be studied in RCTs. Different vaccination schedules might have long-term effects on control of disease, herd effects and serotype replacement by non-vaccine serotypes. Post-introduction surveillance is therefore essential to monitor these outcomes. The challenges of collecting, analysing and interpreting such data are well-recognized. Nevertheless, valuable information could be obtained from studies that harmonize methods and outcome definitions.

2.6 Conclusions

This comprehensive systematic review of RCTs of PCV vaccination schedules found no definitive evidence that any particular PCV schedule is superior to another in its effect on clinical disease, mortality, or carriage outcomes.

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Section 3. Pneumococcal conjugate vaccines

A systematic review of immunological outcome data from randomized controlled trials of childhood schedules 7-, 9-, 10- and 13-valent vaccines

3.1 Overview

3.1.1 Objective

This section of the report presents findings about immunological responses to pneumococcal conjugate vaccines (PCV) studied in randomized controlled trials (RCTs) that directly compare different PCV schedules.

3.1.2 Review methods

A search was made of 12 electronic databases of published articles, trial registers, industry databases and other documents from the earliest citation until August 2009. The search was updated in March 2010.

Items were selected that reported on RCTs in children up to 18 years. The intervention was any vaccination schedule using 7-, 9, 10- or 13-valent PCV.

Comparisons could be between schedules with different numbers of doses, different ages at the start of vaccination, or different intervals between doses.

Structured piloted forms were used to extract available data on: schedule, serotype specific seropositivity (%), geometric mean antibody concentrations (GMC), study characteristics, and potential sources of bias and heterogeneity.

The following immunological outcomes are described: seropositivity (using threshold antibody concentrations of both 0.35µg/ml and 0.20µg/ml), GMC and opsonophagocytic activity (OPA).

Random effects meta-analysis was used to combine results statistically, where appropriate. To compare seropositivity levels between groups of children receiving different schedules, the difference in prevalence of seropositivity was calculated (with 95% confidence intervals, CI). To compare GMC between schedules, the ratio (with 95% CI) of GMCs was calculated in the groups being compared. Between-trial heterogeneity was described using the I^2 statistic where values below 25% represent low levels of heterogeneity, up to 50% moderate; up to 75% high; and more than 75% very high levels.

3.1.3 Results

Of the 31 eligible RCTs identified in searches, 16 reported immunological outcomes in direct comparisons between PCV schedules. The following is a summary of the findings described further in this section of the report.

3.1.3.1 Direct comparisons between PCV schedules

There were 18 different schedule vs schedule comparisons in the 16 included RCTs. All reported GMCs, 12 reported seropositivity and four reported OPA.

a) 2p vs 1p and 3p vs 1p schedules

Schedules containing 1 primary dose were less immunogenic than 2p and 3p schedules at 6 months of age for all serotypes for both seropositivity and GMC (2 RCTs).

After 1 PCV dose, seropositivity levels at around 6 months of age were >65% for serotypes 4, 14, 19F but only 12–30% for serotypes 6B and 23F (2 RCTs).

Differences between 1p and either 2p or 3p schedules in seropositivity and GMC at 12 months and 17 months (1 RCT) were less marked than at 6 months of age.

There were high levels of between-trial heterogeneity for all but 1 serotype. One source of heterogeneity is that, in the RCT with the largest observed differences in seropositivity between comparison groups, the interval between the dates of the last dose and the immunological assessment in each group were different.

b) 3p vs 2p schedules

3p and 2p schedules both resulted in high levels of seropositivity for most serotypes (5 RCTs).

Differences between groups in the percentage of individuals seropositive were generally small, with most differences favouring the 3p schedule. The biggest differences were seen for serotypes 6B and 23F.

Levels of heterogeneity in results between trials were often high.

Differences at 6 months appeared to persist at 12 months (3 RCTs).

The clinical relevance of differences in seropositivity is not well understood.

c) 2p+1 vs 2p schedules

No immunological data from RCTs were available for this comparison.

d) 3p vs 2p+1 schedules

Only one RCT was identified that compared 3p vs 2p+1 schedules.

After the primary series, there were modest differences in seropositivity, favouring the 3p schedule.

At 13 months, antibody concentrations were substantially higher in the 2p+1 group (1 month after the booster) than in the 3p group (7 months after the last primary dose), but these differences were smaller by 19 months.

In trials that included similar 3p schedules and immunological assessments, point estimates of seropositivity at about 12 months were mostly >80%, but were around 50% for serotype 23F.

If the incidence of invasive pneumococcal disease (IPD) is highest in the first year of life, a 2p+1 schedule might not offer substantial individual protection compared to a 3p schedule in immune-competent children. If vaccine-induced herd immunity develops, this scenario might change over time.

e) 3p+1 vs 2p+1 schedules

3p+1 and 2p+1 schedules resulted in similar levels of seropositivity after the booster dose, with the exception of serotypes 23F and 6B (2 RCTs).

GMC ratios generally favoured the 3p+1 schedule, with the highest ratios being for 6B and 23F.

The clinical relevance of the differences in these immunological outcomes is not known. If serotypes 6B or 23F are responsible for a high burden of clinical disease, the observed differences should be considered when choosing a PCV schedule.

f) 3p+1 vs 3p schedules

At 13 months of age, antibody concentrations were substantially higher in the 3p+1 group (1 month after the booster dose) than in the 3p group (7 months after the last primary dose, 2 RCTs), but these differences were smaller by 19 months (1 RCT).

If the incidence of IPD is highest in the second year of life, a 3p+1 schedule might offer more individual protection than a 3p schedule in immune-competent children. If vaccine-induced herd immunity develops, this scenario might change over time.

g) Later vs earlier age at start of primary schedule

Immunological data were reported in four RCTs with very heterogeneous results. Differences in ages between comparison groups at the start of the primary series varied from 2 weeks to 3 months. There were also differences in intervals between the last dose of PCV and immunological assessment, both between comparison groups and between RCTs.

h) 2-month vs 1-month interval between doses in primary schedules

No immunological data from RCTs were available for this comparison.

i) Longer vs shorter interval between primary and booster schedules

Immunological data were reported in two RCTs. The differences between schedules in the age at which the booster dose was given were 3 months in 1 RCT and 2 months in the other.

Antibody concentrations were slightly higher for groups receiving a later booster but CI crossed 1 for all but 2 serotypes.

j) Other comparisons

Other comparisons of schedules examined differences between schedules containing pneumococcal polysaccharide vaccine (PPV) or PCV boosters, or with catch-up doses. Most involved only one trial and did not show marked differences between groups.

3.1.3.2 Comparisons of PCV schedule vs no PCV

There were 26 additional items that compared immunological outcomes between groups vaccinated with PCV and groups that received no PCV. Data from these RCTs were not analysed in this review.

3.1.4 Discussion

3.1.4.1 Strengths and limitations

The main strengths of this review were the wide and comprehensive search strategy, and rigorous methods for selecting studies and extracting data.

A further strength was the collation of data for multiple immunological outcomes at all time points after vaccination for which data were available. Key data are unlikely to have been missed.

A limitation of the data available for this review was the insufficient number of trials to allow a formal examination of the potential causes of statistical between-trial heterogeneity. Potential reasons for heterogeneity, such as interval between last dose and blood sampling, have been suggested.

The lack of standardized reporting of data in RCTs is a major limitation to the systematic synthesis of evidence in this review.

3.1.4.2 Main findings and interpretation

Some differences were found in immunological outcomes following vaccination with different PCV schedules. Schedules with a higher number of primary doses tended to result in higher levels of seropositivity for all analysed serotypes shortly after completing the primary schedule. Differences favouring the schedule with a higher number of doses were more marked for serotypes 6B and 23F in most of these comparisons.

There were high levels of between-trial heterogeneity for many comparisons, but these did not alter the main findings.

3p and 2p schedules both resulted in high levels of seropositivity for most serotypes. Differences between groups were generally small and mostly favoured the 3p schedule at 6 and 12 months (5 RCTs).

Differences in seropositivity between groups receiving 3p or 2p schedules were somewhat smaller after a booster dose of PCV. Both 3p+1 and 2p+1 schedules resulted in high levels of seropositivity for most serotypes (2 RCTs).

Only one RCT was identified that directly compared 3p and 2p+1 schedules. The findings are difficult to interpret because of different intervals between the last dose received and immunological assessment in the 2 groups. If the rapid fall in antibody concentrations after the primary series corresponds to a reduction in protection against clinical disease, a booster dose might be more important. If indirect protection from disease develops through vaccine-induced herd immunity, the need for a booster dose might change over time.

The clinical relevance of differences in immunological outcomes observed in this review between groups receiving different vaccination schedules is not known. The levels of antibodies that provide protection against clinical disease are not known and might differ between serotypes, for different clinical outcomes and in different populations.

The immunological data contained in this review relate primarily to healthy populations. Only trials conducted in Ghana related to high-risk populations, specifically children with sickle-cell disease. The findings of this review might not be generalizable to other high-risk groups.

3.1.4.3 Implications for future research

The timing of vaccination and immunological assessments should be taken into consideration in the design of RCTs comparing different vaccination schedules. The design should allow comparisons between schedules with the same interval between the last vaccination and the assessment, as well as comparisons when children are the same age.

Longer term follow-up of immunological responses to PCV would be useful, in conjunction with clinical and epidemiological data about patterns of pneumococcal disease.

3.1.5 Conclusions

The comprehensive systematic review of RCTs of PCV vaccination schedules found some evidence that schedules containing 2 or 3 doses in the primary series provide better seropositivity and GMC outcomes than schedules with only 1 dose. Differences between other schedules were less marked. The interpretation of differences in immunological outcomes was limited because of uncertainty about their clinical relevance. Optimal schedules are likely to depend on local epidemiology of pneumococcal disease as well as health service delivery of other vaccinations in the National Immunization Programme.

3.2 Introduction

Information on the effects of PCV, particularly on immunological outcomes, is rapidly accumulating as vaccines incorporating increasing numbers of pneumococcal serotypes, or different carrier proteins, become available. Immunogenicity studies of PCV should provide a link between measured immune responses and vaccine efficacy (VE) against clinical disease, although serological correlates of protection are difficult to establish [1]. For protection against IPD, WHO has determined serological criteria for licensure purposes, based on data from three RCTs of 7-valent PCV (PCV7) [3-5] using a standardized enzyme-linked immunosorbent assay (ELISA) [1]. The threshold was determined as a serum IgG antibody concentration of 0.35µg/ml measured 1 month after vaccination for each serotype common to the 7-valent and the new PCV [2]. This updates a previous recommended threshold of 0.20µg/ml [6].

Information about functional antibody, measured as OPA, is also recommended.

Assays and standardization for OPA are not as well established as for IgG antibodies, but limited data suggest that an IgG concentration of ≥0.20µg/ml (determined using an ELISA without 22F pre-adsorption of sera) corresponds approximately to an OPA titre of ≥1:8 for some serotypes [6]. There are a number of methods to assess immune responses, including antibody avidity, cell-mediated immunity and immunological memory [1].

Selected findings from the systematic review, comparing schedules with 3 primary doses vs 2 primary doses, have been published [7]. Within the overall objectives of the systematic review of evidence about PCV, this section presents the results of immunological outcomes studied in RCTs. The general search strategy and methods used are described in the clinical and carriage section 2.1.2, while methods specific to immunological data are described here.

For the selection of studies, two pairs of reviewers independently evaluated articles retrieved in searches conducted in August 2009 and March 2010 for eligibility for inclusion in the review. The selection criteria for these studies are described below.

3.2.1 Inclusion criteria

3.2.1.1 Study design

The following study designs were considered for inclusion: RCT or quasi-RCT, where individuals or groups were randomized to any of the comparison groups listed below.

a) Population

Studies containing data relating to the vaccination of children (up to 18 years).

b) Intervention

Studies relating to vaccination with licensed formulations of PCV (7-, 10- or 13-valent) PCV. The protocol specified that only data from studies using licensed vaccines would be used. However, studies on 9v PCV were subsequently included owing to the limited available clinical data. Trials using the PCV11 were not included as the formulation changed substantially after trials with clinical outcomes were conducted.

3.2.1.2 Comparison groups

The following comparison groups were selected for inclusion:

- different number of doses of PCV;

- different intervals between doses of PCV;
- different ages at the start of a PCV vaccination schedule.

3.2.1.3 Immunogenicity outcomes

Studies reporting any of the following outcomes, or stating that such data would be collected, were eligible for inclusion:

- seropositivity after vaccination, defined as the number of children with antibody levels above a defined threshold;
- seroconversion, defined as either changing from seronegative before vaccination to seropositive after vaccination, or a 4-fold rise in titre/concentration or similar measure;
- geometric mean titre/concentration, or other summary measure, defined as the mean of logarithmic values of antibody concentration;
- mean (or other summary measure) change in titre (or similar measure) in individuals (before vs after vaccination).

3.2.2 Exclusion criteria

Uncontrolled studies, observational intervention studies, dose-finding studies, and animal or laboratory studies were excluded from this section of the review.

3.3 Statistical analysis

3.3.1 Descriptive analysis of immunological outcomes

The features of all included studies are first summarized in tables and figures (Annex 3.1). This study focuses on serotype specific IgG antibody responses to capsular polysaccharides as the indicator of immunogenicity, because these data were most frequently available. The limited available data about OPA is also presented. Other indicators of immune response, e.g. avidity, are not reported here.

a) IgG antibody, seropositivity

Seropositivity was the most frequently reported immunological outcome. For each pneumococcal serotype reported in a study, the percentages of children in each study group with antibody levels above thresholds reported by the authors were calculated. A threshold of 0.35µg/ml was used to define seropositivity in the primary analysis. If this was not reported, a data reporting a cut-off point of 0.20µg/ml was used, the former WHO reference standard [6]. Additionally, limited data suggest that an IgG concentration of ≥0.20µg/ml (determined using an ELISA without 22F pre-adsorption of sera) corresponds approximately to an OPA titre of ≥1:8 for some serotypes [6].

For comparisons between schedules, the absolute difference in seropositivity is reported (the prevalence difference, with 95% CI), subtracting the value in the group receiving fewer doses from the value in the group receiving more doses. The prevalence ratio was not used because, when the percentage seropositive is close to 100% in both groups, the risk ratio is very close to 1, and differences between groups can be difficult to display visually in forest plots.

b) Additional description of RCTs reporting on either 3p or 2p+1 schedules

An additional descriptive analysis was conducted but not described in the review protocol because of the lack of RCTs that directly compared a 3-dose primary series with 2 primary doses and a booster early in the second year.

Eligible trials were only included if they reported the percentage of children with serotype specific antibody concentrations of ≥0.35µg/ml after receiving PCV in either schedule. Similarly, only trials with very similar schedules were included: 3 primary dose series given at about 2, 3, 4 or 3, 4, 5 months; 2 primary doses at 2, 4 or 3, 5 months and a booster at about 12 months. Only results for selected serotypes are reported: 6B; 14; 19F; 23F. Forest plots displaying absolute seropositivity rates for each schedule were generated and patterns examined visually and described. No statistical analyses were done.

c) IgG antibody, geometric mean concentration

GMCs summarize the average antibody concentration level, using logarithmic transformations of the actual values. The transformed values were used to calculate the mean and confidence intervals. The GMC is the exponentiated value of the result and therefore reported in the original units (µg/ml).

d) Opsonophagocytic activity

Assays to measure OPA have not been widely used. Available results are reported as a percentage of individuals with a titre ≥1:8, or as geometric mean titres [6].

3.3.2 Meta-analysis

Data were combined statistically, where appropriate using meta-analysis, which calculates average results across studies, with the final result weighted so that larger studies contribute more than smaller studies. For comparisons of seropositivity, the effect measure that is being combined is the risk difference between two groups receiving different PCV schedules, and for comparisons of GMC the effect measure is the GMC ratio.

DerSimonian and Laird random-effects meta-analyses were used [8] with STATA 10 (StataCorp LP, College Station, Texas, USA). For seropositivity data, meta-analysis was performed on the number of individuals seropositive and seronegative in each comparison group for each study. For GMC data, logarithmic transformations of the reported GMC and confidence intervals were used, as well as the sample size, to calculate the standard deviation of results for each intervention group. The data were then meta-analysed from included studies to produce a combined estimate of non-standardized mean difference between groups on a logarithmic scale. These data were back-transformed to give a combined estimate of the ratio of GMC between comparison groups. It was appropriate to use non-standardized mean differences because all measurements were on the same scale (log µg/ml). The meta-analyses were repeated using the standardized mean differences on the logarithmic scale to take into account the possible influence of factors such as the use of different ELISA tests in different studies. The conclusions were the same in both sets of analyses, so the ratio of GMC between comparison groups is presented as these have a more intuitive interpretation.

Stratum-specific outcomes were examined and between-trial heterogeneity quantified using the I^2 statistic. This can be interpreted as the proportion of the total variation in estimated risk ratios due to between-trial heterogeneity rather than to chance [9]. Low, moderate and high levels of heterogeneity correspond to I^2 values of <25%, <50% and ≥50%, respectively. The level of heterogeneity was taken into account when reporting and interpreting results. The pooled effect estimates were suppressed when the I^2 value was above 50% because these are difficult to interpret when there is a high level of heterogeneity between trial results. Data were not combined statistically when a single study contributed to two or more estimates within strata. Unless otherwise specified, p values relate to tests of heterogeneity.

3.4 Presentation of results

A study name was assigned to each RCT, based on the country or countries in which the trial was conducted and the number of serotypes in the PCV. Actual citations are not used because data might have been collated from several different publications. Annex 3.1 presents all the immunological outcome data in figures and tables. The citations for all publications linked to each study name are listed in Annex 3.2. Selected tables and figures from the annexes are presented in the text for ease of reference, while retaining their original chronology. For descriptive purposes, the basic details of included studies are presented in alphabetical order (Table 3.1 and Appendices 3.1 and 3.2).

3.4.1 Description of schedules

The following abbreviations are used to describe vaccine schedules, using as an example:

3p – 3 doses in the primary (p) vaccination schedule with all doses given before 12 months of age;

+1 – a booster dose of a pneumococcal vaccine. If the booster was PPV, this is noted explicitly;

(2, 3, 4) – the intended ages at vaccination, in months;

(+ b15) – the age at which the booster dose was given, in months.

3.4.2 Order of presentation of comparisons between schedules

Studies and their findings are reported, wherever possible, in a consistent manner, according to the following hierarchy:

- number of doses in the schedule; the first comparisons are with 1-dose schedules; schedules with only a primary vaccination series are reported before those including booster doses;
- type of booster; schedules involving a comparison with no booster are reported first, followed by PPV booster and PCV booster doses;
- valency, starting with PCV7;
- country, in alphabetical order.

3.4.3 Forest plots

Forest plots are used to present the results of meta-analyses comparing seropositivity and displaying the prevalence difference.

Each plot summarizes the available data for a comparison between two different schedules, e.g. 3p vs 2p schedules. The plots present the prevalence differences (with 95% CI), according to serotype, and results for each study are then ordered by vaccine valency and then alphabetical order. If there is no difference between the groups, the risk difference is 0. Where data could be pooled statistically, the combined estimate of the risk difference is presented as an open diamond. The plots also include the raw data, with numbers and percentages seropositive for each comparison. Forest plots for key comparisons are included in the main text, with supplementary data for additional time-points and antibody threshold levels in Annex 3.1.

3.4.4 Tables

Tables are used to present the results of meta-analyses comparing GMC and displaying the GMC ratio.

3.5 Results

3.5.1 Literature search

Of the 3217 items found in searches,16 trials were included that investigated direct comparisons between different PCV schedules and reported at least one immunological outcome.

3.5.2 Description of included studies

The 16 included trials are summarized in Table 3.2. In descriptions of RCTs, Canada1 7v primary and booster trials are counted as one study as only children included in Canada1 7v primary were recruited for Canada1 7v booster.

The included studies involved 4193 children (3888 who received primary vaccination in infancy and 305 toddlers who received only catch-up doses). The studies took place in 15 countries: 9 countries in the WHO European Region, 3 in the Americas, 2 in Africa, and 1 in the Western Pacific. Additional details about the RCTs and outcomes are reported in Annex 3.2.

Seven trials used PCV7 (Canada1 7v, Fiji 7v, Gambia 7v, Germany 7v, Israel 7v, UK1 7v, USA3 7v), six used PCV9 (Ghana infants 9v, Ghana toddlers 9v, Iceland 9v, UK2 9v, UK3 9v, UK4 9v), and three used PCV10 (Chile 10v, Europe 10v, Finland 10v). There were no eligible data available for RCTs of 13-valent PCV.

Table 3.3 shows the range of ELISA used in different studies. In 12 trials that reported seropositivity as an outcome, the WHO recommended threshold of 0.35µg/ml was reported for at least one comparison by eight studies (Fiji 7v, Gambia 7v, Europe 10v, Iceland 9v, Israel 7v, UK2 9v, UK3 9v, UK4 9v). The threshold of 0.20µg/ml was reported in six trials (Chile 10v, Europe 10v, Finland 10v, UK2 9v, UK3 9v, UK4 9v). Details of the ELISA used, or reasons for reporting alternative thresholds, were often not reported. Differences in thresholds limited the number of direct comparisons that could be made.

3.5.2.1 Description of comparisons available for analysis

The RCTs involved 18 types of schedule vs schedule comparisons (Figure 3.1, Table 3.3). The figure shows the studies according to the direct comparisons made within trials and is grouped to show trials examining similar schedules, according to the number of doses. The current WHO recommendation of 3 doses in infancy with no booster was included as a comparison in four trials (Fiji 7v, Ghana infants 9v, Israel 7v, USA3 7v) with 645 infants randomized to 3p+0 groups. Data about outcomes after a 3p schedule were also available from several other RCTs evaluating 3p+1 or 3p+PPV schedules if blood was drawn before administration of the booster dose.

Table 3.1 Summary of included RCTs with schedule–schedule comparisons reporting immunological outcomes, alphabetical order

Study name and PCV valency	Country	Schedules, age at dose in months		Number of participants randomized	Outcomes reported
		Intended	Actual age at administration		
Canada1 primary [10] [1] 7v	Canada	3, 5, 7 2, 4, 6	NR 1st: mean 2.2	124 126	Seropositivity, GMC
Canada1 booster [11] [1] 7v	Canada	3p + b18 3p + b15	18.5 15.5	167 168	Seropositivity, GMC
Chile 10v [12]	Chile	2, 4, 6, + b>18 2 catch-up >18	NR	119 121	Seropositivity, GMC, OPA
Europe 10v [13]	Denmark, Norway, Slovakia, Sweden	2, 3, 4, + b11	2.8, 3.9 ,5.0, 11.2	176	Seropositivity, GMC, OPA
		2, 4, + b11m	2.8, 4.9, 11.1	175	
Fiji 7v [14]	Fiji	1.5, 2.5, 3.5 +/- b12(PPV) 1.5, 3.5 +/- b12(PPV) 3.5 +/- b12(PPV)	NR	136 156 128	Seropositivity, GMC, OPA
Finland 10v [15]	Finland	2, 3, 4, + b14-16 2, 3, 4, + b12-14	NR	101 110	Seropositivity, GMC
Gambia 7v [16]	the Gambia	2, 3, 4 + b10(PPV) 2, 3 + b10(PPV) 2 + b10(PPV)	NR	228 228 228	Seropositivity, GMC, OPA
Germany 7v [17]	Germany	6, 7, 8 + b11-15 2, 3, 4 + b11-15	NR	113 118	GMC [2]
Ghana infants 9v [18]	Ghana	1.5, 2.5, 3.5 + b12 1.5, 2.5, 3.5 + b12(PPV) 1.5, 2.5, 3.5	2.6, 3.9, 4.8, NR 2.4, 3.5, 4.9, NR 2.4, 3.9. 5.2	21 21 20	GMC
Ghana toddlers 9v [19]	Ghana	2 doses PCV (2 months apart) 1 dose PCV + PPV (2 months apart)	14.9, 17.1 14.9, 17.5	46 46	GMC
Iceland 9v [20]	Iceland	3, 4, 5 + b12 3, 4, 5 + b12(PPV) 3, 5 + b12 3, 5 + b12(PPV)	NR	111 [3] 112 [3]	Seropositivity, GMC
Israel 7v [21]	Israel	2, 4, 6 + b12 2, 4, 6 4, 6 + b12	2.1, 4.0, 5.8, 12.5 [4] NR [4] 3.9, 5.7, 12.4	178 178 189	Seropositivity, GMC
UK1 7v [22]	United Kingdom	5, 6, 7 + b13(PPV) 2, 3, 4 + b13(PPV)	NR	120 124	GMC
UK2 9v [23]	United Kingdom	2, 4 + b12 2, 4 + b12(PPV)	NR	88 [3]	Seropositivity, GMC
UK3 9v [23]	United Kingdom	2, 3, 4 + b12 2, 3, 4 + b12(PPV)	NR	84 [3]	Seropositivity, GMC
UK4 9v [23]	United Kingdom	12, 14 + 18(PPV) 12+18 (PPV)	NR	45 47	Seropositivity, GMC
USA3 7v [24]	United States	2-3.5, 4.5, 6.5 1.5-3, 4, 6	1st: median 2.1	188 188	Seropositivity, GMC

Legend:

b – booster; GMC – geometric mean concentration of IgG antibodies; OPA – opsonophagocytic activity; NR – not reported; PCV – pneumococcal conjugate vaccine; PPV – pneumococcal polysaccharide vaccine; seropositivity 3p – 3-dose primary schedule, etc.; +1 – booster dose.

Each RCT has a single primary citation. The citations for all publications linked to each RCT are listed in Annex 3.2.

1 Canada1 7v primary and Canada1 7v booster include the same children, but individuals were randomized for a second time after the primary course. Each intervention group for the booster study therefore contains individuals who received 2, 4, 6m and 3, 5, 7m primary schedules. Results after the booster dose are not reported in a way that allows examination of the original intervention groups. These 2 phases of the study are therefore reported separately, and do not occur in the same analysis. In Canada1 7v primary, there was an additional comparison group for which PCV related outcome data were not reported. This group was therefore not included in the reporting of Canada1 7v primary, but is included in Canada1 7v booster, which accounts for the difference in number of participants in the 2 phases of the study.

2 Results not reported in enough detail to include in analyses (no confidence intervals reported).

3 The number undergoing the randomization process. The numbers randomized to each group are unclear.

4 The ages at administration given for the 3p+1 group appear to relate to both the 3p+1 and the 3p group, but not clearly stated in original publication.

Table 3.2 ELISA assays used and antibody concentration thresholds reported

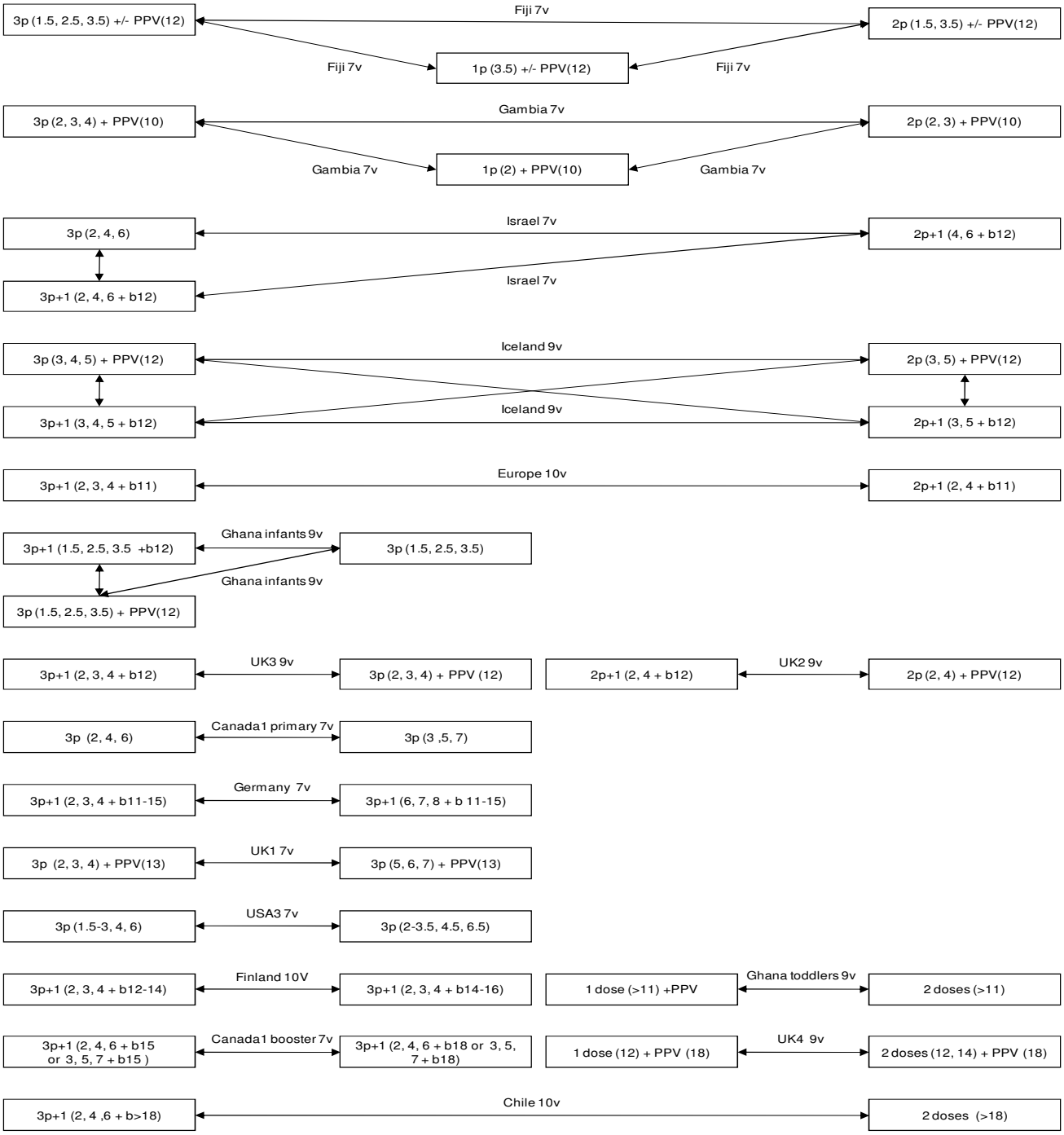
Study	Assay	GMC only	Threshold for ELISA seropositivity, µg/mL[1]						
			0.05	0.15	0.20	0.35	0.50	1.0	5.0
Canada1 7v primary	'standardized ELISA'			✓			✓		
Canada1 7v booster	'published ELISA'			✓			✓		
Chile 10v	"22F-ELISA"		✓		✓				
Europe 10v	ELISA, with 22F pre-adsorption		✓		✓	✓			
Fiji 7v	'modified WHO ELISA' against reference serum 89SF					✓		✓	
Finland 10v	"22F-ELISA"		✓		✓				
Gambia 7v	'ELISA…adapted WHO'					✓			
Germany 7v	"standard ELISA methods"	Yes							
Ghana infants 9v	"ELISA...based on an original assay described by Quataert"	Yes							
Ghana toddler 9v	"ELISA...based on an original assay described by Quataert"	Yes							
Iceland 9v	ELISA, no 22F pre-adsorption					✓			
Israel 7v	ELISA, 22F and C pre-adsorption					✓		✓	✓
UK1 7v	'standard ELISA' against reference serum 89SF	Yes							
UK2-4 9v[2]	ELISA, with 22F pre-adsorption				✓	✓		✓	
USA3 7v	'standardized ELISA'		✓						

Legend:

1 In published articles, not all thresholds are reported for all possible comparisons.

2 Three trials reported separately.

Figure 3.1 Network of RCTs reporting immunological outcomes comparing different PCV schedules in children, according to schedule and comparisons



Legend:

b – booster; p – primary dosing schedule; PCV – pneumococcal conjugate vaccine; PPV – pneumococcal polysaccharide vaccine.

As far as possible, the network is organized as follows:

Left-hand side: 3-dose schedules (3p followed by 3p+1); Right-hand side: 2-dose schedules; Centre: 1-dose schedules.

Study names for each comparison are along the lines connecting each schedule, alphabetical order within schedule groups; arrows connect comparisons, with horizontal lines showing direct schedule–schedule comparisons.

Schedule described as, e.g. 3p – number of doses in primary schedule; +1 – booster dose; (2, 3, 4) – ages in months when vaccine doses intended to be given.

Table 3.3 shows selected comparisons, together with the time points and serotypes for which data are available. Each comparison is identified by a letter, which also appears on accompanying figures or tables. All comparisons are reported in the figures and tables in Annex 3.1 Comparisons highlighted in the table below means they are reported in the main text. Similarly, key forest plots and tables are presented in the main text, while they are included in Annex 3.1.

Table 3.3 Order of description and presentation of comparisons of vaccination schedules in RCTs reporting immunological outcomes

Comparison	Study	Schedules, months	Age at which samples taken[1], months	Age at which 0.35µg/ml available, months	Age at which 0.20µg/ml available, months	Age at which GMC available, months	Age at which OPA available, months
Comparison A 2p vs 1p	Fiji 7v	1.5, 3.5 3.5	4.5, 9, 12, 17	4.5, 9, 12, 17	NR	4.5, 9, 12, 17	4.5, 9, 12, 17
	Gambia 7v[2]	2, 3 2	5.5	5.5	NR	5.5	5.5
Comparison B 3p vs 1p	Fiji 7v	1.5, 2.5, 3.5 3.5	4.5, 9, 12, 17	4.5, 9, 12, 17	NR	4.5, 9, 12, 17	4.5, 9, 12, 17
	Gambia 7v[2]	2, 3, 4 2	5.5	5.5	NR	5.5	5.5
Comparison C 3p vs 2p	Fiji 7v	1.5, 2.5, 3.5 1.5, 3.5	4.5, 9, 12, 17	4.5, 9, 12, 17	NR	4.5, 9, 12, 17	4.5, 9, 12, 17
	Gambia 7v[2]	2, 3, 4 2, 3	5.5	5.5	NR	5.5	5.5
	Israel 7v[2]	2, 4, 6 4, 6	7	7	NR	NR[3]	NR
	Iceland 9v[2]	3, 4, 5 3, 5	6, 12	6, 12	NR	6	NR
	Europe 10v[2]	2, 3, 4 2, 4	6, 11	6	6, 11	6, 11	6, 11
Comparison D 2p + PPV vs 1p + PPV	Fiji 7v	1.5, 3.5 + b12(PPV) 3.5 + b12(PPV)	17	17	NR	17	17
	Gambia 7v	2, 3, 4 + b10(PPV) 2, 3 + b10(PPV)	11, 15	11, 15	NR	11, 15	11, 15
Comparison F 2p + 1 vs 2p + PPV	Iceland 9v	3, 5 + b12 3, 4, 5 + b12(PPV)	13	13	NR	13	NR
	UK2 9v	2, 4 + b12 2, 4 + b12(PPV)	13	NR	NR	13	NR
Comparison G 3p vs 2p + 1	Israel 7v	2, 4, 6 4, 6 + b12	13, 19 (and 1 month post completion: 13 vs 7m)	NR	NR	13, 19 (and 1 month post completion: 13 vs 7m)	NR
Comparison H 3p + PPV vs 1p+ PPV	Fiji 7v	1.5, 2.5, 3.5 + b12(PPV) 3.5 + b12(PPV)	17	17	NR	17	17

Comparison	Study	Schedules, months	Age at which samples taken[1], months	Age at which 0.35µg/ml available, months	Age at which 0.20µg/ml available, months	Age at which GMC available, months	Age at which OPA available, months
	Gambia 7v	2, 3, 4 + b10(PPV) 2 + b10(PPV)	11, 15	11, 15	NR	11, 15	11, 15
Comparison I 3p + PPV vs 2p +PPV	Fiji 7v	1.5, 2.5, 3.5 + b12(PPV) 1.5, 3.5 + b12(PPV)	17	17	NR	17	17
	Gambia 7v	2, 3, 4 + b10(PPV) 2 , 3 + b10(PPV)	11, 15	11, 15	NR	11, 15	11, 15
	Iceland 9v	3, 4, 5 + b12(PPV) 3, 5 + b12 (PPV)	13	13	NR	13	NR
Comparison J 3p + PPV vs 2p + 1	Iceland 9v	3, 4, 5 + b12(PPV) 3, 5 + b12	13	13	NR	13	NR
Comparison K 3p + 1 vs 2p + PPV	Iceland 9v	3, 4, 5 + b12 3, 5 + b12(PPV)	13	13	NR	13	NR
Comparison L 3p + 1 vs 2p + 1	Israel 7v	2, 4, 6 + b12 4, 6 + b12	13, 19	NR	NR	13, 19	NR
	Iceland 9v	3, 5 + b12 3, 4, 5 +b12	13	13	NR	13	NR
	Europe 10v	2, 3, 4 + b11 2, 4 + b11	12	12	12	12	12
Comparison M 3p + 1 vs 3p	Israel 7v	2, 4, 6 + b12 2, 4, 6	13, 19 (and 1 month post completion: 13 vs 7m)	NR	NR	13, 19 (and 1 month post completion: 13 vs 7m)	NR
	Ghana infants 9v	1.5, 2.5, 3.5 + b12 1.5, 2.5, 3.5	13 (and 1 month post completion: 13 vs 4.5m)	NR	NR	13 (and 1 month post completion: 13 vs 4.5m)	NR
Comparison N 3p +1 vs 3p + PPV	Ghana infants 9v	1.5, 2.5, 3.5 + b12 1.5, 2.5, 3.5 + 12(PPV)	13	NR	NR	13	NR
	Iceland 9v	3, 4, 5 + b12 3, 4, 5 + b12(PPV)	13	13	NR	13	NR
	UK3 9v	2, 3, 4 + b12 2, 3, 4 + b12 (PPV)	13	NR	NR	13	NR
Comparison O Late start vs early start	Canada1 7v primary[4]	3, 5, 7 2, 4, 6	1 month post completion: 8 vs 7m	NR	NR	1 month post completion: 8 vs 7m	NR

Comparison	Study	Schedules, months	Age at which samples taken[1], months	Age at which 0.35µg/ml available, months	Age at which 0.20µg/ml available, months	Age at which GMC available, months	Age at which OPA available, months
	Germany 7v	6, 7, 8 + b11-15 2, 3, 4 + b11-15	11-15, 12-16	NR	NR	NR	NR
	UK1 7v	5, 6, 7 2, 3, 4	13	NR	NR	13	NR
	UK1 7v	5, 6, 7 + b13(PPV) 2, 3, 4 + b13(PPV)	14	NR	NR	14	NR
	USA3 7v	1.5-3, 4, 6 2-3.5, 4.5, 6.5	7	NR	NR	7	NR
Comparison Q longer interval between primary and booster	Finland 10v	2, 3, 4 + b14-16 2, 3, 4 + b12-14	1.5 months post completion: 15.5 vs 13.5m	NR	1.5 months post completion: 15.5 vs 13.5m	1.5 months post completion: 15.5 vs 13.5m	NR
vs shorter interval between primary and booster	Canada1 7v booster [4]	3p + b18 3p + b15	1 month post completion: 19 vs 16m	NR	NR	1 month post completion: 19 vs 16m	NR
Comparison R Catch-up vs catch-up	Ghana toddlers 9v	2 doses PCV (2 months apart) 1 dose PCV + PPV (2 months apart)	1 month post completion	NR	NR	1 month post completion	NR
	UK4 9v	12, 14 12	1 month post completion: 15 vs13m	1 month post completion: 15 vs13m	1 month post completion: 15 vs13m	1 month post completion: 15 vs13m	NR
Comparison S 2 + PPV vs 1 + PPV	UK4 9v	12, 14 + b18(PP 12 + b18(PPV)	19	NR	NR	19	NR
Comparison T Primary (+/- booster) vs catch-up	Chile 10v	2, 4, 6, + b>18 2 catch-up >18	1 month post completion: >19	NR	1 month post completion: >19	1 month post completion: >19	1 month post completion: >19

Legend:

b – booster; p – primary schedule; NR – not reported; OPA- opsonophagocytic activity; PPV – pneumococcal polysaccharide vaccine; v – valent.

Shaded grey rows are those reported in main text.

1 Time point at which blood samples taken for assessment.

2 Samples taken before booster dose so comparison of primary schedule also possible.

3 At 7 months of age, 2 intervention groups have received 3 primary doses of PCV. GMCs are reported separately for each 3p group and were not combined for this analysis.

4 Canada1 7v primary and Canada1 7v booster include the same children, but individuals were randomized for a second time after the primary course. Each intervention group for the booster study therefore contains individuals who received 2, 4, 6m and 3, 5, 7m primary schedules. Results after the booster dose are not reported in a way that allows examination of the original intervention groups. These 2 phases of the study are therefore reported separately, and never both occur in the same analysis.

3.5.2.2 Description of methodological features of included RCTs

Table 3.4 summarizes the methodological features of the studies included in this review that could potentially be sources of bias or between-trial heterogeneity. In three studies, the interval between primary doses of PCV differed between comparison groups (Europe 10v, Fiji 7v, Iceland 9v). In two studies, it was not possible to compare groups after the same interval after the last dose of PCV (Gambia 7v, UK1 7v). Only five studies described the method of generation of allocation sequence and had this method assessed as adequate. Only five studies offered some description of how the allocation sequence was concealed, but none described it well enough to be certain that concealment was adequate. Two studies explicitly stated that the laboratory staff that assessed immunological outcomes were blinded. In addition, the Canada1 7v RCT reports stated that outcome assessors were blinded, but it was unclear if this related to laboratory staff as well as those assessing other outcomes. Three studies reported intention-to-treat analyses of immunological data, five reported per protocol analyses and the remainder did not indicate which of these methods was used.

Variation in these features might create heterogeneity between trials. However, there were not enough RCTs to allow investigation of the effect of these features using methods such as stratification or meta-regression.

Table 3.4 Reporting of methodological features of RCTs reporting immunological outcomes, alphabetical order

Study, vaccine (manufacturer)	Intended interval between doses in primary series	Intended interval from last dose PCV/PPV to blood sampling[1]	Adequate randomization sequence generation	Adequate randomization allocation concealment	Blinding of outcome assessors	Intention-to-treat or per protocol analyses[2]
Canada1 7v primary [10][3]	2m	Same in all groups	Unclear, 'randomized'	Unclear, 'randomized'	"With evaluator blinding"	ITT
Canada1 7v booster [11][3]	2m	Same in all groups	Unclear, 'randomized'	Unclear, 'randomized'	"evaluator-blinded"	NR
Chile 10v [12]	2m	Same in all groups	Unclear, 'randomized'	Unclear, 'randomized'	NR	PP
Europe 10v [13]	2p: 2m 3p: 1m	Same in all groups	Unclear, 'randomized'	Unclear, 'randomized'	NR	PP
Fiji 7v [14]	2p: 2m 3p: 1m	Same in all groups	Yes	Unclear (opaque envelopes but not clear if envelope linked to child before opening)	Laboratory staff blinded	NR
Finland 10v [15]	1m	Same in all groups	Unclear, 'randomized'	Unclear, 'randomized'	NR	PP
Gambia 7v [16]	1m	Differs by either 1 or 2 months between groups, until PPV booster	Unclear, 'consecutively randomized'	Unclear, 'consecutively randomized'	NR	ITT

Ghana infants (sickle-cell) 9v [18]	1m	Possible to compare same in all groups, or with differences in intervals of up to 8.5m (after booster)	Yes	Unclear (envelopes used but not clear if envelope linked to child before opening)	NR	NR
Ghana toddlers (sickle-cell) 9v [18]	NA	Same in all groups	Yes	Unclear (envelopes used but not clear if envelope linked to child before opening)	NR	NR
Iceland 9v [20]	2p: 2m 3p: 1m	Same in all groups	Unclear, 'randomized'	Unclear, 'randomized'	NR	PP
Israel 7v [21]	2m	Possible to compare same in all groups, or with differences in intervals of up to 6m (after booster)	Yes	Unclear (opaque envelopes but not clear if envelope linked to child before opening)	NR	NR
UK1 7v [22]	1m	Differs by 3m	Yes	Unclear, not well described	NR	ITT
UK2 infants 9v [23]	2m	Same in all groups	Unclear, 'randomized'	Unclear, 'randomized'	NR	NR
UK3 infants 9v [23]	1m	Same in all groups	Unclear, 'randomized'	Unclear, 'randomized'	NR	NR
UK4 toddlers 9v [23]	NA	Same in all groups	Unclear, 'randomized'	Unclear, 'randomized'	NR	NR
USA3 7v [24]	Approx. 2m	Same in all groups	Not fully randomized, "10% randomness and the center as minimization factor"	Unclear, Internet randomization (not clear if child data entered prior to allocation being given)	Laboratory staff blinded	PP

Legend:

ITT – intention to treat; NA – not applicable; NR – not reported; m – months; p – primary doses; PP – per protocol; PPV – pneumococcal polysaccharide vaccine.

Each RCT has a single primary citation. The citations for all publications linked to each RCT are listed in Annex 3.2. Germany 7v not included in table as there were no data that could be analysed in this review;

1 Where intended interval is categorized as 'same', this applies to all time points. Where one group receives booster PCV and another not, this is listed as 'same' if time between last primary dose and sampling is the same in each group.

2 As reported by authors of included articles.

3 Canada1 7v primary and Canada1 7v booster include the same children, but individuals were randomized for a second time after the primary course. Each intervention group for the booster study therefore contains individuals who received 2, 4, 6m and 3, 5, 7m primary schedules. Results after the booster dose are not reported in a way that allows examination of the original intervention groups. These 2 phases of the study are therefore reported separately, and never both occur in the same analysis.

3.5.3 Immunological outcomes, schedule vs schedule comparisons

3.5.3.1 Comparisons A and B: 2p vs 1p and 3p vs 1p schedules

Summary

- *Schedules containing 1 primary dose were less immunogenic than 2p and 3p schedules at 6 months of age for all serotypes for both seropositivity and GMC (2 RCTs).*
- *After 1 PCV dose, seropositivity to serotypes 6B and 23F at around 6 months of age was only 12–30%.*
- *Differences between 1p and other schedules in seropositivity and GMC at 12 months and 17 months (1 RCT) were less marked.*
- *There were high levels of between-trial heterogeneity for all but 1 serotype. One source of heterogeneity is that, in the RCT with the largest observed differences in seropositivity between comparison groups, the interval between the dates of the last dose and the immunological assessment in each group were different.*

Two trials using PCV7 (Fiji 7v, Gambia 7v) examined the effects of reduced dose schedules, comparing 2p or 3p schedules with a single dose in a total of 1104 infants. The timing of the schedules and of assessments differed. In Fiji 7v, the last dose in each schedule was given at 3.5 months and blood samples taken about 1 month later. In Gambia 7v, the first dose in each schedule was given at 2 months, and blood samples in each group were taken at about 5 months of age; the interval between the last vaccine dose and immunological assessment was therefore 3 months in the 1-dose group and 1 month in the 3-dose group.

a) Seropositivity

Seropositivity defined as antibody concentration ≥0.35µg/ml

For 2p vs 1p schedules, Figures 3.2, 3.3 and 3.4 show the proportions of children seropositive at a threshold of 0.35µg/ml, assessed at about 6, 12 and 17 months of age, respectively. For the comparison of 3p vs 1p schedules, Figures 3.5, 3.6 and 3.7 show proportions seropositive at a threshold of 0.35µg/ml, assessed at about 6, 12 and 17 months of age, respectively.

Infants receiving 2 or 3 primary doses were more likely to have antibody concentrations ≥0.35µg/ml at 6 months than infants receiving 1 dose, especially for serotypes 6B and 23F (Figures 3.2 and 3.5). For almost all serotypes and for both comparisons (2p vs 1p and 3p vs 1p) the differences in seropositivity were 10% or more at 6 months of age.

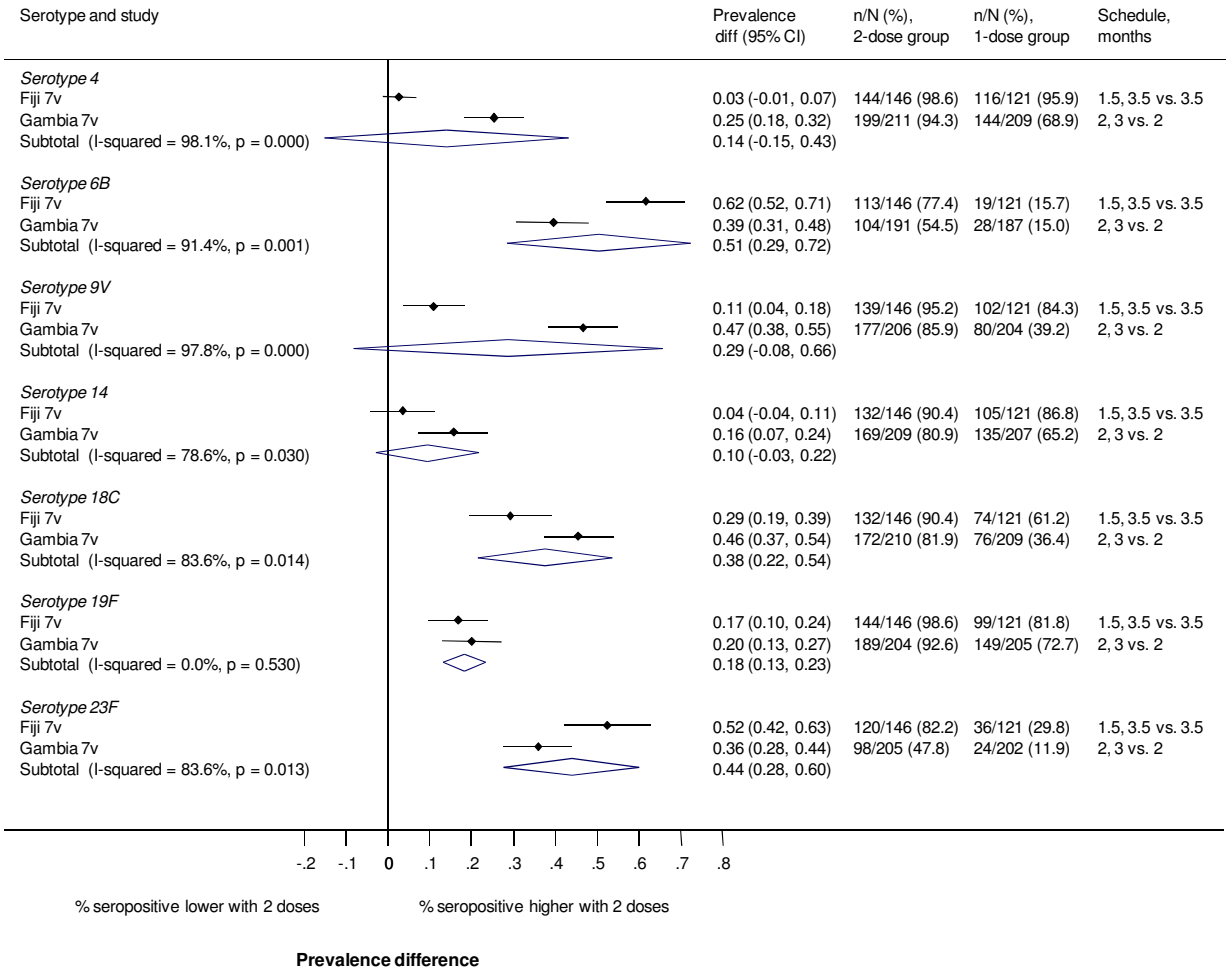
At 12 months of age, only one RCT (Fiji 7v) had data available from groups that did not receive a booster vaccination. Compared to data obtained at 6 months in this RCT, there was some decline in the percentage of individuals seropositive in all three groups (3p, 2p and 1p) for most serotypes. This was most marked for serotypes 18C and 23F for the 3p and 2p groups and serotype 18C in the 1p group. There was also a decline between 12 and 17 months for some serotypes, with changes in serotype 18C being marked for all three groups. Differences between groups became smaller between 6 and 17 months.

There were high levels of heterogeneity between the trials for most serotypes in both comparisons (2p vs 1p and 3p vs 1p). The differences in seropositivity between schedules

were more marked in Gambia 7v than in Fiji 7v, except for serotypes 6B and 23F in the 2p vs 1p schedules.

These data suggest that the larger differences observed in Gambia 7v than in Fiji 7v, especially in the 3p vs 1p schedules at 6 months of age, might be explained by differences in the interval between vaccination and blood sampling in the groups in Gambia 7v. In the groups receiving 3 doses, in which the intervals between last dose and immunological assessments were similar in both RCTs, absolute levels of seropositivity were similar (Figure 3.5).

Figure 3.2 Comparison A. 2p vs 1p schedules, seropositivity at ~6 months, ELISA threshold 0.35ug/ml, by serotype and study

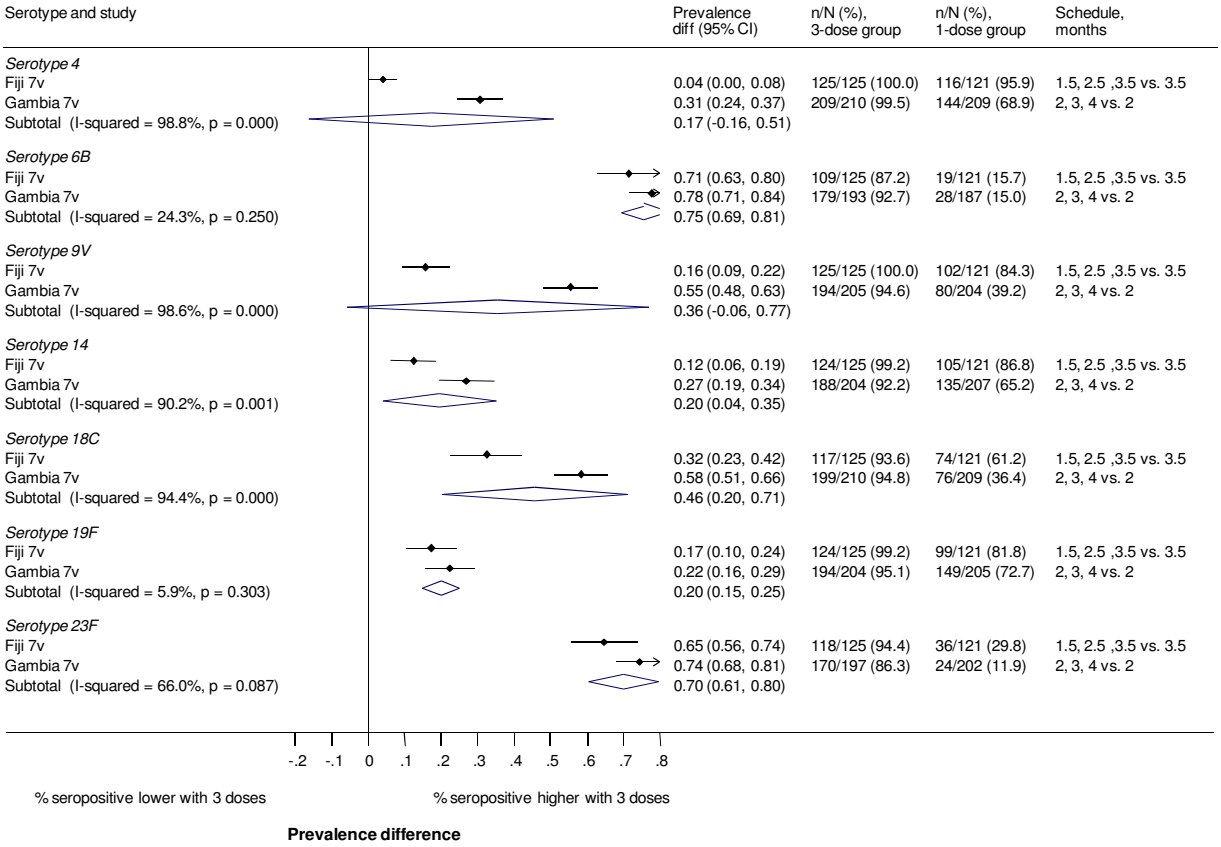


Legend:

n/N – number seropositive/total in group; Prevalence diff – difference in seropositivity between groups, shown as a proportion.

Horizontal axis represents the difference, expressed as a proportion between groups receiving schedules of 2 primary doses vs 1 primary dose. Vertical line through risk difference of 0 shows no difference in levels of seropositivity between groups. Solid black diamonds represent point estimate of prevalence difference; horizontal black line represents 95% confidence interval. Open diamond represents the pooled estimate, combined using random effects meta-analysis; vertical points of diamond represent point estimate and horizontal points represent 95% confidence interval; I-squared value is the level of statistical heterogeneity between trials (<25% low heterogeneity).

Figure 3.5 Comparison B. 3p vs 1p schedules, seropositivity at ~6 months, ELISA threshold 0.35ug/mL, by serotype and study



Legend:

n/N –number seropositive/total in group; Prevalence diff –difference in seropositivity between groups shown as a proportion.

Horizontal axis represents the difference, expressed as a proportion between groups receiving schedules of 3 primary doses vs 1 primary dose. Vertical line through risk difference of 0 shows no difference in levels of seropositivity between groups. Solid black diamonds represent point estimate of prevalence difference; horizontal black line represents 95% confidence interval. Open diamond represents the pooled estimate, combined using random effects meta-analysis; vertical points of diamond represent point estimate and horizontal points represent 95% confidence interval; I-squared value is the level of statistical heterogeneity between trials (<25% low heterogeneity).

Seropositivity defined as antibody concentration ≥ 0.20µg/ml

No studies reported this outcome.

b) Geometric mean antibody concentrations

GMC were reported in Fiji 7v and Gambia 7v. Heterogeneity between results from the trials was high for most serotypes in both comparisons at 6 months of age. Tables 3.5 and 3.6 show individual study results in each intervention group per study. At 6 months, pooled estimates showed that GMC in children receiving 2p or 3p were 3 to 33 times higher than in children receiving 1 dose. The 3p:1p ratios were generally higher than the 2p:1p ratios.

Tables 3.5 and 3.6 also show that GMC were much lower in Fiji 7v at 12 months than at 6 months of age in all comparison groups, but did not fall markedly between 12 and 17 months. GMC ratios showed that children receiving 2 or 3 doses of PCV had similar GMC to those receiving 1 dose by 12 and 17 months of age.

For the comparison of 2p vs 1p schedules at 12 months of age, confidence intervals include the possibility of no difference between the schedules for serotypes 4, 9V, 14 and 19F. By 17 months of age this possibility exists for all serotypes. A similar pattern was seen for the comparison of 3p vs 1p schedules with confidence intervals crossing 1 for serotypes 4, 9V and 19F at 12 months of age and serotypes 4, 6B, 9V and 19F at 17 months of age.

c) Opsonophagocytic antibody seropositivity defined as OPA titre ≥1:8

Figures 3.8, 3.9 and 3.10 show OPA seropositivity results assessed at around 6, 12 and 17 months of age, respectively for comparison A. Figures 3.11, 3.12 and 3.13 show OPA seropositivity results assessed at around the same ages for comparison B.

The patterns described for ELISA data at a threshold of 0.35µg/ml hold largely true for OPA data. The main exception to this is data for serotype 19F in Gambia 7v (data not available for Fiji 7v), where differences between the 3p or 2p group and the 1p group were larger than those seen in ELISA data.

Table 3.5 Comparison A (2p vs 1p). Geometric mean antibody concentrations at ~6, ~9, ~12 and ~17 months, by serotype

Age	Serotype	Study	GMC, µg/ml (95% CI)		Studies in meta-analysis, N	Combined ratio of GMCs from meta-analysis (95% CI)	I^2, %
			2p	1p			
6 months	4	Fiji 7v	5.23 (4.46, 6.13)	2.20 (1.80, 2.70)	2	5.58 (1.01, 30.81)	96.7
		Gambia 7v	2.04 (1.54, 2.70)	0.15 (0.09, 0.24)			
	6B	Fiji 7v	0.86 (0.70, 1.07)	0.19 (0.16, 0.22)	1*	4.53 (3.47, 5.90)	NA
		Gambia 7v	0.05 (0.03, 0.08)	0.00 (0.00, 0.01)			
	9V	Fiji 7v	4.71 (3.88, 5.71)	0.90 (0.74, 1.09)	2	12.10 (2.22, 65.82)	95.6
		Gambia 7v	0.59 (0.41, 0.84)	0.02 (0.01, 0.03)			
	14	Fiji 7v	3.12 (2.42, 4.03)	1.07 (0.89, 1.27)	2	4.05 (1.89, 8.70)	75
		Gambia 7v	1.03 (0.64, 1.65)	0.16 (0.09, 0.26)			
	18C	Fiji 7v	2.67 (2.16, 3.31)	0.58 (0.45, 0.74)	2	14.09 (1.54, 128.76)	98
		Gambia 7v	0.44 (0.30, 0.66)	0.01 (0.01, 0.02)			
	19F	Fiji 7v	7.99 (6.62, 9.64)	0.84 (0.70, 1.00)	2	10.04 (7.95, 12.68)	0
		Gambia 7v	2.16 (1.56, 2.99)	0.17 (0.11, 0.26)			
	23F	Fiji 7v	1.65 (1.29, 2.11)	0.23 (0.20, 0.27)	1*	7.17 (5.38, 9.57)	NA
		Gambia 7v	0.07 (0.04, 0.11)	0.00 (0.00, 0.00)			
9 months	4	Fiji 7v	0.86 (0.67, 1.12)	0.60 (0.42, 0.85)	1	1.43 (0.93, 2.22)	NA
	6B	Fiji 7v	0.81 (0.59, 1.12)	0.39 (0.29, 0.52)	1	2.08 (1.35, 3.20)	NA
	9V	Fiji 7v	0.72 (1.38, 0.56)	0.56 (0.40, 0.77)	1	1.79 (1.14, 2.79)	NA
	14	Fiji 7v	1.93 (1.20, 3.09)	1.11 (0.79, 1.57)	1	1.74 (0.97, 3.12)	NA
	18C	Fiji 7v	0.41 (0.33, 0.53)	0.18 (0.14, 0.24)	1	2.28 (1.59, 3.26)	NA
	19F	Fiji 7v	1.40 (1.05, 1.86)	0.89 (0.61, 1.29)	1	1.57 (0.98, 2.52)	NA
	23F	Fiji 7v	0.44 (0.33, 0.60)	0.24 (0.18, 0.32)	1	1.83 (1.21, 2.78)	NA
12 months	4	Fiji 7v	0.47 (0.40, 0.54)	0.63 (0.50, 0.81)	1	0.75 (0.56, 0.99)	NA
	6B	Fiji 7v	0.76 (0.63, 0.92)	0.57 (0.46, 0.71)	1	1.33 (1.00, 1.78)	NA
	9V	Fiji 7v	0.62 (0.54, 0.71)	0.50 (0.41, 0.62)	1	1.24 (0.97, 1.59)	NA
	14	Fiji 7v	1.52 (1.26, 1.84)	1.16 (0.94, 1.44)	1	1.31 (0.99, 1.74)	NA
	18C	Fiji 7v	0.24 (0.21, 0.28)	0.17 (0.15, 0.20)	1	1.41 (1.15, 1.73)	NA
	19F	Fiji 7v	1.14 (0.95, 1.36)	0.93 (0.76, 1.15)	1	1.23 (0.93, 1.61)	NA
	23F	Fiji 7v	0.42 (0.35, 0.50)	0.26 (0.21, 0.31)	1	1.62 (1.24, 2.10)	NA
17 months	4	Fiji 7v	0.43 (0.33, 0.56)	0.56 (0.39, 0.80)	1	0.77 (0.49, 1.20)	NA
	6B	Fiji 7v	0.78 (0.58, 1.04)	0.62 (0.47, 0.83)	1	1.26 (0.84, 1.89)	NA
	9V	Fiji 7v	0.49 (0.39, 0.62)	0.51 (0.36, 0.71)	1	0.96 (0.64, 1.45)	NA
	14	Fiji 7v	1.12 (0.86, 1.46)	0.93 (0.66, 1.32)	1	1.20 (0.78, 1.86)	NA
	18C	Fiji 7v	0.20 (0.16, 0.25)	0.15 (0.12, 0.19)	1	1.33 (0.97, 1.84)	NA
	19F	Fiji 7v	1.06 (0.82, 1.38)	0.92 (0.66, 1.26)	1	1.15 (0.76, 1.74)	NA
	23F	Fiji 7v	0.43 (0.32, 0.58)	0.32 (0.22, 0.48)	1	1.34 (0.82, 2.19)	NA

Legend:

I^2 value is the level of statistical heterogeneity between trials (<25% low heterogeneity); NA – not applicable.

* Gambia 7v data not included in meta-analysis because of zero values in 1 or more groups.

Table 3.6 Comparison B (3p vs 1p). Geometric mean antibody concentrations at ~6, ~9, ~12 and ~17 months, by serotype

Age	Serotype	Study	GMC, µg/ml (95% CI)		Studies in meta-analysis, N	Combined ratio of GMCs from meta-analysis (95% CI)	I^2, %
			3p	1p			
6 months	4	Fiji 7v	5.47 (4.84, 6.19)	2.20 (1.80, 2.70)	2	8.21 (0.77, 87.28)	98.6
		Gambia 7v	4.16 (3.61, 4.79)	0.15 (0.09, 0.24)			
	6B	Fiji 7v	1.66 (1.33, 2.07)	0.19 (0.16, 0.22)	1*	8.74 (6.65, 11.47)	NA
		Gambia 7v	3.47 (2.41, 4.98)	0.00 (0.00, 0.01)			
	9V	Fiji 7v	4.76 (4.19, 5.40)	0.90 (0.74, 1.09)	2	21.32 (1.35, 337.16)	98.6
		Gambia 7v	1.77 (1.36, 2.29)	0.02 (0.01, 0.03)			
	14	Fiji 7v	5.51 (4.50, 6.76)	1.07 (0.89, 1.27)	2	11.92 (2.19, 64.93)	95.7
		Gambia 7v	4.65 (3.21, 6.72)	0.16 (0.09, 0.26)			
	18C	Fiji 7v	3.20 (2.66, 3.86)	0.58 (0.45, 0.74)	2	33.18 (0.98, 1124.99)	99.4
		Gambia 7v	2.01 (1.53, 2.63)	0.01 (0.01, 0.02)			
	19F	Fiji 7v	5.52 (4.79, 6.36)	0.84 (0.70, 1.00)	2	12.98 (3.29, 51.25)	95.7
		Gambia 7v	4.54 (3.37, 6.10)	0.17 (0.11, 0.26)			
	23F	Fiji 7v	2.93 (2.39, 3.59)	0.23 (0.20, 0.27)	1*	12.74 (9.89, 16.40)	NA
		Gambia 7v	1.50 (1.04, 2.18)	0.00 (0.00, 0.00)			
9 months	4	Fiji 7v	0.79 (0.55, 1.14)	0.60 (0.42, 0.85)	1	1.32 (0.79, 2.19)	NA
	6B	Fiji 7v	0.82 (0.58, 1.17)	0.39 (0.29, 0.52)	1	2.10 (1.33, 3.32)	NA
	9V	Fiji 7v	0.91 (0.71, 1.16)	0.56 (0.40, 0.77)	1	1.63 (1.08, 2.45)	NA
	14	Fiji 7v	3.99 (2.86, 5.57)	1.11 (0.79, 1.57)	1	3.59 (2.23, 5.80)	NA
	18C	Fiji 7v	0.49 (0.37, 0.65)	0.18 (0.14, 0.24)	1	2.72 (1.84, 4.02)	NA
	19F	Fiji 7v	1.04 (0.70, 1.54)	0.89 (0.61, 1.29)	1	1.17 (0.68, 2.01)	NA
	23F	Fiji 7v	0.65 (0.46, 0.94)	0.24 (0.18, 0.32)	1	2.71 (1.71, 4.28)	NA
12 months	4	Fiji 7v	0.48 (0.41, 0.57)	0.63 (0.50, 0.81)	1	0.76 (0.57, 1.02)	NA
	6B	Fiji 7v	0.86 (0.72, 1.03)	0.57 (0.46, 0.71)	1	1.51 (1.14, 2.00)	NA
	9V	Fiji 7v	0.59 (0.51, 0.67)	0.50 (0.41, 0.62)	1	1.18 (0.92, 1.51)	NA
	14	Fiji 7v	2.38 (1.98, 2.86)	1.16 (0.94, 1.44)	1	2.05 (1.55, 2.72)	NA
	18C	Fiji 7v	0.32 (0.27, 0.38)	0.17 (0.15, 0.20)	1	1.88 (1.51, 2.35)	NA
	19F	Fiji 7v	1.05 (0.83, 1.34)	0.93 (0.76, 1.15)	1	1.13 (0.82, 1.55)	NA
	23F	Fiji 7v	0.54 (0.44, 0.66)	0.26 (0.21, 0.31)	1	2.08 (1.57, 2.75)	NA
17 months	4	Fiji 7v	0.35 (0.29, 0.43)	0.56 (0.39, 0.80)	1	0.63 (0.41, 0.94)	NA
	6B	Fiji 7v	0.91 (0.69, 1.21)	0.62 (0.47, 0.83)	1	1.47 (0.98, 2.19)	NA
	9V	Fiji 7v	0.41 (0.34, 0.49)	0.51 (0.36, 0.71)	1	0.80 (0.55, 1.18)	NA
	14	Fiji 7v	1.78 (1.42, 2.24)	0.93 (0.66, 1.32)	1	1.91 (1.26, 2.90)	NA
	18C	Fiji 7v	0.21 (0.18, 0.26)	0.15 (0.12, 0.19)	1	1.40 (1.04, 1.88)	NA
	19F	Fiji 7v	1.19 (0.84, 1.67)	0.92 (0.66, 1.26)	1	1.29 (0.81, 2.07)	NA
	23F	Fiji 7v	0.57 (0.43, 0.75)	0.32 (0.22, 0.48)	1	1.78 (1.10, 2.88)	NA

Legend:

I^2 value is the level of statistical heterogeneity between trials (<25% low heterogeneity); NA – not applicable.

* Gambia 7v data not included in meta-analysis as zero value in 1 or more groups.

3.5.3.2 Comparison C: 3p vs 2p schedules

Summary

- *3p and 2p schedules both resulted in high levels of seropositivity for most serotypes (5 RCTs).*
- *Differences between groups in the percentage of individuals seropositive were generally small, with most differences favouring the 3p schedule.*
- *The biggest differences were seen for serotypes 6B and 23F.*
- *Levels of heterogeneity in results between trials were frequently high.*
- *Differences at 6 months appeared to persist at 12 months (3 RCTs).*
- *The clinical relevance of differences in seropositivity is not well understood.*

Five trials reported comparisons between 3p and 2p dose schedules for at least one immunological outcome, at least one serotype and at least one time point (Europe 10v, Fiji 7v, Gambia 7v, Iceland 9v, Israel 7v). A total of 1867 infants received 2 or 3 primary doses of PCV in these studies.

In all studies except Fiji 7v, infants received a booster of either PCV or PPV after the primary series. In Fiji 7v, about half the children received a booster of PPV and the remainder received no booster. The data presented here relate to assessments after the primary series and before the booster dose.

The interval between doses for the 3p schedules was 1 month in Fiji 7v, Gambia 7v, Europe 10v and Iceland 9v, and 2 months in Israel. The interval between the 2p schedules was 2 months in Fiji 7v, Europe 10v, Iceland 9v and Israel 7v, and 1 month in Gambia 7v. For both schedules in all studies except Gambia 7v, the ~6 month blood sample was taken about 1 month after the last dose. In Gambia 7v, the blood sample was taken 1 month after the last dose in the 3p schedule and 2 months after the last dose in the 2p schedule.

There was statistical evidence of between-trial heterogeneity when comparing the seropositivity risk difference (Figures 3.14, 3.15 and 3.16) and GMC ratios (Table 3.7) for most serotypes. This was most apparent for seropositivity in serotypes 6B and 23F.

a) Seropositivity

Seropositivity defined as antibody concentration ≥0.35µg/ml

Figures 3.14, 3.15 and 3.16 show seropositivity results for comparison C at a threshold of 0.35µg/ml, assessed at about 6, 12 and 17 months of age, respectively.

Five RCTs (Fiji 7v, Gambia 7v, Israel 7v, Iceland 9v, Europe 10v) reported on this outcome at approximately 6 months of age. In addition, two studies reported data at around 12 months of age (Fiji 7v, Iceland 9v), and one study at 17 months of age (Fiji 7v).

At around 6 months of age, the proportion of children seropositive was generally high in both 3p and 2p groups. Differences varied between studies and serotypes but favoured the 3p groups in almost all cases. The largest differences (as well as marked heterogeneity) were seen for serotypes 6B and 23F. For the serotypes with the least between-trial heterogeneity (5 and 19F), differences were small and confidence intervals did not cross the

null. Gambia 7v favoured the 3-dose group more strongly for most serotypes. In this trial, the 3-dose group received PCV 1 month before antibody levels were measured while the 2-dose group received PCV 2 months before; in all other studies the interval between the last vaccine dose and antibody measurement was the same in both arms.

By 12 months of age (Fiji 7v, Iceland 9v), the proportions seropositive had dropped by varying degrees for all serotypes except 6B, where percentages had dropped slightly in Fiji 7v and increased slightly in Iceland 9v (data not shown). Percentages seropositive were around 60% or below for serotypes 4 (Iceland 9v), 9V (Iceland 9v), 18C (both studies) and 23F (both studies). By 17 months (Fiji 7v) the proportions seropositive had dropped further for all serotypes except 9V and 19F, which remained >90%. The prevalence differences between schedules were similar to the differences at 6 months of age.

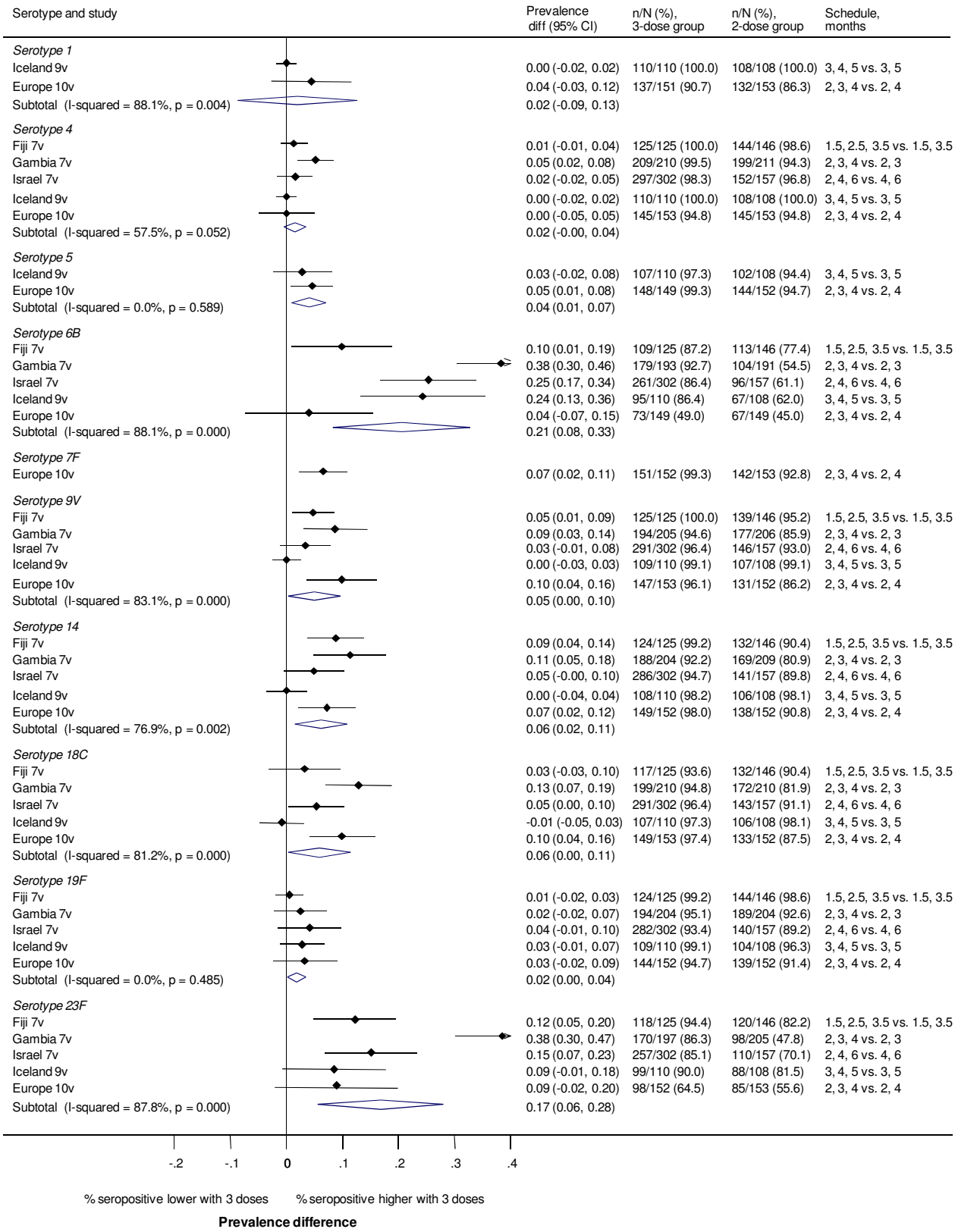
Seropositivity defined as antibody concentration ≥0.20µg/ml

One RCT (Europe 10v) reported on the proportions of children receiving 3p vs 2p schedules who were seropositive at a threshold of 0.20µg/ml at 6 and 11 months of age (Figures 3.17 and 3.18,.

At 6 months of age, the proportions of children seropositive were generally high in both 3p and 2p groups. Differences varied between serotypes but favoured the 3p groups in all cases. The lowest proportions of children seropositive and the largest differences between groups were seen for serotypes 6B and 23F.

At 11 months of age, the proportion seropositive to serotype 1 was lower (Figure 3.18). Increases in the proportions seropositive were seen for serotypes 6B and 23F. A small reduction in the proportion seropositive or no change was seen for the remainder of the serotypes, with changes often being more marked in the 2p group. Prevalence differences between groups increased for all serotypes except 23F.

Figure 3.14 Comparison C. 3p vs 2p schedules, seropositivity at ~6 months, ELISA threshold 0.35ug/ml, by serotype and study



Legend:

n/N – number seropositive/total in group; Prevalence diff – difference in seropositivity between groups shown as a proportion.

Horizontal axis represents the difference, expressed as a proportion between groups receiving schedules of 3 primary doses vs 2 primary doses. Vertical line through risk difference of 0 shows no difference in levels of seropositivity between groups. Solid black

diamonds represent point estimate of prevalence difference; horizontal black line represents 95% confidence interval. Open diamond represents the pooled estimate, combined using random effects meta-analysis; vertical points of diamond represent point estimate and horizontal points represent 95% confidence interval; I-squared value is the level of statistical heterogeneity between trials (<25% low heterogeneity).

b) Geometric mean antibody concentrations

Tables 3.7 shows GMC for groups receiving 3p vs 2p schedules for each serotype in up to four RCTs at around 6, 9, 12 and 17 months of age.

At 6 months, between-trial heterogeneity was high for all serotypes, but the groups receiving 3 primary doses tended to have higher GMC than groups receiving 2 primary doses for all studies and serotypes. Pooled GMC ratios were between 1.05 and 4.83 and 95% CI did not cross 1 except for serotypes 1 and 19F. At 12 months of age, data were available for Fiji 7v and Europe 10v trials and heterogeneity between these trials remained moderate to high. GMC values in both studies and comparison groups had dropped, but differences in GMC ratios tended to persist, with slightly lower pooled ratios than observed at 6 months of age. Results were available for one study at 17 months of age (Fiji 7v). Results were similar to those at 12 months in this RCT.

Table 3.7 Comparison C (3p vs 2p). Geometric mean antibody concentrations at ~6, ~9, ~12 and ~17 months, by serotype, study and time point

Age	Serotype	Study	GMC, µg/ml (95% CI)		Studies in meta-analysis, N[1]	Combined ratio of GMCs from meta-analysis (95% CI)	I^2, %
			3p	2p			
6 months	1	Iceland 9v	3.34 (2.93, 3.80)	3.62 (3.13, 4.19)	2	1.05 (0.82, 1.35)	70.1
		Europe 10v	1.23 (1.07, 1.42)	1.03 (0.90, 1.18)			
	4	Fiji 7v	5.47 (4.84, 6.19)	5.23 (4.46, 6.13)	4	1.32 (1.06, 1.65)	75.7
		Gambia 7v	4.16 (3.61, 4.79)	2.04 (1.54, 2.70)			
		Iceland 9v	2.97 (2.62, 3.38)	2.34 (2.01, 2.74)			
		Europe 10v	1.71 (1.47, 1.99)	1.37 (1.21, 1.55)			
	5	Iceland 9v	1.52 (1.33, 1.74)	1.20 (1.02, 1.41)	2	1.34 (1.16, 1.54)	0
		Europe 10v	1.85 (1.63, 2.10)	1.32 (1.14, 1.52)			
	6B	Fiji 7v	1.66 (1.33, 2.07)	0.86 (0.70, 1.07)	4	4.83 (1.45, 16.14)	97.6
		Gambia 7v	3.47 (2.41, 4.98)	0.05 (0.03, 0.08)			
		Iceland 9v	1.94 (1.48, 2.53)	0.69 (0.52, 0.90)			
		Europe 10v	0.31 (0.25, 0.38)	0.19 (0.15, 0.24)			
	7F	Europe 10v	2.14 (1.90, 2.40)	1.28 (1.13, 1.46)	1	1.67 (1.41, 1.99)	NA
	9V	Fiji 7v	4.76 (4.19, 5.40)	4.71 (3.88, 5.71)	4	1.47 (1.04, 2.07)	87.5
		Gambia 7v	1.77 (1.36, 2.29)	0.59 (0.41, 0.84)			
		Iceland 9v	1.99 (1.74, 2.27)	1.73 (1.47, 2.02)			
		Europe 10v	1.47 (1.29, 1.68)	0.92 (0.81, 1.05)			
	14	Fiji 7v	5.51 (4.50, 6.76)	3.12 (2.42, 4.03)	4	1.87 (1.34, 2.61)	75.3
		Gambia 7v	4.65 (3.21, 6.72)	1.03 (0.64, 1.65)			
		Iceland 9v	6.95 (5.82, 8.29)	4.69 (3.66, 6.02)			
		Europe 10v	2.57 (2.22, 2.97)	1.72 (1.45, 2.05)			
	18C	Fiji 7v	3.20 (2.66, 3.86)	2.67 (2.16, 3.31)	4	2.00 (1.16, 3.47)	93.8
		Gambia 7v	2.01 (1.53, 2.63)	0.44 (0.30, 0.66)			

		Iceland 9v	1.83 (1.60, 2.09)	1.52 (1.33, 1.75)			
		Europe 10v	3.42 (2.87, 4.07)	1.26 (1.06, 1.51)			
	19F	Fiji 7v	5.52 (4.79, 6.36)	7.99 (6.62, 9.64)	4	1.34 (0.82, 2.20)	91.6
		Gambia 7v	4.54 (3.37, 6.10)	2.16 (1.56, 2.99)			
		Iceland 9v	4.19 (3.62, 4.84)	3.20 (2.65, 3.87)			
		Europe 10v	4.43 (3.60, 5.45)	2.43 (1.97, 2.98)			
	23F	Fiji 7v	2.93 (2.39, 3.59)	1.65 (1.29, 2.11)	4	3.03 (1.31, 6.99)	95.1
		Gambia 7v	1.50 (1.04, 2.18)	0.07 (0.04, 0.11)			
		Iceland 9v	1.77 (1.36, 2.31)	0.91 (0.72, 1.14)			
		Europe 10v	0.52 (0.42, 0.63)	0.38 (0.30, 0.47)			
9 months	4	Fiji 7v	0.79 (0.55, 1.14)	0.86 (0.67, 1.12)	1	0.92 (0.59, 1.43)	NA
	6B	Fiji 7v	0.82 (0.58, 1.17)	0.81 (0.59, 1.12)	1	1.01 (0.63, 1.63)	NA
	9V	Fiji 7v	0.91 (0.71, 1.16)	1.00 (0.72, 1.38)	1	0.91 (0.62, 1.34)	NA
	14	Fiji 7v	3.99 (2.86, 5.57)	1.93 (1.20, 3.09)	1	2.07 (1.16, 3.69)	NA
	18C	Fiji 7v	0.49 (0.37, 0.65)	0.41 (0.33, 0.53)	1	1.20 (0.83, 1.73)	NA
	19F	Fiji 7v	1.04 (0.70, 1.54)	1.40 (1.05, 1.86)	1	0.74 (0.46, 1.21)	NA
	23F	Fiji 7v	0.65 (0.46, 0.94)	0.44 (0.33, 0.60)	1	1.48 (0.93, 2.35)	NA
12	1	Europe 10v	0.30 (0.26, 0.34)	0.21 (0.19, 0.24)	1	1.43 (1.20, 1.71)	NA
months	4	Fiji 7v	0.48 (0.41, 0.57)	0.47 (0.40, 0.54)	2	1.28 (0.83, 1.99)	88.9
		Europe 10v	0.64 (0.56, 0.73)	0.40 (0.35, 0.46)			
	5	Europe 10v	0.59 (0.51, 0.68)	0.43 (0.37, 0.50)	1	1.37 (1.11, 1.69)	NA
	6B	Fiji 7v	0.86 (0.72, 1.03)	0.76 (0.63, 0.92)	2	1.32 (0.96, 1.83)	63
		Europe 10v	0.44 (0.36, 0.54)	0.28 (0.23, 0.35)			
	7F	Europe 10v	0.92 (0.81, 1.05)	0.55 (0.49, 0.63)	1	1.67 (1.40, 2.00)	NA
	9V	Fiji 7v	0.59 (0.51, 0.67)	0.62 (0.54, 0.71)	2	1.26 (0.73, 2.20)	94.2
		Europe 10v	0.87 (0.77, 0.99)	0.52 (0.46, 0.60)			
	14	Fiji 7v	2.38 (1.98, 2.86)	1.52 (1.26, 1.84)	2	1.76 (1.40, 2.23)	35.8
		Europe 10v	1.53 (1.27, 1.85)	0.77 (0.64, 0.93)			
	18C	Fiji 7v	0.32 (0.27, 0.38)	0.24 (0.21, 0.28)	2	1.60 (1.11, 2.30)	80.2
		Europe 10v	1.14 (0.96, 1.35)	0.59 (0.50, 0.69)			
	19F	Fiji 7v	1.05 (0.83, 1.34)	1.14 (0.95, 1.36)	2	1.23 (0.70, 2.16)	87.6
		Europe 10v	1.70 (1.41, 2.04)	1.04 (0.87, 1.25)			
	23F	Fiji 7v	0.54 (0.44, 0.66)	0.42 (0.35, 0.50)	2	1.33 (1.09, 1.62)	0
		Europe 10v	0.44 (0.36, 0.54)	0.32 (0.26, 0.40)			
17	4	Fiji 7v	0.35 (0.29, 0.43)	0.43 (0.33, 0.56)	1	0.81 (0.59, 1.13)	NA
months	6B	Fiji 7v	0.91 (0.69, 1.21)	0.78 (0.58, 1.04)	1	1.17 (0.78, 1.75)	NA
	9V	Fiji 7v	0.41 (0.34, 0.49)	0.49 (0.39, 0.62)	1	0.84 (0.62, 1.12)	NA
	14	Fiji 7v	1.78 (1.42, 2.24)	1.12 (0.86, 1.46)	1	1.59 (1.12, 2.25)	NA
	18C	Fiji 7v	0.21 (0.18, 0.26)	0.20 (0.16, 0.25)	1	1.05 (0.79, 1.40)	NA
	19F	Fiji 7v	1.19 (0.84, 1.67)	1.06 (0.82, 1.38)	1	1.12 (0.73, 1.73)	NA
	23F	Fiji 7v	0.57 (0.43, 0.75)	0.43 (0.32, 0.58)	1	1.33 (0.88, 1.99)	NA

Legend:

I^2 value is the level of statistical heterogeneity between trials (<25% low heterogeneity); NA – not applicable.

1 Israel data not included in this analysis; prior to booster, 2 groups that received 3p cannot be combined for GMC data.

c) Opsonophagocytic antibody seropositivity defined as OPA titer ≥1:8

Figures 3.19, 3.20 and 3.21 show OPA seropositivity results assessed at around 6, 12 and 17 months of age, respectively. The patterns described for ELISA data at a threshold of 0.35µg/ml are mostly similar for OPA data. However, somewhat larger differences were seen in seropositivity assessed by OPA between the groups at around 6 months of age for serotype 6B.

3.5.3.3 Comparison G: 3p vs 2p+1 schedules

Summary

- *Only one RCT had compared 3p vs 2p+1 schedules.*
- *After the primary series, there were modest differences in seropositivity, favouring the 3p schedule.*
- *At 13 months, antibody concentrations were substantially higher in the 2p+1 group (1 month after the booster) than in the 3p group (7 months after the last primary dose), but these differences were smaller by 19 months.*
- *In trials that included similar 3p schedules and immunological assessments, point estimates of seropositivity at about 12 months were mostly >80%, but were around 50% for serotype 23F.*
- *If the incidence of IPD is highest in the first year of life, a 2p+1 schedule might not offer substantial protection compared to a 3p schedule in immune-competent children. If vaccine-induced herd immunity develops, this scenario might change over time.*

Only one RCT reported on this comparison (Israel 7v), with children enrolled from August 2005 to June 2006, before the introduction of PCV7 in Israel [21]. The trial compared 3 regimens: 3p+1, 3p, and 2p+1, with the 3p regimen given at 2, 4, and 6 months and the booster at 12 months. In all, 545 infants were randomized, with similar follow up rates. Antibody concentrations were measured at 2, 7, 13, and 19 months. GMC were presented graphically for all serotypes and time points. Seropositivity data were presented using thresholds of 0.35µg/ml and 1.0µg/ml after the primary series, and 1.0µg/ml and 5.0µg/ml after the booster dose.

At 7 months, 1 month after the last primary dose in each group, there were modest differences in seropositivity (5 to 22%) between the groups for serotypes 6B, 14, 18C, 19F and 23F, which favoured the 3p schedule. At 13 months, 1 month after the booster dose in the 2p+1 schedule and 7 months after the last dose in the 3p schedule, antibody concentrations for all serotypes had fallen back towards pre-vaccination levels in the 3p groups. In contrast, antibody concentrations were higher than at 7 months in the 2p+1 group (Table 3.8). There were no samples taken at 12 months in this study, so immunological responses immediately before the booster dose could not be compared between groups.

At 19 months, antibody concentrations in the two groups were more similar, again because of a steeper decline between 13 and 19 months in the 2p+1 than in the 3-dose group for all serotypes. There was statistical evidence of differences favouring the 2p+1 schedule for all serotypes at 19 months when GMCs were compared. This is likely to be a result of the booster dose, but it is unclear what implications this has for clinical disease.

Table 3.8 Comparison G (3p vs 2p+1). Geometric mean antibody concentrations at 13 and 19 months, by serotype

Age	Serotype	Study	GMC, µg/ml (95% CI)		Studies in meta-analysis, N	Combined ratio of GMCs from meta-analysis (95% CI)	I^2, %
			3p	2p+1			
13	4	Israel 7v	0.32 (0.28, 0.37)	4.78 (4.60, 5.50)	1	0.07 (0.06, 0.08)	NA
months	6B	Israel 7v	0.80 (0.65, 0.99)	6.93 (5.36, 8.95)	1	0.12 (0.08, 0.16)	NA
	9V	Israel 7v	0.48 (0.43, 0.54)	3.45 (3.05, 3.91)	1	0.14 (0.12, 0.16)	NA
	14	Israel 7v	1.37 (1.11, 1.69)	12.16 (10.39, 14.22)	1	0.11 (0.09, 0.15)	NA
	18C	Israel 7v	0.32 (0.28, 0.36)	2.80 (2.45, 3.20)	1	0.11 (0.10, 0.14)	NA
	19F	Israel 7v	0.55 (0.44, 0.67)	4.90 (4.08, 5.88)	1	0.11 (0.08, 0.15)	NA
	23F	Israel 7v	0.40 (0.33, 0.48)	3.87 (3.32, 4.52)	1	0.10 (0.08, 0.13)	NA
19	4	Israel 7v	0.14 (0.12, 0.17)	0.48 (0.40, 0.56)	1	0.29 (0.23, 0.37)	NA
months	6B	Israel 7v	0.76 (0.63, 0.93)	1.46 (1.22, 1.76)	1	0.52 (0.40, 0.68)	NA
	9V	Israel 7v	0.35 (0.30, 0.40)	0.55 (0.49, 0.62)	1	0.64 (0.53, 0.77)	NA
	14	Israel 7v	0.90 (0.71, 1.15)	2.00 (1.71, 2.35)	1	0.45 (0.34, 0.60)	NA
	18C	Israel 7v	0.20 (0.17, 0.23)	0.38 (0.33, 0.44)	1	0.53 (0.43, 0.65)	NA
	19F	Israel 7v	0.63 (0.49, 0.82)	1.45 (1.12, 1.87)	1	0.43 (0.30, 0.62)	NA
	23F	Israel 7v	0.29 (0.24, 0.34)	0.65 (0.55, 0.78)	1	0.45 (0.35, 0.57)	NA

Legend:

I^2 value is the level of statistical heterogeneity between trials (<25% low heterogeneity); NA – not applicable.

Description of RCTs reporting on either 3p or 2p+1 schedules

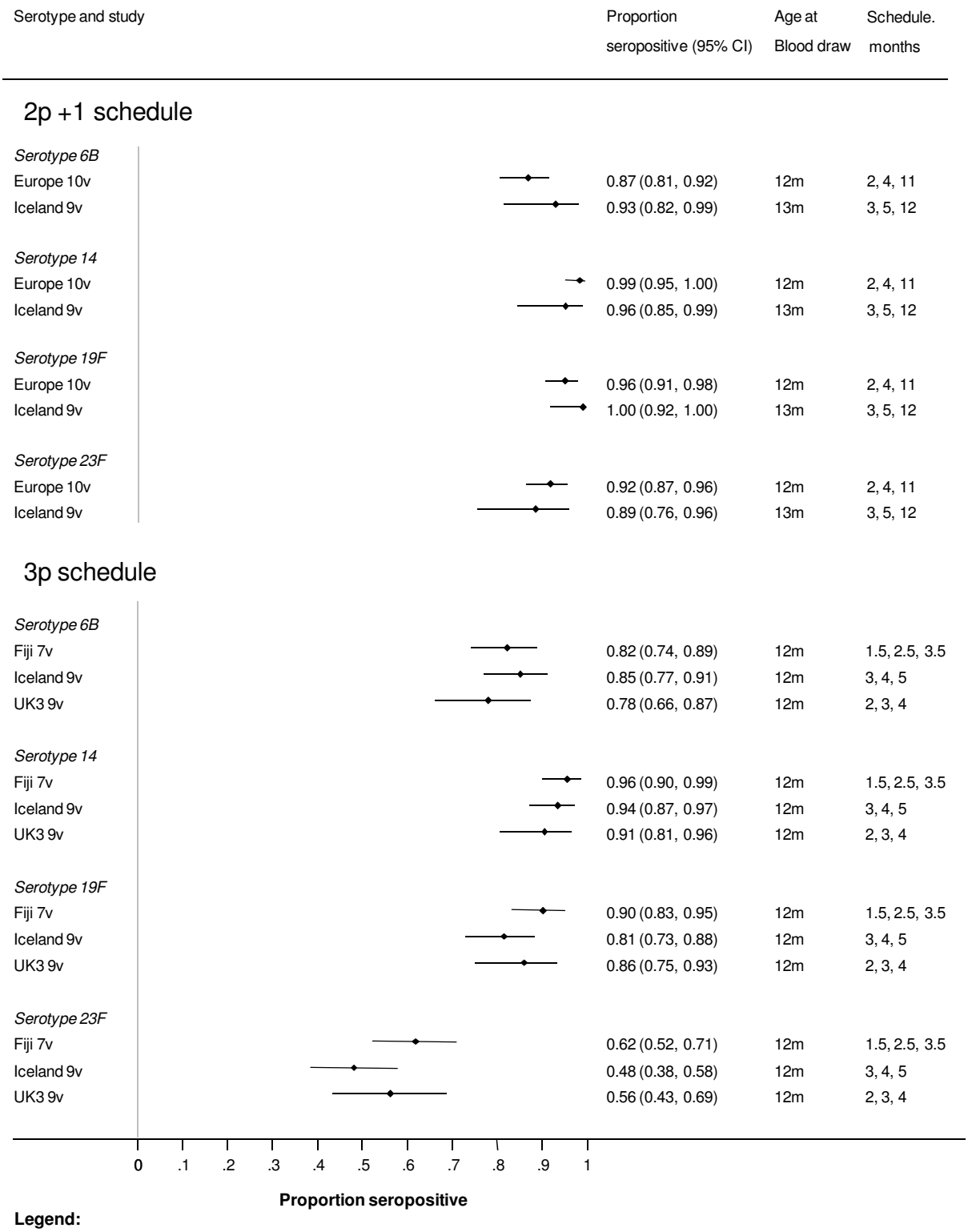
Eligibility criteria for RCTs described here are reported in the methods section (p11). Three additional RCTs reported seropositivity after 3 primary doses (Fiji 7v, Iceland 9v, UK3 9v). The children from the Iceland 9v trial were those receiving a 3p+PPV (12) or a 3p+1 schedule and who had samples taken before the booster dose. Two additional RCTs reported on a 2p+1 schedule (Europe 10v and Iceland 9v). Figure 3.22 shows the proportions seropositive at about 12 months of age (or 1 month after the booster dose if given at 12 months) for both schedules. The Israel 7v trial was not included in the forest plot because results using the 0.35µg/ml threshold after the booster dose were not reported.

At about 12 months of age, proportions of child seropositivity 1 month after receiving the booster dose in a 2p+1 schedule were close to 100% for serotypes 14 and 19F, and slightly lower for serotypes 6B and 23F. In children receiving a 3p schedule and assessed at about 12 months, point estimates for seropositivity for serotypes 14 and 19F ranged from 85 to 96%. For serotype 6B, seropositivity ranged from 78 to 89%, and for serotype 23F from 51 to 62%. The pattern of results for each schedule is consistent with the results of the Israel 7v trial, with somewhat higher seropositivity in children who had received a booster dose closer to the time of assessment.

The results suggest that the optimal schedule might depend on the age distribution of IPD, as well as serotype distribution. The age range over which individual protection occurs might vary with schedule. For example, a schedule with fewer primary doses but with a booster might afford

shorter or less robust protection in the first year of life, but potentially provide better protection in the second year of life than a schedule with more primary doses but no booster. When comparing the 2p+1 to a 3p schedule, antibody concentrations appear to decline markedly after the primary series. If the incidence of IPD is highest in the first year of life, a 2p+1 schedule might not offer substantial benefits over a 3p schedule, as increased antibody levels occur only after the booster dose and would be after the peak incidence of IPD. However, it is not well understood how measured antibody concentrations relate to direct protection against clinical disease, and whether a drop in antibody concentration after the primary course of vaccination corresponds to a drop in protection. Also, if indirect protection from disease develops through vaccine-induced herd immunity, differences between these schedules in terms of clinical disease in the population may change over time.

Figure 3.22 Comparison G (3p vs 2p+1). Absolute seropositivity at ~12 months, ELISA threshold 0.35ug/ml, by schedule, serotype and study



Legend:

Schedules reported as intended age in months for each dose.

Solid black diamonds represent point estimate of prevalence; horizontal black line represents 95% confidence interval.

3.5.3.4 Comparison L: 3p+1 vs 2p+1 schedules

Summary

- *3p+1 and 2p+1 schedules resulted in similar levels of seropositivity after the booster dose, with the exception of serotypes 23F and 6B (2 RCTs).*
- *GMC ratios generally favoured the 3p+1 schedule with the highest ratios being for 6B and 23F.*
- *The clinical relevance of the differences between schedules in these immunological outcomes is not known. If serotypes 6B or 23F are responsible for a high burden of clinical disease, then the observed differences should considered when choosing a PCV schedule.*

Three RCTs reported comparisons of 3p+1 and 2p+1 schedules and at least one immunological outcome (Israel 7v, Iceland 9v, and Europe 10v). The interval between primary doses was 2 months in all of the groups receiving the 2p+1 schedule. Iceland 9v and Europe 10v used 1-month intervals between primary doses in the 3p+1 groups and Israel 7v used 2-month intervals in the 3p+1 group. All groups in the three studies were assessed for antibody levels 1 month after the booster dose. Only the Israel 7v trial included follow-up data for more than 1 month after the last dose of vaccine.

a) Seropositivity

A threshold of 0.35µg/ml was reported for ELISA seropositivity in Iceland 9v and Europe 10v, and a threshold of 0.20µg/ml for Europe 10v only. Thresholds of 1µg/ml and 5µg/ml were reported in Israel 7v (data not shown).

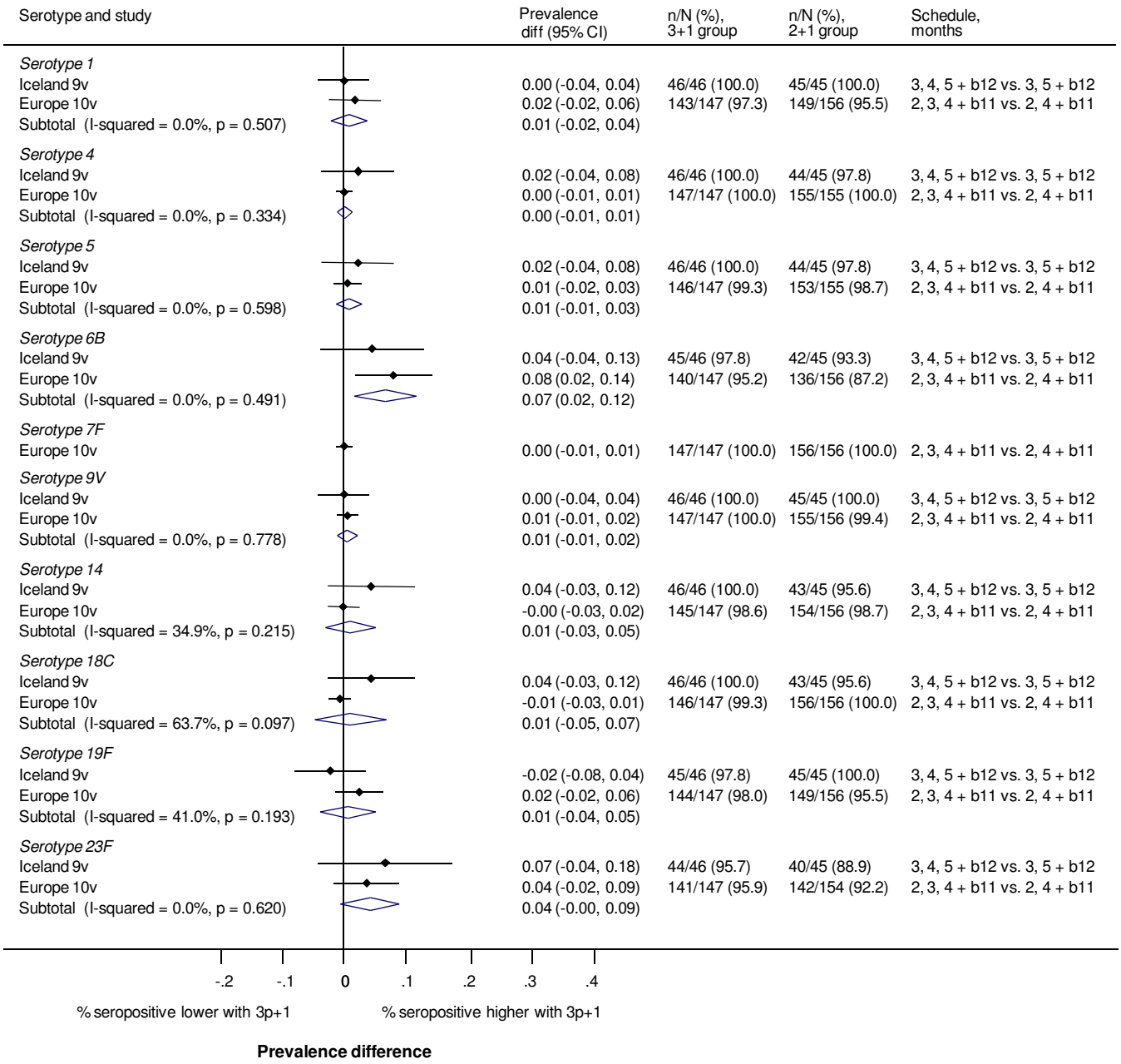
Seropositivity defined as antibody concentration ≥0.35µg/ml

Figure 3.23 shows proportions seropositive at a threshold of 0.35µg/ml assessed 1 month after the booster dose in two RCTs (Iceland 9v and Europe 10v). There was little between-trial heterogeneity (I^2 0% for all serotypes except 14, 18C and 19F). Point estimates for combined prevalence differences were 0–1% for all serotypes except for 6B (difference 7%) and 23F (difference 4%).

Seropositivity defined as antibody concentration ≥0.20µg/ml

Seropositivity at a cut point of 0.20µg/ml was reported in Europe 10v only, 1 month after the booster dose (Figure 3.24). Proportions seropositive were greater than 95% for both schedules for all serotypes except 6B (89% in the group receiving the 2p+1 schedule). Prevalence differences between groups were very similar to those at the 0.35µg/ml threshold.

Figure 3.23 Comparison L (3p+1 vs 2p+1). Seropositivity 1 month after the booster dose, ELISA threshold 0.35ug/ml, by serotype and study



Legend:

n/N – number seropositive/total in group; Prevalence diff – difference in seropositivity between groups shown as a proportion. Horizontal axis represents the difference, expressed as a proportion between groups receiving schedules of 3 primary doses and a booster vs 2 primary doses and a booster. Vertical line through risk difference of 0 shows no difference in levels of seropositivity between groups. Solid black diamonds represent point estimate of prevalence difference; horizontal black line represents 95% confidence interval. Open diamond represents the pooled estimate, combined using random effects meta-analysis; vertical points of diamond represent point estimate and horizontal points represent 95% confidence interval; I-squared value is the level of statistical heterogeneity between trials (<25% low heterogeneity).

Iceland data read from graphs using PlotDigitizer software. Due to resolution of graphs in the original publication, readings might be inaccurate.

b) Geometric mean antibody concentrations

GMC ratios in two RCTs (Iceland 9v and Europe 10v) were heterogeneous for serotypes 4, 9V and 19F 1 month after the booster dose (Table 3.9). Pooled GMC ratios for other serotypes ranged from 1.01 to 1.60, favouring the 3p+1 schedule. The highest ratios were seen for serotypes 6B

(1.60, 95% CI 1.30, 1.98) and 23F (1.34, 95% CI 1.14, 1.59). Confidence intervals for serotypes 6B, 7F, 14, 18C, and 23F did not include 1. One study reported GMC at 19 months of age (Israel 7v, 7 months after vaccination). GMC for all serotypes had dropped markedly in each group between 1 and 7 months after vaccination. GMC ratios comparing 2p+1 and 3p+1 schedules did not change substantially between these time points.

Table 3.9 Comparison L (3p+1 vs 2p+1). Geometric mean antibody concentrations at 1 and 7 months after booster dose, by serotype

Age	Serotype	Study	GMC, µg/ml (95% CI)		Studies in meta-analysis, N	Combined ratio of GMCs from meta-analysis (95% CI)	I^2, %
			3p+1	2p+1			
1 month after booster dose	1	Iceland 9v	4.48 (3.48, 5.78)	4.48 (3.56, 5.65)	2	1.01 (0.85, 1.21)	0
		Europe	1.88 (1.62, 2.17)	1.85 (1.59, 2.15)			
	4	Israel 7v	3.98 (3.40, 4.67)	4.78 (4.60, 5.50)	3	1.00 (0.80, 1.25)	66.1
		Iceland 9v	4.30 (3.43, 5.40)	3.87 (3.04, 4.92)			
		Europe	3.47 (3.03, 3.98)	3.06 (2.68, 3.49)			
	5	Iceland 9v	3.18 (2.60, 3.90)	3.28 (2.65, 4.04)	2	1.12 (0.90, 1.38)	36.1
		Europe	3.21 (2.81, 3.67)	2.65 (2.31, 3.03)			
	6B	Israel 7v	10.99 (8.78, 13.77)	6.93 (5.36, 8.95)	3	1.60 (1.30, 1.98)	0
		Iceland 9v	14.01 (9.41, 20.86)	9.42 (6.34, 14.00)			
		Europe	1.85 (1.54, 2.22)	1.12 (0.88, 1.41)			
	7F	Europe	3.88 (3.45, 4.37)	2.81 (2.51, 3.15)	1	1.38 (1.17, 1.63)	NA
	9V	Israel 7v	3.49 (3.03, 4.01)	3.45 (3.05, 3.91)	3	1.14 (0.94, 1.39)	59
		Iceland 9v	2.55 (2.06, 3.16)	2.39 (1.94, 2.95)			
		Europe	3.97 (3.49, 4.50)	2.95 (2.59, 3.37)			
	14	Israel 7v	12.92 (10.96, 15.22)	12.16 (10.39,	3	1.18 (1.02, 1.36)	0
		Iceland 9v	10.15 (8.20, 12.55)	8.75 (6.37, 12.02)			
		Europe	5.47 (4.68, 6.40)	4.19 (3.62, 4.85)			
	18C	Israel 7v	3.70 (3.17, 4.30)	2.80 (2.45, 3.20)	3	1.26 (1.10, 1.44)	0
		Iceland 9v	2.37 (1.92, 2.92)	1.79 (1.43, 2.24)			
		Europe	7.20 (6.08, 8.52)	6.24 (5.43, 7.18)			
	19F	Israel 7v	4.07 (3.37, 4.91)	4.90 (4.08, 5.88)	3	1.10 (0.82, 1.47)	68.3
		Iceland 9v	4.48 (3.38, 5.93)	3.38 (2.98, 4.93)			
		Europe	6.95 (5.92, 8.17)	5.58 (4.65, 6.69)			
	23F	Israel 7v	5.64 (4.72, 6.72)	3.87 (3.32, 4.52)	3	1.34 (1.14, 1.59)	0.6
		Iceland 9v	4.42 (3.23, 6.06)	2.83 (1.90, 4.23)			
		Europe	2.78 (2.31, 3.35)	2.41 (1.98, 2.94)			
7 after booster dose	4	Israel 7v	0.42 (0.35, 0.50)	0.48 (0.40, 0.56)	1	0.88 (0.68, 1.12)	NA
	6B	Israel 7v	1.97 (1.65, 2.36)	1.46 (1.22, 1.76)	1	1.35 (1.04, 1.74)	NA
	9V	Israel 7v	0.67 (0.58, 0.77)	0.55 (0.49, 0.62)	1	1.22 (1.01, 1.46)	NA
	14	Israel 7v	2.38 (2.00, 2.83)	2.00 (1.71, 2.35)	1	1.19 (0.94, 1.51)	NA
	18C	Israel 7v	0.49 (0.42, 0.57)	0.38 (0.33, 0.44)	1	1.29 (1.05, 1.59)	NA
	19F	Israel 7v	1.00 (0.80, 1.25)	1.45 (1.12, 1.87)	1	0.69 (0.49, 0.97)	NA
	23F	Israel 7v	0.88 (0.73, 1.06)	0.65 (0.55, 0.78)	1	1.35 (1.05, 1.75)	NA

c) Opsonophagocytic antibody seropositivity defined as OPA titre ≥1:8

Figure 3.25 shows OPA seropositivity results assessed at 1 month after the booster dose.

The patterns described for ELISA data at a threshold of 0.35µg/ml were mostly consistent with the results of OPA, except for serotype 5.

Also, the proportions OPA seropositive were generally slightly lower in both groups than for ELISA using the 0.35µg/ml threshold.

3.5.3.5 Comparison M: 3p+1 vs 3p schedules

Summary

- *At 13 months of age, antibody concentrations were substantially higher in the 3p+1 group (1 month after the booster dose) than in the 3p group (7 months after the last primary dose, 2 RCTs), but these differences were smaller by 19 months (1 RCT).*
- *If the incidence of IPD is highest in the second year of life, a 3p+1 schedule might offer more individual protection than a 3p schedule in immune-competent children. If vaccine-induced herd immunity develops, this scenario might change over time.*

Two trials reported this outcome (Israel 7v and Ghana infants 9v). In both studies, blood samples were taken at 13 months of age, 1 month after the 3p+1 group received their booster dose and 7 months after the 3p group received their last primary dose. In Israel 7v, a further blood sample was taken at 19 months of age. Neither study reported seropositivity using the 0.35µg/ml or the 0.20µg/ml cut point. They also did not report OPA outcomes.

a) Geometric mean antibody concentrations

Despite the differences in the populations between the two RCTs (Ghana infants 9v enrolled only children with sickle-cell disease), there was little heterogeneity between study results at 13 months of age. The group that received a booster dose had a GMC for each serotype 5–14 times higher than that in the group without a booster. By 19 months of age, the GMC for each serotype had dropped markedly in the 3p+1 group for all serotypes, and slightly in the 3p group for most serotypes. Ratios of GMC were therefore closer to 1 at 19 months of age than at 13 months of age.

When comparing the 3p+1 to a 3p schedule, antibody concentrations appear to decline markedly after the primary series. If the incidence of IPD is highest in the second year of life, a 3p+1 schedule might offer benefits over a 3p schedule. However, it is not well understood how measured antibody concentrations relate to direct protection from clinical disease, and whether a drop in antibody concentration after the primary course of vaccination corresponds to a drop in protection. Also, if indirect protection from disease develops through vaccine-induced herd immunity, differences between these schedules in terms of clinical disease in the population may change over time.

Table 3.10 Comparison L (3p+1 vs 3p). Geometric mean antibody concentrations at 13 and 19 months of age, by serotype

Age	Serotype	Study	GMC, µg/ml (95% CI)		Studies in meta-analysis, N	Combined ratio of GMCs from meta-analysis (95% CI)	I^2, %
			3p+1	3p			
13 months	1	Ghana infants 9v	4.98 (1.63, 15.20)	0.69 (0.32, 1.50)	1	7.22 (1.86, 28.05)	NA
	4	Israel 7v	3.98 (3.40, 4.67)	0.32 (0.28, 0.37)	2	12.70 (10.32, 15.62)	0
		Ghana infants 9v	8.61 (4.59, 16.17)	0.40 (0.17, 0.96)			
	5	Ghana infants 9v	4.64 (1.32, 16.31)	0.86 (0.36, 2.03)	1	5.40 (1.17, 24.81)	NA
	6B	Israel 7v	10.99 (8.78, 13.77)	0.80 (0.65, 0.99)	2	13.32 (9.86, 18.00)	0
		Ghana infants 9v	9.23 (2.83, 30.03)	1.35 (0.60, 3.06)			
	9V	Israel 7v	3.49 (3.03, 4.01)	0.48 (0.43, 0.54)	2	7.25 (6.06, 8.67)	0
		Ghana infants 9v	3.51 (1.23, 10.06)	0.57 (0.23, 1.39)			
	14	Israel 7v	12.92 (10.96, 15.22)	1.37 (1.11, 1.69)	2	8.10 (4.24, 15.48)	30.2
		Ghana infants 9v	8.15 (2.14, 31.12)	2.06 (1.38, 3.07)			
	18C	Israel 7v	3.70 (3.17, 4.30)	0.32 (0.28, 0.36)	2	11.50 (9.45, 13.98)	0
		Ghana infants 9v	5.17 (1.73, 15.48)	0.61 (0.24, 1.60)			
	19F	Israel 7v	4.07 (3.37, 4.91)	0.55 (0.44, 0.67)	2	7.35 (5.56, 9.74)	0
		Ghana infants 9v	1.91 (0.23, 15.86)	0.43 (0.10, 1.75)			
	23F	Israel 7v	5.64 (4.72, 6.72)	0.40 (0.33, 0.48)	2	14.13 (10.95, 18.22)	0
		Ghana infants 9v	6.56 (2.78, 15.49)	0.43 (0.10, 1.75)			
19	4	Israel 7v	0.42 (0.35, 0.50)	0.14 (0.12, 0.17)	1	3.00 (2.34, 3.85)	NA
months	6B	Israel 7v	1.97 (1.65, 2.36)	0.76 (0.63, 0.93)	1	2.59 (1.99, 3.38)	NA
	9V	Israel 7v	0.67 (0.58, 0.77)	0.35 (0.30, 0.40)	1	1.91 (1.56, 2.34)	NA
	14	Israel 7v	2.38 (2.00, 2.83)	0.90 (0.71, 1.15)	1	2.64 (1.96,	NA

					3.56)	
18C	Israel 7v	0.49 (0.42, 0.57)	0.20 (0.17, 0.23)	1	2.45 (1.98, 3.04)	NA
19F	Israel 7v	1.00 (0.80, 1.25)	0.63 (0.49, 0.82)	1	1.59 (1.13, 2.23)	NA
23F	Israel 7v	0.88 (0.73, 1.06)	0.29 (0.24, 0.34)	1	3.03 (2.35, 3.92)	NA

3.5.3.6 Comparison O: Later vs earlier age at start of primary schedule

Summary

- *Immunological data were reported in four RCTs with very heterogeneous results.*
- *Differences in ages between comparison groups at the start of the primary series varied from 2 weeks to 3 months. There were also differences in intervals between the last dose of PCV and immunological assessment, both between comparison groups and between RCTs.*

Four studies reported a late vs early start comparison as well as at least one immunological outcome (UK1 7v, USA3 7v, Canada1 7v primary, Germany 7v). However, Germany 7v reported only GMCs and no confidence intervals, so data from this study could not be included in any analyses.

Both the schedules compared, as well as the outcomes reported, varied greatly between trials with this comparison. The difference in ages between comparison groups at the start of their primary series varied from 2 weeks (USA3 7v) to 3 months (UK1 7v).

a) Seropositivity

None of these studies reported ELISA seropositivity for antibody concentration thresholds of 0.35µg/ml or 0.20µg/ml.

b) Geometric mean antibody concentrations

All studies reported GMCs, but at different ages and at different times since the last dose of vaccine. The analysis of GMC (Table 3.11) was therefore conducted separately for (a) studies where samples were taken 1 month after the last dose in all groups (at 8 and 7 months of age respectively in the late and early groups of Canada1 7v); (b) studies where samples were taken at 7 months of age (2 weeks and 1 month after the last dose respectively in the late and early groups of USA3 7v); and (c) studies where samples were taken at 13 months of age (6 months and 9 months after the last dose respectively in the late and early groups of UK1 7v).

In Canada1 7v, where all samples were taken 1 month after the last dose, confidence intervals for the ratio of GMC crossed 1 for all serotypes except 6B and 23F. A later start was favoured for serotypes 6B, 18C, 19F and 23F and an early start for the remaining serotypes.

In USA3 7v, the late start group had blood drawn 2 weeks after the last dose of PCV and consistently had lower GMCs than the early group. The latter group had a 1-month interval between the last vaccination and blood draw.

In UK1 7v, there was a 6-month interval between the last dose and blood draw in the late start group, and a 9-month interval in the early start group. The late start group had consistently higher GMCs than the early start group.

Future studies comparing late and early start schedules would benefit from assessing immunogenicity at the same interval since last dose in both groups as well as at the same age (i.e. drawing blood at 2 different time points in 1 of the groups).

Table 3.11 Comparison O (Late start vs early start). Geometric mean antibody concentrations after vaccination, by serotype

Age	Serotype	Study	GMC, µg/ml (95% CI)		Studies in meta-analysis, N	Combined ratio of GMCs from meta-analysis (95% CI)	I^2, %
			Late start	Early start			
1 month post-	4	Canada1 7v, primary	3.51 (3.06, 4.02)	3.84 (3.33, 4.42)	1	0.91 (0.75, 1.11)	NA
PCV	6B	Canada1 7v, primary	5.39 (4.25, 6.85)	3.35 (2.56, 4.40)	1	1.61 (1.12, 2.31)	NA
	9V	Canada1 7v, primary	2.02 (1.75, 2.33)	2.07 (1.76, 2.43)	1	0.98 (0.79, 1.21)	NA
	14	Canada1 7v, primary	5.84 (4.92, 6.94)	6.37 (5.26, 7.71)	1	0.92 (0.71, 1.19)	NA
	18C	Canada1 7v, primary	3.75 (3.22, 4.36)	3.01 (2.50, 3.64)	1	1.25 (0.98, 1.59)	NA
	19F	Canada1 7v, primary	3.52 (2.95, 4.21)	3.30 (2.78, 3.92)	1	1.07 (0.83, 1.37)	NA
	23F	Canada1 7v, primary	2.50 (2.01, 3.11)	1.83 (1.48, 2.27)	1	1.37 (1.01, 1.85)	NA
7 months	4	USA3 7v	1.62 (1.44, 1.83)	2.07 (1.81, 2.37)	1	0.78 (0.65, 0.94)	NA
of age	6B	USA3 7v	0.59 (0.49, 0.72)	0.67 (0.52, 0.87)	1	0.88 (0.64, 1.21)	NA
	9V	USA3 7v	1.11 (0.97, 1.28)	1.60 (1.39, 1.85)	1	0.69 (0.57, 0.85)	NA
	14	USA3 7v	4.51 (3.91, 5.19)	6.32 (5.39, 7.41)	1	0.71 (0.58, 0.88)	NA
	18C	USA3 7v	2.37 (2.06, 2.72)	2.96 (2.53, 3.47)	1	0.80 (0.65, 0.99)	NA
	19F	USA3 7v	0.75 (0.66, 0.86)	1.05 (0.91, 1.22)	1	0.71 (0.59, 0.87)	NA
	23F	USA3 7v	1.29 (1.09, 1.53)	1.81 (1.45, 2.25)	1	0.71 (0.54, 0.94)	NA
13	4	UK1 7v*	0.70 (0.60, 0.88)	0.27 (0.23, 0.31)	1	2.59 (2.03, 3.31)	NA
months	6B	UK1 7v*	1.53 (1.27, 1.84)	0.96 (0.78, 1.24)	1	1.59 (1.18, 2.14)	NA
of age	9V	UK1 7v*	0.66 (0.57, 0.77)	0.33 (0.28, 0.39)	1	2.00 (1.60, 2.50)	NA
	14	UK1 7v*	2.68 (2.29, 3.13)	1.02 (0.79, 1.31)	1	2.63 (1.95,	NA

					3.54)	
18C	UK1 7v*	0.66 (0.56, 0.78)	0.29 (0.24, 0.34)	1	2.28 (1.79, 2.89)	NA
19F	UK1 7v*	0.90 (0.72, 1.12)	0.63 (0.48, 0.82)	1	1.43 (1.01, 2.02)	NA
23F	UK1 7v*	0.54 (0.44, 0.68)	0.27 (0.22, 0.34)	1	2.00 (1.47, 2.72)	NA

Legend:

*Data tables in UK1 7v reports were of low resolution and may have led to small errors in extraction.

3.5.3.7 Comparison P: 2-month vs 1-month interval schedules

Summary

- *No immunological data from RCTs were available for this comparison.*

3.5.3.8 Comparison Q: Longer vs shorter interval between primary and booster

Summary

- *Immunological data were reported in two RCTs. The differences between schedules in the age at which the booster dose was given were 3 months in one RCT and 2 months in the other.*
- *Antibody concentrations were slightly higher for groups receiving a later booster but confidence intervals crossed 1 for all but 2 serotypes.*

Two studies compared a late booster to an early booster (Canada1 7v booster, Finland 10v). The age at which the booster dose was given differed by 3 months in Canada1 7v and 2 months in Finland 10v. The last dose to blood draw interval was consistent within studies.

a) Seropositivity

Neither study reported ELISA seropositivity for the threshold of 0.35µg/ml, and only one reported seropositivity for a threshold of 0.20µg/ml (Finland 10v).

Seropositivity defined as antibody concentration ≥0.35µg/ml

No studies reported this outcome.

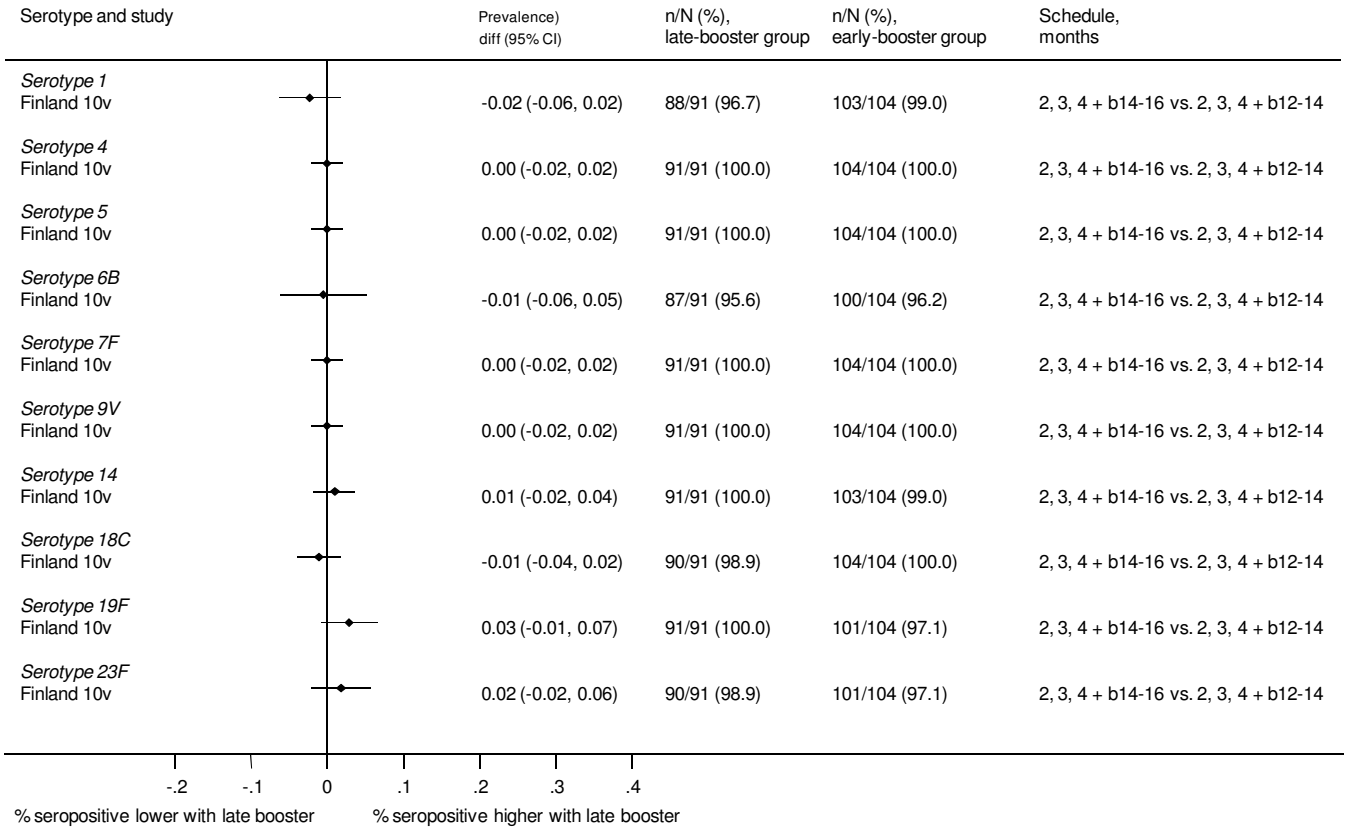
Seropositivity defined as antibody concentration ≥0.20µg/ml

One study reported this outcome (Finland 10v). Figure 3.26 shows seropositivity results at a threshold of 0.20µg/ml assessed at 1.5 months after the booster dose. Proportions of child seropositivity were very high at this threshold (95.6 to 100%), and prevalence differences were small.

b) Geometric mean antibody concentrations

GMC ratios showed little heterogeneity except for serotype 18C (Table 3.12). Late booster dose groups tended to have higher GMCs than early booster groups, but confidence intervals crossed 1 for all but 2 serotypes (4 and 23F).

Figure 3.26 Comparison Q (Longer vs shorter interval between primary and booster). Seropositivity at 1.5 months after the booster dose, ELISA threshold



0.20ug/ml, by serotype and study

Legend:

n/N – number seropositive/total in group; Prevalence diff – difference in seropositivity between groups shown as a proportion.

Horizontal axis represents the difference, expressed as a proportion between groups receiving schedules of 3 primary doses vs 2 primary doses. Vertical line through risk difference of 0 shows no difference in levels of seropositivity between groups. Solid black diamonds represent point estimate of prevalence difference; horizontal black line represents 95% confidence interval. Open diamond represents the pooled estimate, combined using random effects meta-analysis; vertical points of diamond represent point estimate and horizontal points represent 95% confidence interval; I-squared value is the level of statistical heterogeneity between trials (<25% low heterogeneity).

Table 3.12 Comparison Q (Longer vs shorter interval between primary and booster). Geometric mean antibody concentrations 1 month after booster dose, by serotype

Serotype	Study	GMC, µg/ml (95% CI)		Studies in meta-analysis, N	Combined ratio of GMCs from meta-analysis (95%CI)	I^2, %
		Longer interval	Shorter interval			
1	Finland 10v	1.24 (1.04, 1.49)	1.11 (0.96, 1.28)	1	1.12 (0.89, 1.41)	NA
4	Canada1 7v, booster	5.39 (4.62, 6.30)	4.42 (3.77, 5.18)	2	1.21 (1.04, 1.41)	0
	Finland 10v	2.54 (2.16, 2.98)	2.11 (1.83, 2.42)			
5	Finland 10v	1.93 (1.61, 2.32)	1.61 (1.36, 1.89)	1	1.20 (0.94, 1.53)	NA
6B	Canada1 7v, booster	12.26 (10.17, 14.79)	11.10 (9.16, 13.45)	2	1.12 (0.92, 1.37)	0
	Finland 10v	1.63 (1.31, 2.01)	1.42 (1.17, 1.73)			
7F	Finland 10v	2.93 (2.55, 3.36)	2.94 (2.62, 3.30)	1	1.00 (0.83, 1.19)	NA
9V	Canada1 7v, booster	3.49 (3.04, 4.01)	3.16 (2.78, 3.60)	2	1.11 (0.96, 1.28)	0
	Finland 10v	2.60 (2.21, 3.06)	2.33 (2.05, 2.65)			
14	Canada1 7v, booster	11.12 (9.67, 12.79)	11.22 (9.89, 12.74)	2	1.00 (0.86, 1.16)	0
	Finland 10v	4.19 (3.50, 5.01)	4.18 (3.53, 4.97)			
18C	Canada1 7v, booster	2.33 (2.00, 2.72)	2.28 (1.97, 2.63)	2	0.82 (0.54, 1.26)	87.6
	Finland 10v	2.74 (2.30, 3.26)	4.14 (3.66, 4.68)			
19F	Canada1 7v, booster	5.04 (4.36, 5.82)	4.38 (3.79, 5.08)	2	1.06 (0.86, 1.30)	30.7
	Finland 10v	3.94 (3.33, 4.67)	4.23 (3.40, 5.27)			
23F	Canada1 7v, booster	5.74 (4.81, 6.85)	4.81 (3.95, 5.86)	2	1.31 (1.08, 1.58)	0
	Finland 10v	2.41 (2.03, 2.85)	1.68 (1.36, 2.08)			

3.5.3.9 Other comparisons

Summary

Other comparisons examined differences between schedules containing PPV or PCV boosters, or with catch-up doses. Most involved only one trial and did not show marked differences between groups.

3.6 Discussion

The review identified 16 RCTs that compared different PCV schedules and reported at least one immunological outcome. These trials included 4193 children in eligible comparison groups. One trial did not have sufficient data to be included in any statistical analysis (Germany 7v). Among the remaining included trials, there were 18 types of schedule vs schedule comparisons and more than 30 different PCV schedules. Five studies (1498 children) were conducted in developing countries (Chile, Fiji, the Gambia and Ghana).

All studies included in the analyses of immunological outcomes reported GMC, 12 reported seropositivity and 4 reported OPA. Studies that reported seropositivity used a range of ELISA antibody concentration thresholds, which limited the comparisons that could be made between RCTs.

3.6.1 Strengths and limitations

The main strengths of this review were the wide and comprehensive search strategy and rigorous methods for selecting studies and extracting data. Inclusion criteria that specify the design features of studies, interventions and comparison groups in advance make it more likely that comparable studies can be examined.

A further strength of this review is the collation of data for multiple immunological outcomes at all time points after vaccination for which data were available. This means that key data are unlikely to have been missed and it was possible to assess whether findings synthesized from different RCTs or outcomes, for example seropositivity levels and GMCs, were compatible with each other.

A limitation of the data available for this review is that there were insufficient trials to allow a formal examination of the potential causes of between-trial heterogeneity in results using tools such as meta-regression. Potential reasons for heterogeneity, such as interval between last dose and blood sampling, have been suggested. Statistical analyses of the available data, however, would lack the power to show associations between these factors and trial results.

Inconsistent quality in reporting of data in RCT reports is a major limitation to the systematic synthesis of evidence in this review. The CONSORT statement, first published in 1996 and updated in 2010 [25, 26], aims to improve the transparency of reporting of RCTs. Several journals publish RCTs of vaccination that do not endorse the CONSORT statement, such as the Pediatric Infectious Diseases Journal and Clinical Infectious Diseases. Specific items required for the appraisal and synthesis of RCTs were often omitted from published reports. For example, procedures for randomization sequence generation, allocation concealment and implementation were often not reported in adequate detail to assess the risk of bias. Furthermore, meta-analysis cannot be done without an estimate of the precision of the effect measure [27]. However, denominator data and/or confidence intervals that were needed to estimate standard errors were often not reported.

Whilst meta-analysis of seropositivity data can be done to provide a variety of effect estimates, including prevalence differences, risk ratios or odds ratios, the statistical synthesis of GMC data presents challenges. The standard error, which is used for weighting in meta-analysis, is based on the log GMC. Meta-analysis is therefore performed on data on the log scale, usually using a mean difference as the measure of effect. Back-transformation to the original scale returns the ratio of the GMCs. It was therefore not possible to provide the same type of effect estimate for analyses of seropositivity and GMC data. In this review, meta-analyses on GMC data were done using both mean differences and standardized mean differences, with similar results.

An additional issue for GMC data is that comparisons of GMCs following different vaccination schedules can be difficult to interpret when GMC values are well above a particular threshold antibody concentration level.

3.6.2 Main findings and interpretation

Some differences were found in immunological outcomes following vaccination with different PCV schedules. Schedules with a higher number of primary doses tended to result in higher levels of seropositivity for all analysed serotypes shortly after completing the primary schedule. Differences favouring the schedule with more doses were more marked for serotypes 6B and 23F in most of these comparisons.

There were high levels of between-trial heterogeneity for many comparisons, but these did not alter the main findings. One source of heterogeneity resulting from study design was when the time between last vaccine dose and antibody measurement differed between groups. For example, in the analysis of 3p vs 2p schedules at around 6 months of age, the Gambia 7v RCT had a 2-month interval after the last primary dose in the 2p group and a 1-month interval for the 3p group. The larger differences favouring the 3p schedule for most serotypes in this, rather than in the other four RCTs, suggest that these results were more likely to be due to the difference in sampling interval than to differences in immunological responses to the two schedules [7].

3p and 2p schedules both resulted in high levels of seropositivity for most serotypes. Differences between groups were generally small and mostly favoured the 3p schedule at 6 and 12 months (5 RCTs). These differences were usually less than 10%, except for serotypes 6B and 23F. The proportions seropositive in both groups declined over time for most serotypes in the trials that examined this outcome at 12 (2 RCT) and 18 (1 RCT) months of age.

Differences in seropositivity between groups receiving 3p or 2p schedules were somewhat smaller after a booster dose of PCV. Both 3p+1 and 2p+1 schedules resulted in high levels of seropositivity for most serotypes (2 RCTs).

The comparison between 3p and 2p+1 schedules is of interest given that, in 2011, similar numbers of countries reported using each schedule [28]. Only one RCT was identified that directly compared these schedules. It is difficult to interpret differences in immunological outcomes between these schedules, partly because the agreed antibody concentration threshold levels only relate to assessments after the primary course [2], and partly because of different intervals between the last dose received and immunological assessment in the 2 groups. Both schedules contain a total of 3 doses but the timing of the third dose might be important. If the rapid fall in antibody concentrations after the primary series corresponds to a reduction in protection against clinical disease, a booster dose might be more important. Additionally, if indirect protection from disease develops through vaccine-induced herd immunity, the need for a booster dose might change over time. The impact of herd immunity could be explored through infectious disease modeling.

Immunogenicity studies of PCV should provide a link between measured immune responses and vaccine efficacy against clinical disease. The clinical relevance of differences in immunological outcomes observed between groups in this review is not known, for example in the comparison between 3p and 2p schedules (5 RCTs). Seropositivity was defined using a threshold of 0.35µg/ml as an acceptable antibody concentration for all serotypes at all time points [1, 2]. WHO has determined serological criteria for licensure purposes, based on data from 3 RCTs of PCV7 [3-5] and using a standardized ELISA [2]. It is acknowledged that the threshold of 0.35µg/ml was established only for assessments made after a 3-dose primary series [2]. The levels of antibodies that provide protection against clinical disease are not known and might differ between serotypes [29], for different clinical outcomes [30] and in different populations. In addition, there is no known immune correlate of protection against pneumococcal disease for 3 serotypes in extended valency PCVs.

The immunological data contained in this review relate primarily to healthy populations. Only trials conducted in Ghana related to high-risk populations, specifically children with sickle-cell disease. In contrast to clinical data, there are no immunological data from HIV-infected populations. There was some variation in the populations assessed for immunological outcomes because RCTs conducted in both developed and developing countries were included.

3.6.3 Implications for future research

The timing of vaccination and immunological assessments should be taken into consideration in the design of RCTs comparing different vaccination schedules. The design should allow comparisons between

schedules with the same interval between the last vaccination and the assessment, as well as comparisons when children are the same age.

Longer term follow up of immunological responses to PCV would be useful, in conjunction with clinical and epidemiological data about patterns of pneumococcal disease.

3.7 Conclusions

This comprehensive systematic review of RCTs of PCV vaccination schedules found some evidence that schedules containing 2 or 3 doses in the primary series provide better seropositivity and GMC outcomes than schedules with only 1 dose in the primary series. Differences between other schedules were less marked. The interpretation of differences in immunological outcomes was limited because of uncertainty about their clinical relevance. Optimal schedules are likely to depend on local epidemiology of pneumococcal disease as well as health service delivery of other vaccinations in the National Immunization Programme.

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Section 4. Pneumococcal conjugate vaccines

A review of cohort and case–control studies comparing childhood schedules or estimating vaccine effectiveness of 7-, 9-, 10- and 13-valent vaccines

4.1 Overview

4.1.1 Objectives

The objectives of this study were to perform a systematic review of evidence about pneumococcal conjugate vaccines (PCV) from all available sources, to summarize the data available and to identify gaps in evidence. This section of the report presents the results of cohort and case–control studies comparing childhood schedules of vaccination with PCV, or estimating vaccine effectiveness in these schedules.

4.1.2 Review methods

A search was carried out in 12 electronic databases of published articles, trial registers, industry databases and other documents from the earliest citation until August 2009. The search was updated in March 2010.

Items were selected that reported cohort or case–control studies in children aged up to 18 years. The intervention was any vaccination schedule using 7-, 9-, 10- or 13-valent PCV.

Comparisons could be between schedules with different ages at the start of vaccination; different intervals between doses; different number of doses; or any PCV schedule compared with no PCV.

All available data on the following criteria were extracted: schedule, clinical outcomes (invasive pneumococcal disease (IPD); pneumonia; otitis media; mortality); nasopharyngeal carriage of pneumococci; serotype specific seropositivity (%); geometric mean concentrations (GMC); study characteristics; and potential sources of bias and heterogeneity.

Data were summarized descriptively and graphically.

4.1.3 Results

Of the total 3217 eligible items found in the searches, 18 eligible cohort studies and two eligible case–control studies were identified. Fifteen different comparisons of schedules (or schedule vs no PCV) were examined in the cohort studies and 11 in the case–control studies.

4.1.3.1 Direct comparison between PCV schedules

3p vs 2p schedules

- The matched, adjusted odds ratio for vaccine serotype IPD was 1.5 (95% CI 0.54–4.35) with the 2p group as baseline (1 case–control study).
- One month after vaccination, seropositivity was broadly similar between groups. Lowest levels of seropositivity were achieved for serotype 6B (1 cohort study).
- Eight months after vaccination, seropositivity levels were generally lower than at one month post-vaccination in both groups. The lowest levels were seen for serotypes 18C, 4, 9V and 23F. The 3p group tended to have slightly higher levels of seropositivity for most serotypes (1 cohort study).
- Potential biases in the case–control study include issues of control selection common to case–control studies. Confounding could also be present.
- Potential bias in the cohort study could result from comparison groups being in different locations and being recruited in different years. Other biases and confounding could also be present.

3p vs 2p+1 schedules

- The matched, adjusted odds ratio for vaccine serotype IPD was 1.5 (95% CI 0.15–14.6) with 2p+1 as baseline and adjustment for underlying conditions (1 case–control study).
- Potential biases include issues of control selection common to case–control studies. Other biases and confounding could also be present.

3p+1 vs 2p+1 schedules

- The matched, adjusted odds ratio for vaccine serotype IPD was 0 (95% CI 0–10.1) with the 2p+1 group as baseline and adjustment for underlying conditions (1 case–control study).
- GMCs were similar between the 3p+1 and 2p+1 groups. No seropositivity data were reported (1 cohort study).
- Potential bias in the cohort study could result from comparison groups being in different locations and recruited in different years. Other biases and confounding could also be present.

3p+1 vs 3p schedules

- The matched, adjusted odds ratio for vaccine serotype IPD was 0 (95% CI 0–0.87) with the no-booster group as baseline and adjustment for underlying conditions (1 case–control study).
- Potential biases include issues of control selection common to case–control studies. Other biases and confounding could also be present.

2-month vs 1-month interval schedules

- In a 2p schedule with 7-valent PCV, the 2-month interval group (2, 4 schedule) had higher levels of seropositivity 1 month after vaccination than the 1-month interval group (2, 3

schedule). Similar results were seen at 12 months of age prior to the booster (1 cohort study).

- Results for 3p schedules varied by vaccine. For PCV7, the 2-month interval group (2, 4, 6) tended to have a similar or higher percentage seropositive 1 month after vaccination than the 1-month interval group (1.5, 2.5, 3.5), but both groups were similar at 12–18 months of age (1 cohort study). For PCV10, the 2-month interval group tended to have similar or lower percentages seropositive 1 month after vaccination than the 1-month interval group; by 12–18 months of age, all point estimates were lower in the 2-month interval group (1 cohort study).
- Results were consistent for the two cohort studies comparing intervals using PCV7.
- Biases potentially exist if age at outcome assessment differs between groups. Confounding by location and co-administered vaccines might be present as well as other biases.

Catch-up (toddler) vs catch-up, and infant vs catch up schedules

- Clinical and carriage data were scarce for these comparisons.
- Immunogenicity data showed lowest seropositivity levels and most variation between schedules for serotypes 6B and 23F.
- Seropositivity one month after a 7, 11m schedule (PCV10) was lower than after a 12, 24m schedule (PCV10) or a 2, 3 ,4m schedule (PCV10) for serotypes 6B and 23F (1 cohort study).
- Seropositivity one month after either a 2, 3, 4 + 12–15m schedule (PCV10) or a 7, 11 + 12–15m schedule (PCV10) was high for all serotypes (1 cohort study).
- Potential biases include systematic differences between those recruited at different ages and therefore into different intervention groups. Other biases and confounding could also be present.

4.1.3.2 Comparisons of PCV schedule vs no PCV

- Effectiveness was high against vaccine serotype IPD for all 2- or 3-dose infant schedules examined in one case–control study.
- Both a 2p+1 and 3p+1 schedule appeared to have some effectiveness against pneumonia but the outcome reported (clinically or radiologically diagnosed pneumonia) differed between studies, making comparison difficult (2 cohort studies).
- There was less carriage of any serotype after a 3p+1 schedule compared to no vaccination (1 cohort study).
- In one study of toddler vaccination, vaccine serotype carriage did not differ between vaccinated and unvaccinated children (1 cohort study).
- The potential for bias and confounding vary by study.

4.1.4 Discussion

The review identified 18 eligible cohort studies, within which 15 different comparisons of schedules (or a schedule and no PCV) were examined. The review also identified 11 comparisons from within the two eligible case–control studies. Three cohort studies reported clinical disease outcomes, four reported carriage outcomes and eight reported immunological outcomes. Both case–control studies examined IPD.

4.1.4.1 Strengths and limitations

The main strengths of this review were the wide and comprehensive search strategy and rigorous methods for selecting studies and extracting data. Important studies are unlikely to have been missed by this search. The overall number of items retrieved from electronic database searches using broad search terms, without filters to identify specific study designs, was very high compared to the yield of relevant eligible observational studies. Observational studies that examined comparisons between schedules but did not state this in the abstract might still have been excluded.

Observational studies offer advantages, but also disadvantages, over well-conducted randomized trials. Advantages include, but are not limited to, analysing exposures that might be difficult or unethical to examine in RCTs, investigating rare outcomes, filling data gaps that RCTs do not address, and estimating vaccine effectiveness post-licensure. Disadvantages include a greater risk of bias and confounding than in a well-conducted RCT.

Observational study designs not included in this review include surveillance data with population level measures of exposures and outcomes (i.e. ecological studies): ecological studies are particularly prone to biases and confounding and require special care in analysis and interpretation. Studies of the impact of PCV and the methods for analysis are the topic of a separate detailed review.

4.1.4.2 Main findings

Due to low statistical power in the case−control study, confidence intervals for odds ratios for vaccine serotype IPD were wide and crossed 1 for the following comparisons: 3p vs 2p, 3p vs 2p+1 and 3p+1 vs 2p+1. There was some statistical evidence that the 3p+1 schedule was associated with less IPD than a 3p schedule, but the odds ratio was only adjusted for underlying conditions.

Effectiveness was high against vaccine serotype IPD for all 2 or 3 dose infant schedules (in comparison to no vaccination) examined in the case−control studies.

Seropositivity was similar between 3p and 2p groups one month after vaccination, and the 3p group had slightly higher seropositivity estimates for most serotypes eight months after primary vaccination. One month after a booster dose at 12 months, similar GMCs were reported for both groups (no seropositivity reported).

There was some suggestion in the data that a 2-month interval might be associated with better immune responses than 1-month intervals for the 7-valent vaccine, while the reverse might be true for the 10-valent vaccine. However, there is potential confounding from co-administered vaccines.

In comparisons of catch-up (toddler) vaccination schedules with either catch-up schedules or with infant schedules, immunogenicity data showed lowest seropositivity levels and most variation between schedules for serotypes 6B and 23F.

Findings in context with RCTs

When viewed with results from RCTs, several points can be noted:

- One case−control study compared schedules for the prevention of vaccine serotype IPD, which was not possible in the RCTs. However, confidence intervals were very wide and statistical evidence for differences between schedules was limited.

- Results from cohort studies for the comparison of immunogenicity after 3p or 2p schedules are broadly similar to those found in RCTs.
- There were no direct comparisons of 1- and 2-month intervals (where the same number of doses were given in each group) in RCTs, so the information provided by the cohort studies summarizes currently available data.

4.1.4.3 Implications for future research

Systematic reviews investigating vaccination schedules that include case–control and cohort studies can contribute additional clinical data that are not available from RCTs. The added value of including these study designs in literature searches needs to be weighed against the much larger numbers of items retrieved from less specific search strategies.

Primary studies reporting composite clinical outcomes should give descriptive information about the distribution of individual clinical outcomes, even if fully stratified analyses have not been done.

Additional information about the effects of different intervals between doses in a primary schedule would be valuable, particularly for 2-dose primary schedules. RCTs examining different intervals are also needed.

4.1.5 Conclusions

Results from cohort and case–control studies complemented data from RCTs, while not altering the conclusions of the full review of RCTs.

4.2 Introduction

Results from RCTs reporting clinical, carriage and immunological outcomes from eligible studies in the systematic review of PCV schedules are summarized in sections 2 and 3, respectively. However, RCT data about direct comparisons between schedules are scarce, particularly for important clinical outcomes such as pneumonia and IPD.

Observational studies can add to knowledge gained from RCTs, especially to fill gaps in data. Advantages of observational studies include the availability of data from periods after vaccine introduction. This allows the estimation of vaccine effectiveness in a given setting, and incorporates factors such as adequacy of vaccine delivery systems and indirect effects of vaccination (which might also be possible to examine in an RCT, depending on its design). Frequently, due to larger numbers of individuals being eligible for vaccination, more events may also be available for analysis, which is particularly important for rare outcomes. The most important disadvantage of data from observational studies is the increased risk of bias and confounding when compared to well-conducted RCTs. Such biases can result in under- or overestimates of vaccine effectiveness. In some situations, the direction of such biases can be predicted, but often the magnitude and direction of biases cannot be estimated, limiting the interpretation of data from observational sources.

Selected findings from the systematic review, comparing 3p vs 2p schedules, have been published [5]. This section of the report presents the results of cohort and case–control studies that compared childhood schedules or estimated vaccine effectiveness of PCV.

4.3 Methods

General methods for this review, including the search strategy, are described in the clinical and carriage section 2.3. Methods specific to observational data are described here.

4.3.1 Selection of studies

Two pairs of reviewers independently evaluated articles retrieved in the searches for eligibility for inclusion in the review. Observational studies identified as having potentially eligible comparisons in title and abstract screening were included in full text screening for confirmation of eligibility. The selection criteria are described below.

4.3.1.1 Inclusion criteria

a) Study design

Case–control or cohort studies were considered for inclusion. Where two or more exposure cohorts were described in the original publications as part of the same study, this was considered a cohort study for potential inclusion. Cross-sectional studies were excluded, since those identified either presented too few data to allow adequate analysis and interpretation, or involved sampling of different populations before and after PCV introduction, with marked differences in population characteristics. Surveillance studies were excluded as these are the subject of a separate detailed review.

b) Population

The population criteria are described in the clinical and carriage section 2.3.2.1(a).

c) Intervention

Intervention eligibility is as described in the clinical and carriage report, section 2.3.2.1(b).

d) Comparison groups

Only studies that compared groups of individuals with at least one of the following criterion were considered:

- Different number of doses of PCV;
- Different intervals between doses of PCV;
- Different ages at the start of a PCV vaccination schedule;
- Any PCV schedule compared to placebo injection, another vaccine, or nothing (clinical and carriage outcomes only).

e) Outcomes

Studies reporting any of the following outcomes were eligible for inclusion:

- ***Clinical effectiveness:*** Eligible clinical outcomes are those described in the clinical and carriage section 2.3.2.1(d): "Clinical efficacy of effectiveness".
- ***Nasopharyngeal carriage of pneumococci:*** Eligible carriage outcomes are described in the clinical and carriage section 2.3.2.18d) "Nasopharyngeal carriage of pneumococci".
- ***Immunogenicity outcomes:*** Studies eligible for inclusion are as described in the immunological outcomes section 3.2.1.3.

4.3.1.2 Exclusion criteria

Uncontrolled studies, dose-finding studies, and animal or laboratory studies were excluded from this section of the review. In addition, in line with the examination of immunogenicity data from RCTs, studies were excluded from the observational review if they compared PCV to no PCV and presented only immunogenicity data. Studies were also excluded if the PCV comparison was completely confounded by health status, for example if HIV-infected individuals received 2 PCV doses and HIV-uninfected individuals received 1 dose. Finally, studies including only individuals with the outcome in analyses ("case only" studies) were excluded.

4.3.2 Data extraction

Data extraction methods are described in the clinical and carriage section 2.3.3.

4.3.3 Statistical analysis

4.3.4.1 Descriptive analysis

Features of the studies included were first summarized in tables and figures. Cohort and case−control studies are reported separately. Due to the diversity of comparisons in the studies analysed, forest plots were not produced, nor data statistically combined.

4.3.4 Presentation of results

The system used to present the results of the review is described in the clinical and carriage section 2.3.5.

4.4 Results

4.4.1 Literature search

Of the total 3217 items found in the searches, 26 were eligible and related to 20 observational studies. Of these, 18 were cohort and two were case–control studies.

4.4.2 Description of included studies

Of these 18 cohort studies, data are reported from 15 that had at least one eligible comparison and one eligible outcome [6–19]. These studies are summarized in Table 4.1 below. Three of these cohort studies reported clinical disease outcomes, four reported carriage outcomes and eight reported immunological outcomes.

Data from the remaining three cohort studies are not reported because two studies reported carriage as the percentage of positive samples rather than the percentage of individuals carrying *S. pneumoniae* [20, 21]; and one study reported only carriage in adults before and after the introduction of PCV vaccination of children [22].

The two eligible case–control studies (Spain2 obs 7v, USA2 obs 7v) are summarized in Table 4.2 below. One further, large case–control study [23] only included cases of IPD (using individuals with non-vaccine serotype IPD as controls) and was excluded on this basis, but its results are compared with the included case–control studies in the discussion section. Additional details of the cohort and case–control studies are reported in Tables 4.3 and 4.4, respectively.

Table 4.1 Summary of included cohort studies, alphabetical order

Study name and PCV valency	Country	Schedules, age at dose in months		Number of participants	Outcomes reported		
		Intended	Actual age at administration (median)		Clinical	Carriage	Immunogenicity
Finland obs 7v [6]	Finland	2, 4, 6 + b15	NR	30	-	-	SP, GMC
		2, 4, 6 + b15(PPV)		29			
Finland obs 10v [7]	Finland	3, 4, 5 + b12–15	NR	150	Adverse events[1] Mortality	-	SP, GMC, OPA
		7, 11 + b12–15		150			
		12, 23		150			
		>24 (1 dose)		150			
Germany obs 7v [8]	Germany	2, 3, 4 + b12–15	3.1, 4.3, 5.7, 14.6 (both groups)	5609	IPD Pneumonia Otitis media Mortality	-	-
		no PCV and no PPV		1802			
International obs 7v [9]	Poland/Philippines	2, 4, 6 + b12–18	1.9, 3.8, 5.3[2]	103	Adverse events[1] Mortality	-	SP, GMC, OPA
		1.5, 2.5, 3.5 + b12–18	1.8, 2.9, 4.1[2]	100			
International obs 10v [9]	Poland/Philippines	2, 4, 6 + b12–18	1.9, 3.8, 5.3[2]	303	Adverse events[1] Mortality	-	SP, GMC, OPA
		1.5, 2.5, 3.5 + b12–18	1.8, 2.9, 4.1[2]	300			

Study name and PCV valency	Country	Schedules, age at dose in months		Number of participants	Outcomes reported		
		Intended	Actual age at administration (median)		Clinical	Carriage	Immunogenicity
Italy obs 7v [10]	Italy	3, 5 + b11	2.7, 4.6, 11.3	819	IPD Pneumonia Otitis media	-	-
		no PCV and no PPV	NA	752			
Korea obs 7v [11]	Republic of Korea	3p+1 (schedule NR)	NR	200	-	Carriage	-
		no PCV and no PPV		200			
Norway obs 7v [12]	Norway	1 dose (>24m) or 2 doses (12–24m)	NR	56	-	Carriage	-
		no PCV and no PPV		38			
Spain1 obs 7v [13]	Spain	2p or 3p + b12–15[3]	NR	1	-	Carriage	-
		12, 14[3]		52			
		24[3]		2			
		no PCV and no PPV		60			
UK1 obs 7v [14]	United Kingdom	2, 3, 4 + b13(PPV)	NR	267	-	Carriage	-
		no PCV and no PPV		~300			
UK2 obs 7v[4] [15]	United Kingdom	Schedule NR	NR	61	IPD	-	-
		PPV or no PPV		191			
UK3 obs 7v[5] [16]	United Kingdom	2, 4 + b12	2.0, 4.1	239	-	-	SP, GMC, OPA
		2, 3 + b12	2.0, 3.1	154			
UK obs 9v [17]	United Kingdom	2, 3, 4 + b12	NR	≥ 36	-	-	SP, GMC
		2, 4 + b12		≥ 39			
		2, 3, 4 + b12(PPV)		≥ 46			
		2, 4 + b12(PPV)		≥ 39			
USA1 obs 7v[4] [18]	USA	2, 4, 6[6]	2.1, 4.0, 5.5[2]	11	-	-	SP, GMC
		2, 4, 6 + b24(PPV)[6]	2.3, 3.9, 5.7, 24.8[2]	34			
		12[6]	13.4[2]	3			
		12, 24(PPV)[6]	12.3, 24.2[2]	13			
USA obs 7/13v [19]	USA	≥3 doses PCV7 + 2 doses PCV13 >55d apart (15m–24m)	13v doses: 18.0, 20.0[2]	126	-	-	SP, GMC
		≥3 doses PCV7 + 1 dose PCV13 (24m–5y)	13v dose: 3.1y[2]	181			

Legend:

b – booster; GMC – geometric mean concentration (ELISA); IPD – invasive pneumococcal disease; NA – not applicable; NR – not reported; obs – denotes an observational study; OPA – opsonophagocytic activity; PCV – pneumococcal conjugate vaccine; PPV – pneumococcal polysaccharide vaccine; SP - seropositivity (ELISA); 3p – 3 dose primary schedule, etc.; +1 – booster dose; ~ approximate number.

Table excludes one study that reports only outcomes in adults [22], and two studies that report carriage only as the percentage of samples and not of children [20, 21].

1 The adverse events reported include clinical outcomes that are eligible for this review. However, data were not specifically collected for these outcomes, and no case definitions were applied. These data were therefore not considered to reflect the effect of vaccine and are not analysed as such in this review.

2 Mean age in months.

3 Schedule might commence later but with same number of doses and same intervals in primary schedule; PPV also given in some/all groups (unclear).

4 Some or all participants had sickle-cell disease.

5 Randomized controlled trial where randomization pattern was amended during trial. Separate data from before and after protocol amendment not currently available, so data included classed as observational. Boosters given at 12 or 13 months, but post-booster data not currently available.

6 Groups with PPV contain children with sickle-cell disease, groups without PPV contain only children without sickle-cell disease.

Table 4.2 Summary of included case–control studies, alphabetical order

<table>
<tr><th>Study name</th><th>Country</th><th>Comparisons</th><th colspan="2">Number of participants</th><th>Outcome</th></tr>
<tr><th></th><th></th><th></th><th>Cases</th><th>Controls</th><th></th></tr>
<tr><td>Spain2 obs 7v [24]</td><td>Spain</td><td>1 or more doses vs 0
“Complete” vaccination[1] vs 0
“Incomplete” vaccination[1] vs 0</td><td>85</td><td>425</td><td>IPD</td></tr>
<tr><td>USA2 obs 7v [25]</td><td>USA</td><td>
<table>
<tr><th>Infant schedules examined in case–control study:</th><th>no PCV</th><th>2 doses ≤7m</th><th>3 doses ≤7m</th><th>2 doses ≤7m, 1 dose 12-16m</th></tr>
<tr><td>1 dose ≤7m</td><td>+</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>2 doses ≤7m</td><td>+</td><td>-</td><td>+</td><td>+</td></tr>
<tr><td>3 doses ≤7m</td><td>+</td><td>+</td><td>-</td><td>+</td></tr>
<tr><td>2 doses ≤7m, 1 dose 12–16m</td><td>+</td><td>+</td><td>+</td><td>-</td></tr>
<tr><td>1 dose ≤7m, 1 dose 8–11m, 1 dose 12–16m</td><td>+</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>3 doses ≤7m, 1 dose 12–1m</td><td>+</td><td>+</td><td>+</td><td>+</td></tr>
<tr><td>1 dose 7–11m, 2 doses 12–16m</td><td>+</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td colspan="5">Toddler schedules:</td></tr>
<tr><td>1 dose 12–23m</td><td>+</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>2 doses 12–23m</td><td>+</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>1 dose ≥24m</td><td>+</td><td>-</td><td>-</td><td>-</td></tr>
</table>
</td><td>782</td><td>2512</td><td>IPD</td></tr>
</table>

Legend:

obs – denotes an observational study;
+ – Case–control study reports a comparison of the schedules described in column and row;
- – Case–control study does not report the comparison of the schedules described in column and row.
1 Complete vaccination defined as 3 doses if the first dose was given between 2–6 months, or 2 doses if the first dose occurred between 7–23 months, or 1 dose if the first dose occurred at 24 months or more.

The 15 cohort studies reported on involved at least 8966 children who received primary vaccination in infancy and 426 toddlers who received catch-up doses. Twelve of these studies were conducted partially or fully within Europe (Finland obs 7v, Finland obs 10v, Germany obs 7v, International obs 7v, International obs 10v, Italy obs 7v, Norway obs 7v, Spain1 obs 7v, UK1-3 obs 7v, UK obs 9v). In addition, two studies were conducted in the USA (USA1 obs 7v, USA obs 7/13v) and three were conducted either partially or fully in countries in Asia (International obs 7v, International obs 10v, Korea obs 7v).

All but four of the cohort studies related to 7v; two of these four related to 10v (Finland obs 10v, International obs 10v); one to 9v (UK obs 9v) and one combined 7v and 13v PCV (USA obs 7/13v). Six reported at least one clinical outcome (Finland obs 10v, Germany obs 7v, International obs 7v, International obs 10v, Italy obs 7v, UK2 obs 7v); eight reported immunogenicity outcomes (Finland obs 7v, Finland obs 10v, International obs 7v, International obs 10v, UK3 obs 7v, UK obs 9v, USA1 obs 7v, USA obs 7/13v); and four reported carriage outcomes (Korea obs 7v, Norway obs 7v, Spain1 obs 7v, UK1 obs 7v).

The method of allocation to intervention varied between cohort studies. Four were based on age at recruitment (Finland obs 10v, Spain1 obs 7v, USA1 obs 7v, USA obs 7/13v), three on geographic

location (International obs 7v, International obs 10v, UK obs 9v), and two on parental choice (Germany obs 7v, Italy obs 7v). Year of birth was used for allocation in one study (UK2 obs 7v), the day-care centre attended in another (Norway obs 7v), and the inclusion or non-inclusion in a previous study in a further cohort study (UK1 obs 7v). Additionally, one study was randomized to two schedules for the initial period of the study, but due to results of an interim analysis, randomization to one of the schedules was halted (UK3 obs 7v). Results for this study are currently only available for the randomized and non-randomized periods combined, and it is therefore included here as an observational study. The remaining two cohort studies did not report the method of allocation (Finland obs 7v, Korea obs 7v).

The included case–control studies involved 867 cases (all IPD) and 2937 controls. One case-control study was conducted in Spain (Spain2 obs 7v) and the other in the USA (USA2 obs 7v). Both related to 7v PCV and examined cases of IPD. Both studies located cases through surveillance systems. One used hospital birth lists as a sampling frame for controls (matched on hospital and date of birth, Spain2 obs 7v) and the other used a set of birth certificate registries (matched on postcode and same fortnight of birth, USA2 obs 7v).

Table 4.3 shows the comparisons available from the cohort studies, together with the time points at which data are available. Table 4.4 shows comparisons available in case–control studies. Each comparison is identified by a letter, which relates to the same comparison in each section of this review. Comparisons highlighted in the table are those reported in the main text.

Table 4.5 Order of description and presentation of comparisons of vaccination schedules in cohort studies

Comparison	Study	Schedules, months	Time		
			Clinical	Carriage, months	Immunogenicity, months
Schedule vs schedule (comparisons A–T)					
Comparison C 3p vs 2p	UK obs 9v [17]	2, 3, 4 2, 4	-	-	5, 12 5, 12
Comparison I 3p+PPV vs 2p+PPV	UK obs 9v [17]	2, 3, 4 + b12(PPV) 2, 4 + b12(PPV)	-	-	13 13
Comparison L 3p+1 vs 2p+1	UK obs 9v [17]	2, 3, 4 + b12 2, 4 + b12	-	-	13 13
Comparison N 3p+1 vs 3p+PPV	Finland obs 7v [6]	2, 4, 6 + b15 2, 4, 6 + b15(PPV)	-	-	16, 24
Comparison P 2m interval vs 1m interval	International obs 7v [9]	2, 4, 6 + b12–18 1.5, 2.5, 3.5 + b12–18	2–12m, from booster until 6m post-booster 1.5–9.5m, from booster until 6m post-booster	-	7, 12–18, 13–19 4.5, 12–18, 13–19
	International obs 10v [9]	2, 4, 6 + b12–18 1.5, 2.5, 3.5 + b12–18	2–12m, from booster until 6m post-booster 1.5–9.5m, from booster until 6m post-booster	-	7, 12–18, 13–19 4.5, 12–18, 13–19
	UK3 obs 7v [16]	2, 4 2, 3	-	-	5, 12 4, 12
Comparison R Catch-up vs catch-up	Finland obs 10v [7]	7, 11 >24 (1 dose)	Entire study period Entire study period	-	12, pre-booster (12–15) >25m
	Finland obs 10v [7]	7, 11 12, 23	Entire study period Entire study period	-	12, pre-booster (12–15) 24
	Finland obs 10v [7]	7, 11 + b12–15 >24 (1 dose)	Entire study period Entire study period	-	13–16m >25
	Finland obs 10v [7]	7, 11 + b12–15 12, 23	Entire study period Entire study period	-	13–16m 24
	Finland obs 10v [7]	12, 23 >24 (1 dose)	Entire study period Entire study period	-	24 >25
	Spain1 obs 7v [13]	12, 14[1]	-	Unclear	-

Comparison	Study	Schedules, months	Time		
			Clinical	Carriage, months	Immunogenicity, months
		24[1]		Unclear	
Comparison T Primary (+/- booster) vs catch-up	USA1 obs 7v [18]	2, 4, 6[2] 12[2]	-	-	7, 12, 24 13, 24
	Finland obs 10v [7]	3, 4, 5 >24 (1 dose)	-	-	6, pre-booster (12–15) >25
	Finland obs 10v [7]	3, 4, 5 7, 11	-	-	6, pre-booster (12–15) 12, pre-booster (12–15)
	Finland obs 10v [7]	3, 4, 5 12, 23	-	-	6, pre-booster (12–15) 24
	USA1 obs 7v[3] [18]	2, 4, 6 + b24(PPV)[2] 12 + b24(PPV)[2]	-	-	7, 12, 24, 25 13, 24, 25
	Finland obs 10v [7]	3, 4, 5 + b12–15 >24 (1 dose)	Entire study period Entire study period	-	13–16m >25
	Finland obs 10v [7]	3, 4, 5 + b12–15 12, 23	Entire study period Entire study period	-	13–16m 24
	Finland obs 10v [7]	3, 4, 5 + b12–15 7, 11, 12–15	Entire study period Entire study period	-	13–16m 13–16m
Schedule vs no PCV (comparisons U–Z)					
Comparison V3 3p+PPV vs 0	UK1 obs 7v [14]	2, 3, 4 + b13(PPV) no PCV and no PPV	-	mean 33, 40.3 mean 36.4, 39.9	-
Comparison W2 2p+1 vs 0	Italy obs 7v [10]	3, 5 + b11 no PCV and no PPV	6–30m 6–30m	-	-
Comparison W3 3p+1 vs 0	Germany obs 7v [8]	2, 3, 4 + b12–15 no PCV and no PPV	2–27m 2–27m	-	-
	Korea obs 7v [11]	3p+1 (Schedule NR) no PCV and no PPV	-	18–59m 18–59m	-
Comparison W4 1, 2, 3 or 4 doses vs 0	Spain1 obs 7v [13]	2p or 3p + b12–15[1] / 12, 14[1] / 24[1] no PCV and no PPV	-	mean 44.4 mean 38.4	-
Comparison X1 1 catch-up dose vs 0	Norway obs 7v [12]	1 dose (12m – >24m) no PCV and no PPV	-	mean approx. 28.4 mean approx 43.7	-
Comparison Y 1 or 2 catch-up doses vs 0	Norway obs 7v [12]	1 dose (>24m) or 2 doses (12– 24m) no PCV and no PPV	-	mean approx. 34.4 mean approx 49.7	-
Comparison Z Unknown schedule vs 0	UK2 obs 7v[3] [15]	Schedule NR PPV or no PPV	Unclear	-	-
Comparison other	USA obs 7/13V [19]	≥3 doses PCV7 + 2 doses PCV13 >55d apart (15m– 24m) ≥3 doses PCV7 + 1 dose PCV13 (24m– 5y)	-	-	18–27m 25m–5y

Legend:

b – booster; m – months; NR – not reported; obs – denotes an observational study; p – primary schedule; PCV – pneumococcal conjugate vaccine; PPV – pneumococcal polysaccharide vaccine; v – valent; y – years.

Shaded grey rows are those reported in the main text.

1 Schedule might commence later but with same number of doses and same intervals in primary schedule; PPV also given in some/all groups (unclear).

2 Children with sickle-cell disease received PPV in addition to the PCV schedule; children without sickle-cell disease did not.

3 Some or all participants had sickle-cell disease.

Table 4.6 Order of description and presentation of comparisons of vaccination schedules in case–control studies

Comparison	Study	Schedules, months
Comparison C 3p vs 2p	USA2 obs 7v [25]	3 doses ≤ 7m 2 doses ≤ 7m
Comparison E 2p+1 vs 2p	USA2 obs 7v [25]	2 doses ≤ 7m, 1 dose @ 12–16m 2 doses ≤ 7m
Comparison G 3p vs 2p+1	USA2 obs 7v [25]	3 doses ≤ 7m 2 doses ≤ 7m, 1 dose @ 12–16m
Comparison L 3p+1 vs 2p+1	USA2 obs 7v [25]	3 doses ≤ 7m, 1 dose @ 12–16m 2 doses ≤ 7m, 1 dose @ 12–16m
Comparison M 3p +1 vs 3p	USA2 obs 7v [25]	3 doses ≤ 7m, 1 dose @ 12–16m 3 doses ≤ 7m
Comparison U1 1p vs 0	USA2 obs 7v [25]	1 dose ≤ 7m No PCV
Comparison U2 2p vs 0	USA2 obs 7v [25]	2 doses ≤ 7m No PCV
Comparison U3 3p vs 0	USA2 obs 7v [25]	3 doses ≤ 7m No PCV
Comparison W2 2p +1 vs 0	USA2 obs 7v [25]	2 doses ≤ 7m, 1 dose @ 12–16m No PCV
Comparison W3 3p +1 vs 0	USA2 obs 7v [25]	3 doses ≤ 7m, 1 dose @ 12–16m No PCV
Comparison W4 1, 2, 3, or 4 doses vs 0	Spain2 obs 7v [24]	1 or more doses "Complete" vaccination[1] "Incomplete" vaccination[1] No PCV

Legend:

m – months; p – primary schedule; PCV – pneumococcal conjugate vaccine; v – valent.

1 Complete vaccination defined as 3 doses if the first dose was given between 2–6 months, 2 doses if the first dose occurred between 723 months, or 1 dose if the first dose occurred at 24 months or more.

4.4.2.1 Comparison C: 3p vs 2p schedule

Summary

- *The matched, adjusted odds ratio for vaccine-type IPD was 1.5 (95% CI 0.54–4.35) with the 2p group as baseline (1 case–control study).*
- *One month after vaccination, seropositivity was broadly similar between groups. Lowest levels of seropositivity were achieved for serotype 6B (1 cohort study.)*
- *Eight months after vaccination, seropositivity levels were generally lower than at one month post-vaccination in both groups. The lowest levels were seen for serotypes 18C, 4, 9V and 23F. The 3p group tended to have slightly higher levels of seropositivity for most serotypes (1 cohort study).*
- *Potential biases in the case–control study include issues of control selection common to case–control studies. Confounding could also be present.*
- *Potential bias in the cohort study could result from comparison groups being in different locations and recruited in different years. Other biases and confounding could be present.*

One cohort study (UK obs 9v) and one case–control study (USA2 obs 7v) reported on immunogenicity and on IPD, respectively for this comparison.

The case–control study used IPD cases and age- and postcode-matched controls without IPD. The study compared 3 doses of PCV before 7 months of age (no booster) with 2 doses before 7 months (no booster). The matched, adjusted odds ratio for vaccine serotype IPD in children receiving 3 doses was 1.5 (95% CI 0.54–4.35) compared with children receiving 2 doses. This estimate was adjusted for underlying conditions. Fewer variables were adjusted for in this analysis than in the main analyses (comparing vaccination with no vaccination), due to the low numbers of vaccinated cases, which limited statistical power.

The cohort study compared immunogenicity data from two counties in England where different 9v schedules were used. A 3p schedule (2, 3, 4 months) was compared with a 2p schedule (2, 4 months) with broadly similar results at one month after the last primary vaccination (UK obs 9v). Seropositivity at a threshold of 0.35µg/ml ranged from 84% (3-dose group, serotype 6B) to 100% (3p group, serotypes 14 and 19F, and 2p group serotype 1). At a threshold of 0.20µg/ml, all groups and serotypes had seropositivity of 95% or higher with the exception of serotype 6B for the 2-dose group (90%). GMCs were higher in the 3p group for serotypes 6B, 14, 18C and 23F, but with no strong statistical evidence of a difference between groups. GMCs were higher in the 2p group for serotypes 1, 4 and 19F, and there was statistical evidence of a difference for serotype 19F. Results for 3p and 2p groups were similar for the remaining serotypes.

Eight months after vaccination, there were more marked differences between the groups and overall levels of seropositivity had fallen for most serotypes (33–98% seropositivity a threshold of 0.35µg/ml). The 3p group tended to have slightly higher levels of seropositivity at both thresholds for all serotypes, with exception of 19F at the 0.35µg/ml threshold and 19F and 6B at 0.20µg/ml. Seropositivity was lowest for serotype 18C in both groups (33% and 39% in the 2p and 3p groups, respectively at the 0.35µg/ml threshold) and less than 60% of children were seropositive (0.35µg/ml threshold) in both groups for serotypes 4, 9V and 23F. Seropositivity levels above 85% (0.35µg/ml threshold) were seen in the 2p group for serotypes 14 and 19F and in the 3p group for serotypes 1, 5, 14 and 19F. These differences were also reflected in GMCs.

Potential for bias within this comparison

In general, observational studies are more prone to confounding than well-conducted RCTs. As in RCTs, biases may also be introduced if those assessing outcomes are aware of the vaccination status of the individual (or if those assessing vaccination status are aware of the outcome status in case–control studies), and by losses to follow-up (cohort studies). Results of case–control studies can be biased by inappropriate selection of controls that are not representative of the population from which the cases arose.

Specific potential causes of biases in the studies included in this comparison

The comparison groups in the cohort study were in different counties in the United Kingdom and during different time periods (2000–2001 or 2001–2003). This could have introduced bias if systematic differences existed between locations and time periods, such as recruitment processes or exposure to *S. pneumoniae*.

The case–control study had few vaccinated cases, which limited statistical power. Therefore, few potential confounders were included in analyses comparing schedules. This may result in residual confounding by factors such as socioeconomic status and those that might influence both vaccination and the risk of IPD.

4.4.2.2 Comparison G: 3p vs 2p +1 schedules

Summary

- *The matched, adjusted odds ratio for vaccine-type IPD was 1.5 (95% CI 0.15–14.6) with 2p+1 as baseline and adjustment for underlying conditions (1 case–control study).*
- *Potential biases include issues of control selection common to case–control studies. Other biases and confounding could be present.*

One eligible case–control study reported on this comparison (USA2 obs 7v). This study compared 3 doses given before 7 months old (no booster) with 2 doses before 7 months with a booster at 12–16 months. The matched, adjusted odds ratio for vaccine serotype IPD in children who received 3 doses was 1.5 (95% CI 0.15–14.6) compared with 2p+1 doses after adjustment for underlying conditions. As in section 4.4.2.1, fewer variables were adjusted for in this analysis than in the main analyses (comparing vaccination with no vaccination), due to the low numbers of vaccinated cases, which limited statistical power.

Potential for bias within this comparison

Biases described above (4.4.2.1) apply here, both for the case–control study in this comparison and case–control in general.

4.4.2.3 Comparison L: 3p+1 vs 2p+1 schedule

Summary

- *The matched, adjusted odds ratio for vaccine-type IPD was 0 (95% CI 0–10.1) with the 2p+1 group as baseline and adjustment for underlying conditions (1 case–control study).*
- *GMCs were similar between the 3p+1 and 2p+1 groups. No seropositivity data were reported (1 cohort study).*
- *Potential bias in the cohort study could result from comparison groups being in different locations and recruited in different years. Other biases and confounding could also be present.*

One cohort study and one case–control study were eligible and reported on this comparison (UK obs 9v, USA2 obs 7v). The cohort study reported on immunogenicity and the case–control study on IPD.

The cohort study is the same as the one in section 4.4.2.1, with the addition of a booster dose at 12 months. Only GMCs were reported at this time point. These were similar between the 3p+1 and 2p+1 groups with no statistical evidence of differences between groups.

The case–control study compared 3 doses with 2 doses, both before 7 months of age with a booster at 12–16 months. The matched, adjusted odds ratio for vaccine serotype IPD was 0 (95% CI 0–10.1) with the 2p+1 group as baseline and adjustment for underlying conditions. As in section 0, fewer variables were adjusted for in this analysis than in the main analyses (comparing vaccination with no vaccination), due to the low numbers of individuals, which limited statistical power.

Potential for bias within this comparison

Biases described in 4.4.2.1 apply equally to this comparison.

4.4.2.4 Comparison M: 3p +1 vs 3p schedules

Summary

- *The matched, adjusted odds ratio for* vaccine-type IPD *was 0 (95% CI 0–0.87) with the no-booster group as baseline and adjustment for underlying conditions (1 case–control study).*
- *Potential biases include issues of control selection common to case–control studies. Other biases and confounding could be present.*

One case–control study was eligible and reported on this comparison (USA2 obs 7v), which compared 3 doses before 7 months of age plus a booster at 12–16 months, with 3 doses before 7 months without a booster. The matched, adjusted odds ratio for vaccine serotype IPD was 0 (95% CI 0–0.87) with the no-booster group as baseline and adjustment for underlying conditions. As in section 0, fewer variables were adjusted for in this analysis than in the main analyses (comparing vaccination to no vaccination), due to the low numbers of individuals, which limited statistical power.

Potential for bias within this comparison

Biases described in 4.4.2.1 apply to the case–control study in this comparison, as well as case–control studies in general.

4.4.2.5 Comparison P: 2-month vs 1-month interval

Summary

- *In a 2p schedule with PCV7, the 2-month interval group (2, 4m schedule) had higher levels of seropositivity one month after vaccination than the 1-month interval group (2, 3m schedule). Similar results were seen at 12 months of age, prior to the booster (1 cohort study).*
- *Results for 3p schedules varied by vaccine. For PCV7, the 2-month interval group (2, 4, 6m) tended to have a similar or higher percentage seropositive one month after vaccination than the 1-month interval group (1.5, 2.5, 3.5m), but both groups were similar at 12–18 months of age (1 cohort study). For PCV10, the 2-month interval group tended to have similar or lower percentages seropositive at one month after vaccination than the 1-month interval group, and by 12–18 months, all point estimates were lower in the 2-month interval group (1 cohort study).*
- *Results were consistent for the two cohort studies comparing intervals using PCV7.*
- *Biases potentially exist if age at outcome assessment differs between groups. Confounding by location and co-administered vaccines might be present as well as other biases.*

Three cohort studies were eligible and reported on this comparison (International obs 7v, International obs 10v, UK3 obs 7v). One study compared different intervals within a 2-dose schedule (UK3 obs 7v) and two compared intervals within a 3-dose schedule [9].

The first study compared a 2, 4m schedule to a 2, 3m schedule using 7v PCV (UK3 obs 7v). Immunogenicity was assessed at one month after the second dose (5 and 4 months of age,

respectively) and at 12 months of age. Testing was also carried out after a booster dose but data were not reported separately for the different primary vaccination schedules.

One month after the primary course, the percentage seropositive (0.35µg/ml threshold) was higher for all serotypes in the 2, 4m group than the 2, 3m group, with statistical evidence of a difference for serotypes 6B and 23F. These serotypes also had the lowest levels of seropositivity.

At 12 months of age (before the booster dose), the percentage seropositive was higher for all serotypes in the 2, 4m group, but there was no statistical evidence of a difference for any serotype. For GMCs, statistical evidence showed a difference for serotypes 4, 6B and 23F. However, after the booster dose, the primary vaccination schedule no longer had any effect.

The two studies that compared different intervals within a 3-dose schedule were from the same RCT, where children were randomized to either 7v or 10v PCV in Poland and the Philippines (International obs 7v, International obs 10v). A 2, 4, 6m-schedule was used in Poland and a 1.5, 2.5, 3.5m-schedule in the Philippines. Although the intended starting age for these schedules differed by two weeks, the actual ages at first dose were similar between groups (Table 4.2).

At one month after the primary course (approximately 7 months of age and 4.5 months of age for the 2-month interval and 1-month interval groups, respectively), the percentage seropositive at the 0.35µg/ml and 0.20µg/ml thresholds was above 75% for all vaccine serotypes in both studies. Few were below 90% at the 0.35µg/ml threshold. In the 10v study, these were 6B in the 2- and 1-month interval groups and 23F in the 2-month interval group (78.2%, 81.8% and 88.8%, respectively). In the 7v study, only serotype 6B in the 1-month interval group was below 90% seropositivity at the 0.35µg/ml threshold.

In the 10v study, point estimates for percentages (0.35µg/ml threshold) in the 2-month interval group tended to be similar to or lower than the 1-month interval group, with statistical evidence of a difference for serotypes 1 and 5. In the 10v study, GMCs were consistently lower in the 2-month interval group with confidence intervals not overlapping those of the 1-month interval group for any vaccine serotype. In the 7v study, point estimates for percentages (0.35µg/ml threshold) in the 2-month interval group were similar to or higher than the 1-month interval group, with no statistical evidence of a difference for any serotype.

By 12–18 months of age (pre-booster), seropositivity percentages had fallen somewhat (only data for the 0.20µg/ml threshold available). In the 10v study, the values were below 75% for serotype 1 (both groups), serotype 4 (2-month interval group) and serotype 6B (2-month interval group). In the 10v study, the values were below 75% for serotype 4 (both groups), 6B (both groups), and 19F (both groups). In the 10v study, seropositivity point estimates were lower for all vaccine serotypes in the 2-month interval group and confidence intervals did not overlap between groups for serotypes 1, 4, 6B and 18C. Results were more similar between groups in the 7v study with confidence intervals overlapping. Similar patterns were reflected in GMCs in both studies.

Potential for bias within this comparison

Biases described in 4.4.2.1 for the cohort and case–control studies in general also apply here.

Specific potential causes of biases in the studies included in this comparison

For studies where the age at last vaccination differs between groups (i.e. all studies in this comparison), ages will differ when outcomes are examined at a set interval after the last vaccination. In two of the studies in this comparison, a broad range of ages is given for one of the time points for immunogenicity assessment (12–18m), and it is unclear if the average age was similar between groups (International obs 7v, International obs 10v). These issues may affect results if outcomes vary by age, even in the absence of vaccination.

Additionally, the two studies comparing 3-dose schedules are potentially confounded by both country and co-administered vaccines. The children in 1-month interval groups were in the Philippines and received oral polio vaccine (OPV) while those in the 2-month interval groups were in Poland and received inactivated polio vaccine (IPV).

4.4.2.6 Comparisons R and T: Catch-up vs catch-up, and infant vs catch-up schedules

Summary

- *Clinical and carriage data were scarce for these comparisons.*
- *Immunogenicity data showed lowest seropositivity levels and most variation between schedules for serotypes 6B and 23F.*
- *Seropositivity one month after a 7, 11m schedule (PCV10) was lower than after a 12, 24m schedule (PCV10) or a 2, 3, 4m schedule (PCV10) for serotypes 6B and 23F (1 cohort study).*
- *Seropositivity one month after either a 2, 3, 4 + 12−15m schedule (PCV10) or a 7, 11, + 12−15m schedule (PCV10) was high for all serotypes (1 cohort study).*
- *Potential biases include systematic differences between those recruited at different ages and therefore into different intervention groups. Other biases and confounding could also be present.*

Three cohort studies examined either different toddler schedules (Finland obs 10v, Spain1 obs 7v), or infant and toddler schedules (Finland obs 10v, USA1 obs 7v).

One reported clinical data limited to reports of adverse events (Finland obs 10v), one reported carriage (Spain1 obs 7v) and two reported immunogenicity (Finland obs 10v, USA1 obs 7v). One study compared a 3, 4, 5, 12−15m schedule, a 7, 11, 12−15m schedule, a 12 and 23 month schedule and a single dose at 24 months (Finland obs 10v). Another reported a schedule of 2 doses, 2 months apart (given between 12− 24m) compared to a single dose at ≥24m (PPV might also have been given to some individuals, Spain1 obs 7v). The third study compared a 2, 4, 6m schedule to a single dose at 12 months (USA1 obs 7v).

Clinical data were scarce and only collected as adverse event data (Finland obs 10v). Case definitions were not used for these outcomes. The only cohort study that reported adverse event data for this comparison reported two cases of pneumonia in each of the 3, 4, 5, 12−15m schedule, the 7, 11, 12−15m schedule, and the 12 and 23 month schedule groups. There were 150 vaccinated individuals in each group. In the ≥24m group reported no cases of pneumonia.

Carriage data were also scarce in the sole study that reported this outcome (Spain1 obs 7v) [13]. It was unclear when samples were taken. In the 2-dose group (12−24m at vaccination), four children (7.7%) were carrying *S. pneumoniae* when samples were taken, and in the 1-dose group (≥24m at vaccination) one child (50%) was carrying the bacterium. The single child who was vaccinated before 12 months of age was also carrying *S. pneumoniae* when tested.

Immunogenicity data were reported by two studies (Finland obs 10v, USA1 obs 7v). The first study examined PCV10. In this study, data were available one month after either the third dose (3, 4, 5, 12−15m schedule), the second dose (the 7, 11, 12−15m schedule and the 12, 23m schedule) or the first dose (24m schedule). At this time point, levels of seropositivity were generally high (data reported only for the 0.20μg/ml threshold). Seropositivity was above 95% for all groups for serotypes 1, 4, 5, 7F, 9V, 14, 18C and 19F with the exception of the 24m group for serotypes 9V and 14, and the 3, 4, 5, 12−15 group for serotype 19F. For serotype 23F, seropositivity was generally lower at 87.0%, 70.4%, 91.7% and 66.9% for the groups from the lowest to highest age

at start of vaccination. For serotype 6B, seropositivity was 72.5%, 51.1%, 81.2% and 68.6% for the groups from the lowest to highest age at start of vaccination.

Pre- and post-booster data were also available for the 3, 4, 5, 12−15m and the 7, 11, 12−15m schedule. Once again, data were reported only for the 0.20μg/ml threshold. Before the booster, more than 90% of individuals were seropositive for many serotypes. The exceptions were serotypes 1, 6B and 23F for both groups and serotypes 4, 5 and 19F for the 3, 4, 5, 12−15m schedule, where 70−90% of individuals were seropositive. After the booster dose, more that 95% were positive for all serotypes in both groups.

In the second study, sample sizes were very small for healthy children at all time points, limiting precision of results (USA1 obs 7v). Neither a 0.35μg/ml nor a 0.20μg/ml threshold was reported. When considering GMCs amongst healthy children, neither schedule (2, 4, 6m and single dose at 12m) appeared superior when compared at one month after the last vaccination or at around 12 months of age (12m for the 3p+1 group and 13m for the single-dose group). At one month after the last PCV dose, GMCs were lower in the single-dose group than the 3p group for serotypes 6B and 23F, and at around 12 months of age, GMCs were higher in the single-dose group than the 3p group for serotypes 4 and 18C and lower for serotype 6B. By 24 months of age, the point estimates of GMCs were higher in the single-dose group for all serotypes, but confidence intervals were wide.

Potential for bias within this comparison

Biases described in 0 for the cohort and case−control studies in general also apply here.

Specific potential causes of biases in the studies included in this comparison

Group allocation for all studies in this comparison was based on age at recruitment. If systematic differences (in addition to age) exist between those recruited and younger and older ages, results may be biased.

4.4.2.7 Comparisons U to Z: Vaccine effectiveness estimates

Summary

- *Effectiveness was high against vaccine-type IPD for all 2- or 3-dose infant schedules examined in one case−control study.*
- *A 2p+1 and 3p+1 schedule both appeared to have some effectiveness against pneumonia, but the outcome reported (clinically or radiologically diagnosed pneumonia) differed between studies, making comparison difficult (2 cohort studies).*
- *There was less carriage of any serotype after a 3p+1 schedule compared to no vaccination (1 cohort study).*
- *In a study of toddler vaccination, vaccine serotype carriage did not differ between vaccinated and unvaccinated children (1 cohort study).*
- *The potential for bias and confounding vary by study.*

a) Comparison U1: 1p vs no PCV

One case−control study estimated the effectiveness of individual schedules against vaccine serotype IPD (USA2 obs 7v) at 73% (95% CI 43−87) for 1 dose given before 7 months of age.

No data for this comparison were available from cohort studies.

b) Comparison U2: 2p vs no PCV

One case–control study estimated the effectiveness of individual schedules against vaccine serotype IPD (USA2 obs 7v) at 96% (95% CI 88–99) for 2 doses given before 7 months.

No data for this comparison were available from cohort studies.

c) Comparison U3: 3p vs no PCV

One case–control study estimated the effectiveness of individual schedules against vaccine serotype IPD (USA2 obs 7v) at 95% (95% CI 88–98) for 3 doses given before 7 months.

No data for this comparison were available from cohort studies.

d) Comparison W2: 2p+1 vs no PCV

One case–control study estimated the effectiveness of individual schedules against vaccine serotype IPD (USA2 obs 7v) at 98% (95% CI 75–100) for 2 doses given before 7 months and a booster at 12–16 months.

In the cohort study that reported this comparison, a 2p+1 schedule showed a marked effectiveness against radiologically confirmed pneumonia (65%, 95% CI 47, 78), but no protective effect was seen in the period between the primary schedule and the booster dose (Italy obs 7v).

e) Comparison W3: 3p+1 vs no PCV

One case–control study estimated the effectiveness of individual schedules against vaccine serotype IPD (USA2 obs 7v) at 100% (95% CI 94–100) for 3 doses given before 7 months and a booster at 12–16 months (3p+1).

One cohort study examined clinical outcomes for the 3p+1 vs no PCV comparison. The estimate of effectiveness of this schedule against clinical pneumonia from the first dose until the end of two years of follow-up was 24.8% (95% CI 1, 43) in a propensity score matched analysis (Germany obs 7v).

One cohort study investigated carriage for this comparison. There was less carriage of any serotype after a 3p+1 schedule compared to no vaccination (31% of controls and 15% of vaccinees) an unspecified time after vaccination (Korea obs 7v).

f) Comparison Y: 1 or 2 catch-up doses (with or without PPV) vs no PCV

One case–control study estimated the effectiveness of individual schedules against vaccine serotype IPD (USA2 obs 7v) at 93% (95% CI 68–98) for 1 dose at 12–23 months of age, and 96% (95% CI 81–99) for 2 doses at 12–23 months of age (USA2 obs 7v).

Little difference was seen in carriage of vaccine serotypes between toddlers receiving catch-up doses and unvaccinated toddlers in one small cohort study (Norway obs 7v).

g) Other comparisons

Two eligible case–control studies reported results for a comparison of more than 1 dose of PCV to no PCV (Spain2 obs 7v, USA2 obs 7v). The vaccine effectiveness against vaccine serotype IPD for this analysis was 88% (95% CI 9, 98) in all children in Spain2 obs 7v and 96% (95% CI 93, 98) for healthy children and 81% (95% CI 57, 92) for children with co-morbid conditions in USA2 obs 7v.

4.5 Discussion

The review identified 18 eligible cohort studies and two eligible case–control studies. A total of 15 different comparisons of schedules (or a schedule and no PCV) were examined in the cohort studies and 11 in the case–control studies. Three cohort studies reported clinical disease outcomes, four reported carriage outcomes and eight reported immunological outcomes. Both case–control studies examined IPD.

4.5.1 Strengths and limitations

This review of cohort and case–control studies was carried out in the context of a larger review of PCV schedules that searched numerous and diverse databases using broad search terms without filters to identify specific study designs. Important studies are therefore unlikely to have been missed. The overall number of items retrieved from electronic database searches was very high compared to the yield of relevant eligible observational studies. However, observational studies that examined comparisons between schedules without stating this in the abstract might have been excluded.

Observational studies offer advantages as well as disadvantages over well-conducted randomized trials. Advantages include, but are not limited to, the possibility of examining exposures that might be difficult or unethical to examine in RCTs; the investigation of rare outcomes that would otherwise require extremely large RCTs; filling data gaps for questions where no RCTs have been conducted; and the estimation of vaccine effectiveness post-licensure. In this review, the only data about clinical disease outcomes for schedule comparison were from one case–control study [25].

Disadvantages include a greater risk of bias and confounding than in a well-conducted RCT. Such biases can result in under- or overestimates of vaccine effectiveness. In some situations, the direction of such biases can be predicted but frequently the magnitude and direction of biases cannot be estimated, limiting the interpretation of data from observational sources.

Other observational study designs have not been included in this review. The most important of these, in the context of investigating the outcomes of different vaccination schedules, are studies based on surveillance data with population level measures of exposures and outcomes (i.e. ecological studies). Most commonly, such studies estimate incidence before and after the introduction of vaccination in a population. Ecological studies are particularly prone to biases and confounding and require special care in analysis and interpretation. Studies of the impact of PCV and the methods for analysis are the topic of a separate detailed review.

4.5.2 Main findings

Due to low statistical power in the case–control study, confidence intervals for odds ratios for vaccine serotype IPD were wide and crossed 1 for the following comparisons: 3p vs 2p, 3p vs 2p+1, and 3p+1 vs 2p+1. There was some statistical evidence that the 3p+1 schedule was associated with less IPD than a 3p schedule, but the odds ratio was only adjusted for underlying conditions.

Effectiveness was high against vaccine serotype IPD for all 2- or 3-dose infant schedules (in comparison with no vaccination) examined in the case–control studies.

Seropositivity was similar between 3p and 2p groups one month after vaccination, and the 3p group had slightly higher seropositivity estimates for most serotypes eight months after primary vaccination. One month after a booster dose at 12 months, similar GMCs were reported for both groups (no seropositivity reported).

There was some suggestion in the data that a 2-month interval might be associated with better immune responses than 1-month intervals for the 7-valent vaccine, while the reverse might be true for the 10 valent vaccine, but there is potential confounding from co-administered vaccines.

In comparisons of catch-up (toddler) vaccination schedules to other catch-up schedules or to infant schedules, immunogenicity data showed lowest seropositivity levels and most variation between schedules for serotypes 6B and 23F

4.5.3 Findings from other observational studies

Studies examined in this review were restricted to cohort and case–control studies reporting on pre-specified outcomes. Furthermore, studies were not included in this review if they reported only IPD case data, or reported carriage as a percentage of samples and not of individuals. However, the results of these excluded studies were broadly similar to the included studies.

Specifically, two carriage studies were eligible except for the denominator type (samples, not individuals) [20, 21]. The first study examined mainly the carriage of drug-resistant strains, but stated that "no significant differences between vaccinees and the control group in the total carriage rate of pneumococcus" were detected [20]. Vaccinees received 3 doses if aged 6–11 months, 2 doses if aged 12–24 months or 1 dose if older than 24 months. It is not clear if repeated measurement was accounted for in this analysis. The second study concluded that PCV7 serotypes were detected less after third and fourth PCV7 doses. However, longer dosing intervals, particularly in day-care attendees, were associated with higher risk of PCV7 detection in the nasopharynx when comparing a dosing interval longer than 3 months with a shorter interval [21]. Repeated measures were accounted for in this analysis. There was no analysis to assess differences in carriage between 1- or 2-month intervals as examined in other observational studies.

One case–control study was excluded as it only used data from children with IPD [23]. In contrast to the included case–control studies, the odds of vaccination were compared between children with vaccine and with non-vaccine serotype. Results were adjusted for the year in which the IPD occurred. Vaccine effectiveness against vaccine serotype IPD was estimated at 38.8% (95% CI -79.7–79.1) for 1 dose given before 3 months of age, 70.5% (95% CI 28.0–87.9) for 2 doses before 5 months, 76.6% (95% CI 50.4–88.9) for 3 doses before 7 months, and 90.5% (95% CI 17.7–98.9) for 3 doses before 7 months plus a booster at 12–15 months. Additionally, vaccine effectiveness against vaccine serotype IPD for toddler doses were estimated as 55.0% (95% CI -240.7–94.1) for 1 dose between 12 and 24 months and 68.2% (95% CI -219.6–96.8) for 2 doses between the same ages. These estimates are markedly lower than those from the other case–control study reporting effectiveness for these schedules. This might reflect how well the selected controls represent the population from which the cases of vaccine serotype IPD arose in terms of vaccine coverage.

Pelton et al. report a retrospective matched cohort study in the USA, comparing 2 vs 3 primary doses of PCV7 [26]. The outcome was 'lower respiratory tract disease', including bronchitis, bronchiolitis, asthma or wheezing, and pneumonia due to pneumococcal infection or unspecified cause. This study was not included because results were not stratified by diagnosis, and the composite outcome was not one pre-specified in the review. Results showed fewer hospital admissions and outpatient visits for lower respiratory tract disease for children receiving 3 vs 2 primary doses before a booster dose. Outcomes did not differ during the post-booster observation period. These findings are difficult to compare with other studies in the review because of the different outcome definition. More studies which examine the relative effect of vaccination schedules on pneumonia would be useful.

Studies reporting routine surveillance data are the subject of another detailed review and thus are not discussed here.

4.5.4 Findings in relation to RCTs

When viewed with results from RCTs, several points can be noted:

- One case–control study compared schedules for the prevention of vaccine serotype IPD, which was not possible in the RCTs. However, confidence intervals were very wide and statistical evidence for a difference was limited to a comparison of 3p+1 and 3p schedules, adjusted only for underlying conditions (3p+1 was more effective).
- Results from cohort studies for the comparison of immunogenicity after 3p or 2p schedules are broadly similar to those found in RCTs (i.e. there is some suggestion that 3p might be slightly more immunogenic than 2p, but the statistical evidence is not strong).
- A comparison of 3p+1 with 2p+1 showed similar results in both groups in the cohort study, and did not show the differences observed for 6B and 23F in RCTs (however, only GMCs were reported in the cohort studies and the differences in RCTs were seen in seropositivity data).
- There were no direct comparisons of 1- and 2-month intervals (where the same number of doses were given in each group) in RCTs, so the information provided by the cohort studies summarizes currently available data.

4.5.5 Implications for future research

Systematic reviews investigating vaccination schedules that include case–control and cohort studies can contribute clinical data that are not available from RCTs. The added value of including these study designs in literature searches needs to be weighed against the much larger numbers of items retrieved from less specific search strategies.

Primary studies reporting composite clinical outcomes should give descriptive information about the distribution of individual outcomes, even if fully stratified analyses have not been carried out.

Additional information about the effects of different intervals between doses in a primary schedule would be valuable, particularly for 2-dose primary schedules. RCTs examining different intervals are also needed. Observational study designs are well-suited to collecting information on the actual dates of vaccination in practice.

4.6 Conclusions

Results from cohort and case–control studies supplemented the data available from RCTs. The comparisons and outcomes of these observational studies did not alter the conclusions reached from the review of RCTs.

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Annex 1
Search strategy

Embase.com

(

(

('**pneumococcus vaccine**'/syn)

OR

('**pneumococcal vaccine**'/syn)

OR

(**pneumococcal** AND '**vaccine**'/syn)

OR

(('**vaccine**'/syn) AND ('**pneumococcus**'/syn))

OR

((('**vaccine**'/syn) OR ('**immunization**'/syn) OR (**vacc***:ab,ti) OR (**immuni?ation***:ab,ti)) AND (**pneumococc***:ab,ti))

OR

((**pneumococc***:de) AND (**vacc***:de))

OR

((**pneumococc***:de) AND (**immuni?ation***:de))

OR

(**pneumococcal** AND ('**vaccine**'/exp OR '**vaccine**'))

OR

('**pneumococcal vaccine**'/exp OR '**pneumococcal vaccine**')

OR

(**pneumococcal** AND ('**vaccination**'/exp OR '**vaccination**'))

OR

('**pneumococcal vaccination**')

OR

((('**vaccine**'/syn) OR ('**immunization**'/syn) OR (**vacc***:ab,ti) OR (**immuni?ation***:ab,ti)) AND (((**strep***:ab,ti) AND (**pneumoniae**:ab,ti)) OR ('**streptococcus pneumoniae**'/syn))

)

OR

((('vaccine'/syn) OR ('immunization'/syn) OR (vacc*:ab,ti) OR (immuni?ation*:ab,ti)) AND (('pneumococcal infection'/syn) OR ((('infection'/syn) OR (infection*:ab,ti) OR (disease*:ab,ti)) AND (pneumococc*:ab,ti)) OR ((('infection'/syn) OR (infection*:ab,ti) OR (disease*:ab,ti)) AND (((strep*:ab,ti) AND (pneumoniae:ab,ti)) OR ('streptococcus pneumoniae'/syn)))))

)

AND

(('conjugate'/syn) OR (conjug*:ab,ti) OR (conjug*))

Cochrane Library

ID Search Hits

#1 (pneumoco* or strep*) AND (vaccin* OR immuni*) AND conjugate*

#2 MeSH descriptor Pneumococcal Vaccines explode all trees

#3 conjugate*

#4 (#2 AND #3)

#5 (#1 OR #4)

Current Controlled Trials metaRegister of Controlled Trials (mRCT) – active registers

(pneumococc* OR strep*) AND (vaccine* OR immuni*) AND conjugate*

Current Controlled Trials metaRegister of Controlled Trials (mRCT) – archived registers

pneumococc*

UK Clinical Trials Gateway

pneumococc*

WHO : International Clinical Trials Registry Platform Search Portal

(pneumococc* OR strep*) AND (vaccine* OR immuni*) AND conjugate*

AIM

pneumococc$ OR strep$

Lilacs

(pneumococc$ OR strep$) AND (vaccin$ OR immuni$) AND conjugate$

INDMED

(pneumococc$ OR strep$) AND (vaccin$ OR immuni$)

FDA

Search by licensed name – Prevnar only

EMEA

Search European Public Assessment Reports (EPARs) by licensed name – Prevenar and Synflorix

GSK

Compound name: Pneumococcal Polysaccharide Conjugate Vaccine (Adsorbed)

WYETH

redirected to clinicaltrials.gov and clinicalstudyresults.org

Clinicalstudyresults.org

Searched by drug name: prevnar, prevenar, synflorix

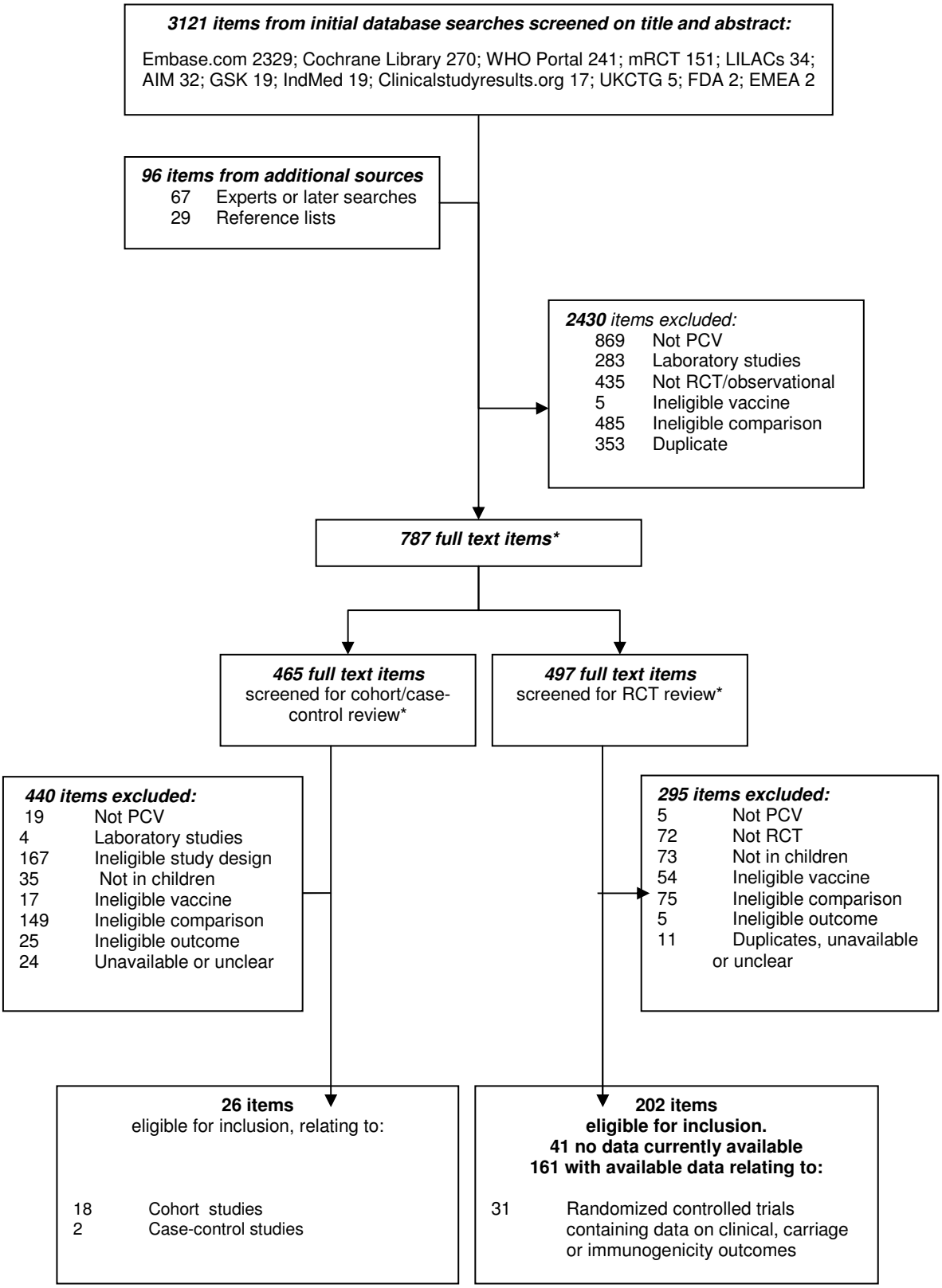
Annex 2.1

A systematic review of clinical and carriage data from randomized controlled trials of childhood schedules using 7-, 9-, 10- and 13-valent pneumococcal conjugate vaccines: Figures and tables

Figures

Tables

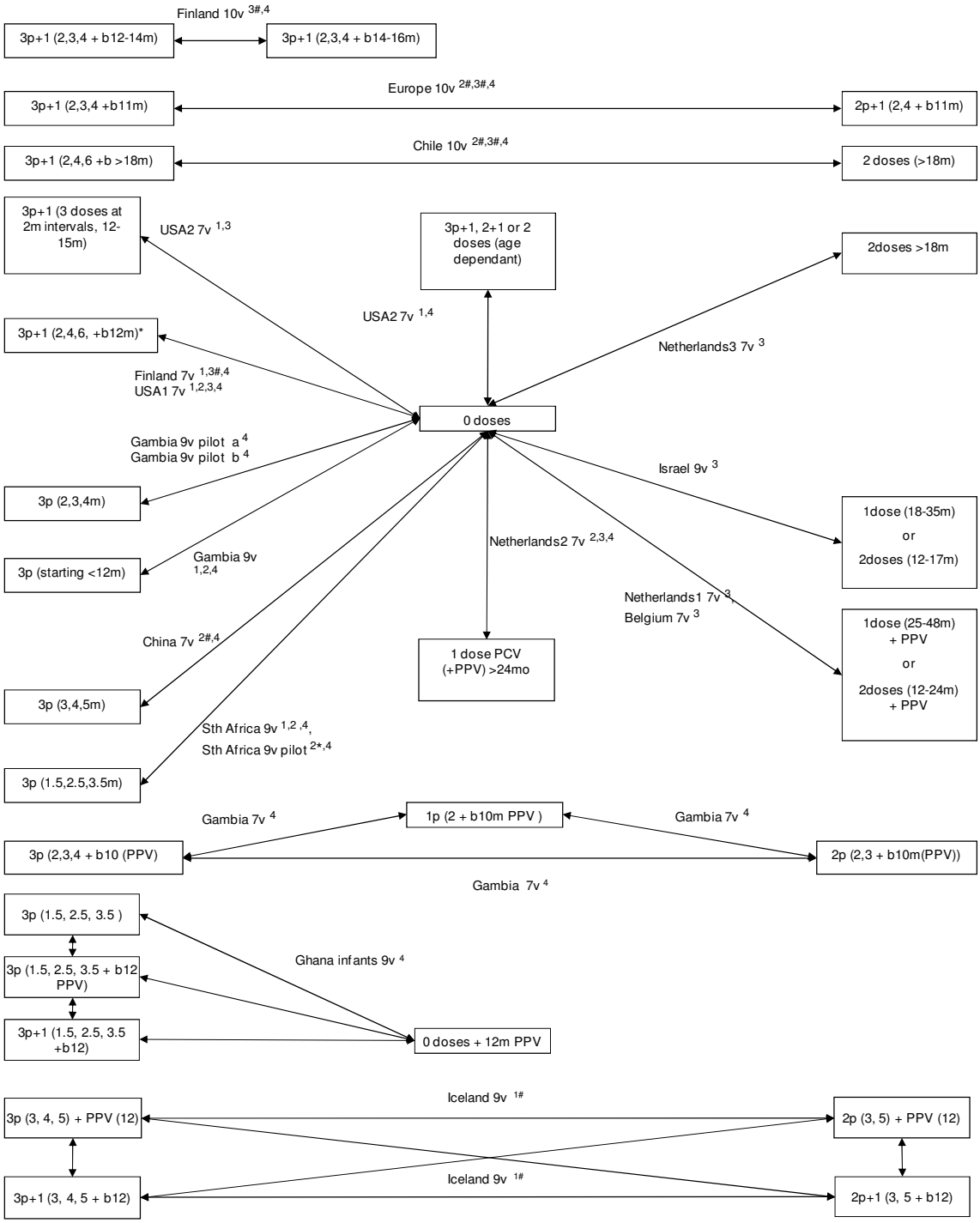
Figure 2.1: Flow chart of studies for full systematic review



* 175 full text items reviewed for eligibility in both RCT and cohort/case-control reviews as potential randomized and observational components

AIM - African Index Medicus; EMEA – European Medicines Agency; FDA – U.S. Food and Drug Administration ; GSK - GlaxoSmithKline ; IndMed - Indexing of Indian Medical Journals ; LILACs - Latin American and Caribbean Health Sciences ; mRCT - metaRegister of Controlled Trials ; PCV - ; RCT – Randomized controlled trial ; WHO Portal – World Health Organization Clinical Trials Search Portal ; UKCTG - UK Clinical Trials Gateway

Figure 2.2: Clinical outcomes following PCV vaccination: comparisons available in included trials



Legend:

PCV – pneumococcal conjugate vaccine; PPV – pneumococcal polysaccharide vaccine; b – booster (PCV unless explicitly stated as PPV);

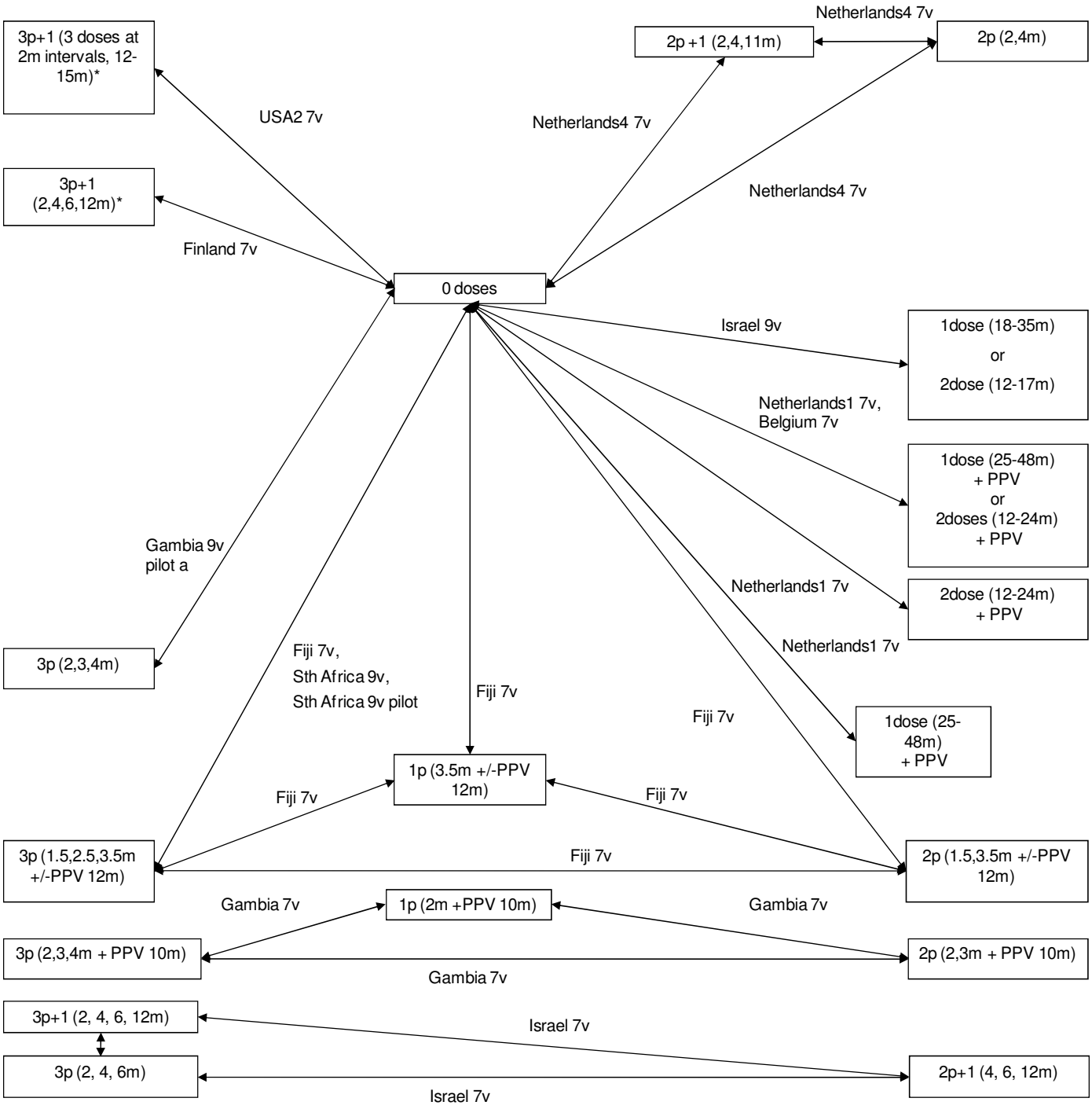
Studies not included in this report if mortality was the only clinical or carriage outcome, and it was reported there were no deaths or mortality data could not be extracted. There are 4 studies in this category: 3 report no deaths [1-3] and for 1 mortality data were not extractable [4];

3p + 1 (2,3,4,11m) Schedule described as, e.g. 3p – number of doses in primary schedule; +1 – booster dose; (2,3,4,11m) – ages when vaccine doses intended to be given;

Study names for each comparison are along the lines connecting each schedule;

Superscript numbers refer to outcomes described: 1 – IPD; 2 – pneumonia; 3 – otitis media; 4 – mortality; # - outcome extracted from reports of (serious) adverse events only; * not reported separately for each intervention group.

Figure 2.3: Carriage of pneumococcal serotypes following PCV vaccination: comparisons available in included trials



Legend:

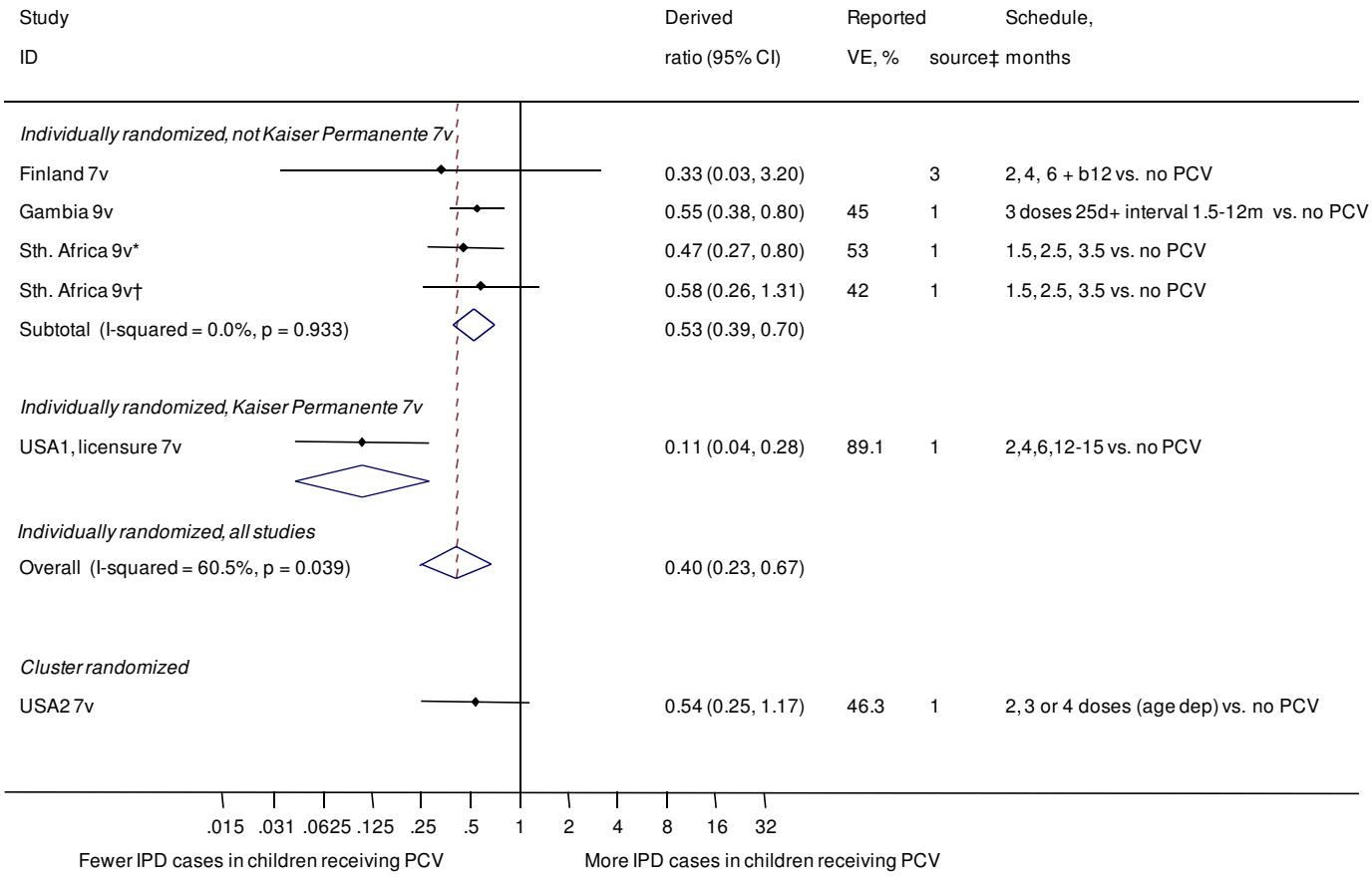
PCV – pneumococcal conjugate vaccine; PPV – pneumococcal polysaccharide vaccine; b – booster (PCV unless explicitly stated as PPV);

3p + 1 (2,3,4,11m) Schedule described as, e.g. 3p – number of doses in primary schedule; +1 – booster dose; (2,3,4,11m) – ages when vaccine doses intended to be given;

Study names for each comparison are along the lines connecting each schedule;

Superscript numbers refer to outcomes described: 1 – IPD; 2 – pneumonia; 3 – otitis media; 4 – mortality; * sample/s also taken before booster dose.

Figure 2.4: Invasive pneumococcal disease, any serotype, intention to treat analysis



Legend:

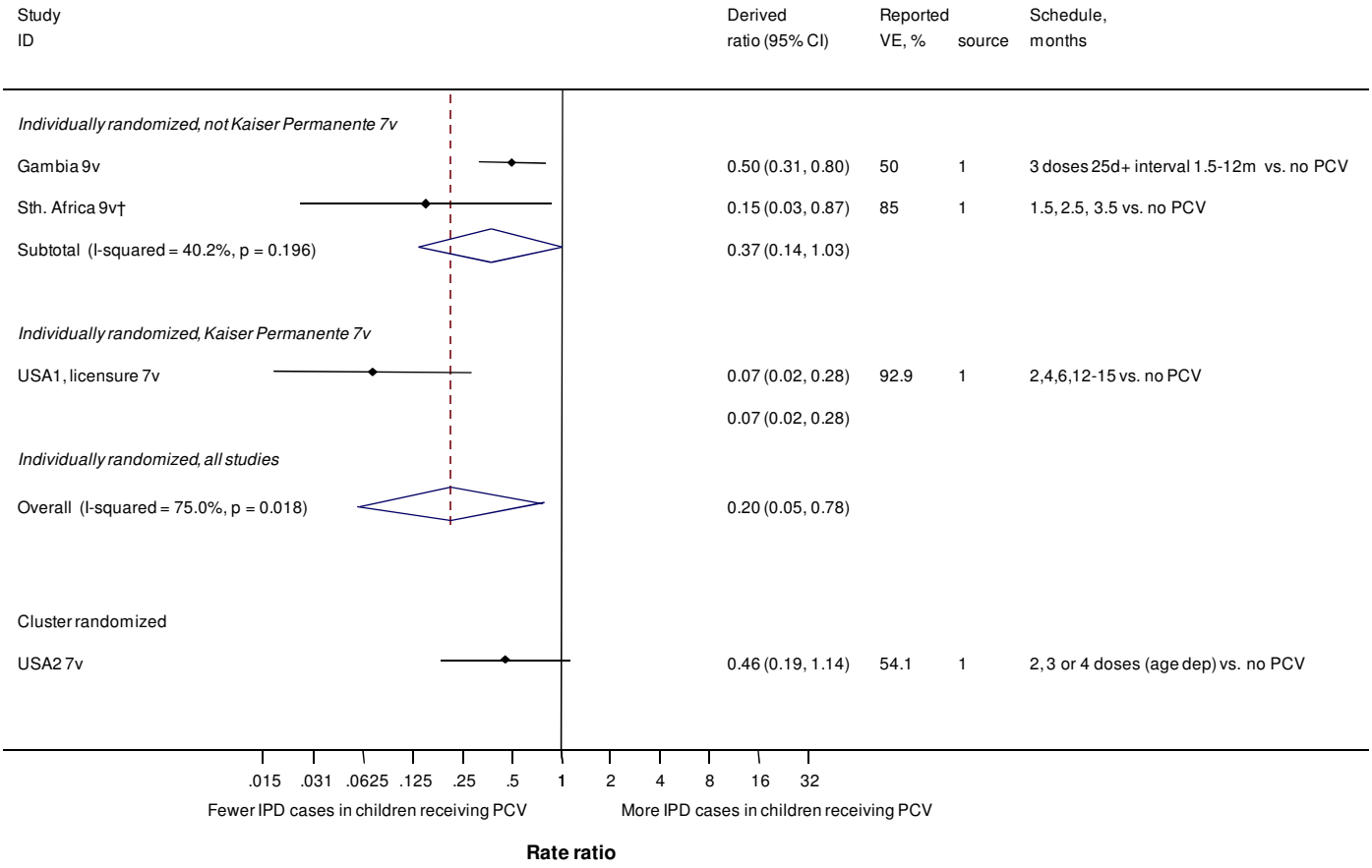
IPD – invasive pneumococcal disease; * HIV-infected; † HIV-uninfected; ‡ Source of derived ratio (1, from a reported VE based on a rate ratio; 2, reported rate ratio; 3, risk ratio calculated from reported cases/events and denominator data).

Horizontal axis represents effect estimate on logarithmic scale, comparing IPD in groups of children receiving PCV *vs.* no PCV; vertical line through 1 shows no difference in IPD incidence between groups; effect estimate might differ between studies, depending on data provided in trial report;

Solid black diamonds represent point estimate of effect estimate ratio; horizontal black line represents 95% confidence interval; points to the left of the vertical black line show a beneficial effect of PCV (fewer cases of IPD in PCV group), points to the right of the line show a detrimental effect of PCV (more cases of IPD in PCV group);

Blue diamond represents the pooled estimate, combined using random effects meta-analysis; vertical points of diamond represent point estimate and horizontal points represent 95% confidence interval; red dashed vertical line represents combined effect amongst individually randomized studies; I^2 value is the level of statistical heterogeneity between trials (<25% low heterogeneity).

Figure 2.5: Invasive pneumococcal disease, any serotype, per-protocol analysis



Legend:

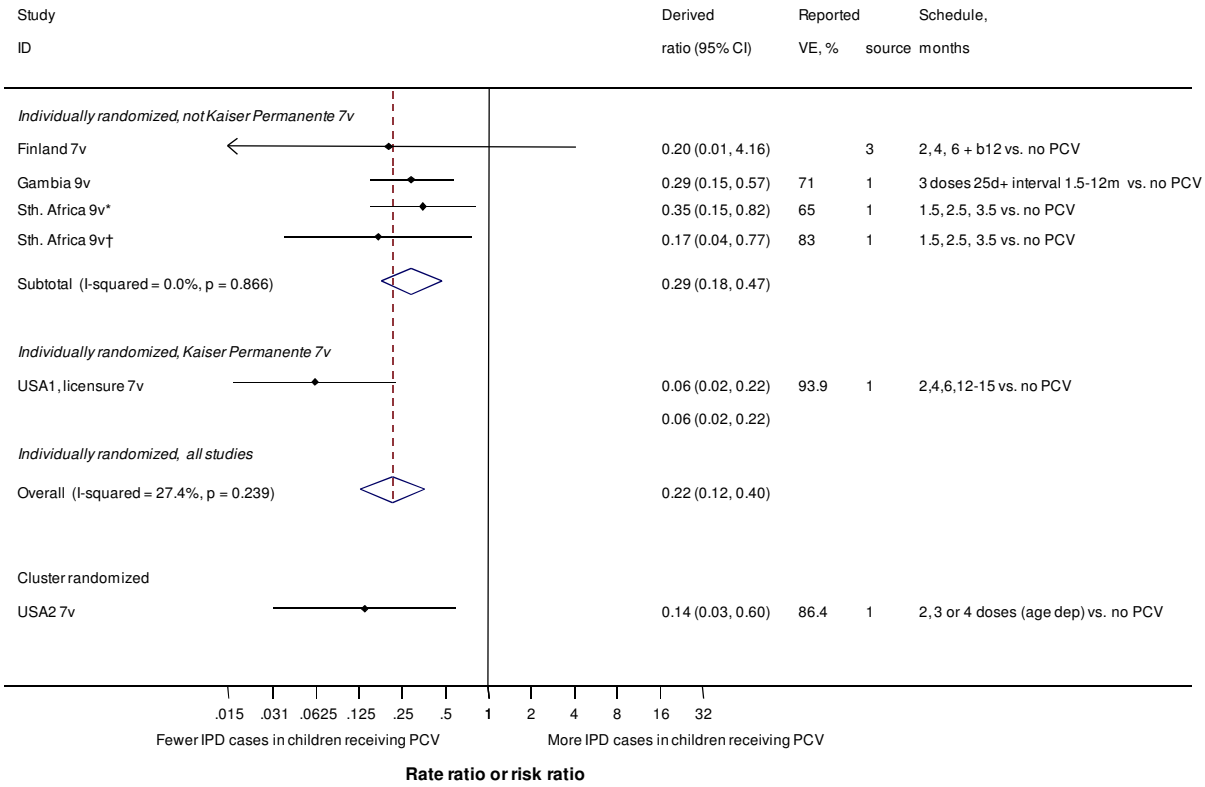
IPD – invasive pneumococcal disease; * HIV-infected; † HIV-uninfected; ‡ Source of derived ratio (1, from a reported VE based on a rate ratio; 2, reported rate ratio; 3, risk ratio calculated from reported cases/events and denominator data).

Horizontal axis represents effect estimate on logarithmic scale, comparing IPD in groups of children receiving PCV *vs.* no PCV; vertical line through 1 shows no difference in IPD incidence between groups; effect estimate might differ between studies, depending on data provided in trial report;

Solid black diamonds represent point estimate of effect estimate ratio; horizontal black line represents 95% confidence interval; points to the left of the vertical black line show a beneficial effect of PCV (fewer cases of IPD in PCV group), points to the right of the line show a detrimental effect of PCV (more cases of IPD in PCV group);

Blue diamond represents the pooled estimate, combined using random effects meta-analysis; vertical points of diamond represent point estimate and horizontal points represent 95% confidence interval; red dashed vertical line represents combined effect amongst individually randomized studies; I^2 value is the level of statistical heterogeneity between trials (<25% low heterogeneity).

Figure 2.6: Invasive pneumococcal disease, vaccine serotype, intention to treat analysis



Legend:

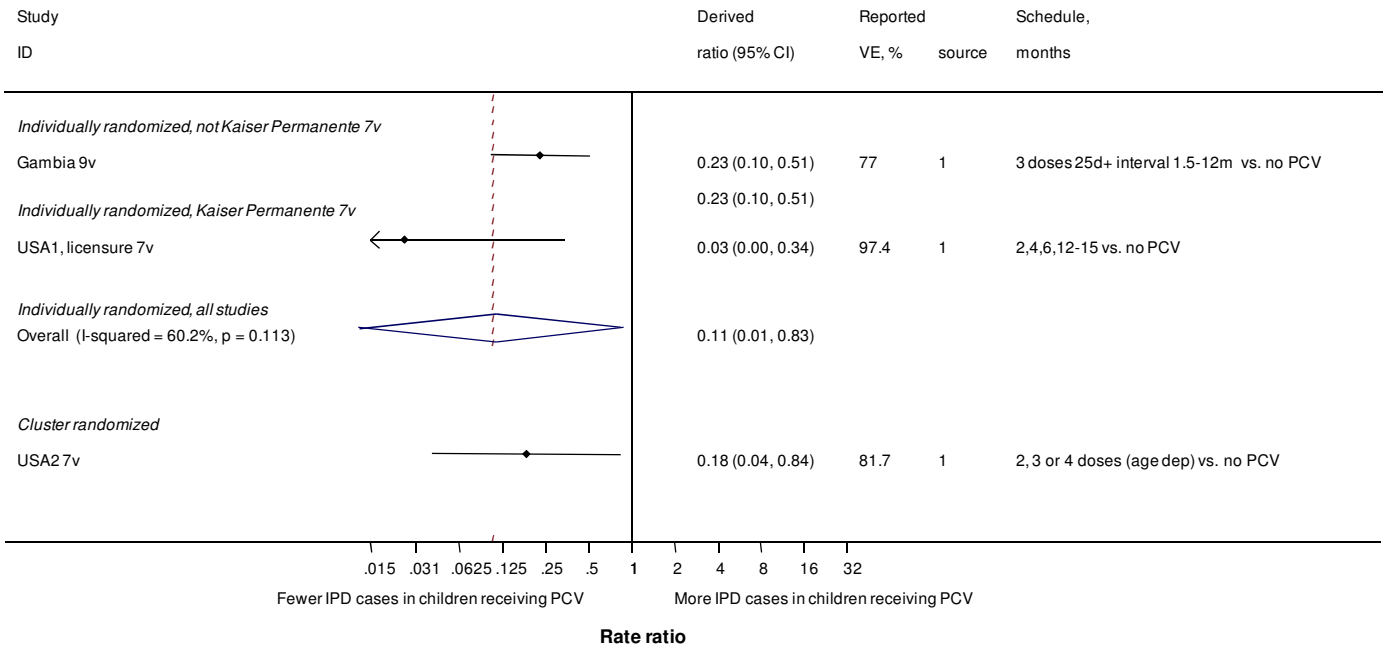
IPD – invasive pneumococcal disease; * HIV-infected; † HIV-uninfected; ‡ Source of derived ratio (1, from a reported VE based on a rate ratio; 2, reported rate ratio; 3, risk ratio calculated from reported cases/events and denominator data).

Horizontal axis represents effect estimate on logarithmic scale, comparing IPD in groups of children receiving PCV *vs.* no PCV; vertical line through 1 shows no difference in IPD incidence between groups; effect estimate might differ between studies, depending on data provided in trial report;

Solid black diamonds represent point estimate of effect estimate ratio; horizontal black line represents 95% confidence interval; points to the left of the vertical black line show a beneficial effect of PCV (fewer cases of IPD in PCV group), points to the right of the line show a detrimental effect of PCV (more cases of IPD in PCV group);

Blue diamond represents the pooled estimate, combined using random effects meta-analysis; vertical points of diamond represent point estimate and horizontal points represent 95% confidence interval; red dashed vertical line represents combined effect amongst individually randomized studies; I^2 value is the level of statistical heterogeneity between trials (<25% low heterogeneity).

Figure 2.7: Invasive pneumococcal disease, vaccine serotype, per-protocol analysis



Legend:

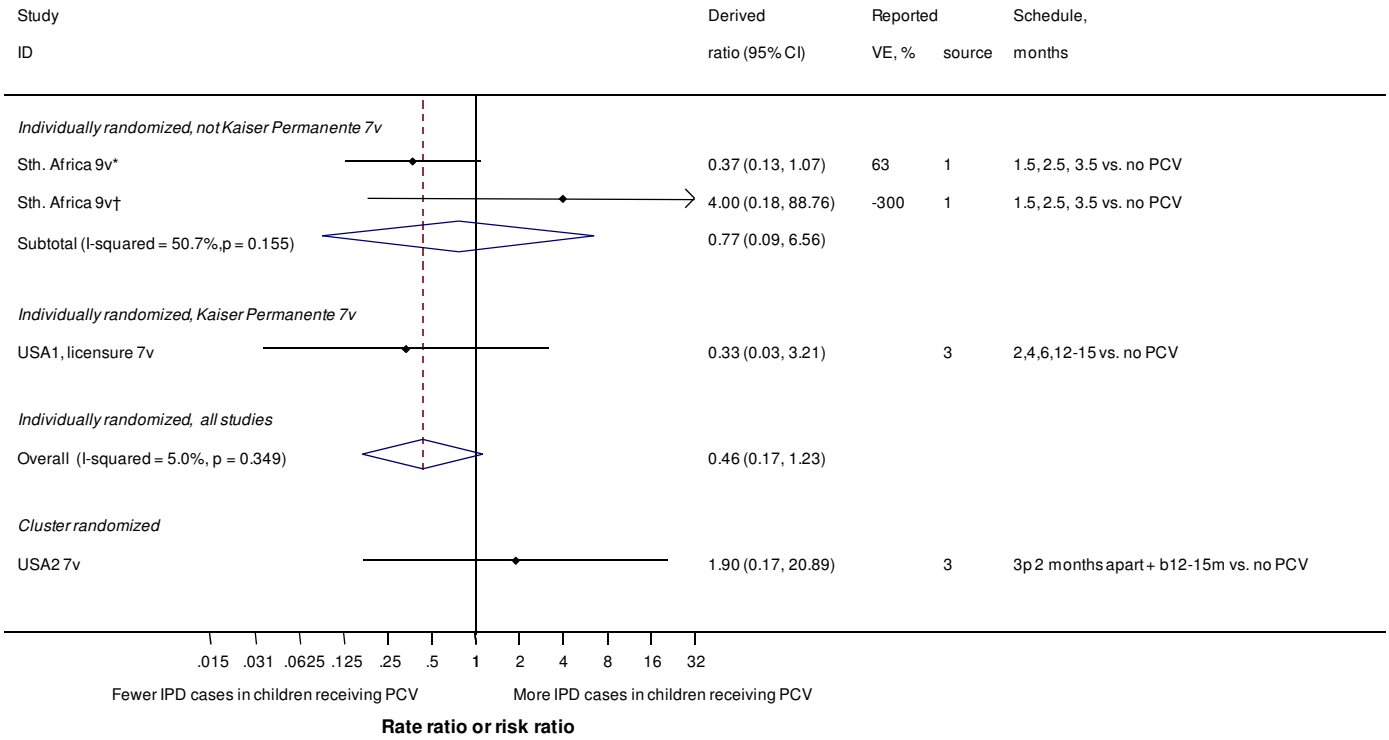
IPD – invasive pneumococcal disease; * HIV-infected; † HIV-uninfected; ‡ Source of derived ratio (1, from a reported VE based on a rate ratio; 2, reported rate ratio; 3, risk ratio calculated from reported cases/events and denominator data).

Horizontal axis represents effect estimate on logarithmic scale, comparing IPD in groups of children receiving PCV *vs.* no PCV; vertical line through 1 shows no difference in IPD incidence between groups; effect estimate might differ between studies, depending on data provided in trial report;

Solid black diamonds represent point estimate of effect estimate ratio; horizontal black line represents 95% confidence interval; points to the left of the vertical black line show a beneficial effect of PCV (fewer cases of IPD in PCV group), points to the right of the line show a detrimental effect of PCV (more cases of IPD in PCV group);

Blue diamond represents the pooled estimate, combined using random effects meta-analysis; vertical points of diamond represent point estimate and horizontal points represent 95% confidence interval; red dashed vertical line represents combined effect amongst individually randomized studies; I^2 value is the level of statistical heterogeneity between trials (<25% low heterogeneity).

Figure 2.8: Invasive pneumococcal disease, vaccine associated serotypes, intention to treat analysis



Legend:

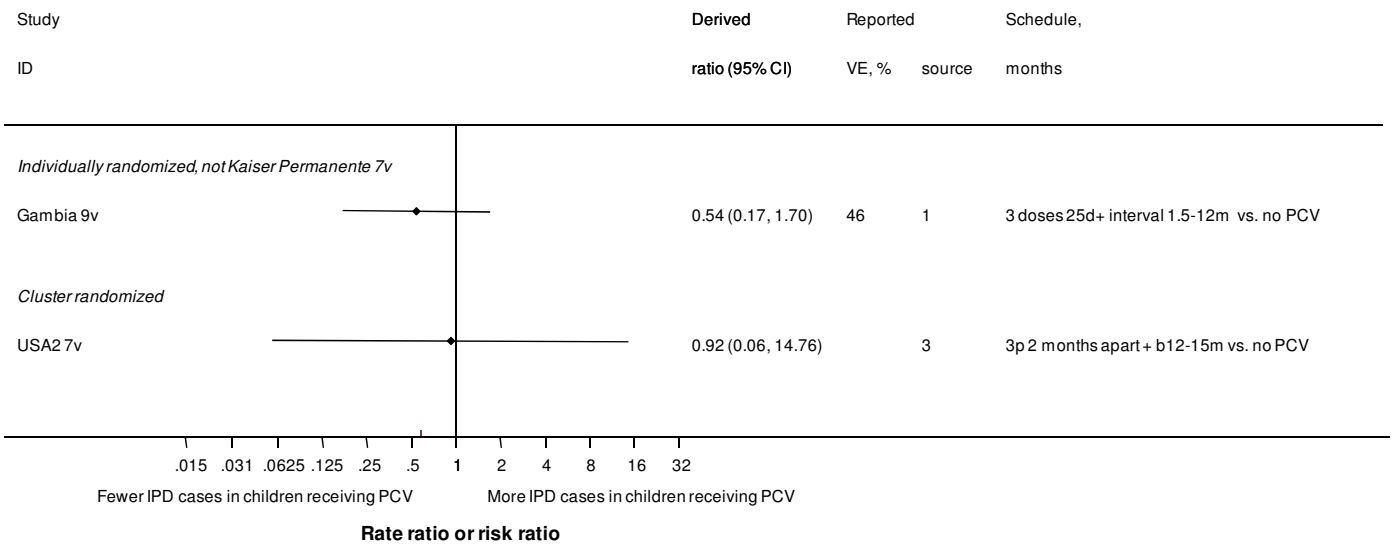
IPD – invasive pneumococcal disease; * HIV-infected; † HIV-uninfected; ‡ Source of derived ratio (1, from a reported VE based on a rate ratio; 2, reported rate ratio; 3, risk ratio calculated from reported cases/events and denominator data).

Horizontal axis represents effect estimate on logarithmic scale, comparing IPD in groups of children receiving PCV *vs.* no PCV; vertical line through 1 shows no difference in IPD incidence between groups; effect estimate might differ between studies, depending on data provided in trial report;

Solid black diamonds represent point estimate of effect estimate ratio; horizontal black line represents 95% confidence interval; points to the left of the vertical black line show a beneficial effect of PCV (fewer cases of IPD in PCV group), points to the right of the line show a detrimental effect of PCV (more cases of IPD in PCV group);

Blue diamond represents the pooled estimate, combined using random effects meta-analysis; vertical points of diamond represent point estimate and horizontal points represent 95% confidence interval; red dashed vertical line represents combined effect amongst individually randomized studies; I^2 value is the level of statistical heterogeneity between trials (<25% low heterogeneity).

Figure 2.9: Invasive pneumococcal disease, vaccine associated serotypes, per-protocol analysis



Legend:

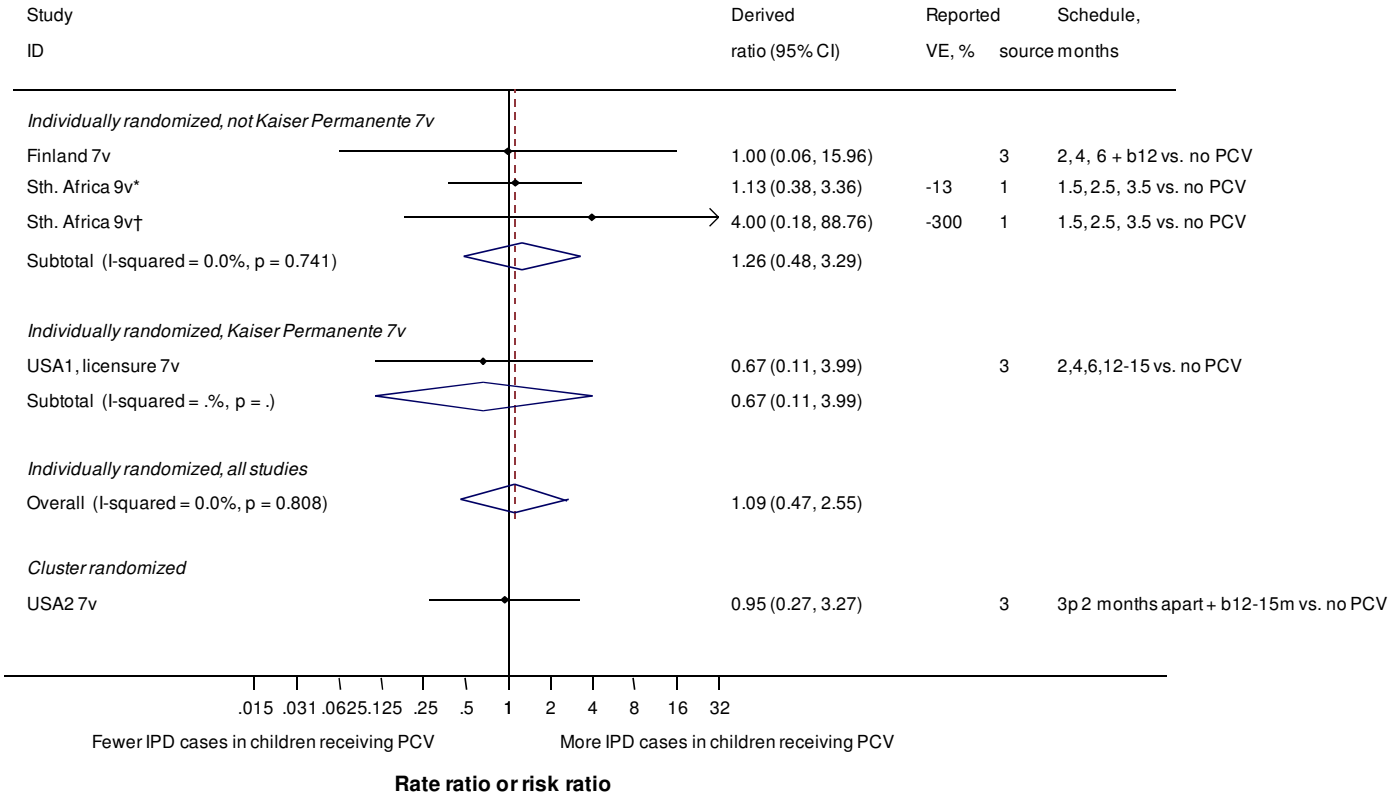
IPD – invasive pneumococcal disease; * HIV-infected; † HIV-uninfected; ‡ Source of derived ratio (1, from a reported VE based on a rate ratio; 2, reported rate ratio; 3, risk ratio calculated from reported cases/events and denominator data).

Horizontal axis represents effect estimate on logarithmic scale, comparing IPD in groups of children receiving PCV *vs.* no PCV; vertical line through 1 shows no difference in IPD incidence between groups; effect estimate might differ between studies, depending on data provided in trial report;

Solid black diamonds represent point estimate of effect estimate ratio; horizontal black line represents 95% confidence interval; points to the left of the vertical black line show a beneficial effect of PCV (fewer cases of IPD in PCV group), points to the right of the line show a detrimental effect of PCV (more cases of IPD in PCV group);

Blue diamond represents the pooled estimate, combined using random effects meta-analysis; vertical points of diamond represent point estimate and horizontal points represent 95% confidence interval; red dashed vertical line represents combined effect amongst individually randomized studies; I^2 value is the level of statistical heterogeneity between trials (<25% low heterogeneity).

Figure 2.10: Invasive pneumococcal disease, non-vaccine serotypes (excluding vaccine associated serotypes), intention to treat analysis



Legend:

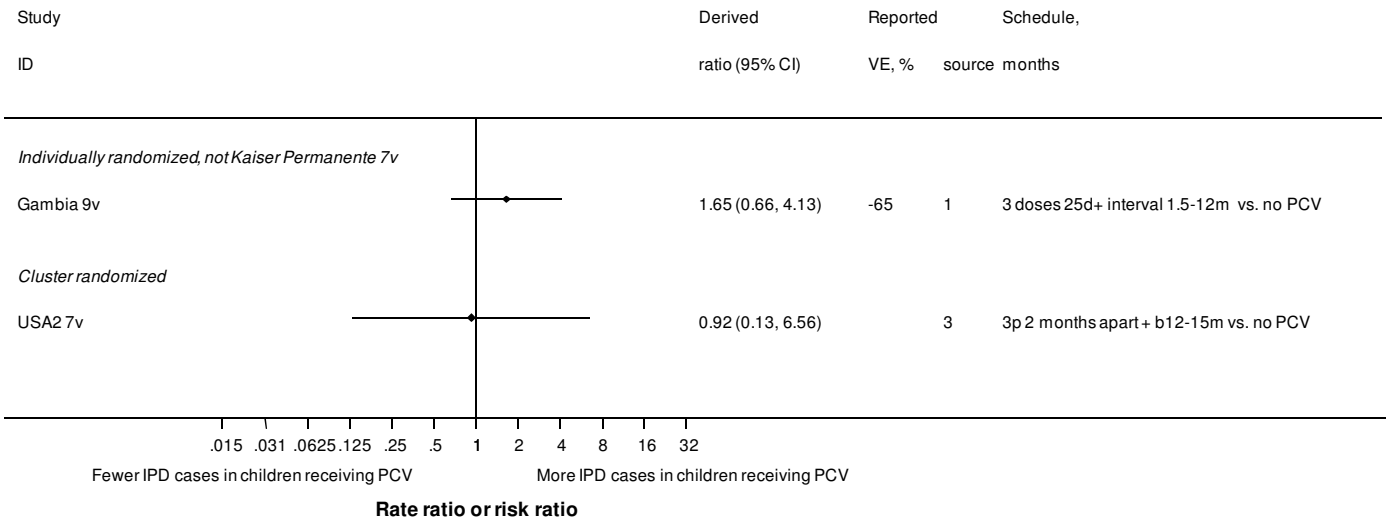
IPD – invasive pneumococcal disease; * HIV-infected; † HIV-uninfected; ‡ Source of derived ratio (1, from a reported VE based on a rate ratio; 2, reported rate ratio; 3, risk ratio calculated from reported cases/events and denominator data).

Horizontal axis represents effect estimate on logarithmic scale, comparing IPD in groups of children receiving PCV *vs.* no PCV; vertical line through 1 shows no difference in IPD incidence between groups; effect estimate might differ between studies, depending on data provided in trial report;

Solid black diamonds represent point estimate of effect estimate ratio; horizontal black line represents 95% confidence interval; points to the left of the vertical black line show a beneficial effect of PCV (fewer cases of IPD in PCV group), points to the right of the line show a detrimental effect of PCV (more cases of IPD in PCV group);

Blue diamond represents the pooled estimate, combined using random effects meta-analysis; vertical points of diamond represent point estimate and horizontal points represent 95% confidence interval; red dashed vertical line represents combined effect amongst individually randomized studies; I^2 value is the level of statistical heterogeneity between trials (<25% low heterogeneity).

Figure 2.11: Invasive pneumococcal disease, non-vaccine serotypes (excluding vaccine associated serotypes), per protocol analysis



Legend:

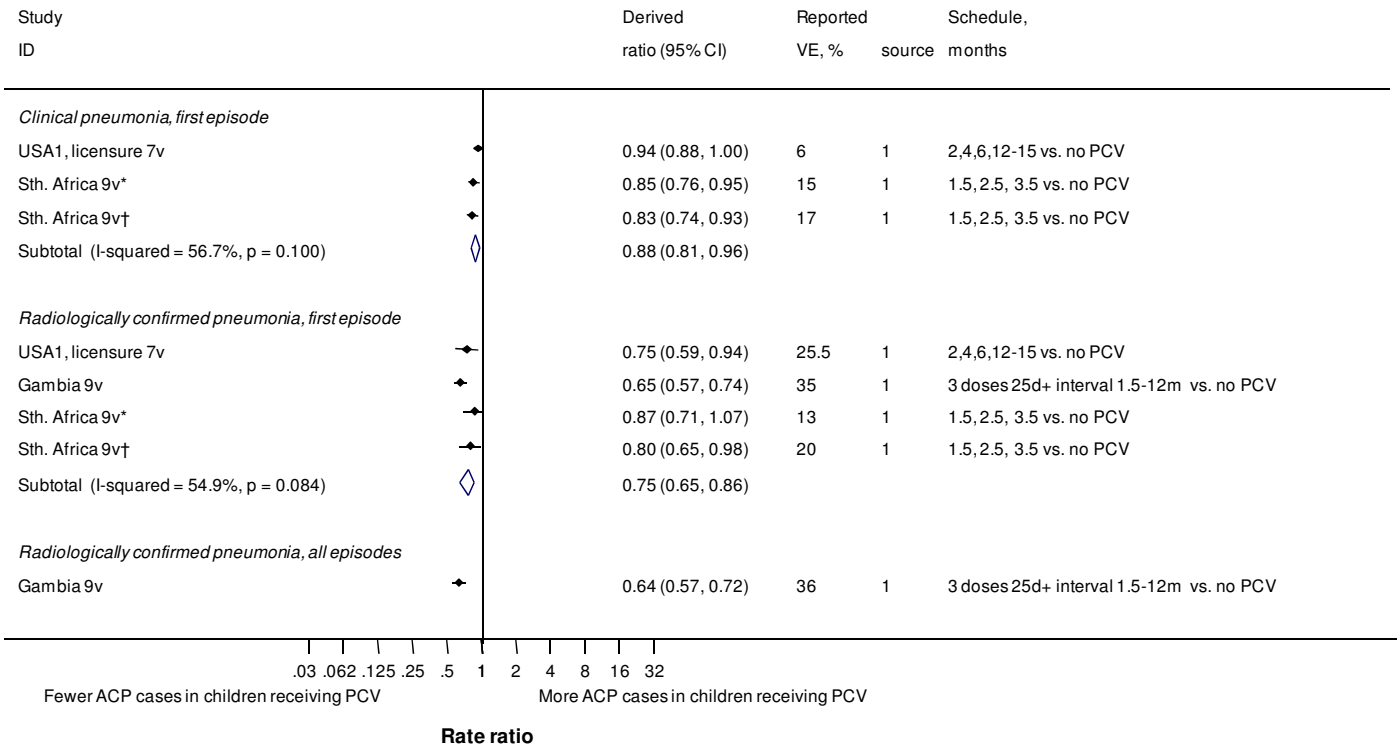
IPD – invasive pneumococcal disease; * HIV-infected; † HIV-uninfected; ‡ Source of derived ratio (1, from a reported VE based on a rate ratio; 2, reported rate ratio; 3, risk ratio calculated from reported cases/events and denominator data).

Horizontal axis represents effect estimate on logarithmic scale, comparing IPD in groups of children receiving PCV *vs.* no PCV; vertical line through 1 shows no difference in IPD incidence between groups; effect estimate might differ between studies, depending on data provided in trial report;

Solid black diamonds represent point estimate of effect estimate ratio; horizontal black line represents 95% confidence interval; points to the left of the vertical black line show a beneficial effect of PCV (fewer cases of IPD in PCV group), points to the right of the line show a detrimental effect of PCV (more cases of IPD in PCV group);

Blue diamond represents the pooled estimate, combined using random effects meta-analysis; vertical points of diamond represent point estimate and horizontal points represent 95% confidence interval; red dashed vertical line represents combined effect amongst individually randomized studies; I^2 value is the level of statistical heterogeneity between trials (<25% low heterogeneity).

Figure 2.12: All-cause pneumonia, intention to treat analysis



Legend:

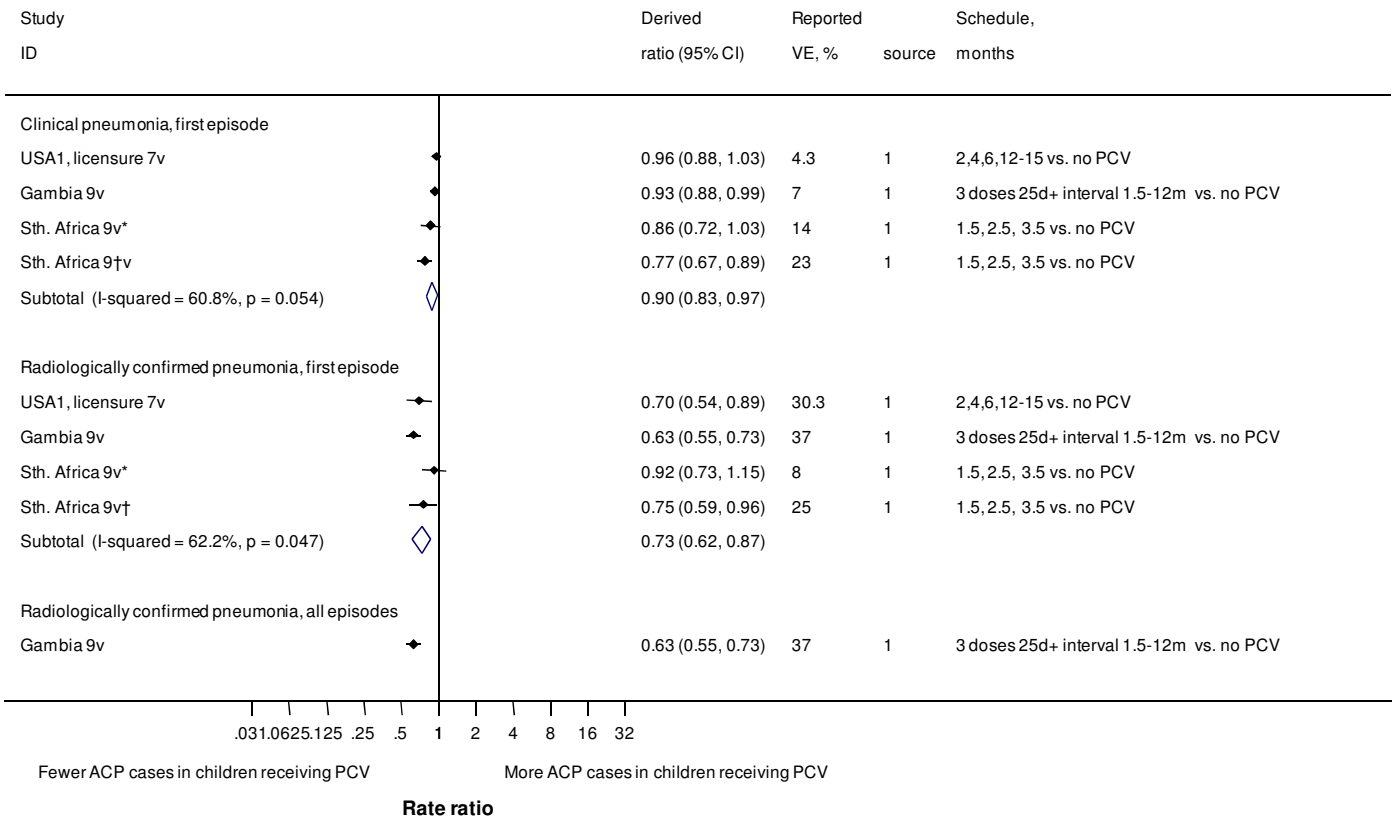
ACP - all-cause pneumonia; * HIV-infected; † HIV-uninfected; ‡ Source of derived ratio (1, from a reported VE based on a rate ratio; 2, reported rate ratio; 3, risk ratio calculated from reported cases/events and denominator data).

Horizontal axis represents effect estimate on logarithmic scale, comparing ACP in groups of children receiving PCV *vs.* no PCV; vertical line through 1 shows no difference in ACP incidence between groups; effect estimate might differ between studies, depending on data provided in trial report;

Solid black diamonds represent point estimate of effect estimate ratio; horizontal black line represents 95% confidence interval; points to the left of the vertical black line show a beneficial effect of PCV (fewer cases of ACP in PCV group), points to the right of the line show a detrimental effect of PCV (more cases of ACP in PCV group);

Blue diamond represents the pooled estimate, combined using random effects meta-analysis; vertical points of diamond represent point estimate and horizontal points represent 95% confidence interval; red dashed vertical line represents combined effect amongst individually randomized studies; I^2 value is the level of statistical heterogeneity between trials (<25% low heterogeneity).

Figure 2.13: All-cause pneumonia, per-protocol analysis



Legend:

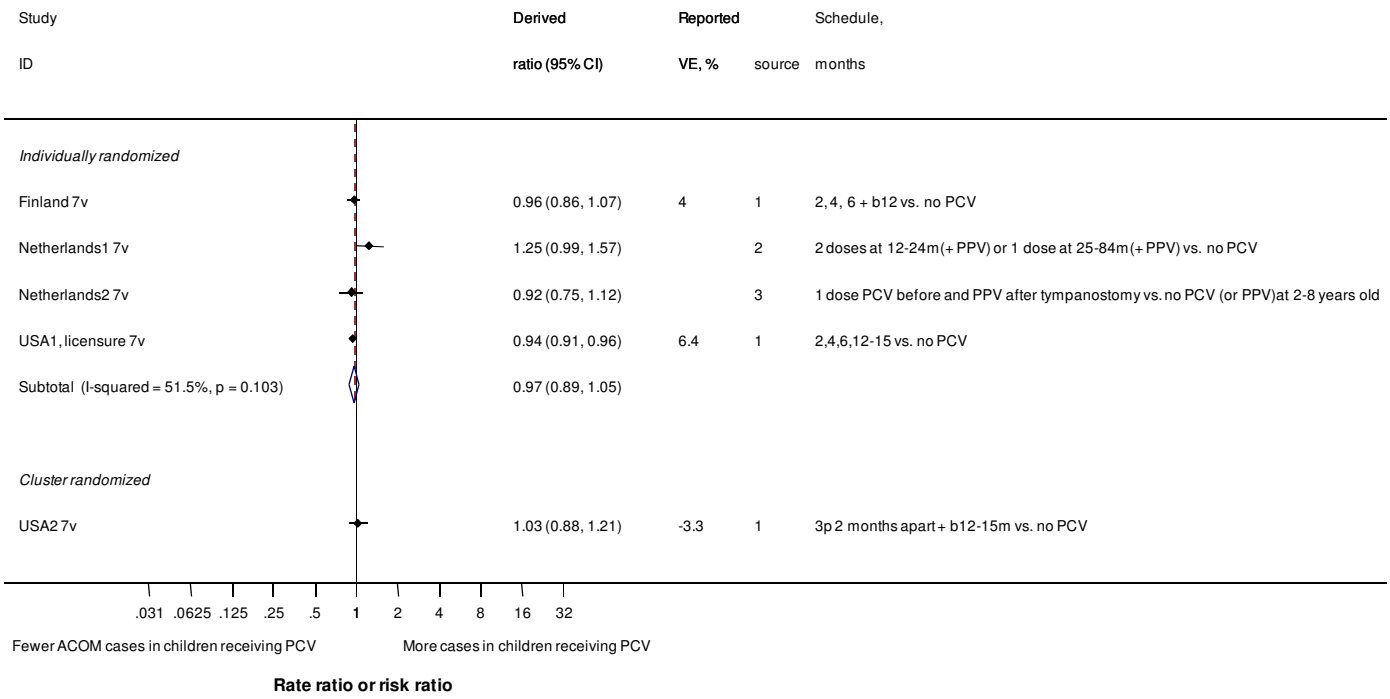
ACP - all-cause pneumonia; * HIV-infected; † HIV-uninfected; ‡ Source of derived ratio (1, from a reported VE based on a rate ratio; 2, reported rate ratio; 3, risk ratio calculated from reported cases/events and denominator data).

Horizontal axis represents effect estimate on logarithmic scale, comparing ACP in groups of children receiving PCV *vs.* no PCV; vertical line through 1 shows no difference in ACP incidence between groups; effect estimate might differ between studies, depending on data provided in trial report;

Solid black diamonds represent point estimate of effect estimate ratio; horizontal black line represents 95% confidence interval; points to the left of the vertical black line show a beneficial effect of PCV (fewer cases of ACP in PCV group), points to the right of the line show a detrimental effect of PCV (more cases of ACP in PCV group);

Blue diamond represents the pooled estimate, combined using random effects meta-analysis; vertical points of diamond represent point estimate and horizontal points represent 95% confidence interval; red dashed vertical line represents combined effect amongst individually randomized studies; I^2 value is the level of statistical heterogeneity between trials (<25% low heterogeneity).

Figure 2.14: Otitis media (all cause), intention to treat analysis



Legend:

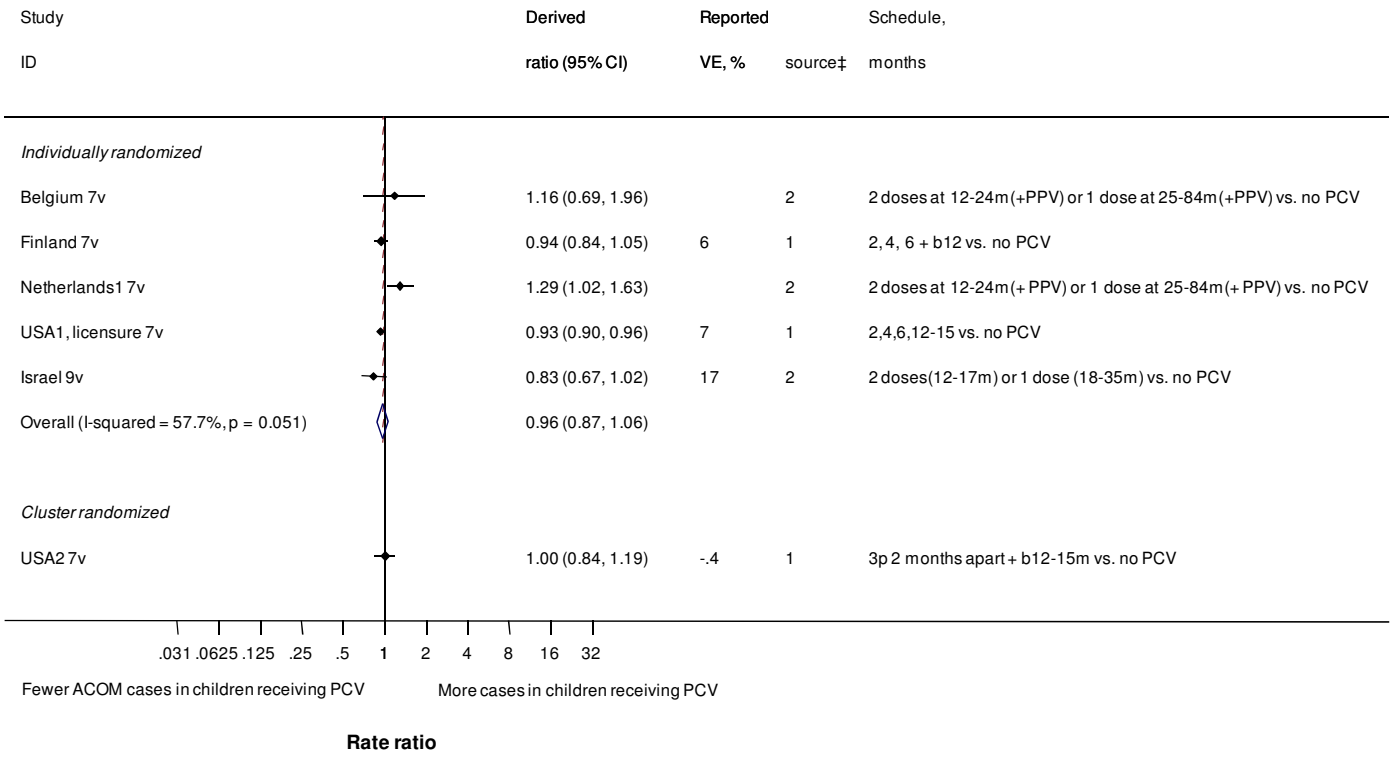
ACOM - all-cause otitis media; * HIV-infected; † HIV-uninfected; ‡ Source of derived ratio (1, from a reported VE based on a rate ratio; 2, reported rate ratio; 3, risk ratio calculated from reported cases/events and denominator data).

Horizontal axis represents effect estimate on logarithmic scale, comparing ACOM in groups of children receiving PCV *vs.* no PCV; vertical line through 1 shows no difference in ACOM incidence between groups; effect estimate might differ between studies, depending on data provided in trial report;

Solid black diamonds represent point estimate of effect estimate ratio; horizontal black line represents 95% confidence interval; points to the left of the vertical black line show a beneficial effect of PCV (fewer cases of ACOM in PCV group), points to the right of the line show a detrimental effect of PCV (more cases of ACOM in PCV group);

Blue diamond represents the pooled estimate, combined using random effects meta-analysis; vertical points of diamond represent point estimate and horizontal points represent 95% confidence interval; red dashed vertical line represents combined effect amongst individually randomized studies; I^2 value is the level of statistical heterogeneity between trials (<25% low heterogeneity).

Figure 2.15: Otitis media (all cause), per-protocol analysis



Legend:

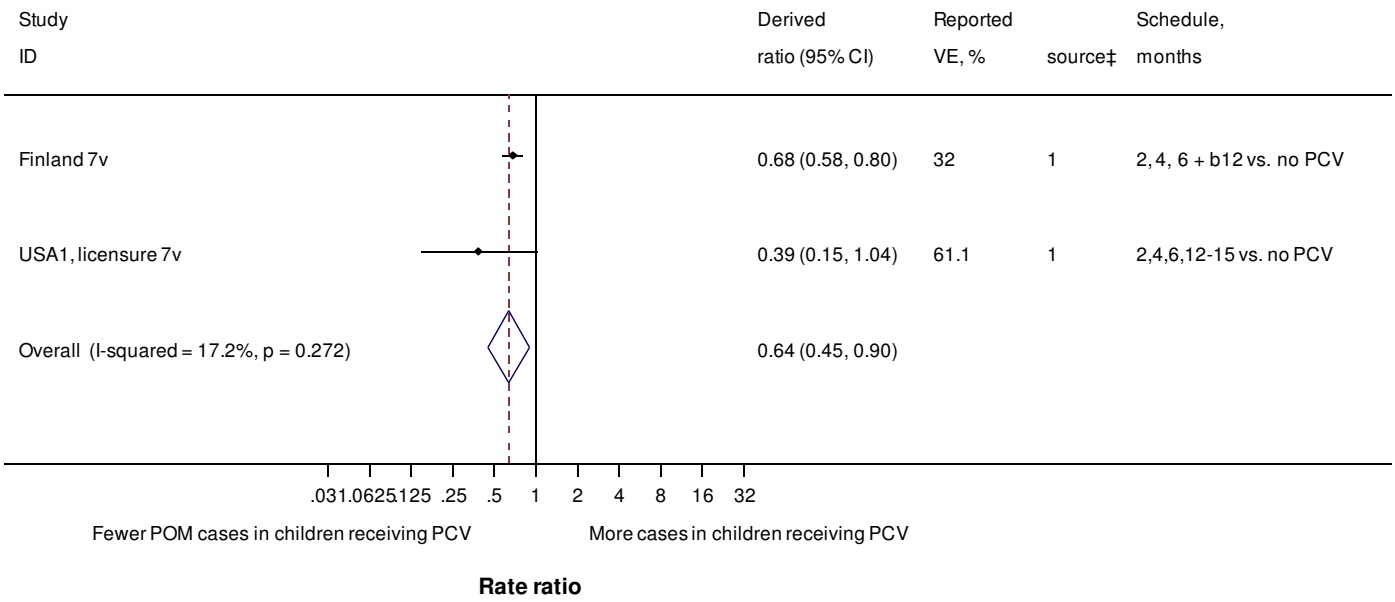
ACOM - all-cause otitis media; * HIV-infected; † HIV-uninfected; ‡ Source of derived ratio (1, from a reported VE based on a rate ratio; 2, reported rate ratio; 3, risk ratio calculated from reported cases/events and denominator data).

Horizontal axis represents effect estimate on logarithmic scale, comparing ACOM in groups of children receiving PCV *vs.* no PCV; vertical line through 1 shows no difference in ACOM incidence between groups; effect estimate might differ between studies, depending on data provided in trial report;

Solid black diamonds represent point estimate of effect estimate ratio; horizontal black line represents 95% confidence interval; points to the left of the vertical black line show a beneficial effect of PCV (fewer cases of ACOM in PCV group), points to the right of the line show a detrimental effect of PCV (more cases of ACOM in PCV group);

Blue diamond represents the pooled estimate, combined using random effects meta-analysis; vertical points of diamond represent point estimate and horizontal points represent 95% confidence interval; red dashed vertical line represents combined effect amongst individually randomized studies; I^2 value is the level of statistical heterogeneity between trials (<25% low heterogeneity).

Figure 2.16: Otitis media (pneumococcal), intention to treat analysis



Legend:

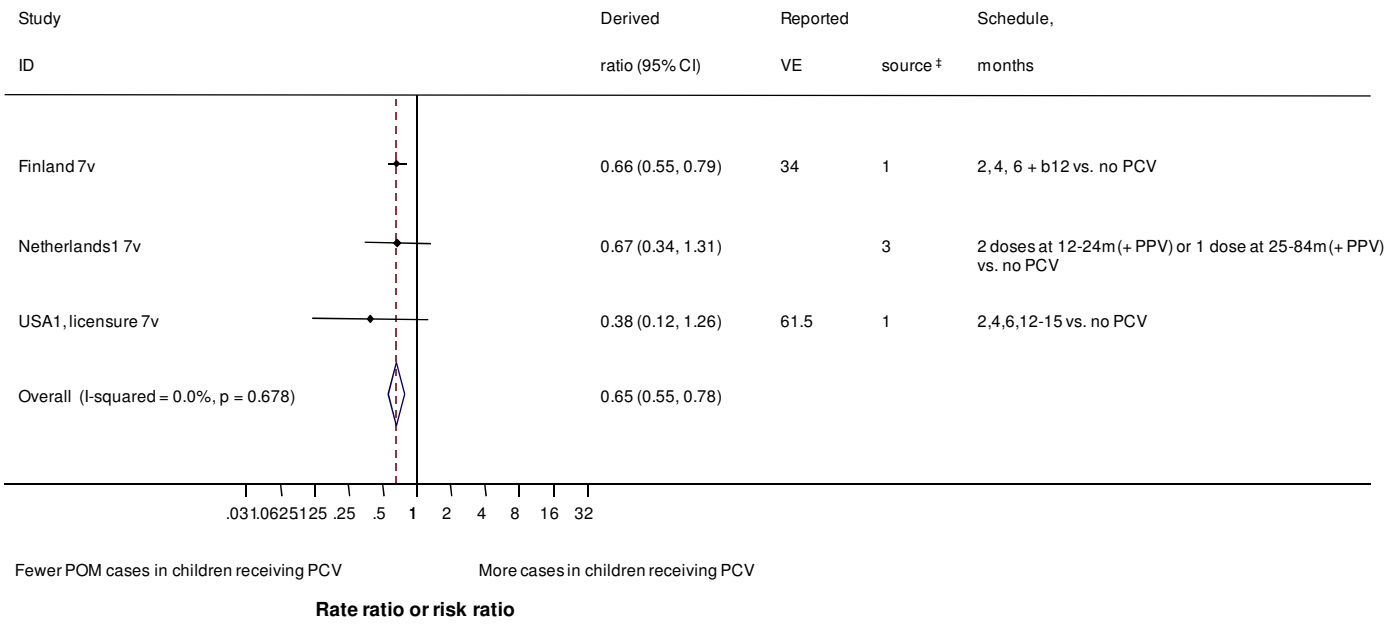
POM - pneumococcal otitis media; * HIV-infected; † HIV-uninfected; ‡ Source of derived ratio (1, from a reported VE based on a rate ratio; 2, reported rate ratio; 3, risk ratio calculated from reported cases/events and denominator data).

Horizontal axis represents effect estimate on logarithmic scale, comparing POM in groups of children receiving PCV *vs.* no PCV; vertical line through 1 shows no difference in POM incidence between groups; effect estimate might differ between studies, depending on data provided in trial report;

Solid black diamonds represent point estimate of effect estimate ratio; horizontal black line represents 95% confidence interval; points to the left of the vertical black line show a beneficial effect of PCV (fewer cases of POM in PCV group), points to the right of the line show a detrimental effect of PCV (more cases of POM in PCV group);

Blue diamond represents the pooled estimate, combined using random effects meta-analysis; vertical points of diamond represent point estimate and horizontal points represent 95% confidence interval; red dashed vertical line represents combined effect amongst individually randomized studies; I^2 value is the level of statistical heterogeneity between trials (<25% low heterogeneity).

Figure 2.17: Otitis media (pneumococcal), per-protocol analysis



Legend:

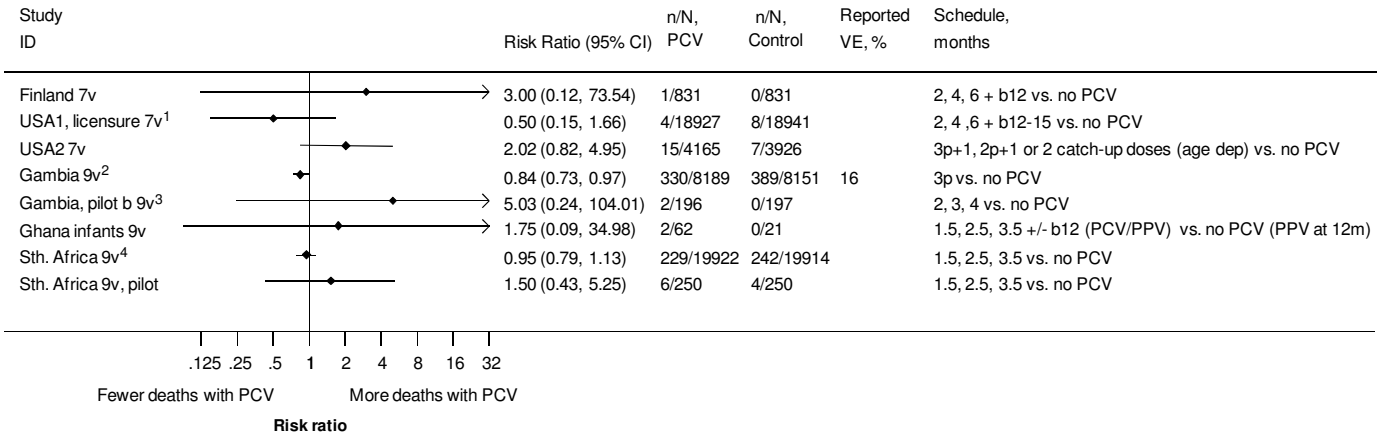
POM - pneumococcal otitis media; * HIV-infected; † HIV-uninfected; ‡ Source of derived ratio (1, from a reported VE based on a rate ratio; 2, reported rate ratio; 3, risk ratio calculated from reported cases/events and denominator data).

Horizontal axis represents effect estimate on logarithmic scale, comparing POM in groups of children receiving PCV *vs.* no PCV; vertical line through 1 shows no difference in POM incidence between groups; effect estimate might differ between studies, depending on data provided in trial report;

Solid black diamonds represent point estimate of effect estimate ratio; horizontal black line represents 95% confidence interval; points to the left of the vertical black line show a beneficial effect of PCV (fewer cases of POM in PCV group), points to the right of the line show a detrimental effect of PCV (more cases of POM in PCV group);

Blue diamond represents the pooled estimate, combined using random effects meta-analysis; vertical points of diamond represent point estimate and horizontal points represent 95% confidence interval; red dashed vertical line represents combined effect amongst individually randomized studies; I^2 value is the level of statistical heterogeneity between trials (<25% low heterogeneity).

Figure 2.18: Mortality, PCV schedule vs. no PCV



Legend:

Horizontal axis represents effect estimate on logarithmic scale, comparing mortality in groups of children receiving PCV *vs.* no PCV; vertical line through 1 shows no difference in IPD incidence between groups;

Solid black diamonds represent point estimate of effect estimate ratio; horizontal black line represents 95% confidence interval; points to the left of the vertical black line show a beneficial effect of PCV (fewer cases of IPD in PCV group), points to the right of the line show a detrimental effect of PCV (more deaths in PCV group);

All risk ratios calculated from reported cases/events and denominator data.

1 Sudden infant death syndrome (SIDS) deaths only

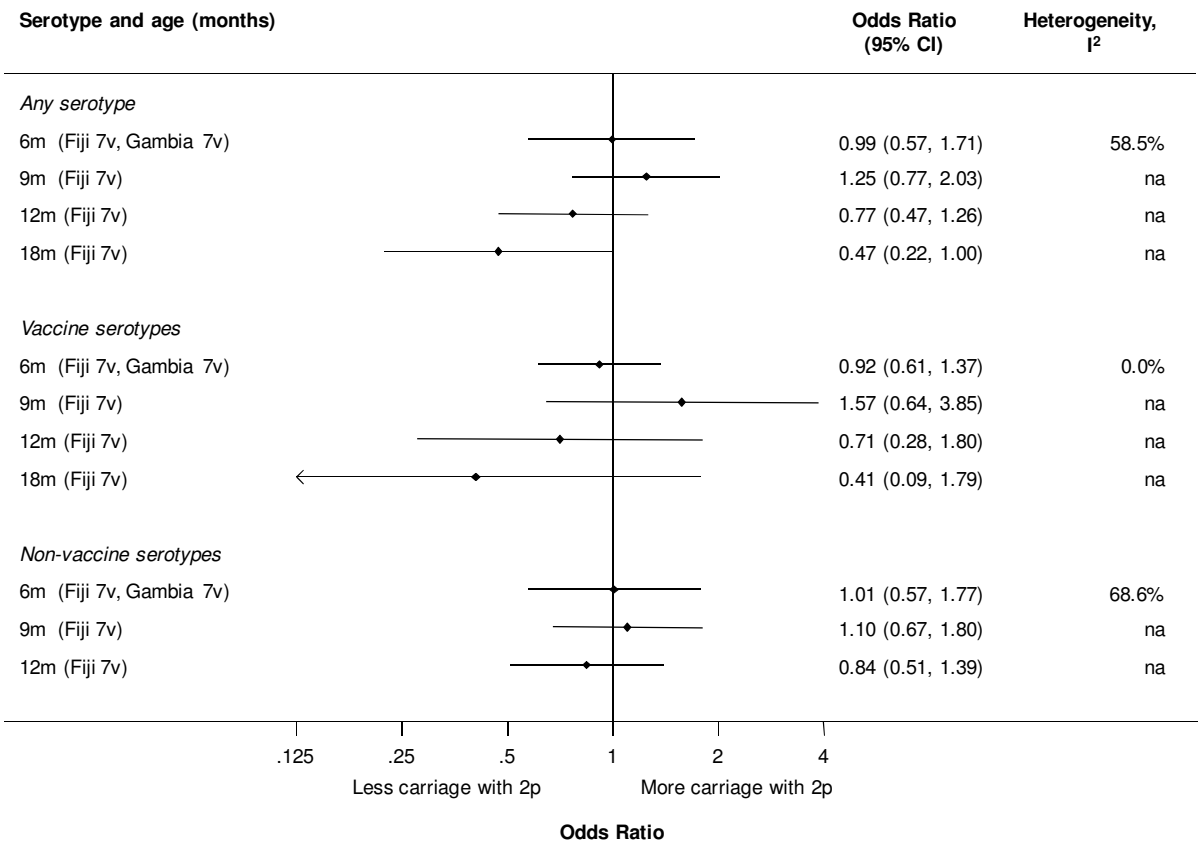
2 Per-protocol data

3 PCV group includes only those in the separate-vaccination group as described in the study.

4 Includes HIV-infected and -uninfected individuals as no denominators available for separate analysis

Studies are not included in this report if mortality was the only clinical or carriage outcome, and it was reported there were no deaths or mortality data were not extractable. There are 4 studies in this category : 3 report no deaths [1-3] and for 1 mortality data were not extractable [4]

Figure 2.19: Nasopharyngeal carriage, comparison A , 2p vs. 1p, by serotype and age tested



Legend:

Ages stated are approximate. For ages at testing for individual studies, see Table 3

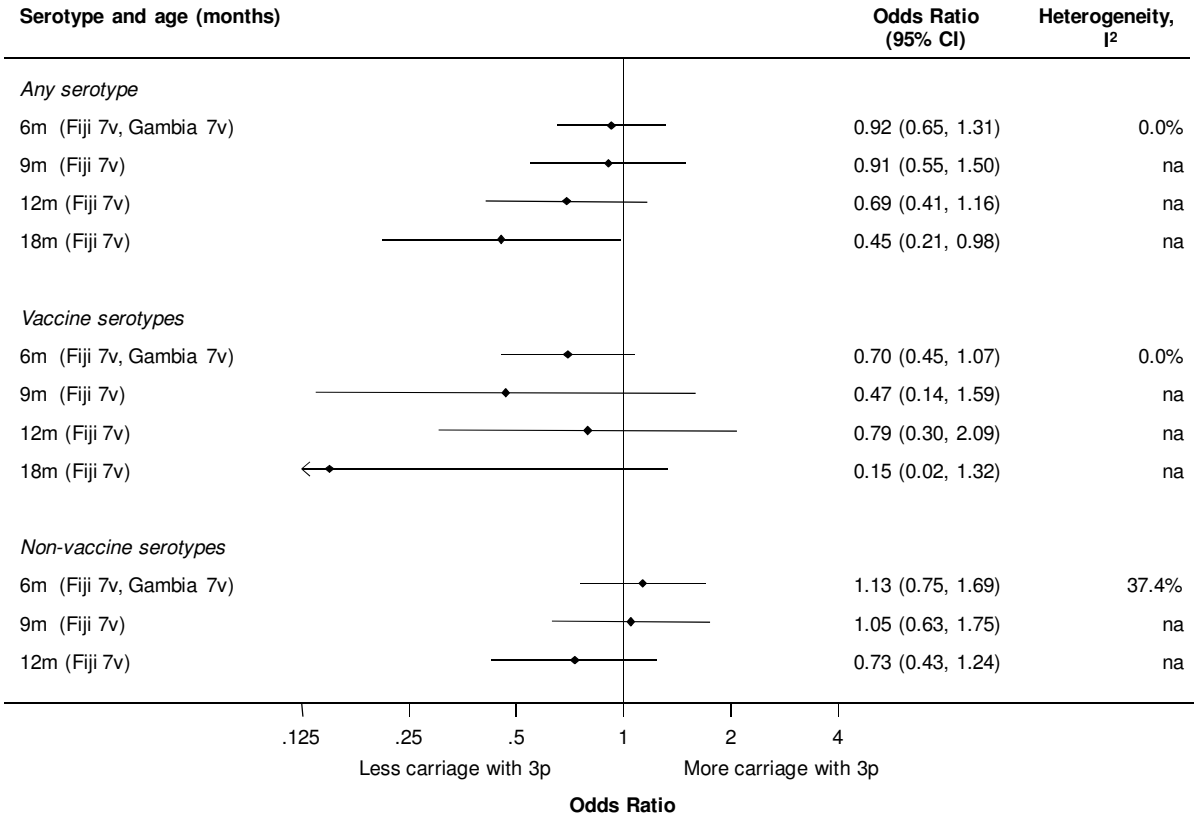
Horizontal axis represents the combined odds ratios from meta-analysis on a logarithmic scale, comparing carriage in groups of children receiving 2p vs. 1p schedules; vertical line through combined odds ratio of 1 shows no difference in levels of carriage between groups.

Solid black diamonds represent point estimate of combined odds ratio; horizontal black line represents 95% confidence interval

The I^2 statistic can be interpreted as the proportion of the total variation in estimated risk ratios due to between-trial heterogeneity rather than to chance [5]. Low, moderate and high levels of heterogeneity correspond to I^2 values of 25%, 50% and 75% respectively.

na - not applicable as only one trial in analysis

Figure 2.20: Nasopharyngeal carriage, comparison B , 3p vs. 1p, by serotype and age tested



Legend:

Ages stated are approximate. For ages at testing for individual studies, see Table 3

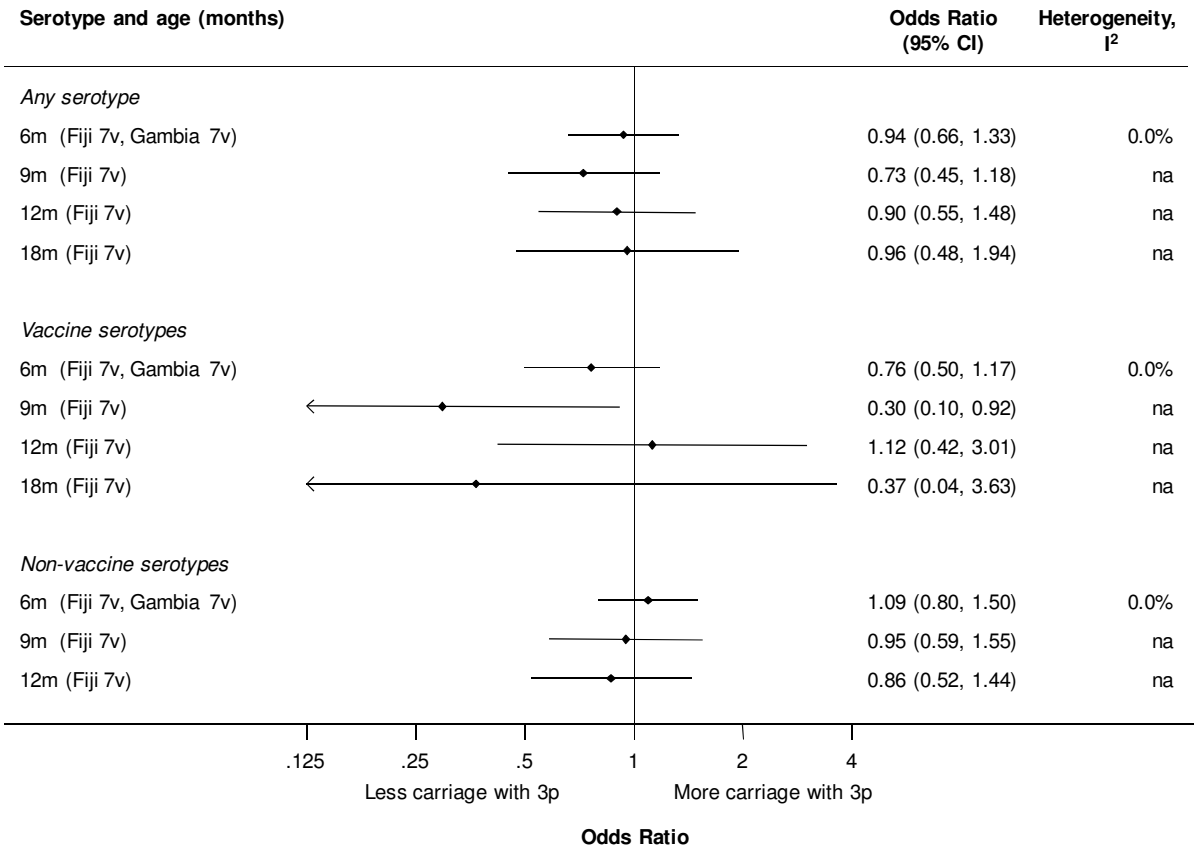
Horizontal axis represents the combined odds ratios from meta-analysis on a logarithmic scale, comparing carriage in groups of children receiving 3p vs. 1p schedules; vertical line through combined odds ratio of 1 shows no difference in levels of carriage between groups.

Solid black diamonds represent point estimate of combined odds ratio; horizontal black line represents 95% confidence interval

The I^2 statistic can be interpreted as the proportion of the total variation in estimated risk ratios due to between-trial heterogeneity rather than to chance [5]. Low, moderate and high levels of heterogeneity correspond to I^2 values of 25%, 50% and 75% respectively.

na - not applicable as only one trial in analysis

Figure 2.21: Nasopharyngeal carriage, comparison C , 3p vs. 2p, by serotype and age tested



Legend:

Ages stated are approximate. For ages at testing for individual studies, see Table 3

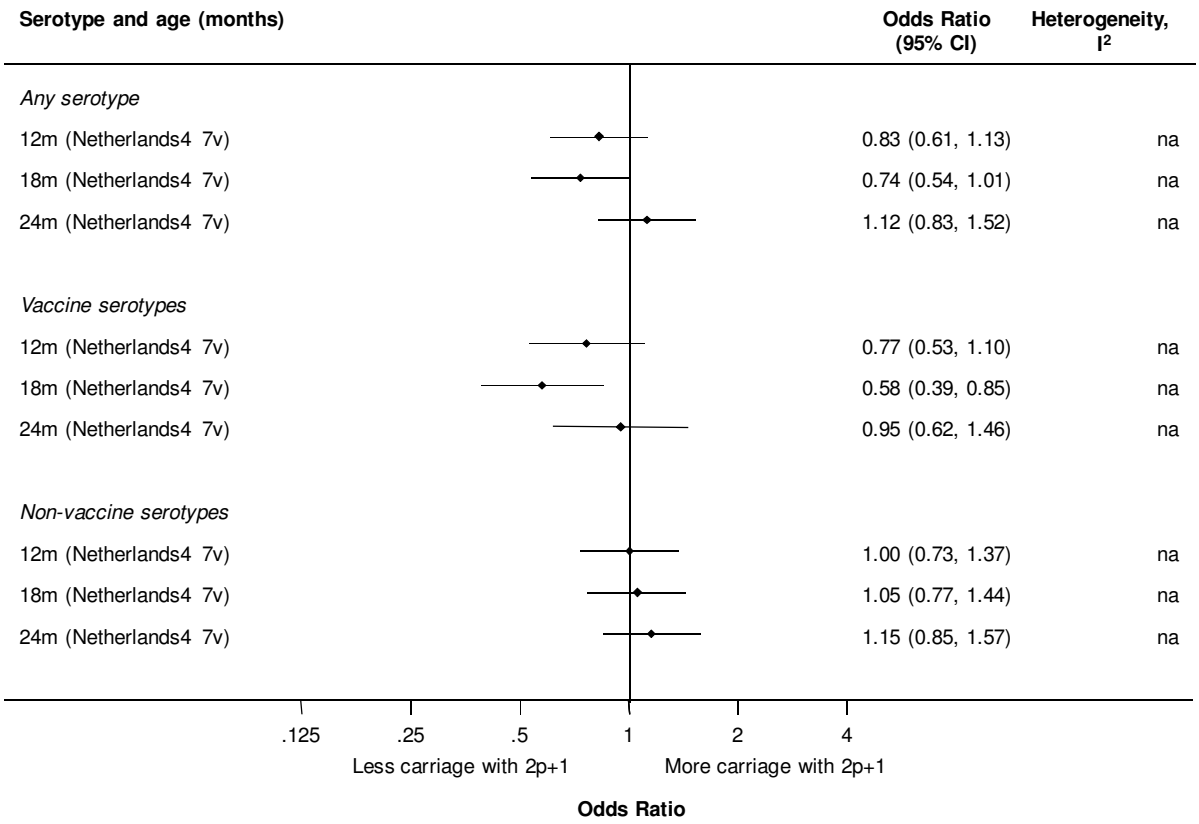
Horizontal axis represents the combined odds ratios from meta-analysis on a logarithmic scale, comparing carriage in groups of children receiving 3p vs. 2p schedules; vertical line through combined odds ratio of 1 shows no difference in levels of carriage between groups.

Solid black diamonds represent point estimate of combined odds ratio; horizontal black line represents 95% confidence interval

The I^2 statistic can be interpreted as the proportion of the total variation in estimated risk ratios due to between-trial heterogeneity rather than to chance [5]. Low, moderate and high levels of heterogeneity correspond to I^2 values of 25%, 50% and 75% respectively.

na - not applicable as only one trial in analysis

Figure 2.22: Nasopharyngeal carriage, comparison E , 2p+1 vs. 2p, by serotype and age tested



Legend:

Ages stated are approximate. For ages at testing for individual studies, see Table 3

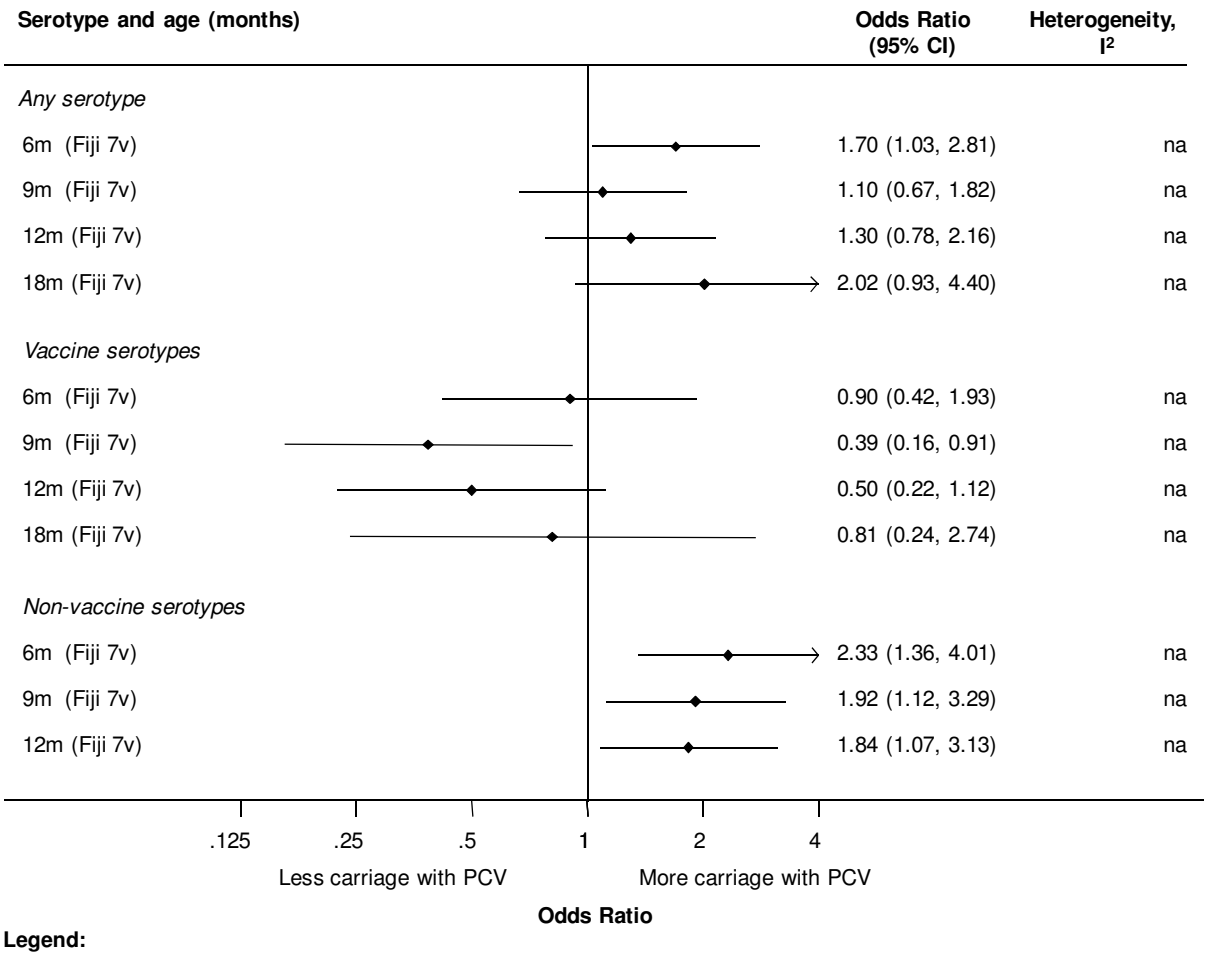
Horizontal axis represents the combined odds ratios from meta-analysis on a logarithmic scale, comparing carriage in groups of children receiving 2p+1 vs. 2p schedules; vertical line through combined odds ratio of 1 shows no difference in levels of carriage between groups.

Solid black diamonds represent point estimate of combined odds ratio; horizontal black line represents 95% confidence interval

The I^2 statistic can be interpreted as the proportion of the total variation in estimated risk ratios due to between-trial heterogeneity rather than to chance [5]. Low, moderate and high levels of heterogeneity correspond to I^2 values of 25%, 50% and 75% respectively.

na - not applicable as only one trial in analysis

Figure 2.23: Nasopharyngeal carriage, comparison U1, 1p vs. no PCV, by serotype and age tested



Legend:

Ages stated are approximate. For ages at testing for individual studies, see Table 3

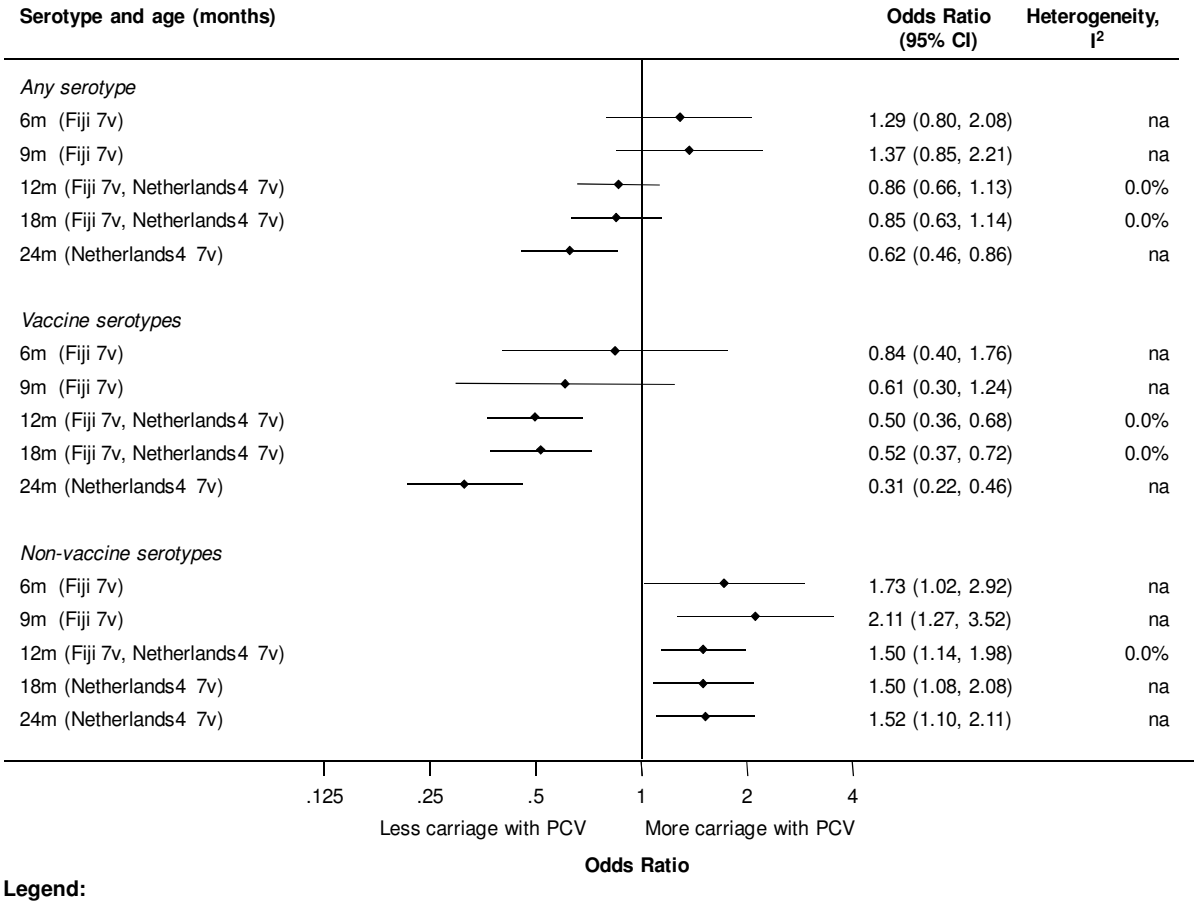
Horizontal axis represents the combined odds ratios from meta-analysis on a logarithmic scale, comparing carriage in groups of children receiving 1p vs. no PCV schedules; vertical line through combined odds ratio of 1 shows no difference in levels of carriage between groups.

Solid black diamonds represent point estimate of combined odds ratio; horizontal black line represents 95% confidence interval .

The I^2 statistic can be interpreted as the proportion of the total variation in estimated risk ratios due to between-trial heterogeneity rather than to chance [5]. Low, moderate and high levels of heterogeneity correspond to I^2 values of 25%, 50% and 75% respectively.

na - not applicable as only one trial in analysis

Figure 2.24: Nasopharyngeal carriage: Comparison U2, 2p vs. no PCV, by serotype and age tested



Legend:

Ages stated are approximate. For ages at testing for individual studies, see Table 3

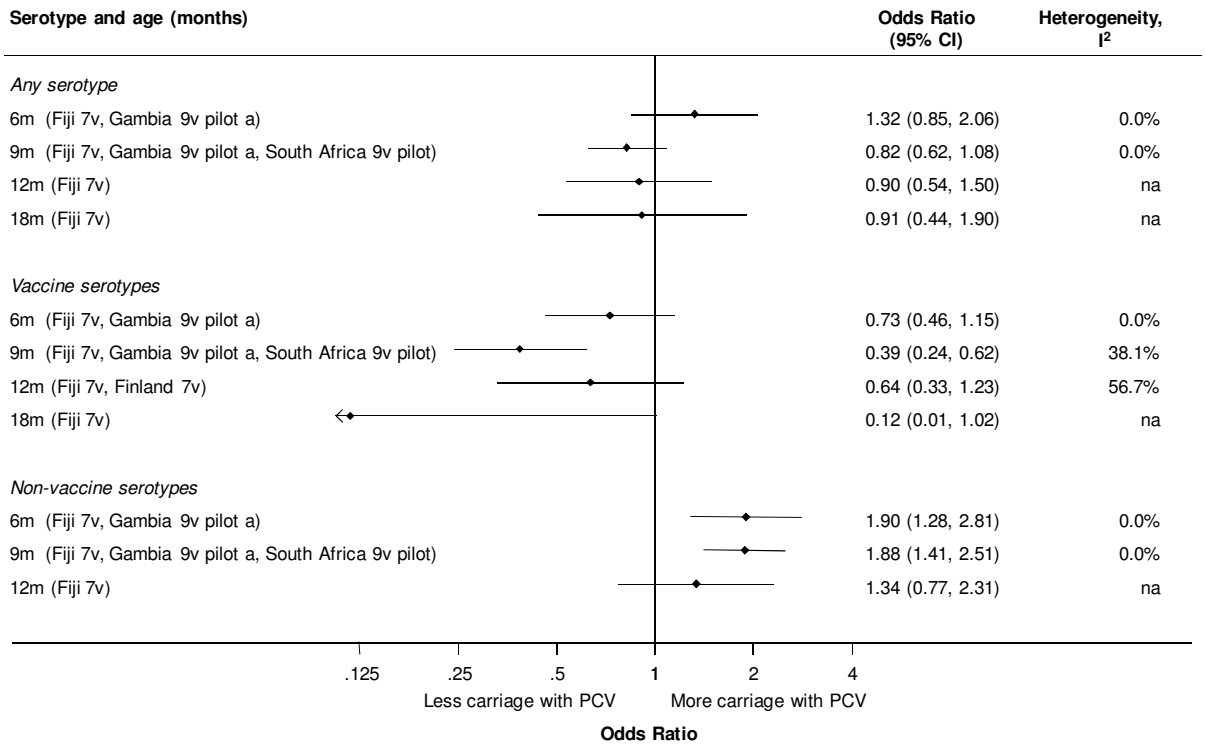
Horizontal axis represents the combined odds ratios from meta-analysis on a logarithmic scale, comparing carriage in groups of children receiving 2p vs. no PCV; vertical line through combined odds ratio of 1 shows no difference in levels of carriage between groups.

Solid black diamonds represent point estimate of combined odds ratio; horizontal black line represents 95% confidence interval

The I^2 statistic can be interpreted as the proportion of the total variation in estimated risk ratios due to between-trial heterogeneity rather than to chance [5]. Low, moderate and high levels of heterogeneity correspond to I^2 values of 25%, 50% and 75% respectively.

na - not applicable as only one trial in analysis

Figure 2.25: Nasopharyngeal carriage, comparison U3, 3p vs. no PCV, by serotype and age tested



Legend:

Ages stated are approximate. For ages at testing for individual studies, see Table 3

USA2 7v not included in this analysis as is a cluster-randomized trial and from a non-randomly selected sub-group.

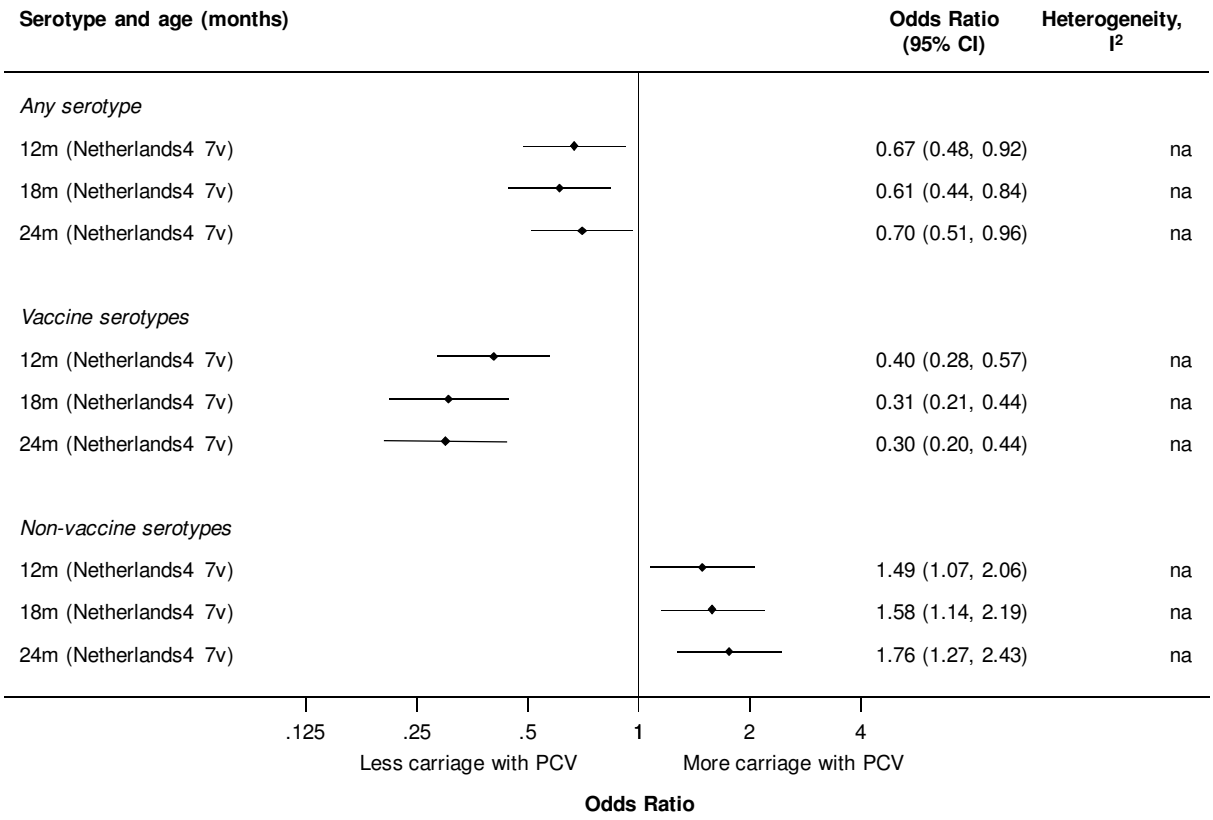
Horizontal axis represents the combined odds ratios from meta-analysis on a logarithmic scale, comparing carriage in groups of children receiving 3p vs. no PCV; vertical line through combined odds ratio of 1 shows no difference in levels of carriage between groups.

Solid black diamonds represent point estimate of combined odds ratio; horizontal black line represents 95% confidence interval

The I^2 statistic can be interpreted as the proportion of the total variation in estimated risk ratios due to between-trial heterogeneity rather than to chance [5]. Low, moderate and high levels of heterogeneity correspond to I^2 values of 25%, 50% and 75% respectively.

na - not applicable as only one trial in analysis

Figure 2.26: Nasopharyngeal carriage, comparison W2, 2p+1 vs. no PCV, by serotype and age tested



Legend:

Ages stated are approximate. For ages at testing for individual studies, see Table 3

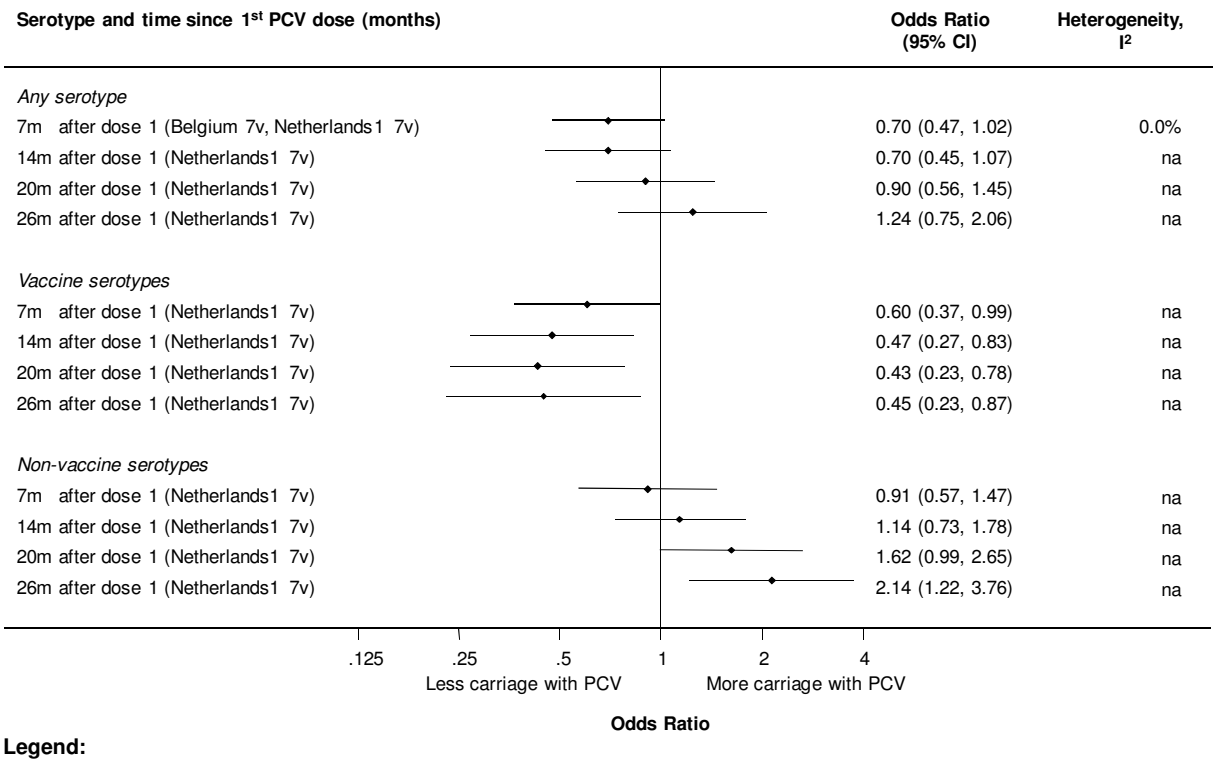
Horizontal axis represents the combined odds ratios from meta-analysis on a logarithmic scale, comparing carriage in groups of children receiving 2p+1 vs. no PCV; vertical line through combined odds ratio of 1 shows no difference in levels of carriage between groups.

Solid black diamonds represent point estimate of combined odds ratio; horizontal black line represents 95% confidence interval

The I^2 statistic can be interpreted as the proportion of the total variation in estimated risk ratios due to between-trial heterogeneity rather than to chance [5]. Low, moderate and high levels of heterogeneity correspond to I^2 values of 25%, 50% and 75% respectively.

na - not applicable as only one trial in analysis

Figure 2.27: Nasopharyngeal carriage, comparison Y, 1 or 2 catch-up doses (with or without PPV) vs. no PCV



Legend:

Horizontal axis represents the combined odds ratios from meta-analysis on a logarithmic scale, comparing carriage in groups of children receiving 1 or 2 catch-up doses vs. no PCV or PPV; vertical line through combined odds ratio of 1 shows no difference in levels of carriage between groups.

Solid black diamonds represent point estimate of combined odds ratio; horizontal black line represents 95% confidence interval

The I^2 statistic can be interpreted as the proportion of the total variation in estimated risk ratios due to between-trial heterogeneity rather than to chance [5]. Low, moderate and high levels of heterogeneity correspond to I^2 values of 25%, 50% and 75% respectively.

na - not applicable as only one trial in analysis

Table 2.1: Pneumococcal serotypes contained in different vaccines

Vaccine	Pneumococcal serotype												
	1	3	4	5	6A	6B	7F	9V	14	18C	19A	19F	23F
7-valent			✓			✓		✓	✓	✓		✓	✓
9-valent	✓		✓	✓		✓		✓	✓	✓		✓	✓
10-valent	✓		✓	✓		✓	✓	✓	✓	✓		✓	✓
13-valent	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Table 2.2: Summary of included studies

Study name and PCV valency[1]	Country	Schedules, age at dose in months		Intervention in no dose group	Number of participants randomized	Outcomes reported
		Intended	Actual age at administration			
Individual randomization						
Belgium 7v [6]	Belgium	2 doses + PPV(12-24m)/ 1dose + PPV (25-84m)	Median 24 (12-76) [2]		38	Otitis media Carriage
		No doses		HepB/ HepA	36	
Chile 10v [7]	Chile	2, 4, 6, + b>18	Not reported		119[3]	Adverse events[4]
		2 catch-up >18			121[3]	Mortality
China 7v [8]	China	3, 4, 5 (DTaP coad)	median 3.5 (3.0-4.0) [2]		296	Adverse events[4] Mortality
		3, 4, 5 (DTaP not coad)	median 3.5 (3.0-4.0) [2]		300	
		No doses	median 3.5 (3.0-4.7) [2]	No additional intervention	204	
Europe 10v [9]	Denmark, Norway, Slovakia, Sweden	2, 3, 4, +b11m	1st: mean 2.8 2nd: mean 3.9 3rd : mean 5.0 Booster: mean 11.2		176	Adverse events[4] Mortality
		2, 4, +b11m	1st: mean 2.8 2nd: mean 4.9 Booster: mean 11.1		175	
Fiji 7v [10]	Fiji	1.5, 2.5, 3.5 +/- b12(PPV)	Not reported		136	Carriage
		1.5, 3.5 +/- b12(PPV)			156	
		3.5 +/- b12(PPV)			128	
		No doses +/- b12(PPV)		No additional intervention	132	
Finland 7v [11]	Finland	2, 4, 6, +b12	Not reported		831	IPD Meningitis
		No doses		Hep B	831	Otitis media Adverse events[4] Mortality Carriage
Finland 10v [12]	Finland	2, 3, 4, + b14-16m	Not reported		101	Adverse events[4]
		2, 3, 4, + b12-14m			110	Mortality
Gambia 7v [13]	The Gambia	2, 3, 4 + b10(PPV)	median 1.7, 3.0, 4.2, 10.5		228	Mortality
		2, 3 + b10(PPV)	media 1.8, 3.0, 10.5		228	Carriage
		2 + b10(PPV)	median 1.8, 10.4		228	

Study name and PCV valency[1]	Country	Schedules, age at dose in months		Intervention in no dose group	Number of participants randomized	Outcomes reported
		Intended	Actual age at administration			
Gambia 9v [14]	The Gambia	3p [5]	Amongst those in per protocol analysis: 1st: median 2.5 (2.0–3.6) 2nd: median 4.1 (3.2–5.5) 3rd: median 5.6 (4.5–7.5)		8718	IPD Meningitis[6] Pneumonia Mortality
		No doses		Placebo	8719	
Gambia 9v pilot a [15]	The Gambia	2, 3, 4	Not reported		103	Mortality[7]
		No doses		IPV	104	Carriage
Gambia 9v pilot b [16]	The Gambia	2, 3, 4 (DTwPHib mixed)	Not reported		197	Mortality
		2, 3 ,4 (DTwPHib sep)			196	
		No doses		Placebo	197	
Ghana infants 9v [17]	Ghana	1.5, 2.5, 3.5 + b12 (PCV/PPV/Hib)	1st: mean 2.5 2nd: mean 3.8 3rd: mean 5.0		62	Mortality
		No doses		Hib conjugate	21	
Iceland 9v [18]	Iceland	3, 4, 5 + b12 3, 4, 5 + b12(PPV)	Not reported		111[8]	Adverse events[4]
		3, 5 + b12 3, 5 + b12(PPV)			112[8]	
Israel 7v [19]	Israel	2, 4, 6 + b12	Not reported		178	Carriage[9]
		2, 4, 6			178	
		4, 6 + b12			189	
Israel 9v [20]	Israel	2 doses (12-17m)/ 1dose (18-35m)	27.9 (IQR 21.6-31.8) [2]		132	Otitis media Carriage
		No doses		MenC	130	
Netherlands1 7v [21]	Netherlands	2 doses + PPV(12-24m)/ 1dose + PPV (25-84m)	Median 25.1 (12-82.3) [2]		190	Otitis media Carriage
		No doses		HepB/ HepA	193	
Netherlands2 7v [22]	Netherlands	1 dose + PPV (>24m)	Mean 64.8m [10]		80	Otitis Media Mortality
		No doses		No additional intervention	81	
Netherlands3 7v [23]	Netherlands	2 doses >18m	Mean 36 [2]		197	Otitis media[11]
		No doses		Placebo	187	

Study name and PCV valency[1]	Country	Schedules, age at dose in months		Intervention in no dose group	Number of participants randomized	Outcomes reported
		Intended	Actual age at administration			
Netherlands4 7v [24]	Netherlands	2, 4, +b11	1st: mean 2.0 (SD 0.26) 2nd: mean 4.3 (SD 0.40) 3rd : mean 11.3 (SD 0.47)		336	Carriage
		2, 4	1st: mean 2.1 (SD 0.35) 2nd: mean 4.3 (SD 0.58)		336	
		No doses		No additional intervention	333	
South Africa 9v [25]	South Africa	1.5, 2.5, 3.5	1st: mean 1.5 (SD 0.28) 2nd: mean 2.6 (SD 0.61) 3rd: mean 3.7 (SD 0.93)		19922	IPD Meningitis Pneumonia Mortality
		No doses		Placebo	19914	Carriage
South Africa 9v pilot [26]	South Africa	1.5, 2.5, 3.5	1st:mean 1.5 (SD 0.14)[12] 2nd: mean 2.5 (SD 0.32)[12] 3rd: mean 3.5 (SD 0.43)[12]		250	Pneumonia[13] Mortality Carriage
		No doses		Placebo	250	
USA1 7v [27]	USA	2, 4, 6, +b12m	Not reported		18927	IPD
		No doses		MenC	18941	Pneumonia Otitis media Mortality
Cluster randomization						
USA2 7v [28]	USA	3p+1 / 2p+1 / 2doses[14]	1st (3p+1 group): mean 2.7 (SD 1.5)		2971/ 315/ 876	IPD Meningitis Otitis media Mortality
		No doses		MenC	2818/ 295/ 813	Carriage

Notes:

b – booster; coad – coadministered (vaccines given at same time); DTaP – diphtheria, tetanus, acellular pertussis vaccine; DTwP – diphtheria, tetanus, whole cell pertussis vaccine; HepA – Hepatitis A vaccine; HepB – Hepatitis B vaccine; Hib – *Haemophilus influenzae* type b vaccine; IPD – invasive pneumococcal disease; IPV - inactivated poliovirus vaccine; IQR – interquartile range; MenC - meningococcus group C conjugate vaccine; Mixed – vaccines given at same time in same syringe; PCV – pneumococcal conjugate vaccine; PPV – pneumococcal polysaccharide vaccine; SD – standard deviation; Sep – vaccines given at same time but at separate sites; 3p – 3 dose primary schedule, etc.; +1 – booster dose.

Studies are not included in this report if mortality was the only clinical or carriage outcome, and it was reported there were no deaths or mortality data could not be extracted. There are 4 studies in this category: 3 report no deaths [1-3] and for 1 mortality data were not extractable [4].

1 A single primary reference is cited for each study. Further references in Appendix 2. Study names were assigned for this review. Several studies have alternative names used elsewhere in literature: Finland 7v, "Finnish Acute Otitis Media"; Belgium 7v, Netherlands1 7v, "Omavax"; " Netherlands3 7v, "Primakid; Netherlands4 7v, "MNOES" or "MINOES"; USA1 7v, "Northern California Kaiser Permanente"; USA2 7v , "Native American" or "American Indian";

2 Age at baseline – not clear if age at first vaccination;

3 as stated in [29], numbers in [7] differ

4 Adverse events include eligible clinical outcomes. Not analyzed because data were not specifically collected as outcomes, no case definitions were applied and data were only collected for periods immediately after vaccination;

5 No set age for doses, children 6-51 weeks given 3 doses at least 25 days apart;

6 Reported together with sepsis, cannot be analyzed separately;

7 Mortality data not reported clearly for each intervention group, and therefore not reported in this review;

8 Number undergoing randomization, numbers in each group unclear;

9 No extractable carriage data as of 1st September 2011; included here as immunogenicity data are available and carriage data will become available;

10 Described as “age” in published article, unclear if at baseline, first vaccination, or another time point;

11 Insufficient data reported to calculate ratios with CI in relevant groups;

12 reported as age “at recruitment”, “at second visit”, and “at the third vaccination”, and is for all participants (PCV group and control group combined);

13 Insufficient data reported to extract separately for each group;

14 Number of doses given to children in vaccinated group age-dependent. No set age for doses: infants enrolled between age 6 weeks and 7 months- 3 doses of vaccine 2 months apart + b12–15 months of age; infants enrolled between 7 and 11 months of age - 2 doses of vaccine 2 months apart + b12–15 months ; infants enrolled between 12 and 23 months of age received 2 doses of vaccine at least 2 months apart.

Table 2.3: Order of description and presentation of comparisons of vaccination schedules

Comparison	Study	Schedules, months	Time at which outcomes measured[1]			
			Clinical	Carriage in all trial participants, months	Carriage in sub-groups, months	Carriage in the community, months
Schedule vs. schedule (comparisons A-T)						
Comparison A 2p vs. 1p	Fiji 7v	1.5, 3.5 3.5	NA	6, 9, 12, 17	NA	NA
	Gambia 7v[2]	2, 3 2	Between enrolment and approx. 15 months of age[3]	5	NA	NA
Comparison B 3p vs. 1p	Fiji 7v	1.5, 2.5, 3.5 3.5	NA	6, 9, 12, 17	NA	NA
	Gambia 7v[2]	2, 3, 4 2	Between enrolment and approx. 15 months of age[3]	5	NA	NA
Comparison C 3p vs. 2p	Fiji 7v	1.5, 2.5, 3.5 1.5, 3.5	NA	6, 9, 12, 17	NA	NA
	Gambia 7v[2]	2, 3, 4 2, 3	Between enrolment and approx. 15 months of age[3]	**5**	NA	NA
	Israel 7v[2]	2, 4, 6 4, 6	NA	NA[5]	NA	NA
	Iceland 9v[2]	3, 4, 5 3, 5	For 28 days after the primary series[4]	NA	NA	NA
	Europe 10v[2]	2, 3, 4 2, 4	During "whole study period", enrolment until 1 month after last primary dose (possibly longer)	NA	NA	NA
Comparison D 2p + PPV vs. 1p +PPV	Fiji 7v	1.5, 3.5 + b12(PPV) 3.5 + b12(PPV)	NA	17	NA	NA
	Gambia 7v	2, 3, 4 + b10(PPV) 2 , 3 + b10(PPV)	Between enrolment and approx. 15 months of age[3]	11, 15	NA	NA
Comparison E 2p + 1 vs. 2p	Netherlands4 7v	2, 4, +b11 2, 4	NA	12, 18, 24	NA	Parents of children sampled at same time as children
Comparison F 2p + 1 vs. 2p + PPV	Iceland 9v	3, 5 + b12 3, 4, 5 + b12(PPV)	For 28 days after the booster dose[4]	NA	NA	NA
Comparison G 3p vs. 2p + 1	Israel 7v	2, 4, 6 4, 6 + b12	NA	NA[5]	NA	NA
Comparison H 3p + PPV vs. 1p+ PPV	Fiji 7v	1.5, 2.5, 3.5 + b12(PPV) 3.5 + b12(PPV)	NA	17	NA	NA
	Gambia 7v	2, 3, 4 + b10(PPV) 2 + b10(PPV)	Between enrolment and approx. 15 months of age[3]	11, 15	NA	NA
Comparison I 3p + PPV vs. 2p +PPV	Fiji 7v	1.5, 2.5, 3.5 + b12(PPV) 1.5, 3.5 + b12(PPV)	NA	17	NA	NA
	Gambia 7v	2, 3, 4 + b10(PPV) 2 , 3 + b10(PPV)	Between enrolment and approx. 15 months of age[3]	11, 15	NA	NA
	Iceland 9v	3, 4, 5 +b12(PPV) 3, 5 + b12 (PPV)	For 28 days after the booster dose[4]	NA	NA	NA

Comparison	Study	Schedules, months	Time at which outcomes measured[1]			
			Clinical	Carriage in all trial participants, months	Carriage in sub-groups, months	Carriage in the community, months
Comparison J 3p + PPV vs. 2p + 1	Iceland 9v	3, 4, 5 +b12(PPV) 3, 5 + b12	For 28 days after the booster dose[4]	NA	NA	NA
Comparison K 3p + 1 vs. 2p +PPV	Iceland 9v	3, 4, 5 +b12 3, 5 + b12(PPV)	For 28 days after the booster dose[4]	NA	NA	NA
Comparison L 3p + 1 vs. 2p +1	Israel 7v	2, 4, 6 + b12 4, 6 + b12	NA	NA[5]	NA	NA
	Iceland 9v	3, 5 + b 12 3, 4, 5 +b 12	For 28 days after booster dose[4]	NA	NA	NA
	Europe 10v	2, 3, 4 + b 11 2, 4 + b 11	„whole study period“, for 1 month after booster received?[4]	NA	NA	NA
Comparison M 3p + 1 vs. 3p	Israel 7v	2, 4, 6 + b12 2, 4, 6	NA	NA[5]	NA	NA
Comparison N 3p + 1 vs. 3p + PPV	Iceland 9v	3, 4, 5 +b12 3, 4, 5 + b12(PPV)	For 28 days after booster dose[4]	NA	NA	NA
Comparison Q longer interval between primary and booster vs. shorter interval between primary and booster	Finland 10v	2, 3, 4 + b 14-16 2, 3, 4 + b 12-14	"extended safety follow-up“ period[4]	NA	NA	NA
Comparison T Primary (+/- booster) vs. catch-up	Chile 10v	2, 4, 6, + b>18 2 catch-up >18	From booster dose until end of extended safety follow-up[4]	NA	NA	NA
Schedule vs. no PCV (comparisons U-Z)						
Comparison U1 1p vs. 0	Fiji 7v	3.5 no PCV and no PPV	NA	6, 9, 12, 17	NA	NA
	South Africa 9v pilot	1.5, 2.5, 3.5 no PCV and no PPV	NA	2.5	NA	NA
Comparison U2 2p vs. 0	Fiji 7v	1.5, 3.5 no PCV and no PPV	NA	6, 9, 12, 17	NA	NA
	Netherlands4 7v	2, 4 no PCV and no PPV	NA	12, 18, 24	NA	Parents of children sampled at same time as children
	South Africa 9v pilot	1.5, 2.5, 3.5 no PCV and no PPV	NA	3.5	NA	NA
Comparison U3 3p vs. 0	China 7v	3, 4, 5 (DTaP coad) 3, 4, 5 (DTaP not coad) no PCV and no PPV	Until maximum 30-50d after 3rd dose	NA	NA	NA
	Fiji 7v	1.5, 2.5, 3.5 no PCV and no PPV	NA	6, 9, 12, 17	NA	NA
	Finland 7v	2, 4, 6 No doses	Otitis outcomes only. Starting time varies between ITT (at randomization) and PP (at 14d after 3rd dose) analyses.	12	NA	NA
	USA2 7v	3p [6] no PCV and no PPV	NA	NA	1 month after 3rd dose, before booster	Household members also sampled at same time as subgroup

Comparison	Study	Schedules, months	Time at which outcomes measured[1]			
			Clinical	Carriage in all trial participants, months	Carriage in sub-groups, months	Carriage in the community, months
	Gambia 9v	3p [7] no PCV and no PPV	Until end study (2 years follow up). Start time varies between ITT (at randomization) and PP (at 14d after 3rd dose) analyses	NA	NA	NA
	Gambia 9v pilot a	2, 3, 4 no PCV and no PPV	Until 1 month after 3rd dose[8]	5, 9	NA	NA
	Gambia 9v pilot b	2, 3, 4 (DTwPHib mixed) 2, 3 ,4 (DTwPHib sep) no PCV and no PPV	"during the surveillance period", until 1 month after dose 3?	NA	NA	NA
	Ghana infants 9v	1.5, 2.5, 3.5 + b12 (PCV/PPV/Hib) No doses	Between enrolment and approx.. 13 months	NA	NA	NA
	South Africa 9v	1.5, 2.5, 3.5 no PCV and no PPV	Until target number of cases reached. Maximum3.7 years.). Start time varies between ITT (at randomization?) and PP (at 14d after 3rd dose)	NA	Mean 5.35 years after 3rd dose	NA
	South Africa 9v pilot	1.5, 2.5, 3.5 no PCV and no PPV	From enrolment until 9 months	2.5, 3.5, 9	NA	NA
	Chile 10v	2, 4, 6 no PCV and no PPV	"whole study period", enrolment until 1 month after last primary dose (possibly longer) [4]	NA	NA	NA
Comparison V1 1p + PPV vs. 0	Fiji 7v	3.5 + b12(PPV) no PCV (+/- 12(PPV))	NA	17	NA	NA
Comparison V2 2p + PPV vs. 0	Fiji 7v	1.5, 3.5 + b12(PPV) no PCV (+/- 12(PPV))	NA	17	NA	NA
Comparison V3 3p + PPV vs. 0	Fiji 7v	1.5, 2.5, 3.5 + b12(PPV) no PCV (+/- 12(PPV))	NA	17	NA	NA
Comparison W2 2p + 1 vs. 0	Netherlands4 7v	2, 4, +b11 no PCV and no PPV	NA	12, 18, 24	NA	Parents of children sampled at same time as children
Comparison W3 3p + 1 vs. 0	Finland 7v	2, 4, 6, +b12m no PCV and no PPV	Until 24 months of age. Starting time varies between ITT (at randomization) and PP (at 14d after 3rd dose) analyses.	18	NA	NA
	USA1 7v	2, 4, 6, +b12m no PCV and no PPV	Until April 1999	NA	NA	NA
	USA2 7v	3p+1 [6] no PCV and no PPV	April 1997 to May 2000	NA	18-24. Also after trial unblinded, cross sectional study conducted	Household members sampled at same time as subgroup before unblinding
	Ghana infants 9v	1.5, 2.5, 3.5 + b12 (PCV/PPV/Hib) no PCV and no PPV	Enrolment until end of follow up, unclear age at which follow up ended	NA	NA	NA
Comparison W4 1, 2, 3, or 4 doses vs. 0	USA2 7v	3p+1 / 2p+1 / 2doses[6] no PCV and no PPV	April 1997 to May 2000	NA		Community study after trial completion

Comparison	Study	Schedules, months	Time at which outcomes measured[1]			
			Clinical	Carriage in all trial participants, months	Carriage in sub-groups, months	Carriage in the community, months
Comparison X1 1 catch up dose vs. 0	Netherlands1 7v	1dose (25-84m) + PPV 7 months later no PCV and no PPV	NA	7, 14, 20, 26 months after 1st dose [9]	NA	NA
	Netherlands2 7v	1 dose + PPV (>24m) no PCV and no PPV	For 6 months after spontaneous extrusion of the TTs	NA	NA	NA
Comparison X2 2 catch up doses vs. 0	Netherlands1 7v	2 doses with 1 month interval (12-24m) + PPV 6 months later no PCV and no PPV	NA	7, 14, 20, 26 months after 1st dose [9]	NA	NA
	Netherlands3 7v	2 doses >18m no PCV and no PPV	From 14 days after the second set of vaccinations, for 18 or 6 months, depending on year of inclusion	NA	NA	NA
Comparison Y 1 or 2 catch up doses vs. 0	Belgium 7v	2 doses with 1 month interval (12-24m) + PPV 6 months later/ 1dose (25-84m) + PPV 7 months later no PCV and no PPV	1 month after complete vaccination until 26 months after vaccination.	7, 14, 20, 26 months after 1st dose [9]	NA	NA
	Netherlands1 7v	2 doses with 1 month interval (12-24m) + PPV 6 months later/ 1dose (25-84m) + PPV 7 months later no PCV and no PPV	1 month after complete vaccination until 26 months after vaccination.	7, 14, 20, 26 months after 1st dose	NA	NA
	Israel 9v	2 doses (12-17m)/ 1dose (18-35m) no PCV and no PPV	2 years, starting 1 month after complete vaccination	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 18 [9]	NA	NA

Notes:

b – booster; coad – coadministered (vaccines given at same time); DTaP – diphtheria, tetanus, acellular pertussis vaccine; DTwP – diphtheria, tetanus, whole cell pertussis vaccine; HepA – Hepatitis A vaccine; HepB – Hepatitis B vaccine; Hib – *Haemophilus influenzae* type b vaccine; IPD – invasive pneumococcal disease; IPV - inactivated poliovirus vaccine; IQR – interquartile range; ITT – intention to treat analysis; MenC - meningococcus group C conjugate vaccine; Mixed – vaccines given at same time in same syringe; NA – not assessed; PCV – pneumococcal conjugate vaccine; PPV – pneumococcal polysaccharide vaccine; PP- per protocol analysis; SD – standard deviation; Sep – vaccines given at same time but at separate sites; TT – tympanic tube; 3p – 3 dose primary schedule, etc.; +1 – booster dose.

Shaded grey rows are comparisons that are reported in main text;

1 All times are in months of age unless otherwise stated. Carriage in all trial participants is carriage data where attempts were made to sample all of those who were randomized and enrolled in the RCT. Carriage in sub-groups is carriage data where a sub-set of those randomized and enrolled in the RCT was selected for sampling. Carriage in the community is carriage data where people such as parents or siblings of trial participants were sampled to assess indirect effects of vaccination.

2 Samples taken before booster dose so comparison of primary schedule also possible;

3 Not possible to distinguish between pre- and post-PPV periods;

4 Adverse events include eligible clinical outcomes. Not analyzed because data were not specifically collected as outcomes, no case definitions were applied and data were only collected for periods immediately after vaccination;

5 No extractable data as of 1st September 2011;

6 Number of dose given to children in vaccinated group age-dependent. No set age for doses: infants enrolled between age 6 weeks and 7 months- 3 doses of vaccine 2 months apart + b12–15 months of age; infants enrolled between 7 and 11 months of age - 2 doses of vaccine 2 months apart + b12–15 months ; infants enrolled between 12 and 23 months of age received 2 doses of vaccine at least 2 months apart;

7 No set age for doses, children 6-51 weeks given 3 doses at least 25 days apart;

8 Data not reported clearly for each intervention group, and therefore not reported in this review

9 Denominators not reported and not possible to calculate; results not included in meta-analyses.

Table 24: Potential sources of heterogeneity, Clinical outcomes

Study and schedule	Control	Year of trial	Developed country	HIV infected	Annual IPD incidence in population before study	Serotypes causing disease in young before start of trial [30]	Randomization sequence adequate	Concealment of allocation adequate	Outcome assessors blinded	Sub-group observed for outcome	Loss to follow up (%)	Effect estimate on which VE based	Length of follow up for outcome
Finland 7v 3p+1 vs. 0 2, 4, 6, +b12 vs. No doses	Hep B	1995-1999	Yes	NR	< 2 years of age: 45.3 per 100,000 [31]	PCV-type: (79.4% IPD) 4 (5.5% IPD) 6 (17.5% IPD) 9 (6% IPD) 14 (18.6% IPD) 18 (8.2% IPD) 19 (17% IPD) 23 (6.6% IPD)	Not well described	Not described	Yes	**IPD:** Unclear **OM:** No	NR	**IPD:** Risk ratio **OM:** Hazard ratio	17.5m
Gambia 9v 3p vs. 0[1]	Placebo	2000-2004	No	Approx 1%	2-11 months of age: 224 per 100,000 [32]	PCV-type: (77.3% IPD) Individual serotypes: 1 (2.9% IPD) 4 (2.9% IPD) 5 (9.5% IPD) 6 (17.1% IPD) 9 (2.9% IPD) 14 (26.7% IPD) 19 (5.7% IPD) 18 (1% IPD) 23 (8.6% IPD)	Yes	Unclear (opaque envelopes but not clear if envelope linked to child before opening)	Yes	**IPD, pneumonia:** Possibly, only detected at hospitals in first 2 years of study	Unclear	Rate ratio	Median 25 m for ITT (range 21-29m)
South Africa 9v (HIV-uninfected) 3p vs. 0 1.5, 2.5, 3.5 vs. No doses	Placebo	1998-2001	No	0%	No age specified, vaccine type IPD only, HIV-infected and uninfected combined: 112 cases per 100,000 [25] Less than 1 year of age, HIV-infected and uninfected combined: 349 per 100,000 [33]	PCV-type: (82.8% IPD) Individual serotypes: 1 (9.4% IPD) 4 (3.8% IPD) 5 (1.9% IPD) 6 (35.8% IPD) 9 (0% IPD) 14 (11.3% IPD) 18 (5.5% IPD) 19 (11.3% IPD) 23 (3.8% IPD)	Yes	Not well described, but probably adequate	Yes	**IPD:** No **Pneumonia:** Only hospitalized individuals included in outcome definition	Unclear	Relative risk	Max. 45 months, mean 28m

Study and schedule	Control	Year of trial	Developed country	HIV infected	Annual IPD incidence in population before study	Serotypes causing disease in young before start of trial [30]	Randomization sequence adequate	Concealment of allocation adequate	Outcome assessors blinded	Sub-group observed for outcome	Loss to follow up (%)	Effect estimate on which VE based	Length of follow up for outcome
South Africa 9v (HIV-infected) 3p vs. 0 1.5, 2.5, 3.5 vs. No doses	Placebo	1998-2001	No	100%	No age specified, vaccine type IPD only, HIV-infected and uninfected combined: 112 cases per 100,000 [25] Less than 1 year of age, HIV-infected and uninfected combined: 349 per 100,000 [33]	PCV-type: (91% IPD) Individual serotypes: 1 (15.5% IPD) 4 (0% IPD) 5 (0% IPD) 6 (20.0% IPD) 9 (2.2% IPD) 14 (20.0% IPD) 18 (0% IPD) 19 (13.3% IPD) 23 (20.0% IPD)	Yes	Not well described, but probably adequate	Yes	**IPD:** No **Pneumonia:** Only hospitalized individuals included in outcome definition	Unclear	Relative risk	Max. 45 months, mean 28m
USA1 7v 3p+1 2, 4, 6, +12 vs. No doses	MenC	1995-1999	Yes	NR	In US children <2 years of age166.9 per 100,000 [34]	PCV-type: (91.1% IPD) Individual serotypes: 4 (6.3% IPD) 6 (15.9% IPD) 9 (9.5% IPD) 14 (19.8% IPD) 19 (19.8% IPD) 18 (10.3% IPD) 23 (9.5% IPD)	Yes	Yes	Yes	**IPD**: No **Clinical pneumonia:** No **Radiologically confirmed pneumonia (WHO criteria):** Yes, approximately 50% of those with clinical pneumonia	NR	Not explicit. Possibly rate ratio	Max. 42 months
USA2 7v 3p+1 / 2p+1 / 2doses vs. 0[2]	MenC	1997-2000	Yes	NR	1-2 years of age: 2396 per 100,000 [35]	PCV-type: (64.9% IPD) Individual serotypes: 4 (7.1% IPD) 6B (5% IPD) 9V (14.3% IPD) 14 (17.1% IPD) 18C (10% IPD) 19F (7.1% IPD) 23F (4.3% IPD)	Not well described, but probably adequate	Yes	Yes, some limited potential for determining community allocation	**IPD:** No **OM:** Yes, approximately 21% of group (randomly selected)	NR	Rate ratio	Max. 32 months

Hep B - Hepatitis B vaccine; IPD – invasive pneumococcal disease; max. – maximum; MenC - *Neisseria meningitidis* group-C protein conjugate vaccine; NR: Not reported; OM – otitis media
1 No set age for doses: Children 6-51 weeks given 3 doses at least 25 days apart
2 Number of dose given to children in vaccinated group age-dependant. No set age for doses: infants enrolled between age 6 weeks and 7 month s- 3 doses of vaccine 2 months apart + b12–15 months of age; infants enrolled between 7 and 11 months of age - 2 doses of vaccine 2 months apart + b12–15 months ; infants enrolled between 12 and 23 months of age received 2 doses of vaccine at least 2 months apart.

Table 2.5:Comparison A, 2p vs. 1p. Carriage data with random-effects meta-analysis as appropriate

Serotype group	Analysis / sub-analysis	Time of sampling	Number of studies	Studies	Schedules, months	PR (95% CI)[1], I^2	OR (95% CI)[1], I^2	RD (95% CI)[1], I^2
Any	*All studies*	Approx. 6 months of age: Fiji 7v, 6 months of age Gambia 7v, 5 months of age	2	Fiji 7v Gambia 7v	1.5, 3.5 vs. 3.5 2, 3 vs. 2	0.98 (0.81, 1.19), 61.3%	0.99 (0.57, 1.71), 58.5%	-0.01 (-0.11, 0.10), 60.3%
	Studies with same age at last vaccination in both groups	6 months of age	1	Fiji 7v	1.5, 3.5 vs. 3.5	0.87 (0.69, 1.10)	0.76 (0.47, 1.22)	-0.07 (-0.19, 0.05)
	Studies with different age at last vaccination between groups	5 months of age	1	Gambia 7v	2, 3 vs. 2	1.05 (0.96, 1.14)	1.32 (0.79, 2.21)	0.04 (-0.03, 0.11)
	All studies	9 months of age	1	Fiji 7v	1.5, 3.5 vs. 3.5	1.11 (0.88, 1.40)	1.25 (0.77, 2.03)	0.05 (-0.07, 0.18)
		12 months of age	1	Fiji 7v	1.5, 3.5 vs. 3.5	0.87 (0.68, 1.13)	0.77 (0.47, 1.26)	-0.07 (-0.19, 0.06)
		17 months of age	1	Fiji 7v	1.5, 3.5 vs. 3.5	0.70 (0.49, 0.99)	0.47 (0.22, 1.00)	-0.19 (-0.37, -0.01)
VT	*All studies*	Approx. 6 months of age: Fiji 7v, 6 months of age Gambia 7v, 5 months of age	2	Fiji 7v Gambia 7v	1.5, 3.5 vs. 3.5 2, 3 vs. 2	0.93 (0.66, 1.30), 0.0%	0.92 (0.61, 1.37), 0.0%	-0.01 (-0.06, 0.04), 0.0%
	Studies with same age at last vaccination in	6 months of age	1	Fiji 7v	1.5, 3.5 vs. 3.5	0.94 (0.48, 1.85)	0.94 (0.44, 2.00)	-0.01 (-0.08, 0.07)

Serotype group	Analysis / sub-analysis	Time of sampling	Number of studies	Studies	Schedules, months	PR (95% CI)[1], I^2	OR (95% CI)[1], I^2	RD (95% CI)[1], I^2
	both groups: Carriage of VT							
	Studies with different age at last vaccination between groups: Carriage of VT	5 months of age	1	Gambia 7v	2, 3 vs. 2	0.93 (0.63, 1.36)	0.91 (0.56, 1.47)	-0.01 (-0.09, 0.06)
	All studies	9 months of age	1	Fiji 7v	1.5, 3.5 vs. 3.5	1.52 (0.67, 3.45)	1.57 (0.64, 3.85)	0.03 (-0.03, 0.10)
		12 months of age	1	Fiji 7v	1.5, 3.5 vs. 3.5	0.72 (0.30, 1.72)	0.71 (0.28, 1.80)	-0.02 (-0.09, 0.04)
		17 months of age	1	Fiji 7v	1.5, 3.5 vs. 3.5	0.43 (0.11, 1.72)	0.41 (0.09, 1.79)	-0.06 (-0.16, 0.04)
NVT	*All studies*	Approx. 6 months of age	1	Fiji 7v	1.5, 3.5 vs. 3.5	0.99 (0.75, 1.29), 65.6%	1.01 (0.57, 1.77), 68.6%	0.00 (-0.13, 0.13), 68.3%
		Fiji 7v, 6 months of age Gambia 7v, 5 months of age		Gambia 7v	2, 3 vs. 2			
	Studies with same age at last vaccination in both groups: Carriage of NVT	6 months of age	1	Fiji 7v	1.5, 3.5 vs. 3.5	0.83 (0.62, 1.12)	0.74 (0.45, 1.21)	-0.07 (-0.19, 0.05)
	Studies with *different age at last vaccination between groups:* Carriage of NVT	5 months of age	1	Gambia 7v[†]	2, 3 vs. 2	1.10 (0.96, 1.25)	1.32 (0.88, 1.97)	0.06 (-0.03, 0.15)
	All studies:	9 months of age	1	Fiji 7v	1.5, 3.5 vs. 3.5	1.06 (0.80, 1.40)	1.10 (0.67, 1.80)	0.02 (-0.10, 0.14)

Serotype group	Analysis / sub-analysis	Time of sampling	Number of studies	Studies	Schedules, months	PR (95% CI)[1], I^2	OR (95% CI)[1], I^2	RD (95% CI)[1], I^2
		12 months of age	1	Fiji 7v	1.5, 3.5 vs. 3.5	0.90 (0.67, 1.21)	0.84 (0.51, 1.39)	-0.04 (-0.16, 0.08)

Unless otherwise stated, all calculations of effect measures are unadjusted and based on the numbers carrying and not carrying the specified serotypes.
Any – all serotypes, without reference to whether they are included in the vaccine used in the trial; PR – prevalence ratio; OR – Prevalence odds ratio; NVT – non-vaccine serotypes including all serotypes which are not in the vaccine used in the individual trial; RD – risk (prevalence) difference; VAT – vaccine associated serotypes, including all serotypes which are not included in the vaccine used in the individual trial, but which are in the same serogroup as one of the vaccine serotypes. VT – vaccine serotypes, including only the specific serotypes which are in the vaccine used in the individual trial.
1 All analyses are random effects meta-analyses. PR and OR less than 1 and a negative RD indicate that the 2p group is less likely to be carrying *Strep. pneumoniae* than the 1p group. The I^2 statistic can be interpreted as the proportion of the total variation in estimated risk ratios due to between-trial heterogeneity rather than to chance [5]. Low, moderate and high levels of heterogeneity correspond to I^2 values of 25%, 50% and 75% respectively.

Table 2.6: Comparison B, 3p vs. 1p. Carriage data with random-effects meta-analysis as appropriate

Serotype group	Analysis / sub-analysis	Time of sampling	Number of studies	Studies	Schedules, months	PR (95% CI)[1], I^2	OR (95% CI)[1], I^2	RD (95% CI)[1], I^2
Any	All studies	Approx. 6 months of age	2	Fiji 7v	1.5, 2.5, 3.5 vs. 3.5	0.99 (0.91, 1.08), 0.0%	0.92 (0.65, 1.31), 0.0%	-0.01 (-0.07, 0.05), 0.0%
		Fiji 7v, 6 months of age Gambia 7v, 5 months of age		Gambia 7v†	2, 3, 4 vs. 2			
	Studies with same age at last vaccination in both groups	6 months of age	1	Fiji 7v	1.5, 2.5, 3.5 vs. 3.5	0.92 (0.72, 1.16)	0.83 (0.51, 1.37)	-0.05 (-0.17, 0.08)
	Studies with different age at last vaccination in groups	5 months of age	1	Gambia 7v†	2, 3, 4 vs. 2	1.00 (0.92, 1.10)	1.02 (0.62, 1.67)	0.00 (-0.07, 0.08)
	All studies	9 months of age	1	Fiji 7v	1.5, 2.5, 3.5 vs. 3.5	0.95 (0.73, 1.23)	0.91 (0.55, 1.50)	-0.02 (-0.15, 0.10)
		12 months of age	1	Fiji 7v	1.5, 2.5, 3.5 vs. 3.5	0.82 (0.62, 1.09)	0.69 (0.41, 1.16)	-0.09 (-0.22, 0.04)
		17 months of age	1	Fiji 7v	1.5, 2.5, 3.5 vs. 3.5	0.68 (0.47, 0.99)	0.45 (0.21, 0.98)	-0.20 (-0.38, -0.01)
VT	All studies	Approx. 6 months of age.	2	Fiji 7v	1.5, 2.5, 3.5 vs. 3.5	0.73 (0.51, 1.06), 0.0%	0.70 (0.45, 1.07), 0.0%	-0.04 (-0.09, 0.01), 0.0%
		Fiji 7v, 6 months of age Gambia 7v, 5 months of age		Gambia 7v†	2, 3, 4 vs. 2			

Serotype group	Analysis / sub-analysis	Time of sampling	Number of studies	Studies	Schedules, months	PR (95% CI)[1], I^2	OR (95% CI)[1], I^2	RD (95% CI)[1], I^2
	Studies with same age at last vaccination in both groups	6 months of age	1	Fiji 7v	1.5, 2.5, 3.5 vs. 3.5	0.89 (0.44, 1.82)	0.88 (0.40, 1.96)	-0.01 (-0.09, 0.06)
	Studies with different age at last vaccination in groups	5 months of age	1	Gambia 7v†	2, 3, 4 vs. 2	0.68 (0.44, 1.05)	0.63 (0.38, 1.06)	-0.06 (-0.13, 0.01)
	All studies	9 months of age	1	Fiji 7v	1.5, 2.5, 3.5 vs. 3.5	0.48 (0.15, 1.56)	0.47 (0.14, 1.59)	-0.04 (-0.09, 0.02)
		12 months of age	1	Fiji 7v	1.5, 2.5, 3.5 vs. 3.5	0.81 (0.33, 1.97)	0.79 (0.30, 2.09)	-0.02 (-0.09, 0.05)
		17 months of age	1	Fiji 7v	1.5, 2.5, 3.5 vs. 3.5	0.16 (0.02, 1.35)	0.15 (0.02, 1.32)	-0.09 (-0.18, 0.01)
NVT	All studies	Approx. 6 months of age: Fiji 7v, 6 months of age Gambia 7v, 5 months of age	1	Fiji 7v Gambia 7v†	1.5, 2.5, 3.5 vs. 3.5 2, 3 vs. 2	1.07 (0.93, 1.22), 8.0%	1.13 (0.75, 1.69), 37.4%	0.03 (-0.06, 0.12), 33.5%
	Studies with same age at last vaccination in both groups	6 months of age	1	Fiji 7v	1.5, 3.5 vs. 3.5	0.93 (0.70, 1.26)	0.89 (0.54, 1.48)	-0.03 (-0.15, 0.09)
	Studies with different age at last vaccination in groups	5 months of age	1	Gambia 7v†	2, 3 vs. 2	1.10 (0.97, 1.26)	1.35 (0.90, 2.02)	0.07 (-0.02, 0.15)
	All studies	9 months of age	1	Fiji 7v	1.5, 2.5, 3.5 vs. 3.5	1.03 (0.76, 1.38)	1.05 (0.63, 1.75)	0.01 (-0.11, 0.14)

Serotype group	Analysis / sub-analysis	Time of sampling	Number of studies	Studies	Schedules, months	PR (95% CI)[1], I^2	OR (95% CI)[1], I^2	RD (95% CI)[1], I^2
		12 months of age	1	Fiji 7v	1.5, 2.5, 3.5 vs. 3.5	0.82 (0.59, 1.14)	0.73 (0.43, 1.24)	-0.08 (-0.20, 0.05)

Unless otherwise stated, all calculations of effect measures are unadjusted and based on the numbers carrying and not carrying the specified serotypes.
Any – all serotypes, without reference to whether they are included in the vaccine used in the trial; PR – prevalence ratio; OR – Prevalence odds ratio; NVT – non-vaccine serotypes including all serotypes which are not in the vaccine used in the individual trial; RD – risk (prevalence) difference; VAT – vaccine associated serotypes, including all serotypes which are not included in the vaccine used in the individual trial, but which are in the same serogroup as one of the vaccine serotypes. VT – vaccine serotypes, including only the specific serotypes which are in the vaccine used in the individual trial.
1 All analyses are random effects meta-analyses. PR and OR less than 1 and a negative RD indicate that the 3p group is less likely to be carrying *Strep. pneumoniae* than the 1p group. The I^2 statistic can be interpreted as the proportion of the total variation in estimated risk ratios due to between-trial heterogeneity rather than to chance [5]. Low, moderate and high levels of heterogeneity correspond to I^2 values of 25%, 50% and 75% respectively.

Table 2.7: Comparison C, 3p vs. 2p. Carriage data with random-effects meta-analysis as appropriate

Serotype group	Analysis / sub-analysis	Time of sampling	Number of studies	Studies	Schedules, months	PR (95% CI)[1], I^2	OR (95% CI)[1], I^2	RD (95% CI)[1], I^2
Any	All studies	Approx. 6 months of age: Fiji 7v, 6 months of age Gambia 7v, 5 months of age	2	Fiji 7v Gambia 7v[†]	1.5, 2.5, 3.5 vs. 1.5, 3.5 2, 3, 4 vs. 2, 3	0.97 (0.90, 1.05), 0.0%	0.94 (0.66, 1.33), 0.0%	-0.02 (-0.08, 0.04), 0.0%
	Studies with same age at last vaccination in both groups	6 months of age	1	Fiji 7v	1.5, 2.5, 3.5 vs. 1.5, 3.5	1.05 (0.83, 1.34)	1.10 (0.69, 1.77)	0.02 (-0.09, 0.14)
	Studies with different age at last vaccination in groups	5 months of age	1	Gambia 7v[†]	2, 3, 4 vs. 2, 3	0.96 (0.88, 1.04)	0.77 (0.46, 1.29)	-0.03 (-0.10, 0.03)
	All studies	9 months of age	1	Fiji 7v	1.5, 2.5, 3.5 vs. 1.5, 3.5	0.86 (0.68, 1.09)	0.73 (0.45, 1.18)	-0.08 (-0.20, 0.04)
		12 months of age	1	Fiji 7v	1.5, 2.5, 3.5 vs. 1.5, 3.5	0.94 (0.71, 1.25)	0.90 (0.55, 1.48)	-0.03 (-0.15, 0.10)
		17 months of age	1	Fiji 7v	1.5, 2.5, 3.5 vs. 1.5, 3.5	0.98 (0.65, 1.47)	0.96 (0.48, 1.94)	-0.01 (-0.18, 0.16)
VT	All studies	Approx. 6 months of age: Fiji 7v, 6 months of age Gambia 7v, 5 months of age	2	Fiji 7v Gambia 7v[†]	1.5, 2.5, 3.5 vs. 1.5, 3.5 2, 3, 4 vs. 2, 3	0.79 (0.55, 1.15), 0.0%	0.76 (0.50, 1.17), 0.0%	-0.03 (-0.08, 0.02), 0.0%

	Studies with same age at last vaccination in both groups	6 months of age	1	Fiji 7v	1.5, 2.5, 3.5 vs. 1.5, 3.5	0.95 (0.47, 1.89)	0.94 (0.43, 2.04)	-0.01 (-0.08, 0.07)
	Studies with different age at last vaccination in groups	5 months of age	1	Gambia 7v[†]	2, 3, 4 vs. 2, 3	0.74 (0.47, 1.14)	0.69 (0.41, 1.17)	-0.05 (-0.12, 0.02)
	All studies	9 months of age	1	Fiji 7v	1.5, 2.5, 3.5 vs. 1.5, 3.5	0.32 (0.11, 0.94)	0.30 (0.10, 0.92)	-0.07 (-0.13, -0.01)
		12 months of age	1	Fiji 7v	1.5, 2.5, 3.5 vs. 1.5, 3.5	1.12 (0.44, 2.80)	1.12 (0.42, 3.01)	0.01 (-0.05, 0.07)
		17 months of age	1	Fiji 7v	1.5, 2.5, 3.5 vs. 1.5, 3.5	0.38 (0.04, 3.54)	0.37 (0.04, 3.63)	-0.03 (-0.09, 0.03)
NVT	All studies	Approx. 6 months of age: Fiji 7v, 6 months of age Gambia 7v, 5 months of age	1	Fiji 7v Gambia 7v[†]	1.5, 2.5, 3.5 vs. 1.5, 3.5 2, 3 vs. 2	1.02 (0.91, 1.15), 0.0%	1.09 (0.80, 1.50), 0.0%	0.02 (-0.05, 0.09), 0.0%
	Studies with same age at last vaccination in both groups	6 months of age	1	Fiji 7v	1.5, 3.5 vs. 3.5	1.12 (0.83, 1.52)	1.20 (0.74, 1.96)	0.04 (-0.07, 0.16)
	Studies with different age at last vaccination in groups	5 months of age	1	Gambia 7v[†]	2, 3 vs. 2	1.01 (0.89, 1.14)	1.02 (0.68, 1.55)	0.01 (-0.08, 0.09)
	All studies	9 months of age	1	Fiji 7v	1.5, 2.5, 3.5 vs. 1.5, 3.5	0.97 (0.74, 1.28)	0.95 (0.59, 1.55)	-0.01 (-0.13, 0.11)
		12 months of age	1	Fiji 7v	1.5, 2.5, 3.5 vs. 1.5, 3.5	0.91 (0.66, 1.26)	0.86 (0.52, 1.44)	-0.03 (-0.15, 0.08)

Unless otherwise stated, all calculations of effect measures are unadjusted and based on the numbers carrying and not carrying the specified serotypes.
Any – all serotypes, without reference to whether they are included in the vaccine used in the trial; PR – prevalence ratio; OR – Prevalence odds ratio; NVT – non-vaccine serotypes including all serotypes which are not in the vaccine used in the individual trial ;RD – risk (prevalence) difference; VAT – vaccine associated serotypes, including all serotypes which are not included in the vaccine used in the individual trial, but which are in the same serogroup as one of the vaccine serotypes. VT – vaccine serotypes, including only the specific serotypes which are in the vaccine used in the individual trial.
1 All analyses are random effects meta-analyses. PR and OR less than 1 and a negative RD indicate that the 3p group is less likely to be carrying *Strep. pneumoniae* than the 2p group. The I^2 statistic can be interpreted as the proportion of the total variation in estimated risk ratios due to between-trial heterogeneity rather than to chance [5]. Low, moderate and high levels of heterogeneity correspond to I^2 values of 25%, 50% and 75% respectively.

Table 2.8: Comparison D, 2p + PPV vs. 1p +PPV. Carriage data with random-effects meta-analysis as appropriate

Serotype group	Analysis / sub-analysis	Time of sampling	Number of studies	Studies	Schedules, months	PR (95% CI)[1], I^2	OR (95% CI)[1], I^2	RD (95% CI)[1], I^2
Any	All studies	11 months of age	1	Gambia 7v	2, 3, 4 + b10(PPV) vs. 2 , 3 + b10(PPV)	0.91 (0.81, 1.03)	0.71 (0.46, 1.11)	-0.07 (-0.15, 0.02)
		15-17 months of age:	2	Fiji 7v	1.5, 3.5 + b12(PPV) vs. 3.5 + b12(PPV)	0.94 (0.80, 1.11), 26.4%	0.73 (0.47, 1.15), 0.0%	-0.04 (-0.10, 0.03), 0.0%
		Fiji 7v, 17 months of age Gambia 7v, 15 months of age		Gambia 7v	2, 3, 4 + b10(PPV) vs. 2 , 3 + b10(PPV)			
	Studies with same age at last vaccination in both groups	17 months of age	1	Fiji 7v	1.5, 3.5 + b12(PPV) vs. 3.5 + b12(PPV)	0.80 (0.55, 1.15)	0.65 (0.32, 1.31)	-0.11 (-0.28, 0.07)
	Studies with different age at last vaccination in groups	15 months of age	1	Gambia 7v	2, 3, 4 + b10(PPV) vs. 2 , 3 + b10(PPV)	0.97 (0.90, 1.05)	0.80 (0.44, 1.43)	-0.03 (-0.09, 0.04)
VT	All studies	11 months of age	1	Gambia 7v	2, 3, 4 + b10(PPV) vs. 2 , 3 + b10(PPV)	0.83 (0.55, 1.25)	0.79 (0.48, 1.31)	-0.04 (-0.11, 0.04)
		15-17 months of age:	2	Fiji 7v	1.5, 3.5 + b12(PPV) vs. 3.5 + b12(PPV)	0.77 (0.50, 1.21), 1.6%	0.73 (0.45, 1.21), 0.0%	-0.04 (-0.10, 0.01), 0.0%
		Fiji 7v, 17 months of age Gambia 7v, 15 months of age		Gambia 7v	2, 3, 4 + b10(PPV) vs. 2 , 3 + b10(PPV)			
	Studies with same age at last vaccination in both groups	17 months of age	1	Fiji 7v	1.5, 3.5 + b12(PPV) vs. 3.5 + b12(PPV)	0.35 (0.07, 1.75)	0.33 (0.06, 1.78)	-0.05 (-0.14, 0.03)

Serotype group	Analysis / sub-analysis	Time of sampling	Number of studies	Studies	Schedules, months	PR (95% CI)[1], I^2	OR (95% CI)[1], I^2	RD (95% CI)[1], I^2
	Studies with different age at last vaccination in groups	15 months of age	1	Gambia 7v	2, 3, 4 + b10(PPV) vs. 2 , 3 + b10(PPV)	0.83 (0.53, 1.28)	0.79 (0.47, 1.34)	-0.03 (-0.11, 0.04)
NVT	All studies	11 months of age	1	Gambia 7v	2, 3, 4 + b10(PPV) vs. 2 , 3 + b10(PPV)	0.92 (0.77, 1.10)	0.83 (0.56, 1.23)	-0.05 (-0.14, 0.05)
		15 months of age:	1	Gambia 7v	2, 3, 4 + b10(PPV) vs. 2 , 3 + b10(PPV)	1.00 (0.88, 1.12)	0.99 (0.64, 1.53)	-0.00 (-0.09, 0.09)

Unless otherwise stated, all calculations of effect measures are unadjusted and based on the numbers carrying and not carrying the specified serotypes.
Any – all serotypes, without reference to whether they are included in the vaccine used in the trial; PR – prevalence ratio; OR – Prevalence odds ratio; NVT – non-vaccine serotypes including all serotypes which are not in the vaccine used in the individual trial ;RD – risk (prevalence) difference; VAT – vaccine associated serotypes, including all serotypes which are not included in the vaccine used in the individual trial, but which are in the same serogroup as one of the vaccine serotypes. VT – vaccine serotypes, including only the specific serotypes which are in the vaccine used in the individual trial.
1 All analyses are random effects meta-analyses. PR and OR less than 1 and a negative RD indicate that the 2p group is less likely to be carrying *Strep. pneumoniae* than the 1p group. The I^2 statistic can be interpreted as the proportion of the total variation in estimated risk ratios due to between-trial heterogeneity rather than to chance [5]. Low, moderate and high levels of heterogeneity correspond to I^2 values of 25%, 50% and 75% respectively.

Table 2.9: Comparison E: 2p+1 vs. 2p. Carriage data with random-effects meta-analysis as appropriate

Serotype group	Analysis / sub-analysis	Time of sampling	Number of studies	Studies	Schedules, months	PR (95% CI)[1], I^2	OR (95% CI)[1], I^2	RD (95% CI)[1], I^2
Any	All studies	12 months of age	1	Netherlands4 7v	2, 4, +b11 vs. 2, 4	0.93 (0.82, 1.05)	0.83 (0.61, 1.13)	-0.05 (-0.12, 0.03)
		18 months of age	1	Netherlands4 7v	2, 4, +b11 vs. 2, 4	0.88 (0.78, 1.00)	0.74 (0.54, 1.01)	-0.07 (-0.15, 0.00)
		24 months of age	1	Netherlands4 7v	2, 4, +b11 vs. 2, 4	1.05 (0.92, 1.20)	1.12 (0.83, 1.52)	0.03 (-0.05, 0.10)
VT	All studies	12 months of age	1	Netherlands4 7v	2, 4, +b11 vs. 2, 4	0.81 (0.61, 1.08)	0.77 (0.53, 1.10)	-0.05 (-0.11, 0.02)
		18 months of age	1	Netherlands4 7v	2, 4, +b11 vs. 2, 4	0.64 (0.47, 0.88)	0.58 (0.39, 0.85)	-0.09 (-0.15-, 0.03)
		24 months of age	1	Netherlands4 7v	2, 4, +b11 vs. 2, 4	0.96 (0.66, 1.38)	0.95 (0.62, 1.46)	-0.01 (-0.06, 0.05)
NVT	All studies	12 months of age	1	Netherlands4 7v	2, 4, +b11 vs. 2, 4	1.00 (0.82, 1.22)	1.00 (0.73, 1.37)	0.00 (-0.07, 0.07)
		18 months of age	1	Netherlands4 7v	2, 4, +b11 vs. 2, 4	1.03 (0.86, 1.24)	1.05 (0.77, 1.44)	0.01 (-0.06, 0.09)
		24 months of age	1	Netherlands4 7v	2, 4, +b11 vs. 2, 4	1.09 (0.91, 1.30)	1.15 (0.85, 1.57)	0.03 (-0.04, 0.11)

Unless otherwise stated, all calculations of effect measures are unadjusted and based on the numbers carrying and not carrying the specified serotypes.
Any – all serotypes, without reference to whether they are included in the vaccine used in the trial; PR – prevalence ratio; OR – Prevalence odds ratio; NVT – non-vaccine serotypes including all serotypes which are not in the vaccine used in the individual trial ;RD – risk (prevalence) difference; VAT – vaccine associated serotypes, including all serotypes which are not included in the vaccine used in the individual trial, but which are in the same serogroup as one of the vaccine serotypes. VT – vaccine serotypes, including only the specific serotypes which are in the vaccine used in the individual trial.
1 All analyses are random effects meta-analyses. PR and OR less than 1 and a negative RD indicate that the 2p+1 group is less likely to be carrying *Strep. pneumoniae* than the 2p group. The I^2 statistic can be interpreted as the proportion of the total variation in estimated risk ratios due to between-trial heterogeneity rather than to chance [5]. Low, moderate and high levels of heterogeneity correspond to I^2 values of 25%, 50% and 75% respectively.

Table 2.10: Comparison H, 3p+ppv vs. 1p+ppv. Carriage data with random-effects meta-analysis as appropriate

Serotype group	Analysis / sub-analysis	Time of sampling	Number of studies	Studies	Schedules, months	PR (95% CI)[1], I^2	OR (95% CI)[1], I^2	RD (95% CI)[1], I^2
Any	All studies	11 months of age	1	Gambia 7v	2, 3, 4 + b10(PPV) vs. 2 + b10(PPV)	0.94 (0.83, 1.05)	0.78 (0.50, 1.21)	-0.05 (-0.13, 0.04)
		Approx. 18 months of age	2	Fiji 7v	1.5, 2.5, 3.5 + b12(PPV) vs. 3.5 + b12(PPV)	0.92 (0.85, 1.00), 0.0%	0.61 (0.39, 0.96), 0.0%	-0.07 (-0.14, -0.00), 0.0%
		Fiji 7v, 17 months of age Gambia 7v, 15 months of age		Gambia 7v	2, 3, 4 + b10(PPV) vs. 2 + b10(PPV)			
	Studies with same age at last vaccination in both groups	17 months of age	1	Fiji 7v	1.5, 2.5, 3.5 + b12(PPV) vs. 3.5 + b12(PPV)	0.78 (0.51, 1.18)	0.62 (0.29, 1.34)	-0.12 (-0.30, 0.07)
	Studies with different age at last vaccination in groups	15 months of age	1	Gambia 7v	2, 3, 4 + b10(PPV) vs. 2 + b10(PPV)	0.93 (0.85, 1.01)	0.60 (0.34, 1.06)	-0.06 (-0.13, 0.01)
VT	All studies	11 months of age	1	Gambia 7v	2, 3, 4 + b10(PPV) vs. 2 + b10(PPV)	0.50 (0.30, 0.81)	0.44 (0.25, 0.78)	-0.10 (-0.17, -0.03)
		Approx. 18 months of age	2	Fiji 7v	1.5, 2.5, 3.5 + b12(PPV) vs. 3.5 + b12(PPV)	0.65 (0.41, 1.02), 0.0%	0.60 (0.36, 1.02), 0.0%	-0.05 (-0.11, 0.00), 0.0%
		Fiji 7v, 17 months of age Gambia 7v, 15 months of age		Gambia 7v	2, 3, 4 + b10(PPV) vs. 2 + b10(PPV)			
	Studies with same age at last vaccination in both groups	17 months of age	1	Fiji 7v	1.5, 2.5, 3.5 + b12(PPV) vs. 3.5 + b12(PPV)	0.48 (0.10, 2.37)	0.46 (0.09, 2.48)	-0.04 (-0.13, 0.05)

Serotype group	Analysis / sub-analysis	Time of sampling	Number of studies	Studies	Schedules, months	PR (95% CI)[1], I^2	OR (95% CI)[1], I^2	RD (95% CI)[1], I^2
	Studies with different age at last vaccination in groups	15 months of age	1	Gambia 7v	2, 3, 4 + b10(PPV) vs. 2 + b10(PPV)	0.67 (0.42, 1.07)	0.62 (0.36, 1.08)	-0.06 (-0.13, 0.01)
NVT	All studies	11 months of age	1	Gambia 7v	2, 3, 4 + b10(PPV) vs. 2 + b10(PPV)	1.07 (0.91, 1.25)	1.17 (0.79, 1.75)	0.04 (-0.06, 0.13)
		15 months of age	1	Gambia 7v	2, 3, 4 + b10(PPV) vs. 2 + b10(PPV)	0.96 (0.85, 1.09)	0.88 (0.57, 1.36)	-0.03 (-0.11, 0.06)

Unless otherwise stated, all calculations of effect measures are unadjusted and based on the numbers carrying and not carrying the specified serotypes.
Any – all serotypes, without reference to whether they are included in the vaccine used in the trial; PR – prevalence ratio; OR – Prevalence odds ratio; NVT – non-vaccine serotypes including all serotypes which are not in the vaccine used in the individual trial ;RD – risk (prevalence) difference; VAT – vaccine associated serotypes, including all serotypes which are not included in the vaccine used in the individual trial, but which are in the same serogroup as one of the vaccine serotypes. VT – vaccine serotypes, including only the specific serotypes which are in the vaccine used in the individual trial.
1 All analyses are random effects meta-analyses. PR and OR less than 1 and a negative RD indicate that the 2p+1 group is less likely to be carrying *Strep. pneumoniae* than the 2p group. The I^2 statistic can be interpreted as the proportion of the total variation in estimated risk ratios due to between-trial heterogeneity rather than to chance [5]. Low, moderate and high levels of heterogeneity correspond to I^2 values of 25%, 50% and 75% respectively.

Table 2.11: Comparison I, 3p + PPV vs. 2p +PPV. Carriage data with random-effects meta-analysis as appropriate

Serotype group	Analysis / sub-analysis	Time of sampling	Number of studies	Studies	Schedules, months	PR (95% CI)[1], I^2	OR (95% CI)[1], I^2	RD (95% CI)[1], I^2
Any	All studies	11 months of age	1	Gambia 7v	2, 3, 4 + b10(PPV) vs. 2 , 3 + b10(PPV)	1.03 (0.90, 1.16)	1.09 (0.71, 1.68)	0.02 (-0.07, 0.11)
		Approx. 18 months of age	2	Fiji 7v	1.5, 2.5, 3.5 + b12(PPV) vs. 1.5, 3.5 + b12(PPV)	0.96 (0.88, 1.04), 0.0%	0.82 (0.53, 1.27), 0.0%	-0.03 (-0.10, 0.03), 0.0%
		Fiji 7v, 17 months of age Gambia 7v, 15 months of age		Gambia 7v	2, 3, 4 + b10(PPV) vs. 2 , 3 + b10(PPV)			
	Studies with same age at last vaccination in both groups	17 months of age	1	Fiji 7v	1.5, 2.5, 3.5 + b12(PPV) vs. 1.5, 3.5 + b12(PPV)	0.98 (0.63, 1.52)	0.96 (0.45, 2.03)	-0.01 (-0.19, 0.17)
	Studies with different age at last vaccination in groups	15 months of age	1	Gambia 7v	2, 3, 4 + b10(PPV) vs. 2 , 3 + b10(PPV)	0.96 (0.88, 1.04)	0.76 (0.44, 1.30)	-0.04 (-0.11, 0.04)
VT	All studies	11 months of age	1	Gambia 7v	2, 3, 4 + b10(PPV) vs. 2 , 3 + b10(PPV)	0.60 (0.36, 1.01)	0.56 (0.31, 1.01)	-0.07 (-0.13, -0.00)
		Approx. 18 months of age	2	Fiji 7v	1.5, 2.5, 3.5 + b12(PPV) vs. 1.5, 3.5 + b12(PPV)	0.84 (0.52, 1.35), 0.0%	0.82 (0.47, 1.42), 0.0%	-0.01 (-0.06, 0.04), 0.0%
		Fiji 7v, 17 months of age Gambia 7v, 15 months of age		Gambia 7v	2, 3, 4 + b10(PPV) vs. 2 , 3 + b10(PPV)			
	Studies with same age at last vaccination in both groups	17 months of age	1	Fiji 7v	1.5, 2.5, 3.5 + b12(PPV) vs. 1.5, 3.5 + b12(PPV)	1.37 (0.20, 9.37)	1.38 (0.19, 10.17)	0.01 (-0.06, 0.08)

Serotype group	Analysis / sub-analysis	Time of sampling	Number of studies	Studies	Schedules, months	PR (95% CI)[1], I^2	OR (95% CI)[1], I^2	RD (95% CI)[1], I^2
	Studies with different age at last vaccination in groups	15 months of age	1	Gambia 7v	2, 3, 4 + b10(PPV) vs. 2 , 3 + b10(PPV)	0.81 (0.49, 1.33)	0.78 (0.44, 1.39)	-0.03 (-0.10, 0.04)
NVT	All studies	11 months of age	1	Gambia 7v	2, 3, 4 + b10(PPV) vs. 2 , 3 + b10(PPV)	1.16 (0.98, 1.38)	1.41 (0.95, 2.11)	0.08 (-0.01, 0.18)
		15 months of age	1	Gambia 7v	2, 3, 4 + b10(PPV) vs. 2 , 3 + b10(PPV)	0.97 (0.85, 1.10)	0.89 (0.57, 1.38)	-0.02 (-0.11, 0.07)

Unless otherwise stated, all calculations of effect measures are unadjusted and based on the numbers carrying and not carrying the specified serotypes.
Any – all serotypes, without reference to whether they are included in the vaccine used in the trial; PR – prevalence ratio; OR – Prevalence odds ratio; NVT – non-vaccine serotypes including all serotypes which are not in the vaccine used in the individual trial ;RD – risk (prevalence) difference; VAT – vaccine associated serotypes, including all serotypes which are not included in the vaccine used in the individual trial, but which are in the same serogroup as one of the vaccine serotypes. VT – vaccine serotypes, including only the specific serotypes which are in the vaccine used in the individual trial.
1 All analyses are random effects meta-analyses. PR and OR less than 1 and a negative RD indicate that the 3p group is less likely to be carrying *Strep. pneumoniae* than the 2p group. The I^2 statistic can be interpreted as the proportion of the total variation in estimated risk ratios due to between-trial heterogeneity rather than to chance [5]. Low, moderate and high levels of heterogeneity correspond to I^2 values of 25%, 50% and 75% respectively.

Table 2.12: Potential sources of heterogeneity, Carriage

Study	Year of trial	Developed country	HIV infected	Randomization sequence adequate	Concealment of allocation adequate	Outcome assessors blinded	Multiple colonies serotyped?	Sub-group or all randomized included in carriage study?	Level of carriage prevaccination	Time since last dose PCV at sample closest to 12 months of age[1]	
Belgium 7v **1 or 2 catch up doses vs. 0** 2 doses (12-24m) + PPV/ 1dose (24-48m) + PPV vs. No doses	1999-2002	Yes	No (immune-deficiency an exclusion criterion)	Yes	Not well described	Yes	Yes	All	vaccine type 25% any type 42%	NA	All older than 12m at vaccination
Fiji 7v **3p vs. 2p vs. 1p vs. 0**[2] 1.5, 2.5, 3.5 [2] vs. 1.5, 3.5 [2] vs. 3.5 [2] vs. No doses [2]	NR	No	No (or few, those with HIV infected mother excluded)	Yes	Unclear (opaque envelopes but not clear if envelope linked to child before opening)	Yes	Not clear (says "single colonies" rather than 1 colony)	All	NR	8.5m	Based on 12m sample
Finland 7v **3p+1 vs. 0** 2, 4, 6, +b12 vs. No doses	1995-1999	Yes	NR	Not well described	Not described	NR	NR	All	NR	6m	Based on 12m sample
Gambia 7v **3p vs. 2p vs. 1p** 2, 3, 4 + b10(PPV) vs. 2, 3 + b10(PPV) vs. 2 + b10(PPV)	NR	No	NR	Not well described, 'consecutively randomized'	Not described	Yes	NR but appears to be multiple as "any serotype" numbers are less than any PPV + any non-PPV	All	vaccine type 19% any type75-82%	9m (1 dose group) 8m (2 dose group) 7m (1 dose group)	Based on 11m sample

Study	Year of trial	Developed country	HIV infected	Randomization sequence adequate	Concealment of allocation adequate	Outcome assessors blinded	Multiple colonies serotyped?	Sub-group or all randomized included in carriage study?	Level of carriage prevaccination	Time since last dose PCV at sample closest to 12 months of age[1]	
Gambia 9v, pilot a **3p vs. 0** 2, 3, 4 vs. No doses	NR	No	No (or few, those with blood transfusion or HIV infected mother or excluded)	Yes	Not well described, but probably adequate	NR	Yes (at least 5 tested from optochin sensitivity and probably these then serotyped)	All	NR	5m	Based on 9m sample
Netherlands1 7v **1 or 2 catch up doses vs. 0** 2 doses (12-24m) + PPV/ 1dose (24-48m) + PPV vs. No doses	1998-2002	Yes	No (immune-deficiency an exclusion criterion)	Yes	Not well described	Yes	Not clearly stated but probably multiple colonies	All	vaccine type 24% any type 49%	NA	All older than 12m at vaccination
Netherlands4 7v **2p+1 vs. 2p vs. 0** 2, 4, +b11 vs. 2, 4 vs. No doses	2005-2008	Yes	NR	Not well described, but probably adequate	Not well described, but probably adequate	NR	No (1 per plate)	All	vaccine type 5% any type 17%	8m (2p group) 1m (2+1 group)	Based on 12m samples
South Africa 9v **3p vs. 0** 1.5, 2.5, 3.5 vs. No doses	1998-2001	No	HIV-infected individuals analyzed separately	Yes	Not well described, but probably adequate	Yes	NR	Sub-group: 9.4% of those randomized. A randomly selected 20% invited to participate	NR	NA	No 12 months of age sample
South Africa 9v, pilot **3p vs. 0** 1.5, 2.5, 3.5 vs. No doses	NR	No	0.6% strong positive at 9m	Not described	Not described	Yes	NR	All	vaccine type NR any type 49%	5.5m	Based on 9m sample

Study	Year of trial	Developed country	HIV infected	Randomization sequence adequate	Concealment of allocation adequate	Outcome assessors blinded	Multiple colonies serotyped?	Sub-group or all randomized included in carriage study?	Level of carriage prevaccination	Time since last dose PCV at sample closest to 12 months of age[1]	
USA2 7v **3p+1 vs. 0**[3]	1997-2000	Yes	NR	Not well described, but probably adequate	Yes	Yes	Yes (4 per plate)	Sub-group: 10% of those enrolled at <7 months. Not randomly selected	NR	1-6.5m	Based on 12-15m sample
USA2 7v, cross-sectional study **3p+1 vs. 0**[3]	1997-2000 (samples collected 2001-2002)	Yes	NR	Not well described, but probably adequate	Yes	NR	No, single colony	Sub-group: 12% of those enrolled at <7 months. Not randomly selected	NR	Varies depending on when recruited to main study	

Pnc: pneumococci; NA – not applicable; NR: not reported
1 based on the sample closest to 12 months of age
2 half of each group administered PPV at 12 months of age
3 No set age for doses: infants enrolled between age 6 weeks and 7 month s were given3 doses of vaccine 2 months apart + b12–15 months of age;

Table 2.13: Comparison U1, 1p vs. 0. Carriage data with random-effects meta-analysis as appropriate

Serotype group	Analysis / sub-analysis	Time of sampling	Number of studies	Studies	Schedules, months	PR (95% CI)[1], I^2	OR (95% CI)[1], I^2	RD (95% CI)[1], I^2
Any	All studies	2.5 months of age	1	South Africa 9v pilot	1.5 (, 2.5, 3.5) vs. no PCV and no PPV	1.01 (0.83, 1.23)	1.02 (0.71, 1.45)	0.00 (-0.08, 0.09)
		6 months of age	1	Fiji 7v	3.5 vs. no PCV and no PPV	1.32 (1.01, 1.71)	1.70 (1.03, 2.81)	0.13 (0.01, 0.25)
		9 months of age	1	Fiji 7v	3.5 vs. no PCV and no PPV	1.05 (0.81, 1.36)	1.10 (0.67, 1.82)	0.02 (-0.10, 0.15)
		12 months of age	1	Fiji 7v	3.5 vs. no PCV and no PPV	1.15 (0.88, 1.49)	1.30 (0.78, 2.16)	0.07 (-0.06, 0.19)
		18 months of age	1	Fiji 7v	3.5 vs. no PCV and no PPV	1.40 (0.97, 2.02)	2.02 (0.93, 4.40)	0.17 (-0.01, 0.36)
VT	All studies	6 months of age	1	Fiji 7v	3.5 vs. no PCV and no PPV	0.91 (0.46, 1.79)	0.90 (0.42, 1.93)	-0.01 (-0.09, 0.07)
		9 months of age	1	Fiji 7v	3.5 vs. no PCV and no PPV	0.43 (0.20, 0.93)	0.39 (0.16, 0.91)	-0.09 (-0.17, -0.01)
		12 months of age	1	Fiji 7v	3.5 vs. no PCV and no PPV	0.54 (0.27, 1.11)	0.50 (0.22, 1.12)	-0.07 (-0.16, 0.01)
		18 months of age	1	Fiji 7v	3.5 vs. no PCV and no PPV	0.83 (0.28, 2.45)	0.81 (0.24, 2.74)	-0.02 (-0.14, 0.10)
NVT	All studies	6 months of age	1	Fiji 7v	3.5 vs. no PCV and no PPV	1.76 (1.22, 2.55)	2.33 (1.36, 4.01)	0.19 (0.07, 0.30)

	9 months of age	1	Fiji 7v	3.5 vs. no PCV and no PPV	1.54 (1.08, 2.20)	1.92 (1.12, 3.29)	0.15 (0.03, 0.26)
	12 months of age	1	Fiji 7v	3.5 vs. no PCV and no PPV	1.48 (1.04, 2.09)	1.84 (1.07, 3.13)	0.14 (0.02, 0.26)

Unless otherwise stated, all calculations of effect measures are unadjusted and based on the numbers carrying and not carrying the specified serotypes.
Any – all serotypes, without reference to whether they are included in the vaccine used in the trial; PR – prevalence ratio; OR – Prevalence odds ratio; NVT – non-vaccine serotypes including all serotypes which are not in the vaccine used in the individual trial ;RD – risk (prevalence) difference; VAT – vaccine associated serotypes, including all serotypes which are not included in the vaccine used in the individual trial, but which are in the same serogroup as one of the vaccine serotypes. VT – vaccine serotypes, including only the specific serotypes which are in the vaccine used in the individual trial.
1 All analyses are random effects meta-analyses. PR and OR less than 1 and a negative RD indicate that the 1p group is less likely to be carrying *Strep. pneumoniae* than the 0-dose group. The I^2 statistic can be interpreted as the proportion of the total variation in estimated risk ratios due to between-trial heterogeneity rather than to chance [5]. Low, moderate and high levels of heterogeneity correspond to I^2 values of 25%, 50% and 75% respectively.

Table 2.14: Comparison U2, 2p vs. 0. Carriage data with random-effects meta-analysis as appropriate

Serotype group	Analysis / sub-analysis	Time of sampling	Number of studies	Studies	Schedules, months	PR (95% CI)[1], I^2	OR (95% CI)[1], I^2	RD (95% CI)[1], I^2
Any	All studies	3.5 months of age	1	South Africa 9v pilot	1.5, 2.5, 3.5 vs. no PCV and no PPV	0.91 (0.76, 1.09)	0.83 (0.58, 1.18)	-0.05 (-0.13, 0.04)
		6 months of age	1	Fiji 7v	1.5, 3.5 vs. no PCV and no PPV	1.15 (0.88, 1.50)	1.29 (0.80, 2.08)	0.06 (-0.06, 0.18)
		9 months of age	1	Fiji 7v	1.5, 3.5 vs. no PCV and no PPV	1.17 (0.92, 1.47)	1.37 (0.85, 2.21)	0.08 (-0.04, 0.20)
		12 months of age	2	Fiji 7v	1.5, 3.5 vs. no PCV and no PPV	0.94 (0.84, 1.04), 0.0%	0.86 (0.66, 1.13), 0.0%	-0.04 (-0.10, 0.03), 0.0%
				Netherlands4 7v	2, 4 vs. no PCV and no PPV			
		Approx 18 months of age Fiji 7v, 17 months old Netherlands4 7v, 18 months old	2	Fiji 7v	1.5, 3.5 vs. no PCV and no PPV	0.94 (0.84, 1.05), 0.0%	0.85 (0.63, 1.14), 0.0%	-0.04 (-0.11, 0.03), 0.0%
				Netherlands4 7v	2, 4 vs. no PCV and no PPV			
		24 months of age	1	Netherlands4 7v	2, 4 vs. no PCV and no PPV	0.83 (0.73, 0.94)	0.62 (0.46, 0.86)	-0.11 (-0.19, -0.04)
VT	All studies	6 months of age	1	Fiji 7v	1.5, 3.5 vs. no PCV and no PPV	0.86 (0.45, 1.65)	0.84 (0.40, 1.76)	-0.02 (-0.09, 0.06)
		9 months of age	1	Fiji 7v	1.5, 3.5 vs. no PCV and no PPV	0.65 (0.35, 1.21)	0.61 (0.30, 1.24)	-0.06 (-0.14, 0.02)

Serotype group	Analysis / sub-analysis	Time of sampling	Number of studies	Studies	Schedules, months	PR (95% CI)[1], I^2	OR (95% CI)[1], I^2	RD (95% CI)[1], I^2
		12 months of age	2	Fiji 7v	1.5, 3.5 vs. no PCV and no PPV	0.57 (0.38, 0.87), 34.7%	0.50 (0.36, 0.68), 0.0%	-0.12 (-0.17, -0.07), 0.0%
				Netherlands4 7v	2, 4 vs. no PCV and no PPV			
		Approx 18 months of age:	2	Fiji 7v	1.5, 3.5 vs. no PCV and no PPV	0.63 (0.50, 0.80), 0.0%	0.52 (0.37, 0.72), 0.0%	-0.11 (-0.17, -0.06), 0.0%
		Fiji 7v, 17 months old Netherlands4 7v, 18 months old		Netherlands4 7v	2, 4 vs. no PCV and no PPV			
		24 months of age	1	Netherlands4 7v	2, 4 vs. no PCV and no PPV	0.42 (0.31, 0.56)	0.31 (0.22, 0.46)	-0.21 (-0.27, -0.14)
NVT	All studies	6 months of age	1	Fiji 7v	1.5, 3.5 vs. no PCV and no PPV	1.47 (1.01, 2.13)	1.73 (1.02, 2.92)	0.11 (0.01, 0.22)
		9 months of age	1	Fiji 7v	1.5, 3.5 vs. no PCV and no PPV	1.62 (1.16, 2.28)	2.11 (1.27, 3.52)	0.17 (0.06, 0.28)
		12 months of age	2	Fiji 7v	1.5, 3.5 vs. no PCV and no PPV	1.31 (1.09, 1.58), 0.0%	1.50 (1.14, 1.98), 0.0%	0.09 (0.03, 0.15), 0.0%
				Netherlands4 7v	2, 4 vs. no PCV and no PPV			
		18 months of age	1	Netherlands4 7v	2, 4 vs. no PCV and no PPV	1.30 (1.05, 1.61)	1.50 (1.08, 2.08)	0.09 (0.02, 0.16)
		24 months of age	1	Netherlands4 7v	2, 4 vs. no PCV and no PPV	1.32 (1.06, 1.63)	1.52 (1.10, 2.11)	0.10 (0.02, 0.17)

Unless otherwise stated, all calculations of effect measures are unadjusted and based on the numbers carrying and not carrying the specified serotypes.

Any – all serotypes, without reference to whether they are included in the vaccine used in the trial; PR – prevalence ratio; OR – Prevalence odds ratio; NVT – non-vaccine serotypes including all serotypes which are not in the vaccine used in the individual trial ;RD – risk (prevalence) difference; VAT – vaccine associated serotypes, including all serotypes which are not included in the vaccine used in the individual trial, but which are in the same serogroup as one of the vaccine serotypes. VT – vaccine serotypes, including only the specific serotypes which are in the vaccine used in the individual trial.

1 All analyses are random effects meta-analyses. PR and OR less than 1 and a negative RD indicate that the 2p group is less likely to be carrying *Strep. pneumoniae* than the 0-dose group. The I^2 statistic can be interpreted as the proportion of the total variation in estimated risk ratios due to between-trial heterogeneity rather than to chance [5]. Low, moderate and high levels of heterogeneity correspond to I^2 values of 25%, 50% and 75% respectively.

Table 2.15: Comparison U3, 3p vs. 0. Carriage data with random-effects meta-analysis as appropriate

Serotype group	Analysis / sub-analysis	Time of sampling	Number of studies	Studies	Schedules, months	PR (95% CI)[1], I^2	OR (95% CI)[1], I^2	RD (95% CI)[1], I^2
Any	All studies	Approx 6 months of age/ 1 month after 3rd dose	3	Fiji 7v	1.5, 2.5, 3.5 vs. no PCV and no PPV	0.99 (0.86, 1.13), 59.2%	0.97 (0.58, 1.62), 58.6%	-0.01 (-0.09, 0.08), 60.0%
				Gambia 9v pilot a	2, 3, 4 vs. no PCV and no PPV			
				USA2 7v	3p no PCV and no PPV			
	1 month interval between doses, individually randomized, all randomized individuals	Approx 6 months of age/ 1 month after 3rd dose	2	Fiji 7v	1.5, 2.5, 3.5 vs. no PCV and no PPV	1.08 (0.82, 1.41), 74.2%	1.32 (0.85, 2.06), 0.0%	0.03 (-0.07, 0.13), 51.5%
				Gambia 9v pilot a	2, 3, 4 vs. no PCV and no PPV			
	2 month interval between doses: Cluster randomized, sub-set of enrolled individuals	Approx 6 months of age/ 1 month after 3rd dose	1	USA2 7v	3p no PCV and no PPV	0.88 (0.76, 1.01)[2]	0.70 (0.48, 1.03)[2]	-0.08 (-0.17, 0.01)[2]
							0.77 (0.59, 1.00)[2,3]	
	All studies	9 months of age	3	Fiji 7v	1.5, 2.5, 3.5 vs. no PCV and no PPV	0.94 (0.87, 1.03), 0.0%	0.82 (0.62, 1.08), 0.0%	-0.04 (-0.10, 0.02), 0.0%

Serotype group	Analysis / sub-analysis	Time of sampling	Number of studies	Studies	Schedules, months	PR (95% CI)[1], I^2	OR (95% CI)[1], I^2	RD (95% CI)[1], I^2
				Gambia 9v pilot a	2, 3, 4 vs. no PCV and no PPV			
				South Africa 9v pilot	1.5, 2.5, 3.5 vs. no PCV and no PPV			
		12 months of age	2	Fiji 7v	1.5, 2.5, 3.5 vs. no PCV and no PPV	0.97 (0.85, 1.11), 0.0%	0.93 (0.68, 1.26), 0.0%	-0.02 (-0.09, 0.06), 0.0%
				USA2 7v	3p no PCV and no PPV			
	1 month interval	12 months of age	1	Fiji 7v	1.5, 2.5, 3.5 vs. no PCV and no PPV	0.94 (0.70, 1.26)	0.90 (0.54, 1.50)	-0.03 (-0.15, 0.10)
	2 month interval	12 months of age	1	USA2 7v	3p no PCV and no PPV	0.98 (0.84, 1.14)[2]	0.95 (0.64, 1.39)[2]	-0.20 (-0.11, 0.08)[2]
							0.86 (0.50, 1.48)[2,3]	
	All studies	17 months of age	1	Fiji 7v	1.5, 2.5, 3.5 vs. no PCV and no PPV	0.95 (0.62, 1.44)	0.91 (0.44, 1.90)	-0.02 (-0.20, 0.16)
		Mean 5.3 years after 3rd dose	2	South Africa 9V	1.5, 2.5, 3.5 vs. no PCV and no PPV	0.96 (0.80, 1.15)[4], 0.0%	0.88 (0.57, 1.36)[4], 0.0%	-0.03 (-0.13, 0.08)[4], 0.0%
	HIV-uninfected	Mean 5.3 years after 3rd dose	1	South Africa 9V	1.5, 2.5, 3.5 vs. no PCV and no PPV	0.93 (0.73, 1.17)[4]	0.86 (0.53, 1.38)[4]	-0.04 (-0.16, 0.08)[4]
	HIV-infected	Mean 5.3 years after 3rd dose	1	South Africa 9V	1.5, 2.5, 3.5 vs. no PCV and no PPV	1.01 (0.76, 1.13)[4]	1.02 (0.38, 2.75)[4]	0.00 (-0.20, 0.21)[4]
VT	All studies	Approx 6 months of age/ 1 month after 3rd dose	3	Fiji 7v	1.5, 2.5, 3.5 vs. no PCV and no PPV	0.71 (0.47, 1.05), 66.4%	0.57 (0.39, 0.85), 24.7%	-0.08 (-0.16, -0.00), 55.5%

Serotype group	Analysis / sub-analysis	Time of sampling	Number of studies	Studies	Schedules, months	PR (95% CI)[1], I^2	OR (95% CI)[1], I^2	RD (95% CI)[1], I^2
				Gambia 9v pilot a	2, 3, 4 vs. no PCV and no PPV			
				USA2 7v	3p no PCV and no PPV			
	1 month interval between doses, individually randomized, all randomized individuals	Approx 6 months of age/ 1 month after 3rd dose	2	Fiji 7v	1.5, 2.5, 3.5 vs. no PCV and no PPV	0.86 (0.69, 1.07), 0.0%	0.73 (0.46, 1.15), 0.0%	-0.04 (-0.11, 0.03), 0.0%
				Gambia 9v pilot a	2, 3, 4 vs. no PCV and no PPV			
	2 month interval between doses: Cluster randomized, sub-set of enrolled individuals	Approx 6 months of age/ 1 month after 3rd dose	1	USA2 7v	3p no PCV and no PPV	0.51 (0.34, 0.74)[2]	0.42 (0.26, 0.68)[2]	-0.14 (-0.21, -0.06)[2]
							0.40 (0.23, 0.67)[2,3]	
	All studies	9 months of age	3	Fiji 7v	1.5, 2.5, 3.5 vs. no PCV and no PPV	0.51 (0.27, 0.97), 88.2%	0.39 (0.24, 0.62), 38.1%	-0.15 (-0.20, -0.10), 0.0%
				Gambia 9v pilot a	2, 3, 4 vs. no PCV and no PPV			
				South Africa 9v pilot	1.5, 2.5, 3.5 vs. no PCV and no PPV			
	All studies	12 months of age	3	Fiji 7v	1.5, 2.5, 3.5 vs. no PCV and no PPV	0.57 (0.34, 0.95), 72.8%	0.51 (0.28, 0.95), 75.1%	-0.08 (-0.16, 0.00), 81.9%

Serotype group	Analysis / sub-analysis	Time of sampling	Number of studies	Studies	Schedules, months	PR (95% CI)[1], I^2	OR (95% CI)[1], I^2	RD (95% CI)[1], I^2
				Finland 7v	2, 4, 6, vs. No doses			
				USA2 7v	3p no PCV and no PPV			
	1 month interval	12 months of age	1	Fiji 7v	1.5, 2.5, 3.5 vs. no PCV and no PPV	0.44 (0.20, 0.96)	0.40 (0.17, 0.94)	-0.09 (-0.17, -0.01)
	2 month interval	12 months of age	2	Finland 7v	2, 4, 6 vs. No doses	0.83 (0.63, 1.09)	0.81 (0.59, 1.10)	-0.02 (-0.05, 0.01)
				USA2 7v	3p no PCV and no PPV	0.42 (0.27, 0.66)[2]	0.36 (0.21, 0.60)[2] 0.51 (0.34, 0.78)[2,3]	-0.14 (-0.22, -0.07)[2]
	All studies	17 months of age	1	Fiji 7v	1.5, 2.5, 3.5 vs. no PCV and no PPV	0.14 (0.02, 1.07)	0.12 (0.01, 1.02)	-0.11 (-0.20, -0.01)
		Mean 5.3 years after 3rd dose	1	South Africa 9V	1.5, 2.5, 3.5 vs. no PCV and no PPV	0.93 (0.52, 1.68)[4], 60.4%	0.91 (0.41, 2.02)[4], 52.3%	-0.02 (-0.16, 0.12)[4], 41.0%
	HIV-uninfected	Mean 5.3 years after 3rd dose	1	South Africa 9V	1.5, 2.5, 3.5 vs. no PCV and no PPV	0.68 (0.39, 1.20)[4]	0.64 (0.33, 1.24)[4]	-0.06 (-0.15, 0.03)[4]
	HIV-infected	Mean 5.3 years after 3rd dose	1	South Africa 9V	1.5, 2.5, 3.5 vs. no PCV and no PPV	1.23 (0.76, 1.99)[4]	1.45 (0.59, 3.56)[4]	0.09 (-0.13, 0.31)[4]
NVT	All studies	Approx 6 months of age/ 1 month after 3rd dose	3	Fiji 7v	1.5, 2.5, 3.5 vs. no PCV and no PPV	1.30 (0.99, 1.71), 58.2%	1.51 (1.01, 2.26), 50.9%	0.10 (0.01, 0.18), 44.9%
				Gambia 9v pilot a	2, 3, 4 vs. no PCV and no PPV			

Serotype group	Analysis / sub-analysis	Time of sampling	Number of studies	Studies	Schedules, months	PR (95% CI)[1], I^2	OR (95% CI)[1], I^2	RD (95% CI)[1], I^2
				USA2 7v	3p no PCV and no PPV			
	1 month interval between doses, individually randomized, all randomized individuals	Approx 6 months of age/ 1 month after 3rd dose	2	Fiji 7v	1.5, 2.5, 3.5 vs. no PCV and no PPV	1.51 (1.17, 1.95), 0.0%	1.90 (1.28, 2.81), 0.0%	0.14 (0.06, 0.23), 0.0%
				Gambia 9v pilot a	2, 3, 4 vs. no PCV and no PPV			
	2 month interval between doses: Cluster randomized, sub-set of enrolled individuals	Approx 6 months of age/ 1 month after 3rd dose	1	USA2 7v	3p no PCV and no PPV	1.06 (0.86, 1.31)[2]	1.11 (0.76, 1.60)[2] 0.72 (0.43, 1.23)[2,3]	0.02 (-0.07, 0.12)[2]
	All studies	9 months of age	3	Fiji 7v	1.5, 2.5, 3.5 vs. no PCV and no PPV	1.55 (1.27, 1.90), 0.0%	1.88 (1.41, 2.51), 0.0%	0.13 (0.07, 0.19), 0.0%
				Gambia 9v pilot a	2, 3, 4 vs. no PCV and no PPV			
				South Africa 9v pilot	1.5, 2.5, 3.5 vs. no PCV and no PPV			
	All studies	12 months of age	2	Fiji 7v	1.5, 2.5, 3.5 vs. no PCV and no PPV	1.20 (1.01, 1.43), 0.0%	1.38 (1.01, 1.89), 0.0%	0.08 (0.00, 0.15), 0.0%
				USA2 7v	3p no PCV and no PPV			

Serotype group	Analysis / sub-analysis	Time of sampling	Number of studies	Studies	Schedules, months	PR (95% CI)[1], I^2	OR (95% CI)[1], I^2	RD (95% CI)[1], I^2
	1 month interval: Carriage of NVT	12 months of age	1	Fiji 7v	1.5, 2.5, 3.5 vs. no PCV and no PPV	1.22 (0.84, 1.77)	1.34 (0.77, 2.31)	0.06 (-0.06, 0.18)
	2 month interval: Carriage of NVT	12 months of age	1	USA2 7v	3p no PCV and no PPV	1.20 (0.98, 1.46)[2]	1.41 (0.96, 2.05)[2] 1.02 (0.61, 1.72)[2,3]	0.09 (-0.01, 0.18)[2]
	All studies	Mean 5.3 years after 3rd dose	2	South Africa 9V	1.5, 2.5, 3.5 vs. no PCV and no PPV	1.00 (0.74, 1.36)[4], 0.0%	0.99 (0.63, 1.56)[4], 0.0%	-0.01 (-0.10, 0.09)[4], 0.0%
	HIV-uninfected	Mean 5.3 years after 3rd dose	1	South Africa 9V	1.5, 2.5, 3.5 vs. no PCV and no PPV	1.07 (0.77, 1.48)[4]	1.10 (0.67, 1,82)[4]	0.02 (-0.90, 0.14)[4]
	HIV-infected	Mean 5.3 years after 3rd dose	1	South Africa 9V	1.5, 2.5, 3.5 vs. no PCV and no PPV	0.71 (0.33, 1.56)[4]	0.63 (0.23, 1.79)[4]	-0.09 (-0.28, 0.11)[4]
VT +6A	All studies	7 months of age	1	USA2 7v	3p no PCV and no PPV	0.54 (0.39, 0.75)[2]	0.44 (0.28, 0.68)[2] 0.42 (0.25, 0.69)[2,3]	-0.16 (-0.24, -0.08)[2]
		12 months of age	1	USA2 7v	3p no PCV and no PPV	0.52 (0.38, 0.72)[2]	0.41 (0.26, 0.63)[2] 0.48 (0.22, 1.02)[2,3]	-0.18 (-0.26, -0.09)[2]
VAT	All studies	7 months of age	1	USA2 7v	3p no PCV and no PPV	1.03 (0.64, 1.66)[2]	1.03 (0.60, 1.79)[2] 0.74 (0.37, 1.49)[2,3]	0.00 (-0.06, 0.07)[2]

Serotype group	Analysis / sub-analysis	Time of sampling	Number of studies	Studies	Schedules, months	PR (95% CI)[1], I^2	OR (95% CI)[1], I^2	RD (95% CI)[1], I^2
		12 months of age	1	USA2 7v	3p no PCV and no PPV	0.73 (0.47, 1.13)[2]	0.69 (0.41, 1.15)[2] 0.73 (0.26, 2.07)[2,3]	-0.05 (-0.12, 0.02)[2]
NVT-VAT	All studies	7 months of age	1	USA2 7v	3p no PCV and no PPV	1.07 (0.81, 1.42)[2]	1.10 (0.74, 1.65)[2] 0.73 (0.40, 1.34)[2,3]	0.02 (-0.06, 0.11)[2]
		12 months of age	1	USA2 7v	3p no PCV and no PPV	1.56 (1.17, 2.10)[2]	1.90 (1.26, 2.89)[2] 1.62 (0.93, 2.83)[2,3]	0.14 (0.05, 0.22)[2]

Unless otherwise stated, all calculations of effect measures are unadjusted and based on the numbers carrying and not carrying the specified serotypes.
Any – all serotypes, without reference to whether they are included in the vaccine used in the trial; PR – prevalence ratio; OR – Prevalence odds ratio; NVT – non-vaccine serotypes including all serotypes which are not in the vaccine used in the individual trial ;RD – risk (prevalence) difference; VAT – vaccine associated serotypes, including all serotypes which are not included in the vaccine used in the individual trial, but which are in the same serogroup as one of the vaccine serotypes. VT – vaccine serotypes, including only the specific serotypes which are in the vaccine used in the individual trial.
1 All analyses are random effects meta-analyses. PR and OR less than 1 and a negative RD indicate that the 3p group is less likely to be carrying *Strep. pneumoniae* than the 0-dose group. The I^2 statistic can be interpreted as the proportion of the total variation in estimated risk ratios due to between-trial heterogeneity rather than to chance [5]. Low, moderate and high levels of heterogeneity correspond to I^2 values of 25%, 50% and 75% respectively.
2 Data from a sub-group of trial participants, randomization not maintained
3 Odds ratios reported by trial authors controlling for household- and community-level clustering; the number of children who were not colonized with any pneumococcus serotype was used as the denominator in calculations
4 Data from a randomly selected sub-group of trial participants

Table 2.16: Comparison W2, 2p + 1 vs. 0. Carriage data with random-effects meta-analysis as appropriate

Serotype group	Analysis / sub-analysis	Time of sampling	Number of studies	Studies	Schedules, months	PR (95% CI)[1], I^2	OR (95% CI)[1], I^2	RD (95% CI)[1], I^2
Any	All studies	12 months of age	1	Netherlands4 7v	2, 4, +b11 vs. no PCV and no PPV	0.86 (0.76, 0.97)	0.67 (0.48, 0.92)	-0.09 (-0.17, -0.02)
	All studies	18 months of age	1	Netherlands4 7v	2, 4, +b11 vs. no PCV and no PPV	0.83 (0.73, 0.94)	0.61 (0.44, 0.84)	-0.12 (-0.19, -0.04)
	All studies	24 months of age	1	Netherlands4 7v	2, 4, +b11 vs. no PCV and no PPV	0.87 (0.77, 0.99)	0.70 (0.51, 0.96)	-0.08 (-0.16, -0.01)
VT	All studies	12 months of age	1	Netherlands4 7v	2, 4, +b11 vs. no PCV and no PPV	0.52 (0.41, 0.68)	0.40 (0.28, 0.57)	-0.18 (-0.25, -0.11)
	All studies	18 months of age	1	Netherlands4 7v	2, 4, +b11 vs. no PCV and no PPV	0.41 (0.31, 0.55)	0.31 (0.21, 0.44)	-0.22 (-0.29, -0.15)
	All studies	24 months of age	1	Netherlands4 7v	2, 4, +b11 vs. no PCV and no PPV	0.40 (0.29, 0.54)	0.30 (0.20, 0.44)	-0.21 (-0.28, -0.15)
NVT	All studies	12 months of age	1	Netherlands4 7v	2, 4, +b11 vs. no PCV and no PPV	1.30 (1.05, 1.63)	1.49 (1.07, 2.06)	0.09 (0.02, 0.16)
	All studies	18 months of age	1	Netherlands4 7v	2, 4, +b11 vs. no PCV and no PPV	1.34 (1.09, 1.66)	1.58 (1.14, 2.19)	0.10 (0.03, 0.18)
	All studies	24 months of age	1	Netherlands4 7v	2, 4, +b11 vs. no PCV and no PPV	1.43 (1.16, 1.76)	1.76 (1.27, 2.43)	0.13 (0.06, 0.20)

Unless otherwise stated, all calculations of effect measures are unadjusted and based on the numbers carrying and not carrying the specified serotypes.
Any – all serotypes, without reference to whether they are included in the vaccine used in the trial; PR – prevalence ratio; OR – Prevalence odds ratio; NVT – non-vaccine serotypes including all serotypes which are not in the vaccine used in the individual trial ;RD – risk (prevalence) difference; VAT – vaccine associated serotypes, including all serotypes which are not included in the vaccine used in the individual trial, but which are in the same serogroup as one of the vaccine serotypes. VT – vaccine serotypes, including only the specific serotypes which are in the vaccine used in the individual trial.
1 All analyses are random effects meta-analyses. PR and OR less than 1 and a negative RD indicate that the 2p+1 group is less likely to be carrying *Strep. pneumoniae* than the 0-dose group. The I^2 statistic can be interpreted as the proportion of the total variation in estimated risk ratios due to between-trial heterogeneity rather than to chance [5]. Low, moderate and high levels of heterogeneity correspond to I^2 values of 25%, 50% and 75% respectively.

Table 2.17: Comparison W3, 3p + 1 vs. 0. Carriage data with random-effects meta-analysis as appropriate

Serotype group	Analysis / sub-analysis	Time of sampling	Number of studies	Studies	Schedules, months	PR (95% CI)[1], I^2	OR (95% CI)[1], I^2	RD (95% CI)[1], I^2
Any	All studies	USA2 7v, 18-24 months of age	1	USA2 7v	3p+1 vs. no PCV and no PPV	1.16 (1.02, 1.32)[2]	1.56 (1.06, 2.31)[2] 1.42 (0.91, 2.19)[2,3]	0.10 (0.01, 0.19)[2]
	All studies	Cross sect (various ages)	1	USA2 7v	3p+1 vs. no PCV and no PPV	1.06 (0.94, 1.19)[2]	1.16 (0.85, 1.57)[2]	0.03 (-0.04, 0.11)[2]
VT	All studies	Approx. 18 months of age Finland 7v , 18 months of age USA2 7v, 18-24 months of age	2	Finland 7v USA2 7v [2]	2, 4, 6, +b12m vs. no PCV and no PPV 3p+1 vs. no PCV and no PPV	0.60 (0.48, 0.75), 0.0%	0.55 (0.43, 0.71), 0.0%	-0.07 (-0.10, -0.04), 0.0%
	Individually randomized, all randomized individuals	18 months of age	1	Finland 7v	2, 4, 6, +b12m vs. no PCV and no PPV	0.59 (0.45, 0.77)	0.55 (0.40, 0.74)	-0.07 (-0.10, -0.03)
	Cluster randomized, sub-set of enrolled individuals	18-24 months of age	1	USA2 7v	3p+1 vs. no PCV and no PPV	0.63 (0.43, 0.91)[2]	0.56 (0.35, 0.89)[2] 0.81 (0.51, 1.31)[2,3]	-0.09 (-0.16, -0.02)[2]
	All studies	Cross sect (various ages)	1	USA2 7v	3p+1 vs. no PCV and no PPV	0.60 (0.41, 0.87)[2]	0.55 (0.36, 0.85)[2]	-0.07 (-0.12, -0.02)[2]
NVT	All studies	USA2 7v, 18-24 months of age	1	USA2 7v	3p+1 vs. no PCV and no PPV	1.50 (1.24, 1.82)[2]	2.26 (1.55, 3.28)[2]	0.20 (0.11, 0.29)[2]

Serotype group	Analysis / sub-analysis	Time of sampling	Number of studies	Studies	Schedules, months	PR (95% CI)[1], I^2	OR (95% CI)[1], I^2	RD (95% CI)[1], I^2
							1.67 (1.02 , 2.78)[2,3]	
VT+6A	All studies	18 months of age	1	USA2 7v	3p+1 no PCV and no PPV	0.70 (0.51, 0.94)[2]	0.61 (0.40, 0.92)[2]	-0.10 (-0.18, -0.02)[2]
							0.88 (0.58, 1.33)[2,3]	
VAT	All studies	18 months of age	1	USA2 7v	3p+1 no PCV and no PPV	1.22 (0.81, 1.85)[2]	1.27 (0.78, 2.08)[2]	0.03 (-0.03, 0.10)[2]
							1.78 (1.25, 2.53)[2,3]	
		Cross sect (various ages)	1	USA2 7v	3p+1 vs. no PCV and no PPV	1.00 (0.70, 1.42)[2]	1.00 (0.65, 1.51)[2]	-0.00 (-0.05, 0.05)[2]
NVT-VAT	All studies	18 months of age	1	USA2 7v	3p+1 no PCV and no PPV	1.67 (1.27, 2.19)[2]	2.15 (1.44, 3.20)[2]	0.17 (0.08, 0.25)[2]
							2.02 (1.23, 2.33)[2,3]	
		Cross sect (various ages)	1	USA2 7v	3p+1 vs. no PCV and no PPV	1.32 (1.06, 1.62)[2]	1.52 (1.11, 2.08)[2]	0.09 (0.02, 0.16)[2]

Unless otherwise stated, all calculations of effect measures are unadjusted and based on the numbers carrying and not carrying the specified serotypes.
Any – all serotypes, without reference to whether they are included in the vaccine used in the trial; PR – prevalence ratio; OR – Prevalence odds ratio; NVT – non-vaccine serotypes including all serotypes which are not in the vaccine used in the individual trial ;RD – risk (prevalence) difference; VAT – vaccine associated serotypes, including all serotypes which are not included in the vaccine used in the individual trial, but which are in the same serogroup as one of the vaccine serotypes. VT – vaccine serotypes, including only the specific serotypes which are in the vaccine used in the individual trial.
1 All analyses are random effects meta-analyses. PR and OR less than 1 and a negative RD indicate that the 3p+1 group is less likely to be carrying *Strep. pneumoniae* than the 0-dose group. The I^2 statistic can be interpreted as the proportion of the total variation in estimated risk ratios due to between-trial heterogeneity rather than to chance [5]. Low, moderate and high levels of heterogeneity correspond to I^2 values of 25%, 50% and 75% respectively.
2 Data from a sub-group of trial participants, randomization not maintained
3 Odds ratios reported by trial authors controlling for household- and community-level clustering; the number of children who were not colonized with any pneumococcus serotype was used as the denominator in calculations

Table 2.18: Comparison Y, 1 or 2 catch up doses vs. 0. Carriage data with random-effects meta-analysis as appropriate

Serotype group	Analysis / sub-analysis	Time of sampling	Number of studies	Studies	Schedules, months	PR (95% CI)[1], I^2	OR (95% CI)[1], I^2	RD (95% CI)[1], I^2
Any	All studies	7 months after first vaccination	2	Netherlands1 7v	2 doses (12-24m) + PPV 6 months later/ 1dose (24-48m)) + PPV 6 months later no PCV and no PPV	0.84 (0.69, 1.01), 0.0%	0.70 (0.47, 1.02), 0.0%	-0.09 (-0.18, 0.00), 0.0%
				Belgium 7v	2 doses (12-24m) + PPV 6 months later/ 1dose (24-48m)) + PPV 6 months later no PCV and no PPV			
		14 months after first vaccination	1	Netherlands1 7v	2 doses (12-24m) + PPV 6 months later/ 1dose (24-48m)) + PPV 6 months later no PCV and no PPV	0.85 (0.71, 1.03)	0.70 (0.45, 1.07)	-0.09 (-0.19, 0.02)
		20 months after first vaccination	1	Netherlands1 7v	2 doses (12-24m) + PPV 6 months later/ 1dose (24-48m)) + PPV 6 months later no PCV and no PPV	0.96 (0.79, 1.16)	0.90 (0.56, 1.45)	-0.03 (-0.14, 0.09)
		26 months after first vaccination	1	Netherlands1 7v	2 doses (12-24m) + PPV 6 months later/ 1dose (24-48m)) + PPV 6 months later no PCV and no PPV	1.11 (0.87, 1.41)	1.24 (0.75, 2.06)	0.05 (-0.07, 0.18)
VT	All studies	7 months after first vaccination	1	Netherlands1 7v	2 doses (12-24m) + PPV 6 months later/ 1dose (24-48m)) + PPV 6 months later no PCV and no PPV	0.68 (0.46, 1.00)	0.60 (0.37, 0.99)	-0.09 (-0.18, -0.00)
		14 months after first vaccination	1	Netherlands1 7v	2 doses (12-24m) + PPV 6 months later/ 1dose (24-48m)) + PPV 6 months later no PCV and no PPV	0.54 (0.34, 0.86)	0.47 (0.27, 0.83)	-0.11 (-0.19, -0.03)
		20 months after first vaccination	1	Netherlands1 7v	2 doses (12-24m) + PPV 6 months later/ 1dose (24-48m)) + PPV 6 months later no PCV and no PPV	0.51 (0.31, 0.83)	0.43 (0.23, 0.78)	-0.14 (-0.23, -0.04)

Serotype group	Analysis / sub-analysis	Time of sampling	Number of studies	Studies	Schedules, months	PR (95% CI)[1], I^2	OR (95% CI)[1], I^2	RD (95% CI)[1], I^2
		26 months after first vaccination	1	Netherlands1 7v	2 doses (12-24m) + PPV 6 months later/ 1dose (24-48m)) + PPV 6 months later no PCV and no PPV	0.52 (0.30, 0.90)	0.45 (0.23, 0.87)	-0.12 (-0.22, -0.02)
NVT	All studies	7 months after first vaccination	1	Netherlands1 7v	2 doses (12-24m) + PPV 6 months later/ 1dose (24-48m)) + PPV 6 months later no PCV and no PPV	0.94 (0.66, 1.33)	0.91 (0.57, 1.47)	-0.02 (-0.11, 0.07)
		14 months after first vaccination	1	Netherlands1 7v	2 doses (12-24m) + PPV 6 months later/ 1dose (24-48m)) + PPV 6 months later no PCV and no PPV	1.09 (0.81, 1.46)	1.14 (0.73, 1.78)	0.03 (-0.07, 0.13)
		20 months after first vaccination	1	Netherlands1 7v	2 doses (12-24m) + PPV 6 months later/ 1dose (24-48m)) + PPV 6 months later no PCV and no PPV	1.36 (0.99, 1.87)	1.62 (0.99, 2.65)	0.11 (-0.00, 0.22)
		26 months after first vaccination	1	Netherlands1 7v	2 doses (12-24m) + PPV 6 months later/ 1dose (24-48m)) + PPV 6 months later no PCV and no PPV	1.70 (1.14, 2.53)	2.14 (1.22, 3.76)	0.16 (0.04, 0.27)
NVT-VAT	All studies	7 months after first vaccination	1	Belgium 7v	2 doses (12-24m) + PPV 6 months later/ 1dose (24-48m)) + PPV 6 months later no PCV and no PPV	3.30 (0.74, 14.76)	3.88 (0.74, 20.23)	0.14 (-0.02, 0.29)
VT+VAT	All studies	7 months after first vaccination	1	Belgium 7v	2 doses (12-24m) + PPV 6 months later/ 1dose (24-48m)) + PPV 6 months later no PCV and no PPV	0.71 (0.27, 1.82)	0.65 (0.20, 2.12)	-0.07 (-0.26, 0.12)

Unless otherwise stated, all calculations of effect measures are unadjusted and based on the numbers carrying and not carrying the specified serotypes.
Denominators not available for Israel 9v so data not included in analyses. Denominators available only for 7 months post-vaccination for Belgium 7v; data from other time points not included in analyses.
Any – all serotypes, without reference to whether they are included in the vaccine used in the trial; PR – prevalence ratio; OR – Prevalence odds ratio; NVT – non-vaccine serotypes including all serotypes which are not in the vaccine used in the individual trial ;RD – risk (prevalence) difference; VAT – vaccine associated serotypes, including all serotypes which are not included in the vaccine used in the individual trial, but which are in the same serogroup as one of the vaccine serotypes. VT – vaccine serotypes, including only the specific serotypes which are in the vaccine used in the individual trial.

1 All analyses are random effects meta-analyses. PR and OR less than 1 and a negative RD indicate that the catch-up dose group is less likely to be carrying *Strep. pneumoniae* than the 0-dose group. The I^2 statistic can be interpreted as the proportion of the total variation in estimated risk ratios due to between-trial heterogeneity rather than to chance [5]. Low, moderate and high levels of heterogeneity correspond to I^2 values of 25%, 50% and 75% respectively.

Annex 2.2
A systematic review of clinical and carriage data from randomized controlled trials of childhood schedules using 7-, 9-, 10- and 13-valent pneumococcal conjugate vaccines: Included studies, detailed summary (alphabetical order)

Study details	Participant characteristics	Schedule A / schedule B / schedule C	Schedule A population characteristics	Schedule B population characteristics	Schedule C population characteristics	Outcomes					
						Mortality	IPD	Meningitis	Pneumonia	Otitis media	carriage
Belgium 7v [6]											
Location: Belgium **Recruitment dates:** 1999-2002 **Vaccine used:** 7v PCV; Prevnar **Funding:** Netherlands Organization for Health Research and development; Zilveren Kruis-Achmea; vaccine supplied by Wyeth	**Inclusion criteria:** 1—7 years of age with a history of frequent AOM. **Exclusion criteria:** underlying illnesses including immuno-compromising conditions, previous pneumococcal vaccination or documented hypersensitivity to any of the vaccine components.	**A:** 2 doses at 1 month interval (12-24m) + PPV 6 months later or 1 dose (25-84m) + PPV 7 months later **B:** No doses **Additional information:** HepA given in group B with same schedule as PCV.	**N=**38 **Median age at randomization:** 24 m (range 12-76.1m) **Mean age at first study dose:** NR **Gender (M/F):** 22/16	**N=**36 **Median age at randomization:** 22.3m (range 12.2-54.2m) **Mean age at first study dose:** NR **Gender (M/F):** 22/14						✓	✓
Chile 10v [7, 29, 36-39]											
Location: Chile **Recruitment dates:** Aug 2007-Mar 2008 **Vaccine used:** 10v PCV; Synflorix **Funding:** GSK	**Inclusion criteria:** Healthy infants aged 8-16w; informed consent; free of obvious health problems . **Exclusion criteria:** investigational or non-registered drug or non-study vaccine use; history of diseases covered by study vaccines immune deficiency.	**A:** 2, 4, 6 + b>18m **B:** 2 "catch up" at >18m **Additional information:** Group A: HAV co-administered with DTaP-HBV-IPV/Hib followed by PCV. Group B: PCV co-administered with DTaP-HBV-IPV/Hib followed by HAV. (Also had HAV at 2, 4, 6m). DTaP-HBV- IPV/Hib at 2, 4, 6m, HAV at 12m for all.	**N= 119** (as stated in [29], numbers in [7] differ) **Mean age at randomization:** 18.3 ± 0.44m **Mean age at first study dose:** NR **Gender (M/F):** 45/39	**N= 121**(as stated in [29], numbers in [7] differ) **Mean age at randomization:** 18.3 ± 0.50m **Mean age at first study dose:** NR **Gender (M/F):** 35/44		✓					
China 7v [8, 40]											

Study details	Participant characteristics	Schedule A / schedule B / schedule C	Schedule A population characteristics	Schedule B population characteristics	Schedule C population characteristics	Outcomes					
						Mortality	IPD	Meningitis	Pneumonia	Otitis media	carriage
Location: China **Recruitment dates: 2006-2007** **Vaccine used:** 7v PCV; Prevnar **Funding:** Wyeth	**Inclusion criteria:** healthy, Chinese, aged 3-4 months (90-120 days) at enrollment, and had not received his/her first dose of DTaP. **Exclusion criteria:** weight <2 S.D. for age and history of neurological disorders including personal and family history of convulsion or epilepsy (including febrile seizure).	**A**: 3, 4, 5 (DTaP co-administered) **B:** 3, 4, 5 (DTaP not co-administered) **C:** No doses **Additional information:** DTaP administered as follows: A: 3, 4, 5m B: 1 week after each PCV dose C: 3, 4, 5m	**N=**296 **Median age at randomization:** 3.5m (range 3.0-4.0m) **Mean age at first study dose:** NR **Gender (M/F):** 163/133	**N=**300 **Median age at randomization:** 3.5m (range 3.0-4.0m) **Mean age at first study dose:** NR **Gender (M/F):** 158/142	**N=**204 **Median age at randomization: 3.5m (range 3.0-4.7m)** **Mean age at first study dose:** NR **Gender (M/F):** 123/81	✓					
Europe 10v [9, 38, 41-43]											
Location: Denmark; Norway; Slovakia; Sweden **Recruitment dates:** Jan 2006-Jan 2007 **Vaccine used:** 10v PCV; Synflorix **Funding:** GSK	**Inclusion criteria:** Healthy infants aged 8-16w; informed consent; free of obvious health problems; gestation 36-42 weeks. **Exclusion criteria:** investigational or non-registered drug or non-study vaccine use; previous pneumococcal vaccine; history of diseases covered by study vaccines immune deficiency.	**A:** 2, 3, 4 + b11m **B:** 2, 4 + b11m **Additional information:** DTaP-HepB-IPV/Hib or DTaP-IPV/Hib at 2, 3, 4 m according to country.	**N=** 176 **Mean age at randomization:** NR **Mean age at first study dose:** 12.1 ± 1.90 weeks **Gender (M/F):** 91/85	**N=** 175 **Mean age at randomization:** NR **Mean age at first study dose:** 12.0 ± 1.91weeks **Gender (M/F):** 89/86		✓					
Fiji 7v [10, 44-49]; and pre-publication manuscript											

Study details	Participant characteristics	Schedule A / schedule B / schedule C	Schedule A population characteristics	Schedule B population characteristics	Schedule C population characteristics	Outcomes					
						Mortality	IPD	Meningitis	Pneumonia	Otitis media	carriage
Location: Fiji **Recruitment dates:** not reported **Vaccine used:** 7v PCV; Prevnar **Funding:** NIAID + NHMRC; other vaccines donated by GSK and CSL Biotherapies; unclear if vaccine donated by Wyeth	**Inclusion criteria:** Healthy infants aged 6-8w; no significant maternal or perinatal disease history, residing in health centre area; family anticipated lived in study area for 2 years. **Exclusion criteria:** allergy to vaccine components; allergic reaction to previous vaccine; HIV positive mother; immuno-deficiency; thrombocytopenia or coagulation disorder; immunosuppressive drugs; received blood product since birth; any diseases.	**A:** 1.5, 2.5, 3.5 m **B:** 1.5, 3.5 m **C:** 3.5 m D: No doses **Additional information:** DTwP, HepB Hib + OPV given at 1.5, 2.5, 3.5 months; MMR at 12 months, PPV to half children in each group at 12m.	**N=** 136 **Median age at randomization:** 6.7 weeks **Mean age at first study dose:** NR **Gender (M/F):** 71/65	**N=** 156 **Median age at randomization:** 6.4 weeks **Mean age at first study dose:** NR **Gender (M/F):** 70/86	**N=** 128 **Median age at randomization:** 6.5weeks **Mean age at first study dose:** NR **Gender (M/F):** 59/69						✓
Finland 7v [11, 50-67]											
Location: Finland **Recruitment dates:** 1995-1997 **Vaccine used: 7**v PCV; Prevnar **Funding:** Merck; Pasteur Merieux; Connaught and Wyeth Lederle	**Inclusion criteria:** NR in main articles, appears to be healthy infants **Exclusion criteria:** NR in main articles	**A:** 2, 4, 6, +b12 **B:** No doses **Additional information:** HepB given in group B with same schedule as PCV in group A.	**N=**831 **Mean age at randomization:** NR **Mean age at first study dose:** NR **Gender (M/F):** 435/396	**N=**831 **Mean age at randomization:** NR **Mean age at first study dose:** NR **Gender (M/F):** 428/403		✓	✓	✓		✓	✓
Finland 10v [12, 38, 68, 69]											

Study details	Participant characteristics	Schedule A / schedule B / schedule C	Schedule A population characteristics	Schedule B population characteristics	Schedule C population characteristics	Outcomes					
						Mortality	IPD	Meningitis	Pneumonia	Otitis media	carriage
Location: Finland **Recruitment dates:** Oct 2006-Dec 2007 **Vaccine used:** 10v PCV; Synflorix **Funding:** GSK	**Inclusion criteria:** healthy; 12-14m at time of first vaccine; received ≥1 dose 10val PCV in study; informed consent.. **Exclusion criteria:** investigational or non-registered drug or non-study vaccine use; any extra PCV after primary study; immune-suppressed; exposure to or infection with vaccine diseases history of neurological disease.	**A:** (2, 3, 4) + b14-16m **B:** (2, 3, 4) + b12-14m **Additional information:** Group A: PCV co-administered with MMRV at 12-14m, MMRV and DTaP-HepB-IPV/Hib at 14-16 m. Group B: MMRV co-administered with DTaP-HepB-IPV/Hib at 12-14m, and PCV + MMRV at 14-16m Group C: Not analyzed in this review.	**N=** 101 **Mean age at randomization:** 12.3 ± 0.50 m **Mean age at first study dose:** NR **Gender (M/F):** 49/52	**N=** 110 **Mean age at randomization:** 12.3 ± 0.48 m **Mean age at first study dose:** NR **Gender (M/F):** 61/49		✓					
Gambia 7v [13, 70] and pre-publication manuscript											
Location: Gambia **Recruitment dates:** 2007-2007 **Vaccine used:** 7v PCV; Prevnar **Funding:** WHO (funding); MRC sponsor	**Inclusion criteria:** Infants presenting for first routine DTP/Hib vaccination; informed consent. **Exclusion criteria:** Known HIV infected mother; neurological abnormality; no consent; established pneumococcal disease.	**A:** 2, 3, 4 m **B:** 2, 3 m **C:** 2 m **Additional information:** Routine EPI vaccinations including DTP, Hib, OPV and HepB given at 2, 3, 4m; PPV booster given at 10m.	**N=** 228 **Mean age at randomization:** NR **Mean age at first study dose:** NR **Gender (M/F):** 107/120	**N=** 228 **Mean age at randomization:** NR **Mean age at first study dose:** NR **Gender (M/F):** 105/123	**N=** 228 **Mean age at randomization:** NR **Mean age at first study dose:** NR **Gender (M/F):** 113/115	✓					✓
Gambia 9v [14, 71-77] and 1 related reference [78]											

Study details	Participant characteristics	Schedule A / schedule B / schedule C	Schedule A population characteristics	Schedule B population characteristics	Schedule C population characteristics	Outcomes					
						Mortality	IPD	Meningitis	Pneumonia	Otitis media	carriage
Location: The Gambia **Recruitment dates:** 2000-2003 **Vaccine used:** 9v PCV; (Wyeth) **Funding:** National Institute of Allergy and Infection Disease, vaccines supplied by Wyeth	**Inclusion criteria:** NR **Exclusion criteria:** non-residence in study area; previous receipt of diphtheria-pertussis-tetanus/Haemophilus influenzae type b (DPT/Hib) or DPT vaccine; age younger than 40 days or older than 364 days; inclusion in a previous vaccine trial; or serious chronic illness.	**A:** 3p (No set age for doses: Children 6-51 weeks given 3 doses at least 25 days apart). **B:** No doses **Additional information:** Placebo in control group.	**N=**8718 **Mean age at randomization:** NR **Mean age at first study dose:** NR, but of those in per protocol analysis - 2.50m (1.97-3.60m) **Gender (M/F):** NR, but of those in per protocol analysis, 4100/4089	**N=**8719 **Mean age at randomization:** NR **Mean age at first study dose:** NR, but of those in per protocol analysis - 2.50m (1.97-3.60m) **Gender (M/F):** NR, but of those in per protocol analysis, 4074/4077		✓	✓	✓	✓		
Gambia 9v pilot a [15]											
Location: The Gambia **Recruitment dates:** NR **Vaccine used:** 9v PCV; (Wyeth) **Funding:** NR. Vaccine supplied by Wyeth; Pasteur Mérieux	**Inclusion criteria:** 8-12 weeks of age **Exclusion criteria:** age >12 weeks, under-nutrition, an acute febrile illness, congenital cardiac disease, history of blood transfusion and known maternal HIV infection.	**A:** 2,3,4m **B:** No doses **Additional information:** IPV at 2, 3, 4m in control group	**N=**103 **Mean age at randomization:** NR **Mean age at first study dose:** NR **Gender (M/F):** NR	**N=**104 **Mean age at randomization:** NR **Mean age at first study dose:** NR **Gender (M/F):** NR		✓					✓
Gambia 9v pilot b [16]											

Study details	Participant characteristics	Schedule A / schedule B / schedule C	Schedule A population characteristics	Schedule B population characteristics	Schedule C population characteristics	Outcomes					
						Mortality	IPD	Meningitis	Pneumonia	Otitis media	carriage
Location: The Gambia **Recruitment dates:** NR **Vaccine used:** 9v PCV; (Wyeth) **Funding:** NR. Vaccine supplied by Wyeth	**Inclusion criteria:** NR **Exclusion criteria:** NR	**A:** 2, 3, 4m **B:** 2, 3, 4m **C:** No doses **Additional information:** In group A DTwPHib and PCV mixed in same syringe, in group B DTwPHib administered in separate syringe to PCV, in group C only DTwPHib administered (with placebo).	**N=197** **Mean age at randomization:** NR **Mean age at first study dose:** NR **Gender (M/F):** NR	**N=196** **Mean age at randomization:** NR **Mean age at first study dose:** NR **Gender (M/F):** NR	**N=197** **Mean age at randomization:** NR **Mean age at first study dose:** NR **Gender (M/F):** NR	✓					
Ghana infants 9v [17] and pre-publication manuscript											
Location: Ghana **Recruitment dates:** 1997-2000 **Vaccine used:** 9v PCV; (Wyeth) **Funding:** United Kingdom Department for International Development	**Inclusion criteria:** Infants with sickle-cell disease. **Exclusion criteria:** an acute febrile illness; under-nutrition (weight for age,<80%); a severe chronic illness; a congenital malformation or defect; non-resident in the Kumasi metropolis, fever of >38^{o}C.	**A:** 1.5, 2.5, 3.5 + b12 **B:** 1.5, 2.5, 3.5 + PPV(12) **C:** 1.5, 2.5, 3.5 + Hib **D:** no doses **Additional information:** All groups received PCV co-administered with their EPI vaccines.	**N=** 21 **Mean age at randomization:** 2.2m (all groups) **Mean age at first study dose:** 2.6m **Gender (M/F):** 14/7	**N=** 21 **Mean age at randomization:** 2.2m (all groups) **Mean age at first study dose:** 2.4m **Gender (M/F):** **13**/8	**N=** 20 **Mean age at randomization:** 2.2m (all groups) **Mean age at first study dose:** 2.4m **Gender (M/F):** 11/9	✓					
Iceland 9v [18, 79, 80]											

Study details	Participant characteristics	Schedule A / schedule B / schedule C	Schedule A population characteristics	Schedule B population characteristics	Schedule C population characteristics	Outcomes					
						Mortality	IPD	Meningitis	Pneumonia	Otitis media	carriage
Location: Iceland **Recruitment dates:** not reported **Vaccine used:** 9vPnC-MnCC (Wyeth) **Funding:** Wyeth	**Inclusion criteria:** healthy term infants **Exclusion criteria:** NR	**A:** 3, 4, 5 + b12m (PCV/PPV) **B:** 3, 5 + b12m (PCV/PPV) **Additional information:** Children boosted with either PCV or PPV. PPV boosted children also got MnCC booster (CRM197). DTaP-IPV/Hib at 3, 5, 12m for all infants.	**N=** 111 **Mean age at randomization:** NR **Mean age at first study dose:** NR **Gender (M/F):** NR	**N=** 112 **Mean age at randomization:** NR **Mean age at first study dose:** NR **Gender (M/F):** NR			Only adverse events				
Israel 7v [19, 81-88]											
Location: Israel **Recruitment dates:** Aug 2005-Mar 2008 **Vaccine used:** 7v PCV; Prevnar **Funding:** Wyeth	**Inclusion criteria:** Healthy infants , 2m ± 3w; informed consent. **Exclusion criteria:** Born at <35w; acute disease; metabolic disorder or congenital abnormality of clinical importance; previous serious reaction to a vaccine; HIV infected; fever >38.0 ˚C.	**A:** 2, 4, 6 + b12m **B:** 2, 4, 6 **C:** 4, 6 + b12m **Additional information:** DTaP-IPV/Hib at 2, 4, 6, 12m; MMR at 12m	**N=** 178 **Mean age at randomization:** NR **Mean age at first study dose:** 2.1 ± 0.2m **Gender (M/F):** 93/85	**N=** 178 **Mean age at randomization:** NR **Mean age at first study dose:** 2.1 ± 0.2m **Gender (M/F):** 93/85	**N=** 189 **Mean age at randomization:** NR **Mean age at first study dose:** 3.9 ± 0.3m **Gender (M/F):** 88/101						✓
Israel 9v [20, 89-95]											

Study details	Participant characteristics	Schedule A / schedule B / schedule C	Schedule A population characteristics	Schedule B population characteristics	Schedule C population characteristics	Outcomes					
						Mortality	IPD	Meningitis	Pneumonia	Otitis media	carriage
Location: Israel **Recruitment dates:** 1996-1997 **Vaccine used:** 9v PCV (Wyeth) **Funding:** Wyeth; Israel Ministry of Health	**Inclusion criteria:** Healthy boys and girls. **Exclusion criteria:** Received or were expected to receive any vaccine or immunoglobulin within 8 weeks of study vaccination, any known or suspected impairment of immunologic function, major congenital malformation or serious chronic disease, known hypersensitivity to any component of the study vaccines, previously vaccinated with any pneumococcal or meningococcal vaccine.	**A:** 2 doses (12-17m) / 1dose (18-35m) **B:** No doses **Additional information:** MenC vaccine in control group with same schedule as PCV in intervention group.	**N=**19 (2 doses) **N=** 113(1 dose) **Mean age at randomization:** NR, but median age at enrollment 27.9m (inter-quartile range 21.6-31.8m) **Mean age at first study dose:** NR **Gender (M/F):** 76/56	**N=** 16 (2 doses) **N=** 114 (1 dose) **Mean age at randomization:** NR, but median age at enrollment 27.8m (inter-quartile range 21.8-32.1m) **Mean age at first study dose:** NR **Gender (M/F):** 68/62						✓	✓
Netherlands1 7v [21, 96-106]											
Location: The Netherlands **Recruitment dates:** 1998-2002 **Vaccine used:** 7v PCV; Prevnar **Funding:** Netherlands Organization for Health Research and development; Zilveren Kruis-Achmea; vaccine supplied by Wyeth	**Inclusion criteria:** two or more episodes of AOM in the year before study entry, and age 1–7 years. **Exclusion criteria:** primary or secondary immunodeficiency, cystic fibrosis, immotile cilia syndrome, craniofacial abnormalities such as cleft palate, chromosomal abnormalities such as Down's syndrome, and severe adverse events during previous vaccinations.	**A:** 2 doses at 1 month interval (12-24m) + PPV 6 months later or 1 dose (25-84m) + PPV 7 months later **B:** No doses **Additional information:** Control group received HepB if 12-24m, HepA if 25-84m.	**N=**83 (2 doses+ PPV) **N=**107 (1 dose +PPV) **Mean age at randomization:** NR, but "median age" 25.1m, range (12-82.3m) **Mean age at first study dose:** NR **Gender (M/F):** 118/72	**N=**79 (2 doses+ PPV) **N=**114 (1 dose +PPV) **Mean age at randomization:** NR, but "median age" 25.1m, range (12-82.3m) **Mean age at first study dose:** NR **Gender (M/F):** 119/74						✓	✓
Netherlands2 7v [22, 107, 108]											

Study details	Participant characteristics	Schedule A / schedule B / schedule C	Schedule A population characteristics	Schedule B population characteristics	Schedule C population characteristics	Outcomes					
						Mortality	IPD	Meningitis	Pneumonia	Otitis media	carriage
Location: The Netherlands **Recruitment dates:** 2000-2002 **Vaccine used:** 7v PCV; Prevenar **Funding:** NR	**Inclusion criteria:** ages between 2 and 8 years and persistent bilateral OME diagnosed with either a type B (flat) tympanogram or a type C2 tympanogram with otoscopic evidence of middle-ear effusion. **Exclusion criteria:** signs of acute otitis media, cleft palate, Down syndrome, known immune disorder other than IgA or IgG deficiency, chronic inhalation corticosteroid therapy, or use of antiallergic drugs.	**A:** 1 dose + PPV (>24m) **B:** No doses **Additional information:** Group A received PCV before tympanostomy and PPV after, Group B received tympanostomy only.	**N=**80 **Mean age at randomization:** NR, but "mean age" 64.8m **Mean age at first study dose:** NR **Gender (M/F):** 47/33	**N=**81 **Mean age at randomization:** NR, but "mean age" 62.4m **Mean age at first study dose:** NR **Gender (M/F):** 44/37		✓				✓	
Netherlands3 7v [23, 109-113]											
Location: The Netherlands **Recruitment dates:** 2003-2005 **Vaccine used:** 7v PCV; Prevenar **Funding:** Netherlands Organization for Health Research and development; vaccine supplied by Wyeth	**Inclusion criteria:** age 18 to 72 months with a previously diagnosed RTI, registered according to the International Classification of Primary Care. **Exclusion criteria:** chronic asthma or recurrent wheezing treated with corticosteroids; other disorders predisposing to recurrent RTIs, such as Down syndrome and cleft palate; and clinically significant hypersensitivity to eggs.	**A:** 2 doses >18m **B:** No doses **C:** No doses **Additional information:** Placebo in group B, HepB and placebo in group C Groups A and B received trivalent subunit influenza.	**N=**197 **Mean age at randomization:** NR, but "mean age" 36m **Mean age at first study dose:** NR **Gender (M/F):** 116/81	**N=**187 **Mean age at randomization:** NR, but "mean age" 37.1m **Mean age at first study dose:** NR **Gender (M/F):** 104/83	**N=**195 **Mean age at randomization:** NR, but "mean age" 37.1m **Mean age at first study dose:** NR **Gender (M/F):** 98/97					✓	
Netherlands4 7v [24, 114-119]											

Study details	Participant characteristics	Schedule A / schedule B / schedule C	Schedule A population characteristics	Schedule B population characteristics	Schedule C population characteristics	Outcomes					
						Mortality	IPD	Meningitis	Pneumonia	Otitis media	carriage
Location: The Netherlands **Recruitment dates:** 2005-2006 **Vaccine used:** 7v PCV; Prevnar **Funding:** Dutch Ministry of Health	**Inclusion criteria:** younger than 12 weeks, not yet having received any infant vaccination and living in the study region. **Exclusion criteria:** known immunodeficiency, craniofacial or chromosomal abnormalities, language barrier, or expected relocation within the follow-up period.	**A:** 2, 4, b11 **B:** 2, 4 **C:** no doses **Additional information:** Control group received no placebo.	**N=**336 **Mean age at randomization:** NR **Mean age at first study dose:** 2.0m (SD 0.26) **Gender (M/F):** 171/165	**N=**336 **Mean age at randomization:** NR **Mean age at first study dose:** 2.1m (SD 0.35) **Gender (M/F):** 176/160	**N=**333 **Mean age at randomization:** NR **Mean age at first study dose:** reported as "not applicable" by investigators **Gender (M/F):** 160/171 (2 excluded from reporting, see [24])						✓
South Africa 9v [25, 120-128];											
Location: South Africa **Recruitment dates:** 1998-2000 **Vaccine used:** 9v PCV (Wyeth) **Funding:** Wyeth; World Health Organization	**Inclusion criteria:** unvaccinated or had received only Bacille Calmette–Guérin and oral poliovirus vaccine at birth. **Exclusion criteria:** progressive underlying neurologic disorder, a history of seizures or infantile spasms, or a low likelihood of receiving three doses of vaccine because they were apt to move from Soweto.	**A:** 1.5, 2.5, 3.5 **B:** No doses **Additional information:** Placebo in control group.	**N=**19922 **Mean age at randomization:** NR **Mean age at first study dose:** 1.54m (SD 0.28m) **Gender (M/F):** 10,021/9901	**N=**19914 **Mean age at randomization:** NR **Mean age at first study dose:** 1.54m (SD 0.28m) **Gender (M/F):** 9,937/9,977		✓	✓	✓	✓		✓
South Africa 9v Pilot [26, 129-131]											

Study details	Participant characteristics	Schedule A / schedule B / schedule C	Schedule A population characteristics	Schedule B population characteristics	Schedule C population characteristics	Outcomes					
						Mortality	IPD	Meningitis	Pneumonia	Otitis media	carriage
Location: South Africa **Recruitment dates:** NR **Vaccine used:** 9v PCV (Wyeth) **Funding:** Wyeth	**Inclusion criteria:** NR **Exclusion criteria:** NR	**A:** 1.5, 2.5, 3.5 **B:** No doses **Additional information:** Placebo in control group.	**N=**250 **Mean age at randomization:** 1.5m (SD 0.14m) for both PCV and control group combined **Mean age at first study dose:** NR, but likely the same as age at randomization **Gender (M/F):** NR	**N=**250 **Mean age at randomization:** 1.5m (SD 0.14m) for both PCV and control group combined **Mean age at first study dose:** NR, but likely the same as age at randomization **Gender (M/F):** NR		✓			✓		✓
USA1 7v [27, 52, 65-67, 132-145]											
Location: USA **Recruitment dates:** 1995-1998 **Vaccine used:** 7v PCV; Prevnar **Funding:** Wyeth	**Inclusion criteria:** Healthy infants **Exclusion criteria:** sickle cell disease, known immunodeficiency, any serious chronic or progressive disease, a history of seizures or a history of either pneumococcal or meningococcal disease.	**A:** 2, 4, 6, +b12m **B:** No doses **Additional information:** MenC vaccine in control group with same schedule as PCV in intervention group.	**N=**18927 **Mean age at randomization:** NR **Mean age at first study dose:** Reported only as age at start of ITT follow up - 2.15m (SD 0.37m) **Gender (M/F):** 9766/9161	**N=**18941 **Mean age at randomization:** NR **Mean age at first study dose:** Reported only as age at start of ITT follow up - 2.14m (SD 0.36m) **Gender (M/F):** 9679/9262		✓	✓		✓	✓	
USA2 7v [28, 146-160]											

Study details	Participant characteristics	Schedule A / schedule B / schedule C	Schedule A population characteristics	Schedule B population characteristics	Schedule C population characteristics	Outcomes					
						Mortality	IPD	Meningitis	Pneumonia	Otitis media	carriage
Cluster randomized trial **Location**: USA **Recruitment dates:** 1997-2000 **Vaccine used:** 7v PCV; Prevnar **Funding:** USAID, national institute of Health; Wyeth	**Inclusion criteria:** Children aged between 6 weeks and 24 months **Exclusion criteria:** hypersensitivity to any components of the vaccine; contraindications specified on the manufactures' package inserts for any routine non-study vaccines that the child would receive; any medical condition which might interfere with the assessment of the study objectives; or a moderate or severe illness with or without fever until resolved.	**A:** 3p+1 / 2p+1 / 2doses (Number of PCV doses given to children in vaccinated group age-dependant. No set age for doses: infants enrolled between age 6 weeks and 7 months- 3 doses 2 months apart + b12–15 months of age; infants enrolled between 7 and 11 months of age - 2 doses 2 months apart + b12–15, infants enrolled between 12 and 23 months of age 2 doses at least 2 months apart). **B:** No doses **Additional information:** MenC vaccine in control group with same schedule as PCV in intervention group.	**N=**2974 (3p+1) **N=**315 (2p+1) **N=**876 (2 doses) **Mean age at randomization:** Not applicable (clusters not individuals randomized) **Mean age at first study dose:** 3p+1 group - 2.7m (SD 1.5m); Other groups NR **Gender (M/F):** NR **3p+1 group -** 1508/1466 Other groups NR	**N=**2818 (3p+1**)** **N=**295 (2p+1) **N=**813 (2 doses) **Mean age at randomization:** Not applicable (clusters not individuals randomized) **Mean age at first study dose:** 3p+1 group - 2.8m (SD 1.6m); Other groups NR **Gender (M/F):** NR **3p+1 group -** 1375/1433 Other groups NR		✓	✓	✓		✓	✓

NR Data for this outcome not reported and not planned for this study

DTP - diphtheria, tetanus and pertussis vaccine; DTaP- diphtheria, tetanus and acellular pertussis vaccine; DTwP- diphtheria, tetanus and whole-cell pertussis vaccine; EPI - Expanded Program on Immunization; HAV/HepA - hepatitis A vaccine; HepB - hepatitis B vaccine; Hib - Haemophilus influenzae vaccine; IPV - inactivated polio vaccine; m - months; MenC - meningococcal group C vaccine; MMR - measles mumps rubella vaccine; OPV- oral polio vaccine; PCV - pneumococcal conjugate vaccine; PPV - pneumococcal polysaccharide vaccine

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Annex 3.1

A systematic review of immunological outcome data from randomized controlled trials of childhood schedules using 7-, 9-, 10- and 13-valent pneumococcal conjugate vaccines: Figures and tables

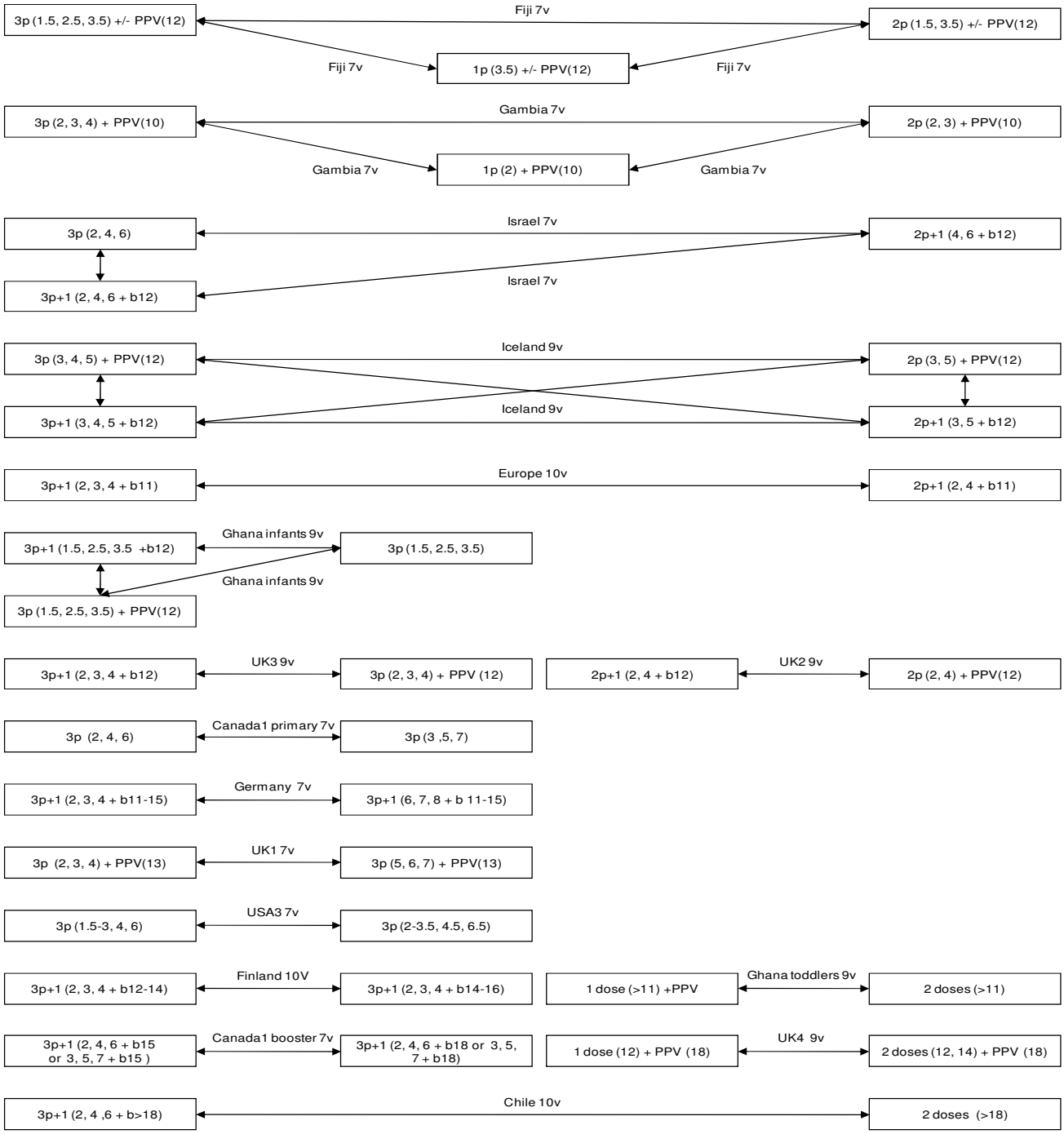
Figures

Tables

Annex 3.2

Description of main characteristics of RCTs comparing PCV schedules and reporting immunological outcomes

Figure 3.1: Network of randomized controlled trials with immunogenicity outcomes comparing different PCV schedules in children, according to schedule and comparisons



Legend:

As far as possible, the network is organized as follows:

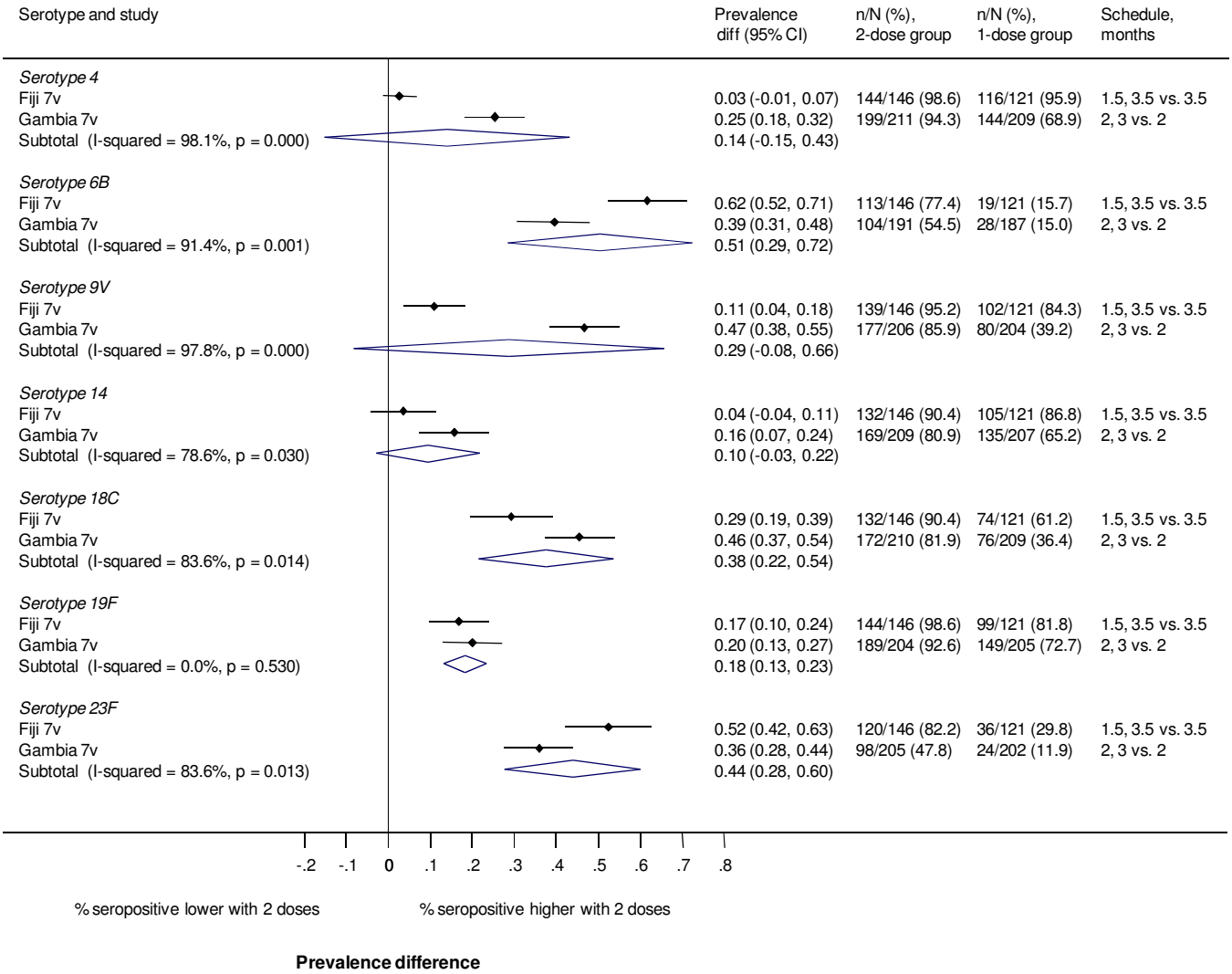
Left hand side: 3 dose schedules (3p followed by 3p+1); Right hand side: 2 dose schedules; Centre: 1 dose schedules;

Study names for each comparison are along the lines connecting each schedule, alphabetical order within schedule groups; arrows connect comparisons, with horizontal lines showing direct schedule-schedule comparisons;

Schedule described as, e.g. 3p – number of doses in primary schedule; +1 – booster dose; (2, 3, 4) – ages in months when vaccine doses intended to be given;

Abbreviations: b – booster; p – primary dosing schedule; PCV – pneumococcal conjugate vaccine; PPV – pneumococcal polysaccharide vaccine

Figure 3.2: Comparison A. 2p vs. 1p schedules, seropositivity at ~6 months, ELISA threshold 0.35ug/mL, by serotype and study

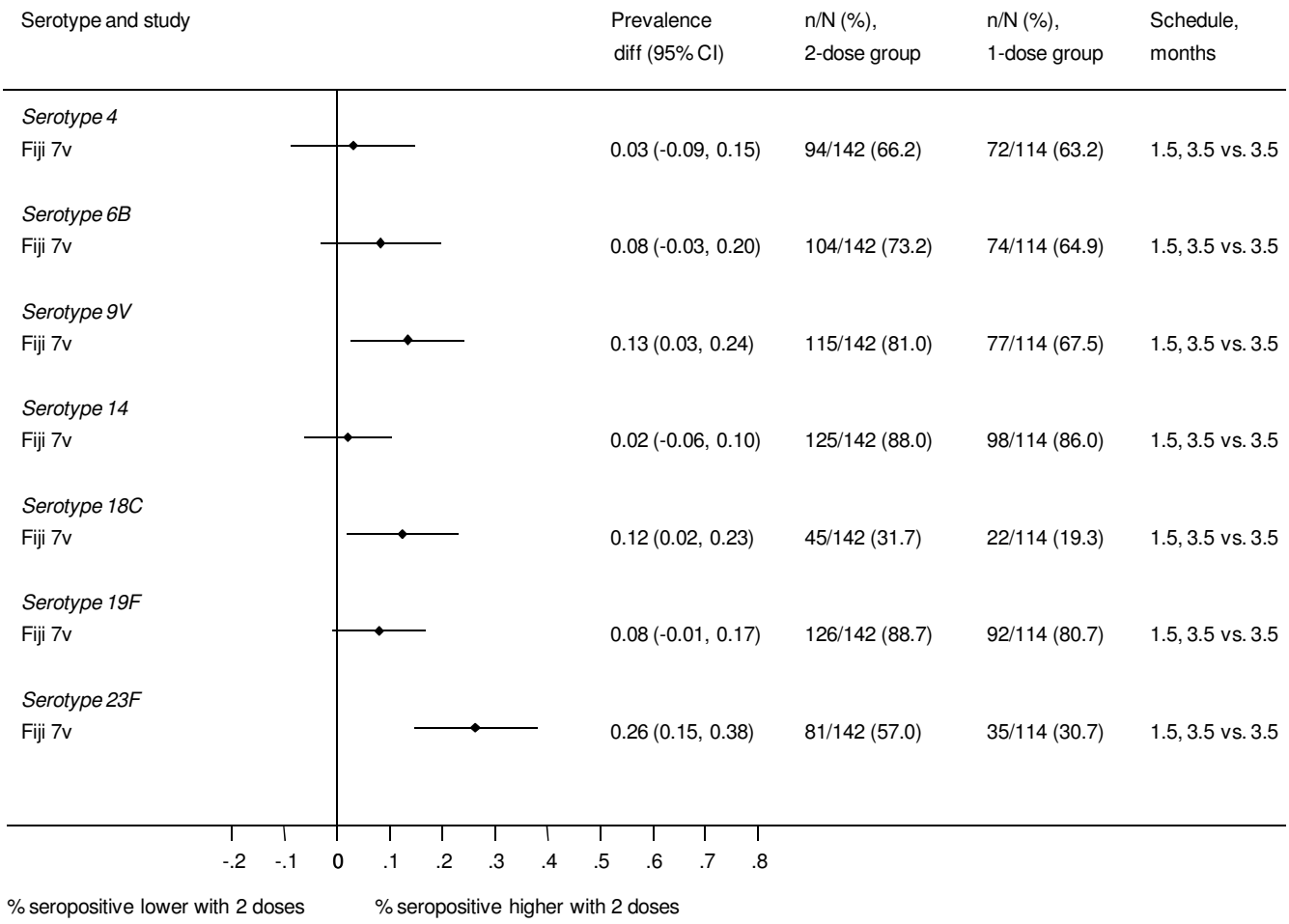


Legend:

n/N - number seropositive/total in group. Prevalence diff - difference in seropositivity between groups shown as a proportion.

Horizontal axis represents the difference, expressed as a proportion between groups receiving schedules of 2 primary doses vs. 1 primary dose. Vertical line through risk difference of 0 shows no difference in levels of seropositivity between groups. Solid black diamonds represent point estimate of prevalence difference; horizontal black line represents 95% confidence interval. Open diamond represents the pooled estimate, combined using random effects meta-analysis; vertical points of diamond represent point estimate and horizontal points represent 95% confidence interval; I2 value is the level of statistical heterogeneity between trials (<25% low heterogeneity).

Figure 3.3: Comparison A. 2p vs. 1p schedules, seropositivity at ~12 months, ELISA threshold 0.35ug/mL, by serotype and study

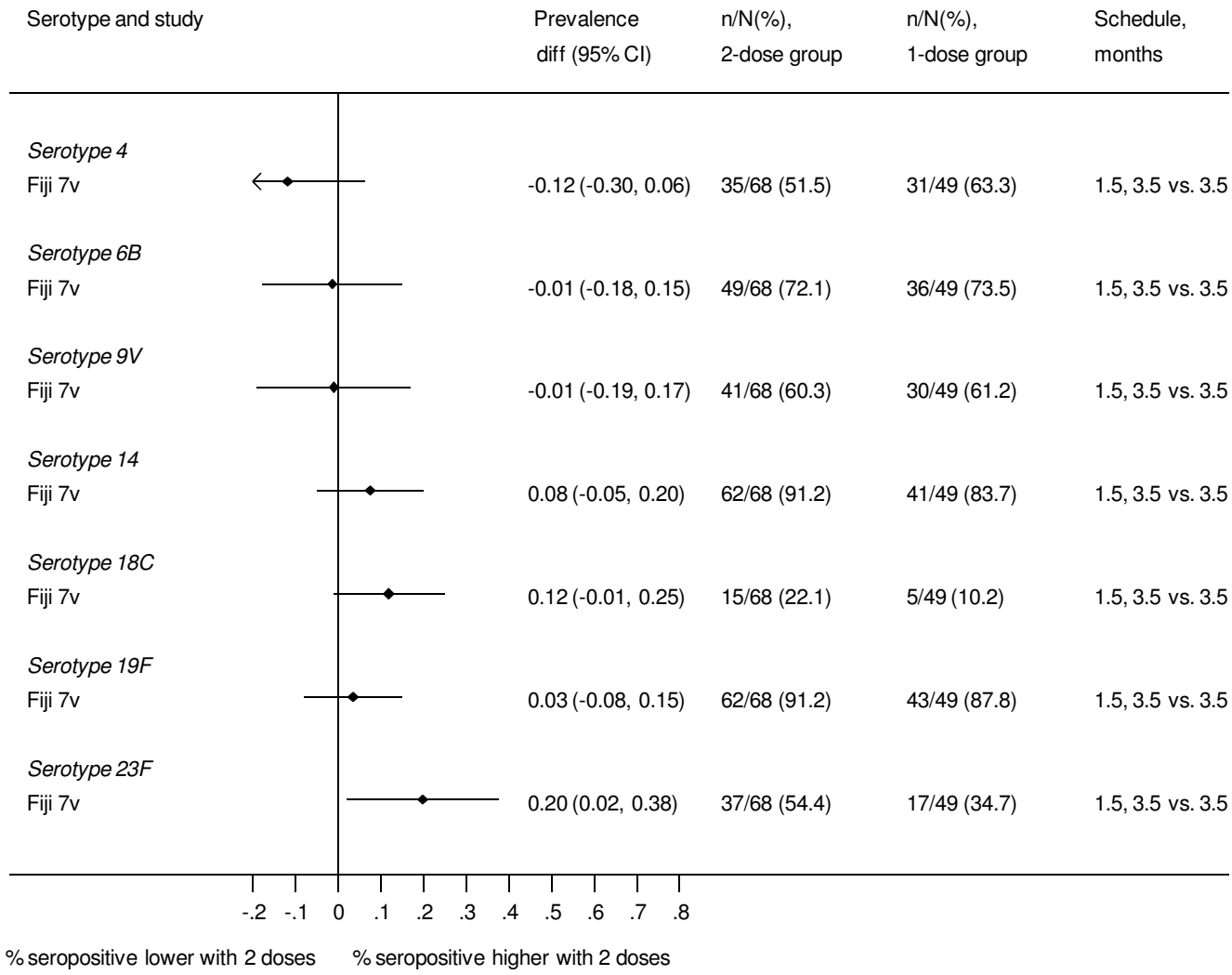


Legend:

n/N - number seropositive/total in group. Prevalence diff - difference in seropositivity between groups shown as a proportion.

Horizontal axis represents the difference, expressed as a proportion between groups receiving schedules of 2 primary doses vs. 1 primary dose. Vertical line through risk difference of 0 shows no difference in levels of seropositivity between groups. Solid black diamonds represent point estimate of prevalence difference; horizontal black line represents 95% confidence interval. Open diamond represents the pooled estimate, combined using random effects meta-analysis; vertical points of diamond represent point estimate and horizontal points represent 95% confidence interval; I2 value is the level of statistical heterogeneity between trials (<25% low heterogeneity).

Figure 3.4: Comparison A. 2p vs. 1p schedules, seropositivity at ~17 months, ELISA threshold 0.35ug/mL, by serotype and study

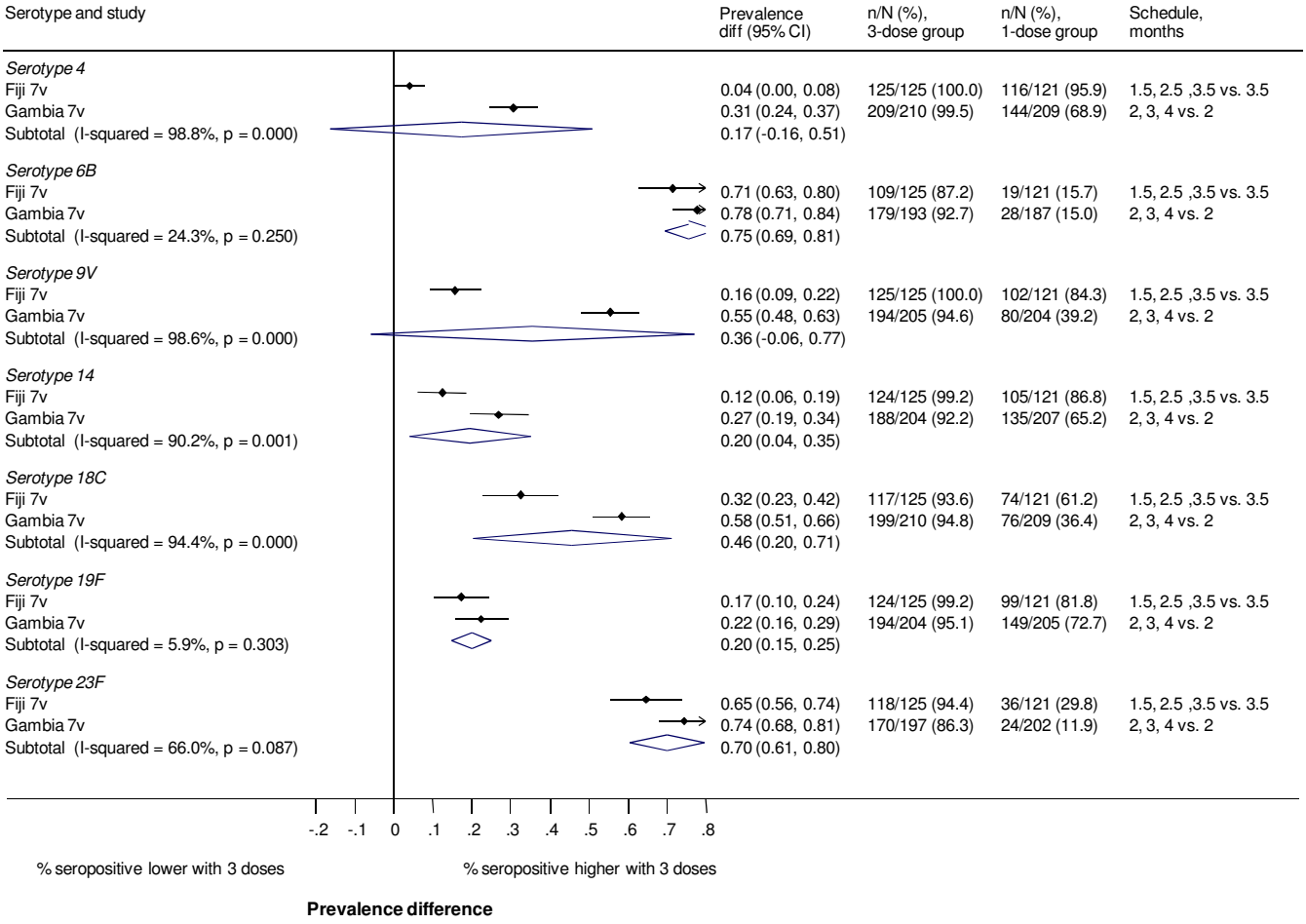


Legend:

n/N - number seropositive/total in group. Prevalence diff - difference in seropositivity between groups shown as a proportion.

Horizontal axis represents the difference, expressed as a proportion between groups receiving schedules of 2 primary doses vs. 1 primary doses. Vertical line through risk difference of 0 shows no difference in levels of seropositivity between groups. Solid black diamonds represent point estimate of prevalence difference; horizontal black line represents 95% confidence interval. Open diamond represents the pooled estimate, combined using random effects meta-analysis; vertical points of diamond represent point estimate and horizontal points represent 95% confidence interval; I2 value is the level of statistical heterogeneity between trials (<25% low heterogeneity).

Figure 3.5: Comparison B. 3p vs. 1p schedules, seropositivity at ~6 months, ELISA threshold 0.35ug/mL, by serotype and study

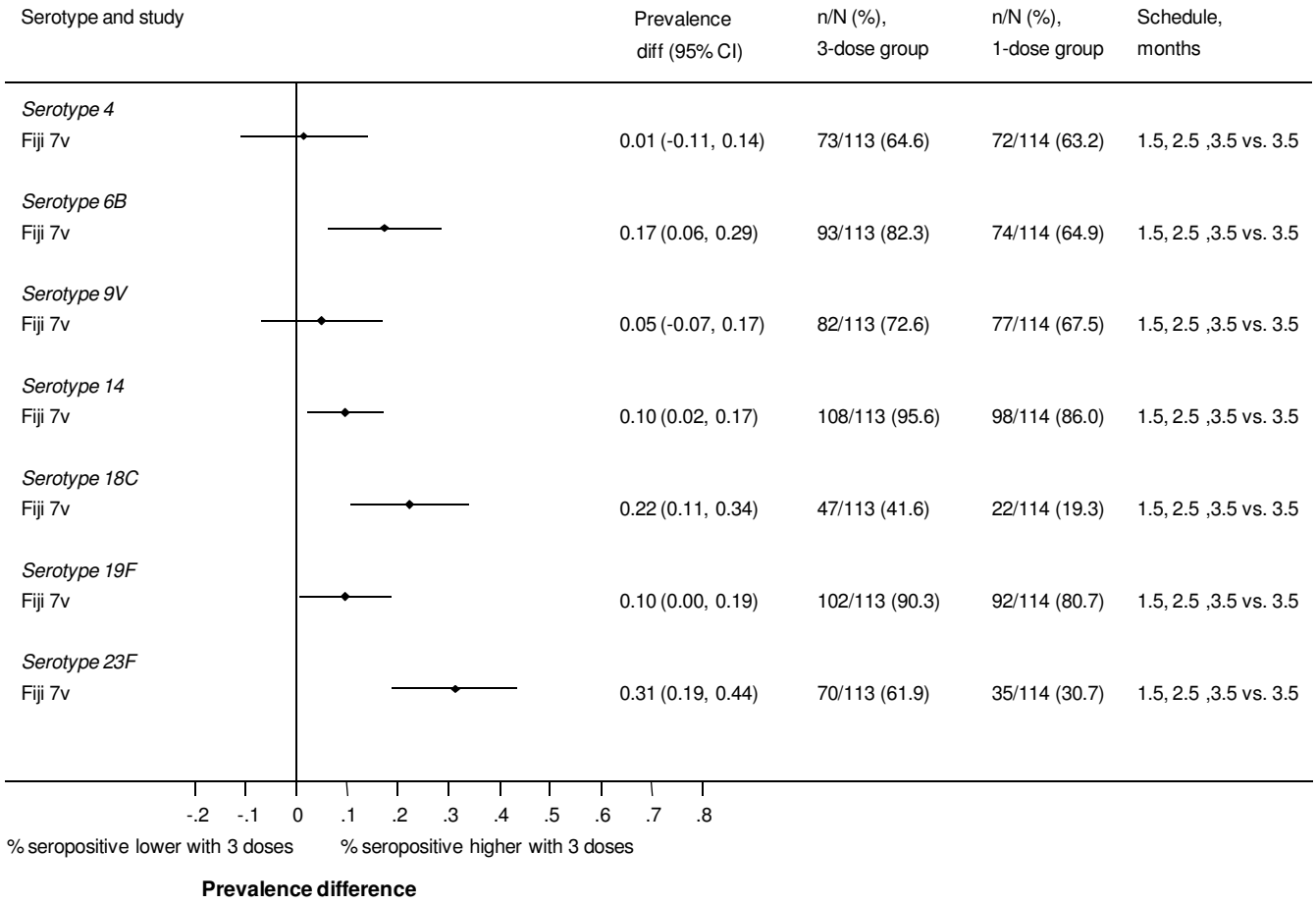


Legend:

n/N - number seropositive/total in group. Prevalence diff - difference in seropositivity between groups shown as a proportion.

Horizontal axis represents the difference, expressed as a proportion between groups receiving schedules of 3 primary doses vs. 1 primary dose. Vertical line through risk difference of 0 shows no difference in levels of seropositivity between groups. Solid black diamonds represent point estimate of prevalence difference; horizontal black line represents 95% confidence interval. Open diamond represents the pooled estimate, combined using random effects meta-analysis; vertical points of diamond represent point estimate and horizontal points represent 95% confidence interval; I2 value is the level of statistical heterogeneity between trials (<25% low heterogeneity).

Figure 3.6: Comparison B. 3p vs. 1p schedules, seropositivity at ~12 months, ELISA threshold 0.35ug/mL, by serotype and study

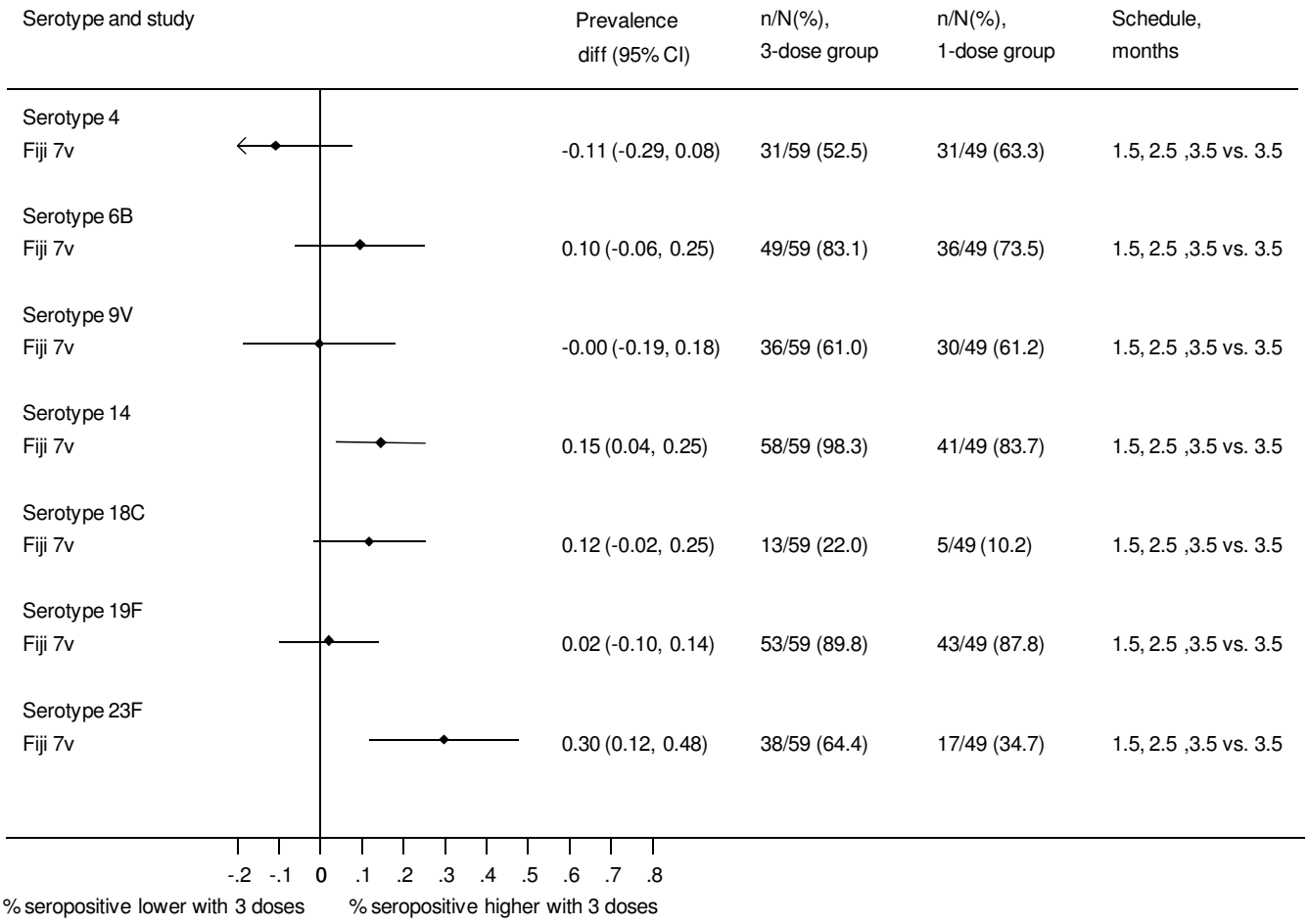


Legend:

n/N - number seropositive/total in group. Prevalence diff - difference in seropositivity between groups shown as a proportion.

Horizontal axis represents the difference, expressed as a proportion between groups receiving schedules of 3 primary doses vs. 1 primary dose. Vertical line through risk difference of 0 shows no difference in levels of seropositivity between groups. Solid black diamonds represent point estimate of prevalence difference; horizontal black line represents 95% confidence interval. Open diamond represents the pooled estimate, combined using random effects meta-analysis; vertical points of diamond represent point estimate and horizontal points represent 95% confidence interval; I2 value is the level of statistical heterogeneity between trials (<25% low heterogeneity).

Figure 3.7: Comparison B. 3p vs. 1p schedules, seropositivity at ~17 months, ELISA threshold 0.35ug/mL, by serotype and study

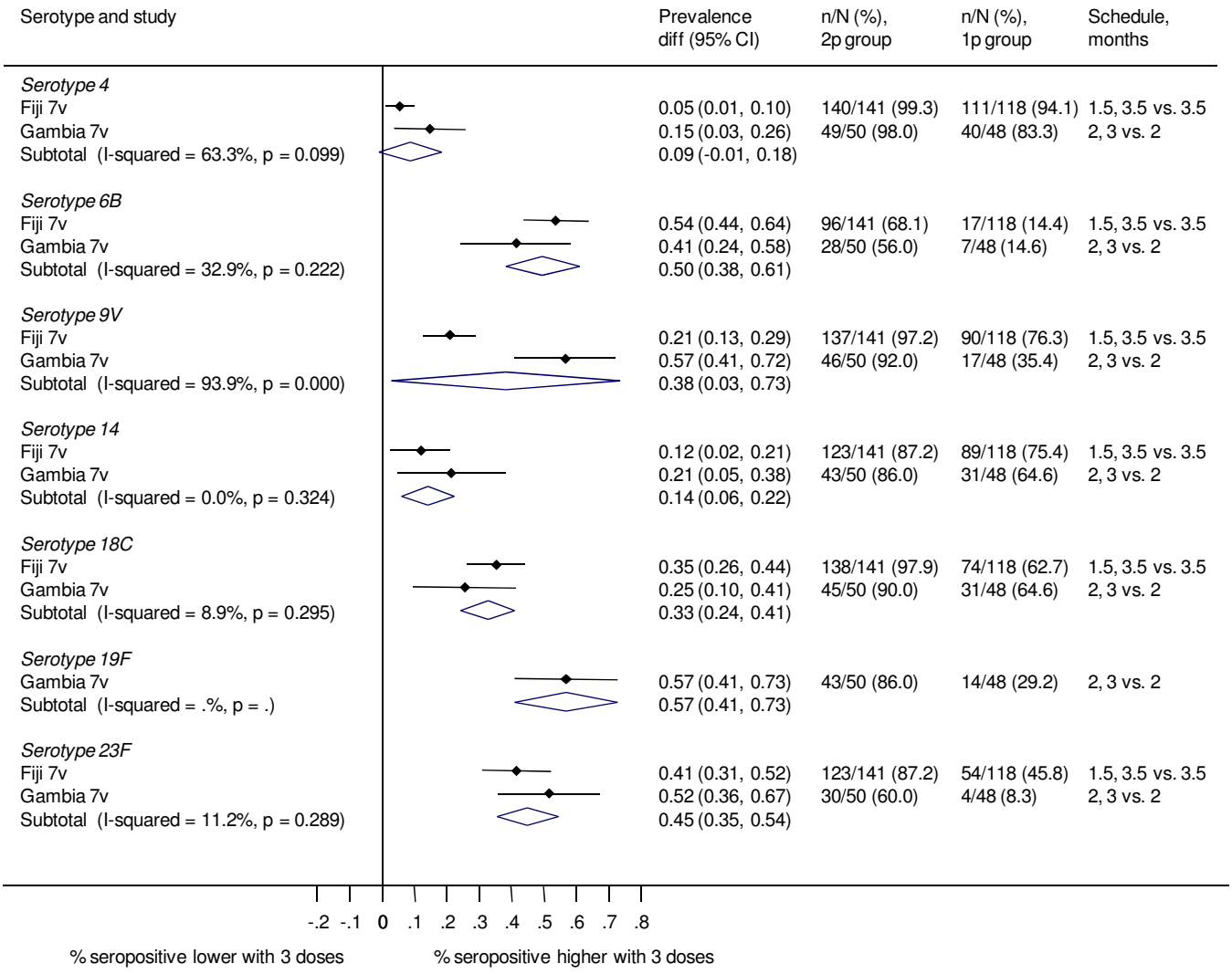


Legend:

n/N - number seropositive/total in group. Prevalence diff - difference in seropositivity between groups shown as a proportion.

Horizontal axis represents the difference, expressed as a proportion between groups receiving schedules of 3 primary doses vs. 1 primary dose. Vertical line through risk difference of 0 shows no difference in levels of seropositivity between groups. Solid black diamonds represent point estimate of prevalence difference; horizontal black line represents 95% confidence interval. Open diamond represents the pooled estimate, combined using random effects meta-analysis; vertical points of diamond represent point estimate and horizontal points represent 95% confidence interval; I2 value is the level of statistical heterogeneity between trials (<25% low heterogeneity).

Figure 3.8: Comparison A. 2p vs. 1p schedules, OPA seropositivity at ~6 months, OPA threshold 1:8, by serotype and study

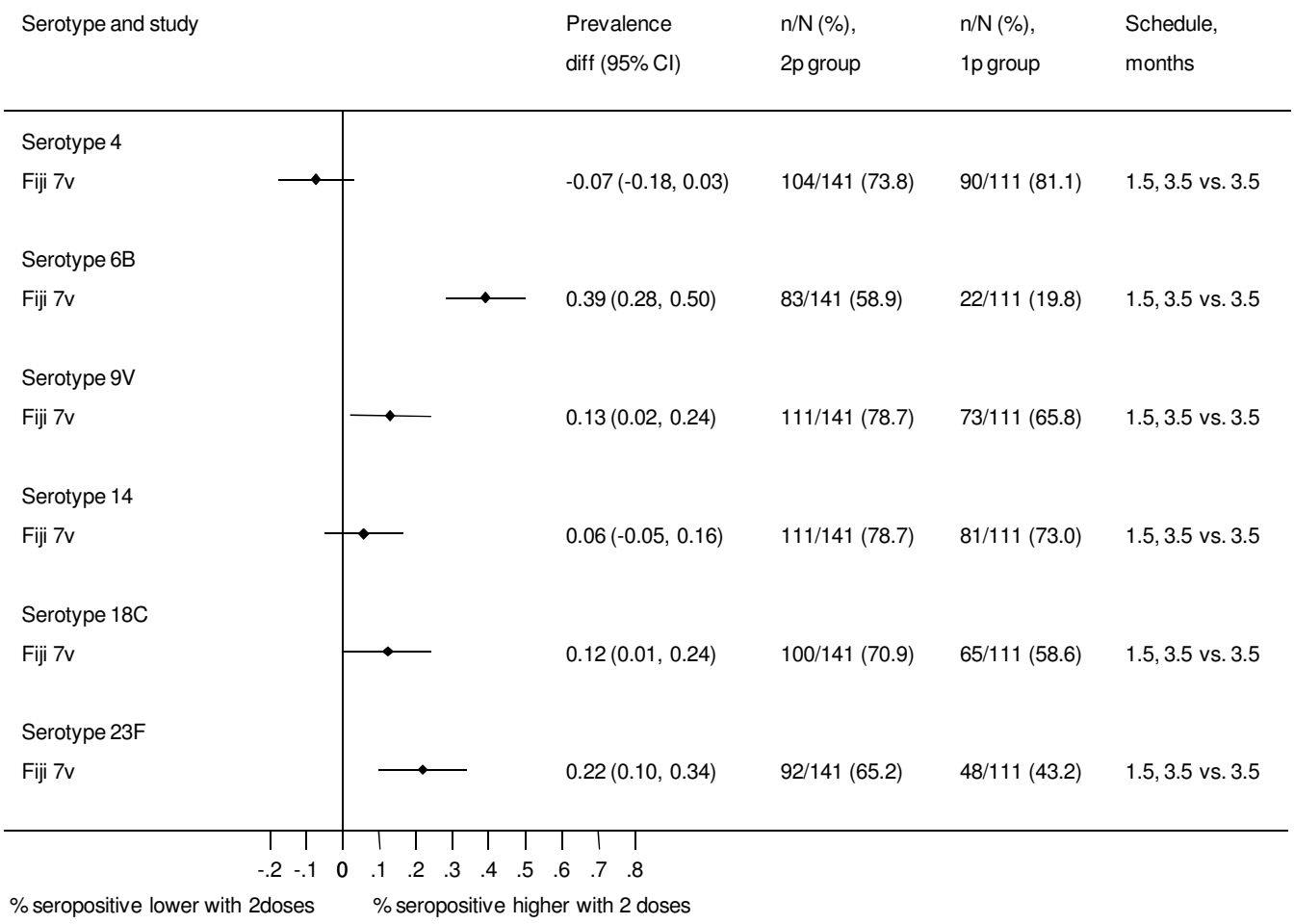


Legend:

n/N - number OPA >1:8/total in group. Prevalence diff - difference in seropositivity between groups shown as a proportion.

Horizontal axis represents the difference, expressed as a proportion between groups receiving schedules of 2 primary doses vs. 1primary dose. Vertical line through risk difference of 0 shows no difference in levels of seropositivity between groups. Solid black diamonds represent point estimate of prevalence difference; horizontal black line represents 95% confidence interval. Open diamond represents the pooled estimate, combined using random effects meta-analysis; vertical points of diamond represent point estimate and horizontal points represent 95% confidence interval; I2 value is the level of statistical heterogeneity between trials (<25% low heterogeneity).

Figure 3.9: Comparison A. 2p vs. 1p schedules, OPA seropositivity at ~12 months, OPA threshold 1:8, by serotype and study

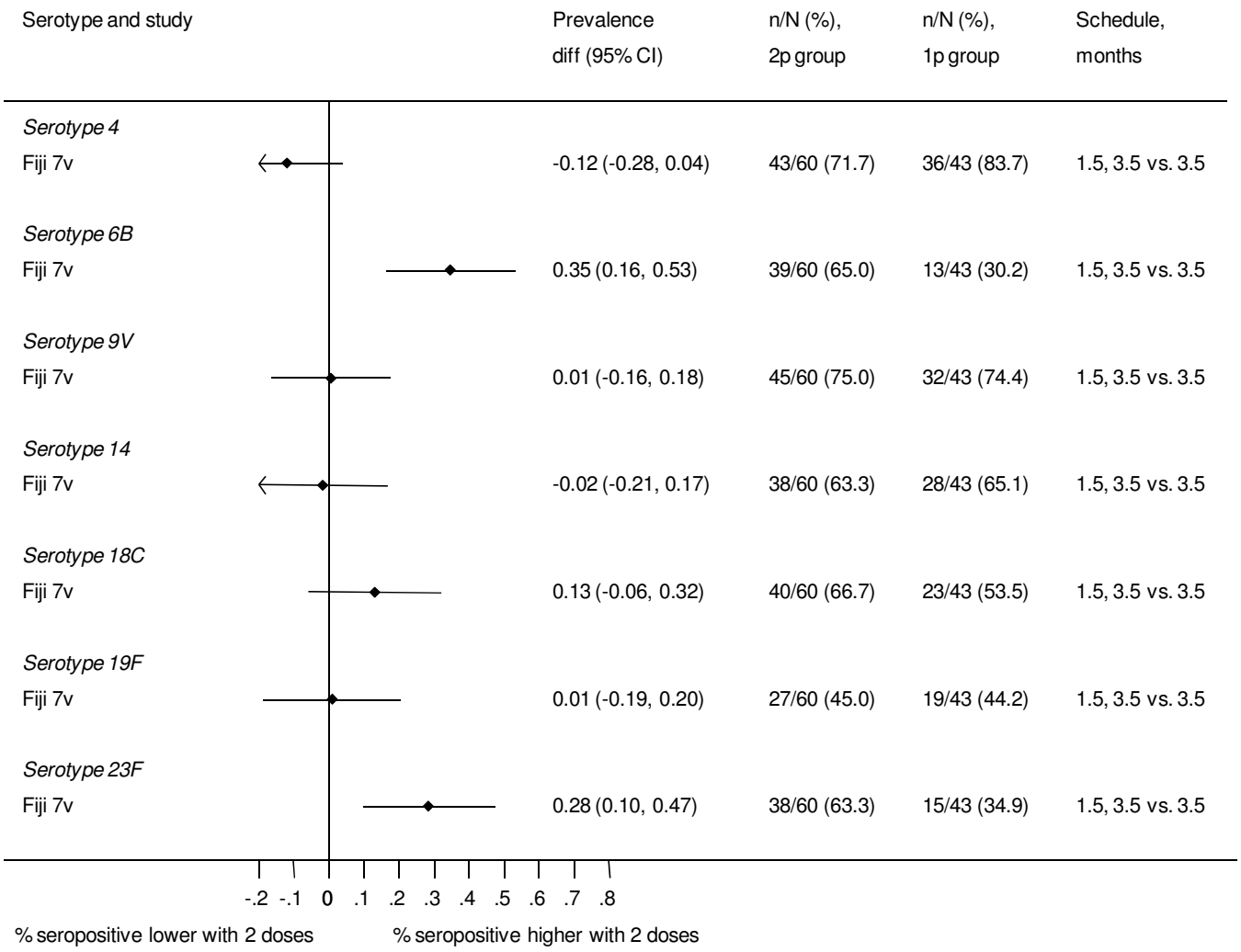


Legend:

n/N - number OPA >1:8/total in group. Prevalence diff - difference in seropositivity between groups shown as a proportion.

Horizontal axis represents the difference, expressed as a proportion between groups receiving schedules of 2 primary doses vs. 1primary dose. Vertical line through risk difference of 0 shows no difference in levels of seropositivity between groups. Solid black diamonds represent point estimate of prevalence difference; horizontal black line represents 95% confidence interval. Open diamond represents the pooled estimate, combined using random effects meta-analysis; vertical points of diamond represent point estimate and horizontal points represent 95% confidence interval; I2 value is the level of statistical heterogeneity between trials (<25% low heterogeneity).

Figure 3.10: Comparison A. 2p vs. 1p schedules, OPA seropositivity at ~17 months, OPA threshold 1:8, by serotype and study

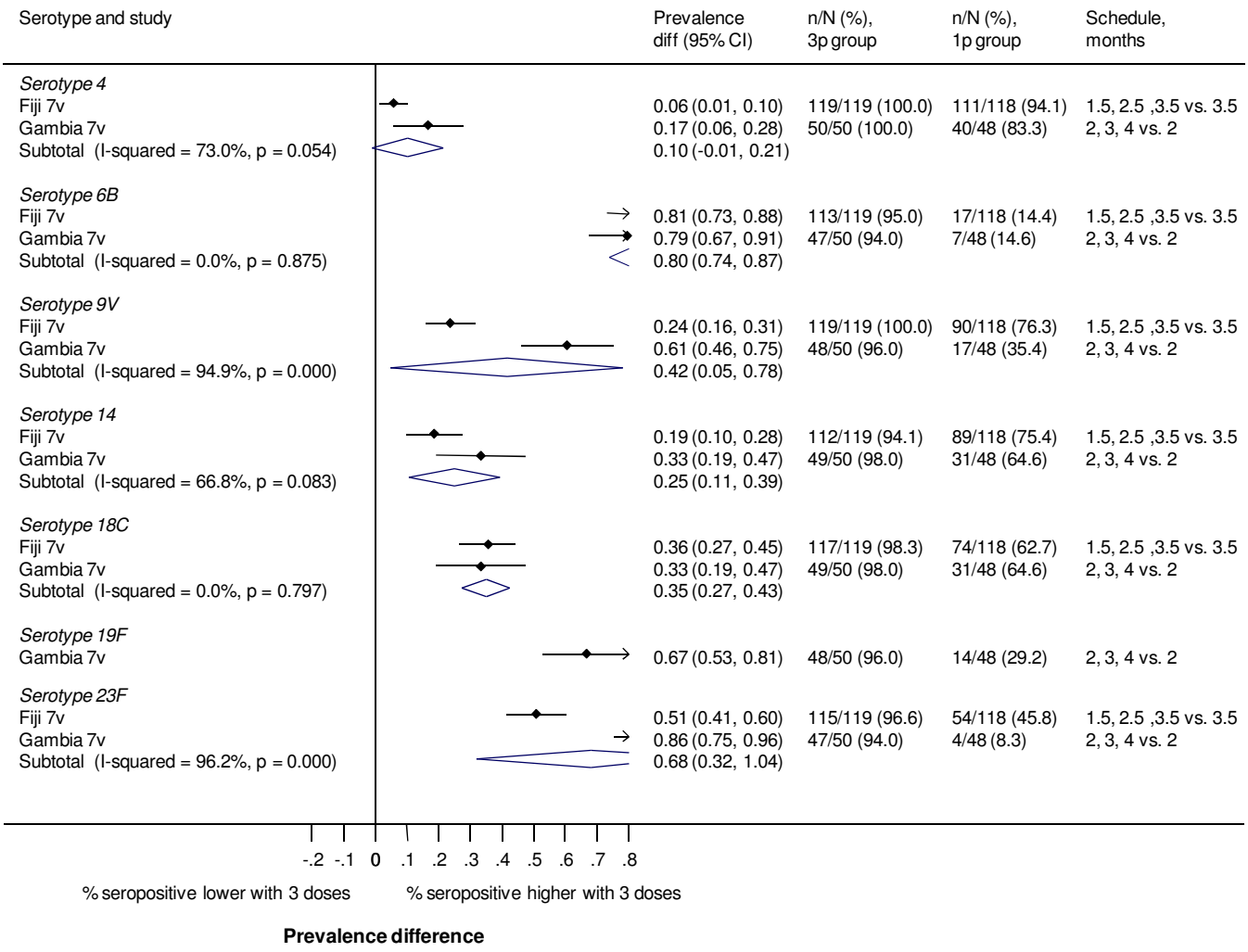


Legend:

n/N - number OPA >1:8/total in group. Prevalence diff - difference in seropositivity between groups shown as a proportion.

Horizontal axis represents the difference, expressed as a proportion between groups receiving schedules of 2 primary doses vs. 1primary dose. Vertical line through risk difference of 0 shows no difference in levels of seropositivity between groups. Solid black diamonds represent point estimate of prevalence difference; horizontal black line represents 95% confidence interval. Open diamond represents the pooled estimate, combined using random effects meta-analysis; vertical points of diamond represent point estimate and horizontal points represent 95% confidence interval; I2 value is the level of statistical heterogeneity between trials (<25% low heterogeneity).

Figure 3.11: Comparison B. 3p vs. 1p schedules, OPA seropositivity at ~6 months, OPA threshold 1:8, by serotype and study

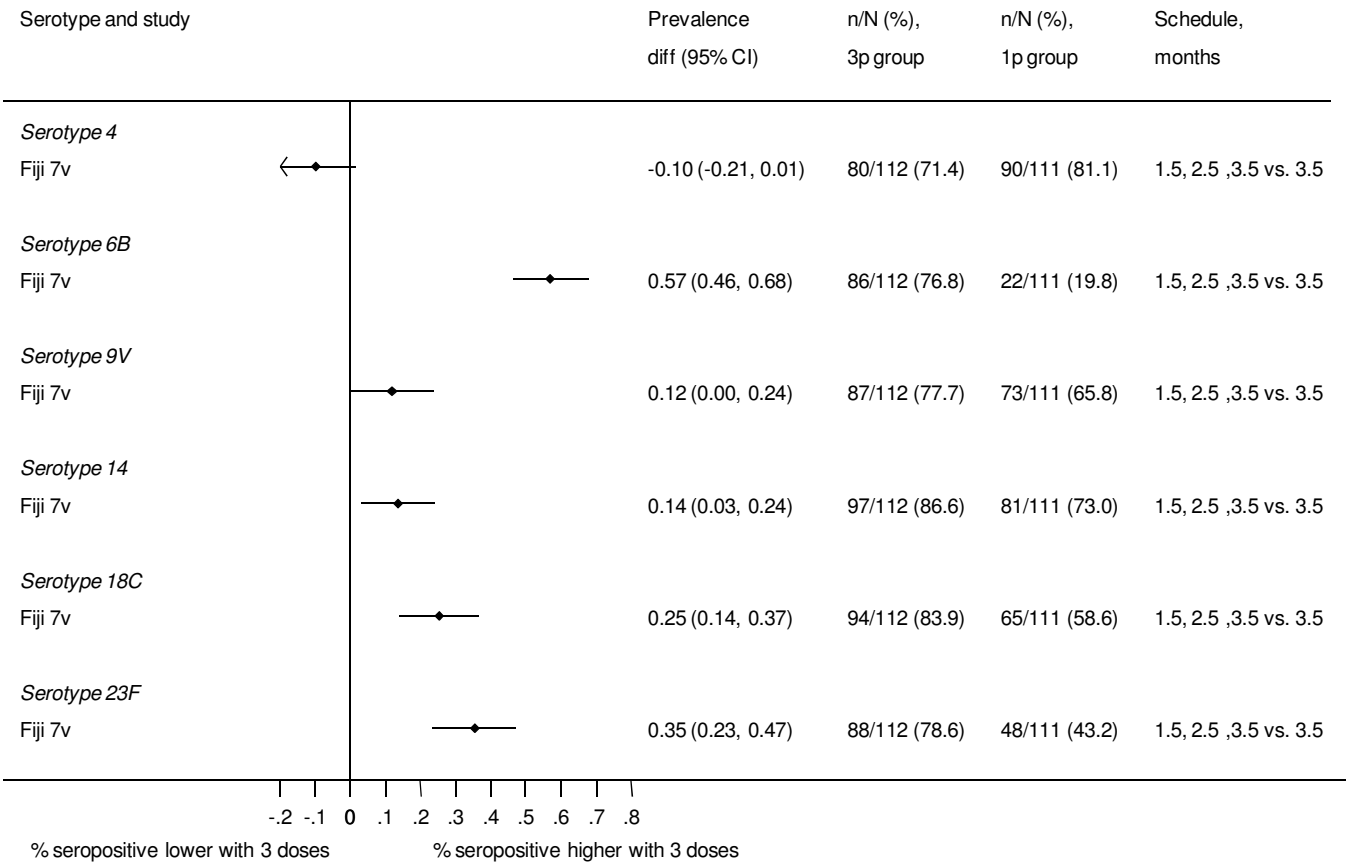


Legend:

n/N - number OPA >1:8/total in group. Prevalence diff - difference in seropositivity between groups shown as a proportion.

Horizontal axis represents the difference, expressed as a proportion between groups receiving schedules of 3 primary doses vs. 1primary dose. Vertical line through risk difference of 0 shows no difference in levels of seropositivity between groups. Solid black diamonds represent point estimate of prevalence difference; horizontal black line represents 95% confidence interval. Open diamond represents the pooled estimate, combined using random effects meta-analysis; vertical points of diamond represent point estimate and horizontal points represent 95% confidence interval; I2 value is the level of statistical heterogeneity between trials (<25% low heterogeneity).

Figure 3.12: Comparison B. 3p vs. 1p schedules, OPA seropositivity at ~12 months, OPA threshold 1:8, by serotype and study

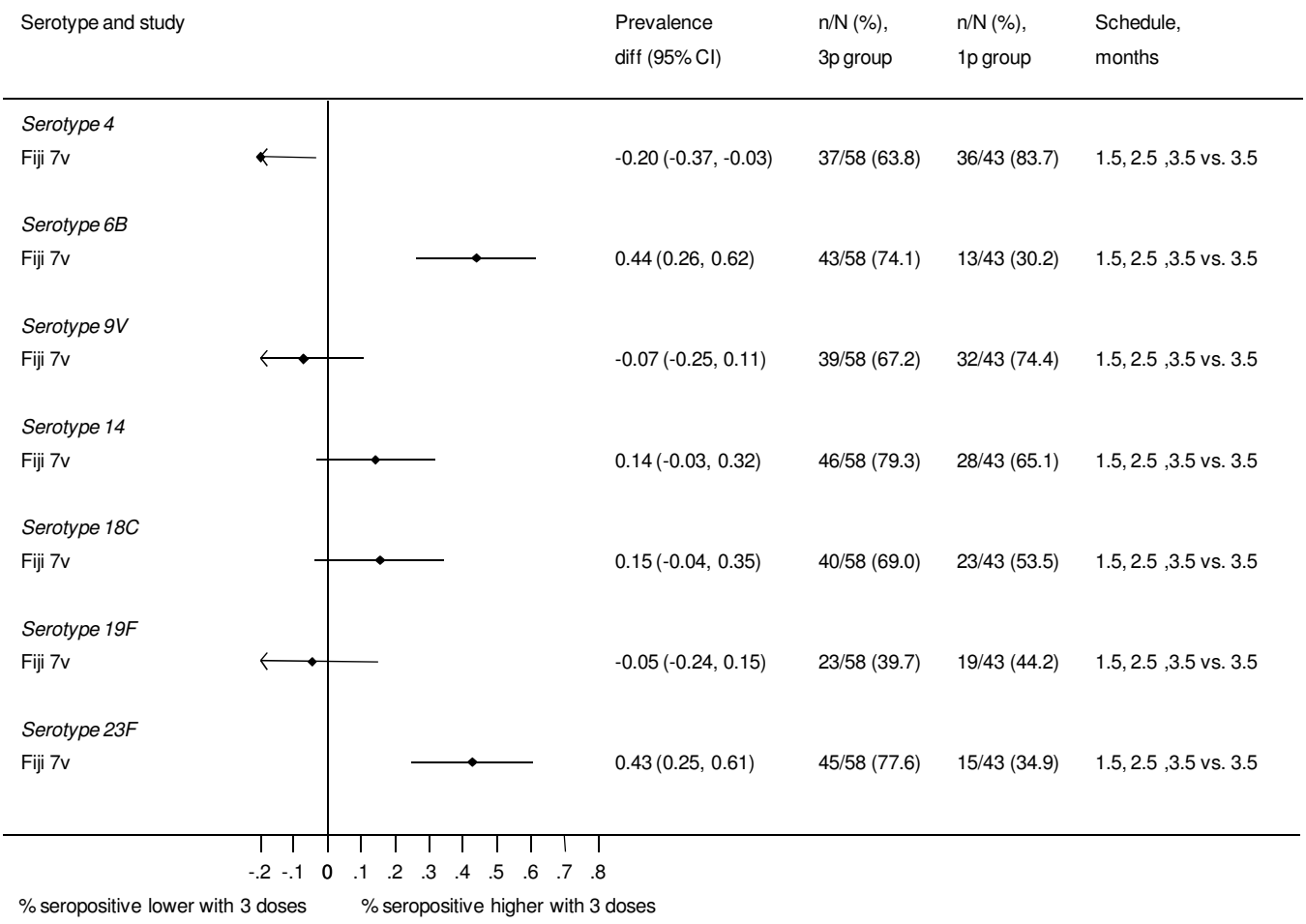


Legend:

n/N - number OPA >1:8/total in group. Prevalence diff - difference in seropositivity between groups shown as a proportion.

Horizontal axis represents the difference, expressed as a proportion between groups receiving schedules of 3 primary doses vs. 1primary dose. Vertical line through risk difference of 0 shows no difference in levels of seropositivity between groups. Solid black diamonds represent point estimate of prevalence difference; horizontal black line represents 95% confidence interval. Open diamond represents the pooled estimate, combined using random effects meta-analysis; vertical points of diamond represent point estimate and horizontal points represent 95% confidence interval; I2 value is the level of statistical heterogeneity between trials (<25% low heterogeneity).

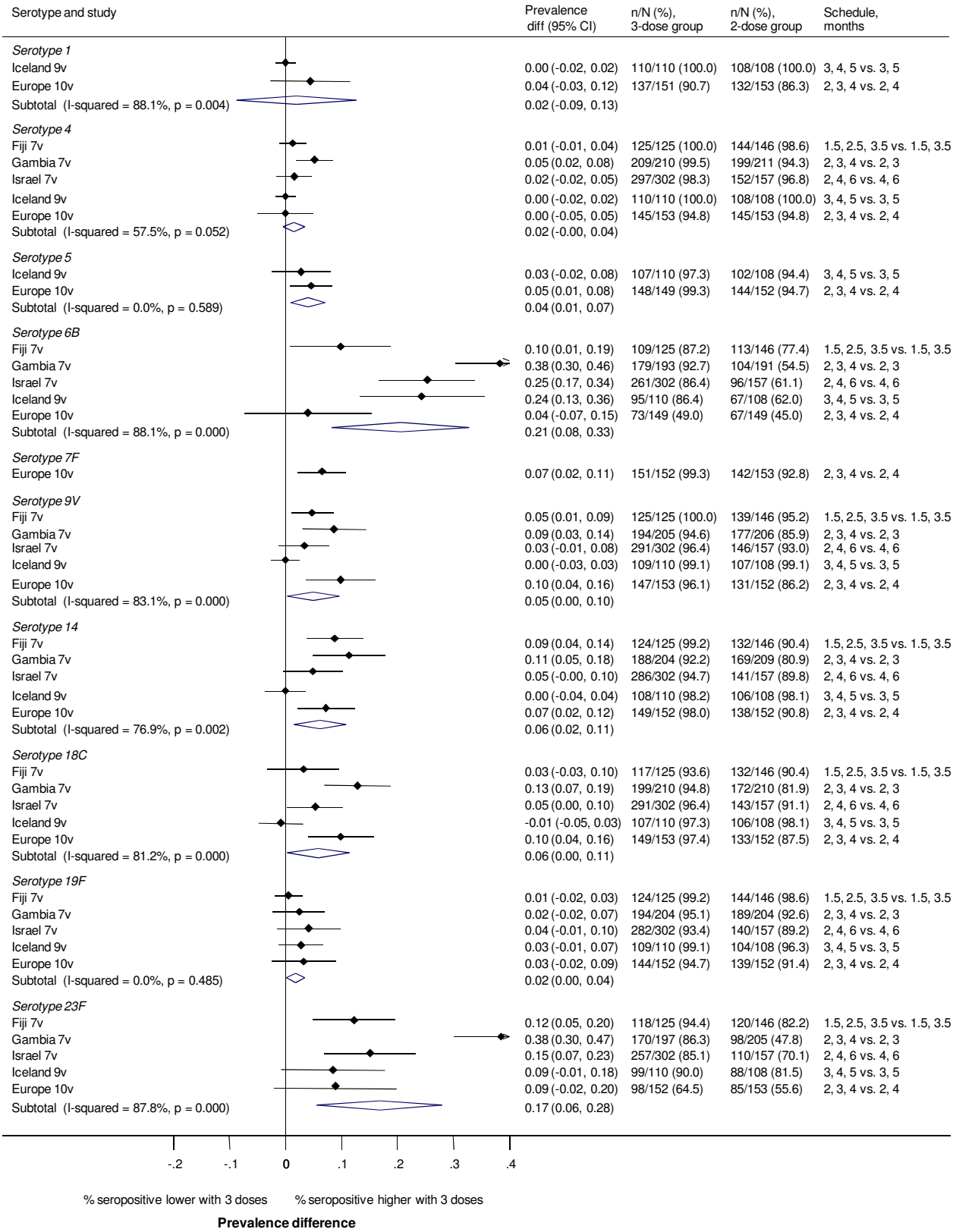
Figure 3.13: Comparison B. 3p vs. 1p schedules, OPA seropositivity at ~17 months, OPA threshold 1:8, by serotype and study



Legend:

n/N - number OPA >1:8/total in group. Prevalence diff - difference in seropositivity between groups shown as a proportion. Horizontal axis represents the difference, expressed as a proportion between groups receiving schedules of 3 primary doses vs. 1primary dose. Vertical line through risk difference of 0 shows no difference in levels of seropositivity between groups. Solid black diamonds represent point estimate of prevalence difference; horizontal black line represents 95% confidence interval. Open diamond represents the pooled estimate, combined using random effects meta-analysis; vertical points of diamond represent point estimate and horizontal points represent 95% confidence interval; I2 value is the level of statistical heterogeneity between trials (<25% low heterogeneity).

Figure 3.14: Comparison C. 3p vs. 2p schedules, seropositivity at ~6 months, ELISA threshold 0.35ug/mL, by serotype and study

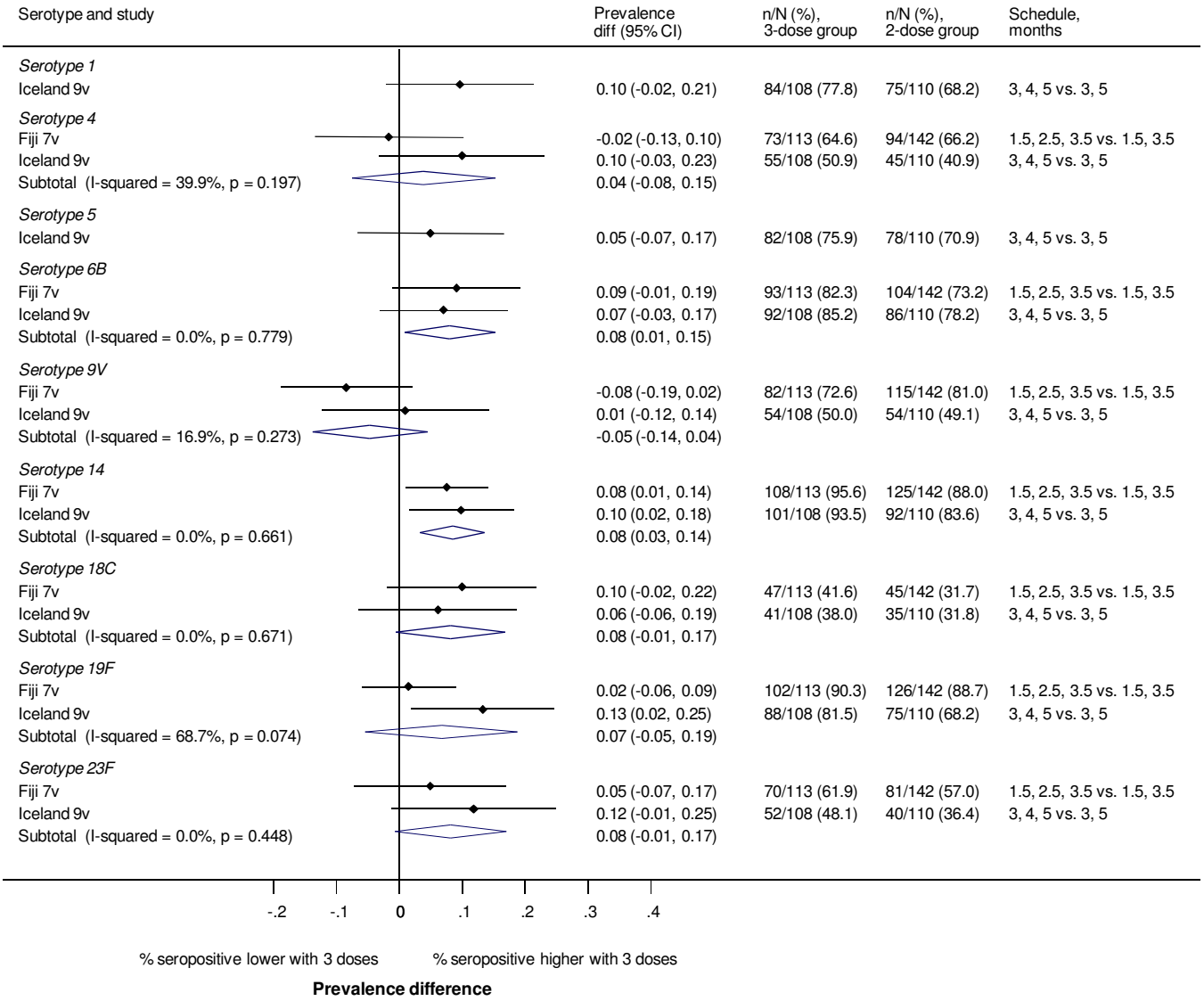


Legend:

n/N - number seropositive/total in group. Prevalence diff - difference in seropositivity between groups shown as a proportion.

Horizontal axis represents the difference, expressed as a proportion between groups receiving schedules of 3 primary doses vs. 2 primary doses. Vertical line through risk difference of 0 shows no difference in levels of seropositivity between groups. Solid black diamonds represent point estimate of prevalence difference; horizontal black line represents 95% confidence interval. Open diamond represents the pooled estimate, combined using random effects meta-analysis; vertical points of diamond represent point estimate and horizontal points represent 95% confidence interval; I2 value is the level of statistical heterogeneity between trials (<25% low heterogeneity).

Figure 3.15: Comparison C. 3p vs. 2p schedules, seropositivity at ~12 months, ELISA threshold 0.35ug/mL, by serotype and study



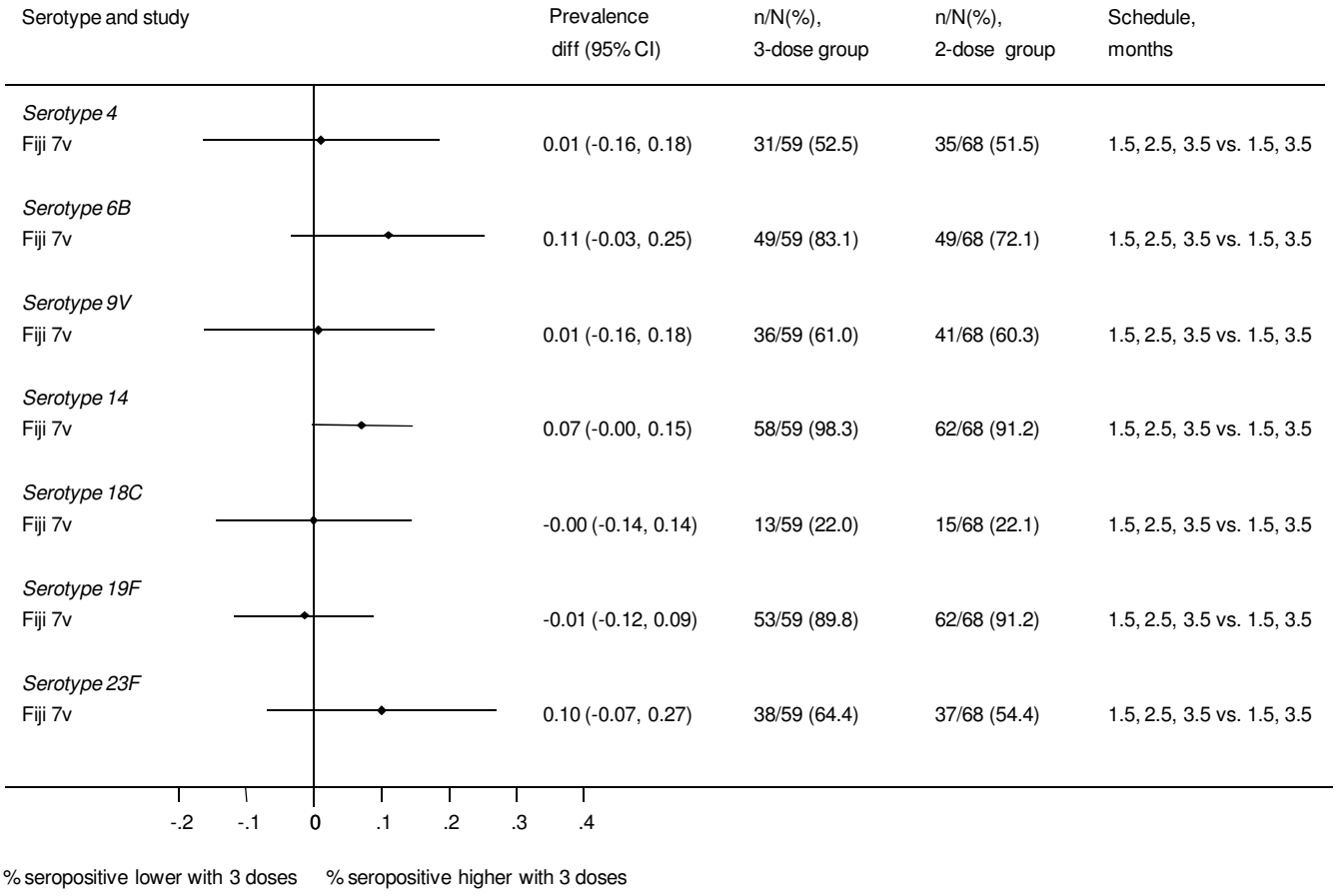
Legend:

n/N - number seropositive/total in group. Prevalence diff - difference in seropositivity between groups shown as a proportion.

Horizontal axis represents the difference, expressed as a proportion between groups receiving schedules of 3 primary doses vs. 2 primary doses. Vertical line through risk difference of 0 shows no difference in levels of seropositivity between groups. Solid black diamonds represent point estimate of prevalence difference; horizontal black line represents 95% confidence interval. Open diamond represents the pooled estimate, combined using random effects meta-analysis; vertical points of diamond represent point estimate and horizontal points represent 95% confidence interval; I2 value is the level of statistical heterogeneity between trials (<25% low heterogeneity).

Iceland data read from graphs using PlotDigitizer software. Due to resolution of graphs in the original publication, readings are prone to a degree of error.

Figure 3.16: Comparison C. 3p vs. 2p schedules, seropositivity at ~17 months, ELISA threshold 0.35ug/mL, by serotype and study

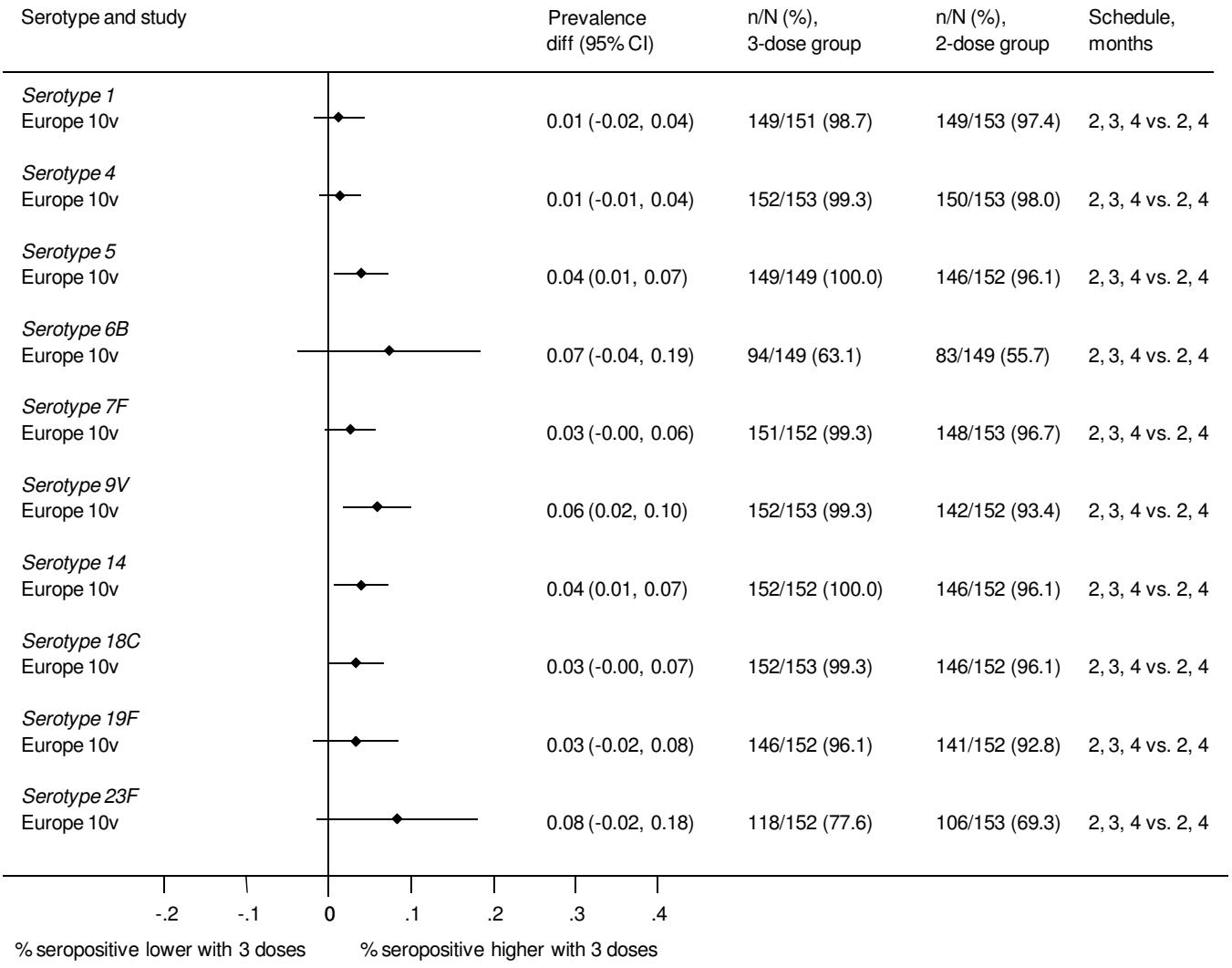


Legend:

n/N - number seropositive/total in group. Prevalence diff - difference in seropositivity between groups shown as a proportion.

Horizontal axis represents the difference, expressed as a proportion between groups receiving schedules of 3 primary doses vs. 2 primary doses. Vertical line through risk difference of 0 shows no difference in levels of seropositivity between groups. Solid black diamonds represent point estimate of prevalence difference; horizontal black line represents 95% confidence interval. Open diamond represents the pooled estimate, combined using random effects meta-analysis; vertical points of diamond represent point estimate and horizontal points represent 95% confidence interval; I2 value is the level of statistical heterogeneity between trials (<25% low heterogeneity).

Figure 3.17: Comparison C. 3p vs. 2p schedules, seropositivity at ~6 months, ELISA threshold 0.20ug/mL, by serotype and study

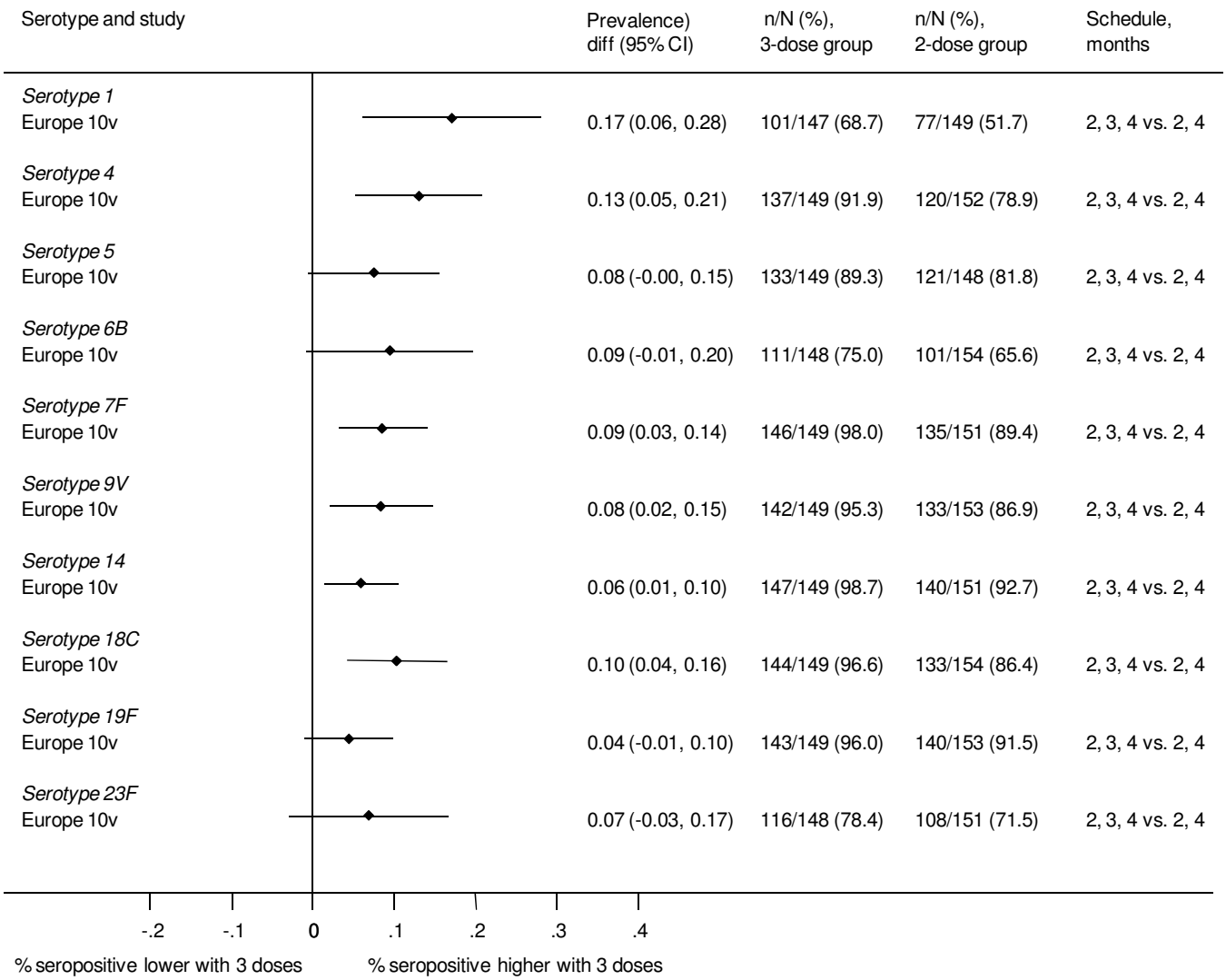


Legend:

n/N - number seropositive/total in group. Prevalence diff - difference in seropositivity between groups shown as a proportion.

Horizontal axis represents the difference, expressed as a proportion between groups receiving schedules of 3 primary doses vs. 2 primary doses. Vertical line through risk difference of 0 shows no difference in levels of seropositivity between groups. Solid black diamonds represent point estimate of prevalence difference; horizontal black line represents 95% confidence interval. Open diamond represents the pooled estimate, combined using random effects meta-analysis; vertical points of diamond represent point estimate and horizontal points represent 95% confidence interval; I2 value is the level of statistical heterogeneity between trials (<25% low heterogeneity).

Figure 3.18: Comparison C. 3p vs. 2p schedules, seropositivity at ~12 months, ELISA threshold 0.20ug/mL, by serotype and study

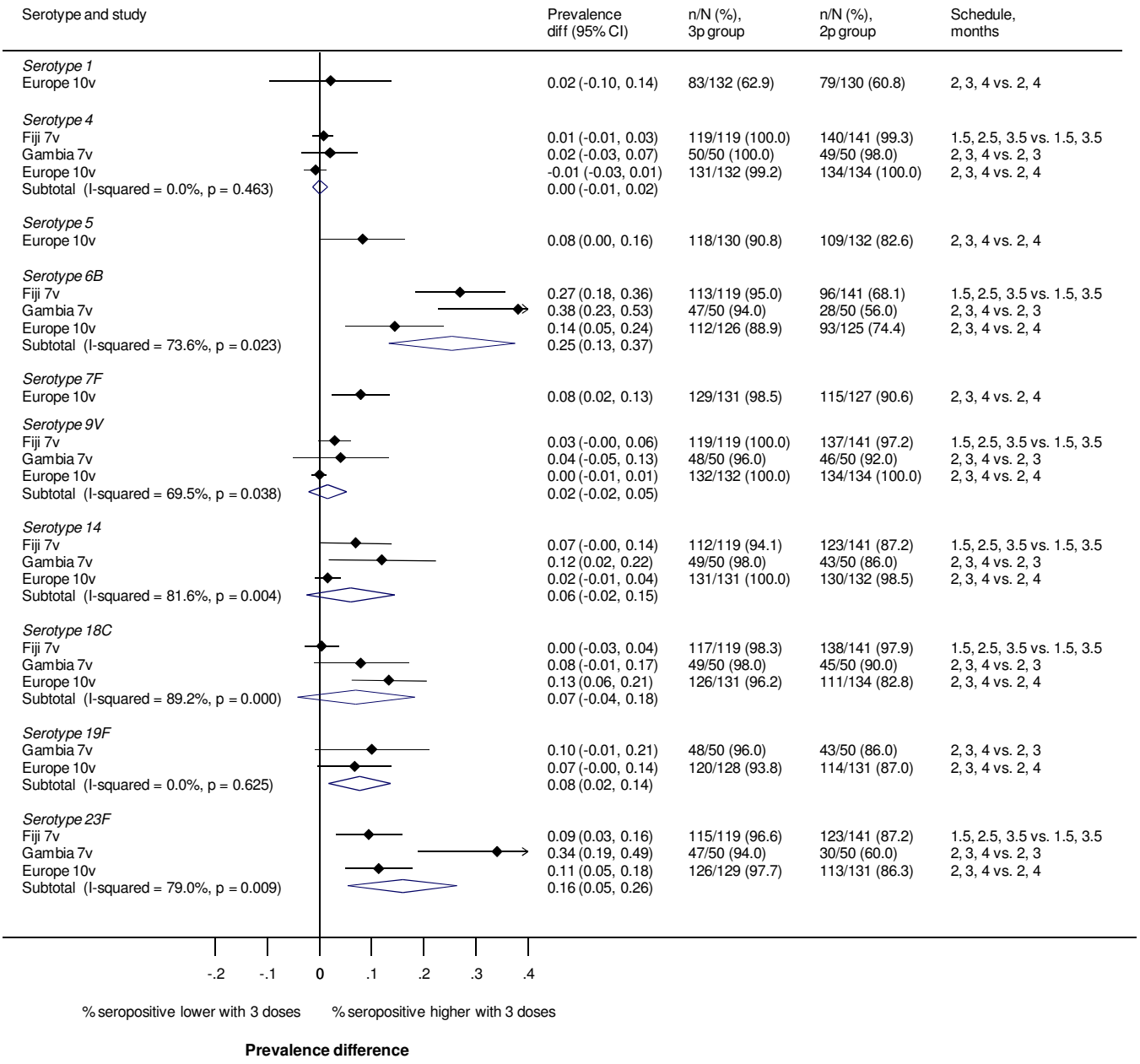


Legend:

n/N - number seropositive/total in group. Prevalence diff - difference in seropositivity between groups shown as a proportion.

Horizontal axis represents the difference, expressed as a proportion between groups receiving schedules of 3 primary doses vs. 2 primary doses. Vertical line through risk difference of 0 shows no difference in levels of seropositivity between groups. Solid black diamonds represent point estimate of prevalence difference; horizontal black line represents 95% confidence interval. Open diamond represents the pooled estimate, combined using random effects meta-analysis; vertical points of diamond represent point estimate and horizontal points represent 95% confidence interval; I2 value is the level of statistical heterogeneity between trials (<25% low heterogeneity).

Figure 3.19: Comparison C. 3p vs. 2p schedules, OPA seropositivity at ~6 months, OPA threshold 1:8, by serotype and study

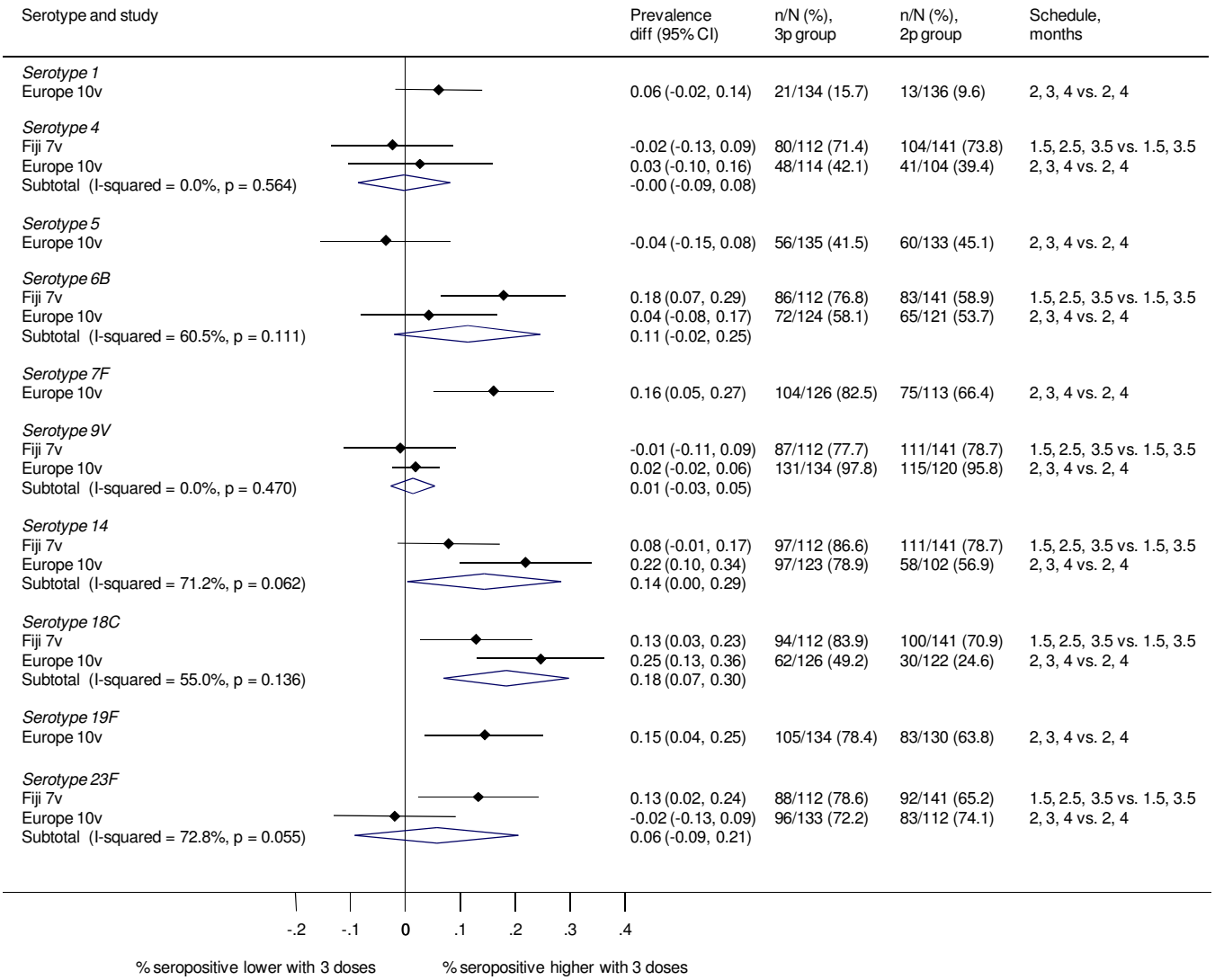


Legend:

n/N - number OPA >1:8/total in group. Prevalence diff - difference in seropositivity between groups shown as a proportion.

Horizontal axis represents the difference, expressed as a proportion between groups receiving schedules of 3 primary doses vs. 2primary doses. Vertical line through risk difference of 0 shows no difference in levels of seropositivity between groups. Solid black diamonds represent point estimate of prevalence difference; horizontal black line represents 95% confidence interval. Open diamond represents the pooled estimate, combined using random effects meta-analysis; vertical points of diamond represent point estimate and horizontal points represent 95% confidence interval; I2 value is the level of statistical heterogeneity between trials (<25% low heterogeneity).

Figure 3.20: Comparison C. 3p vs. 2p schedules, OPA seropositivity at ~12 months, OPA threshold 1:8, by serotype and study

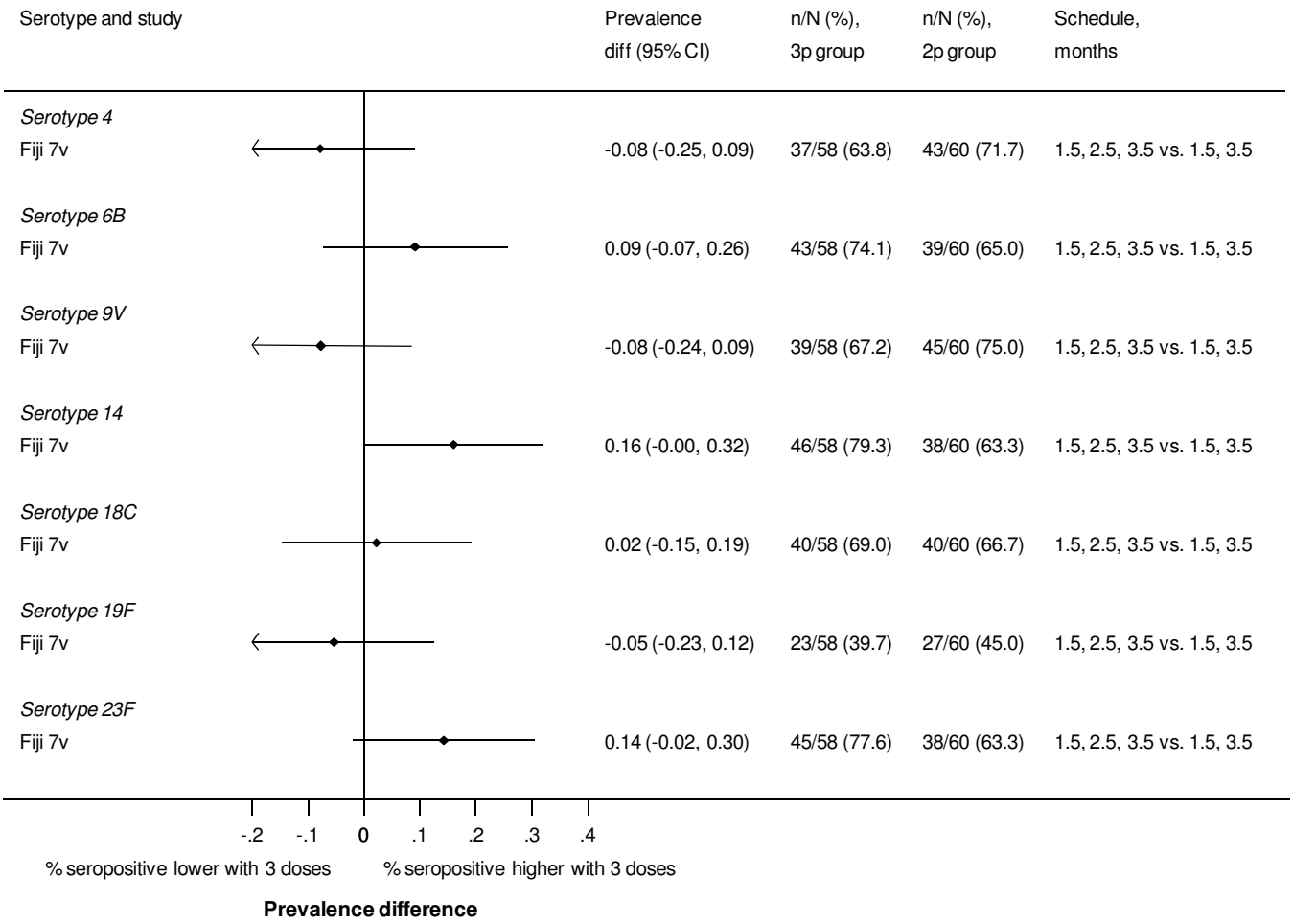


Legend:

n/N - number OPA >1:8/total in group. Prevalence diff - difference in seropositivity between groups shown as a proportion.

Horizontal axis represents the difference, expressed as a proportion between groups receiving schedules of 3 primary doses vs. 2primary doses. Vertical line through risk difference of 0 shows no difference in levels of seropositivity between groups. Solid black diamonds represent point estimate of prevalence difference; horizontal black line represents 95% confidence interval. Open diamond represents the pooled estimate, combined using random effects meta-analysis; vertical points of diamond represent point estimate and horizontal points represent 95% confidence interval; I2 value is the level of statistical heterogeneity between trials (<25% low heterogeneity).

Figure 3.21: Comparison C. 3p vs. 2p schedules, OPA seropositivity at ~17 months, OPA threshold 1:8, by serotype and study

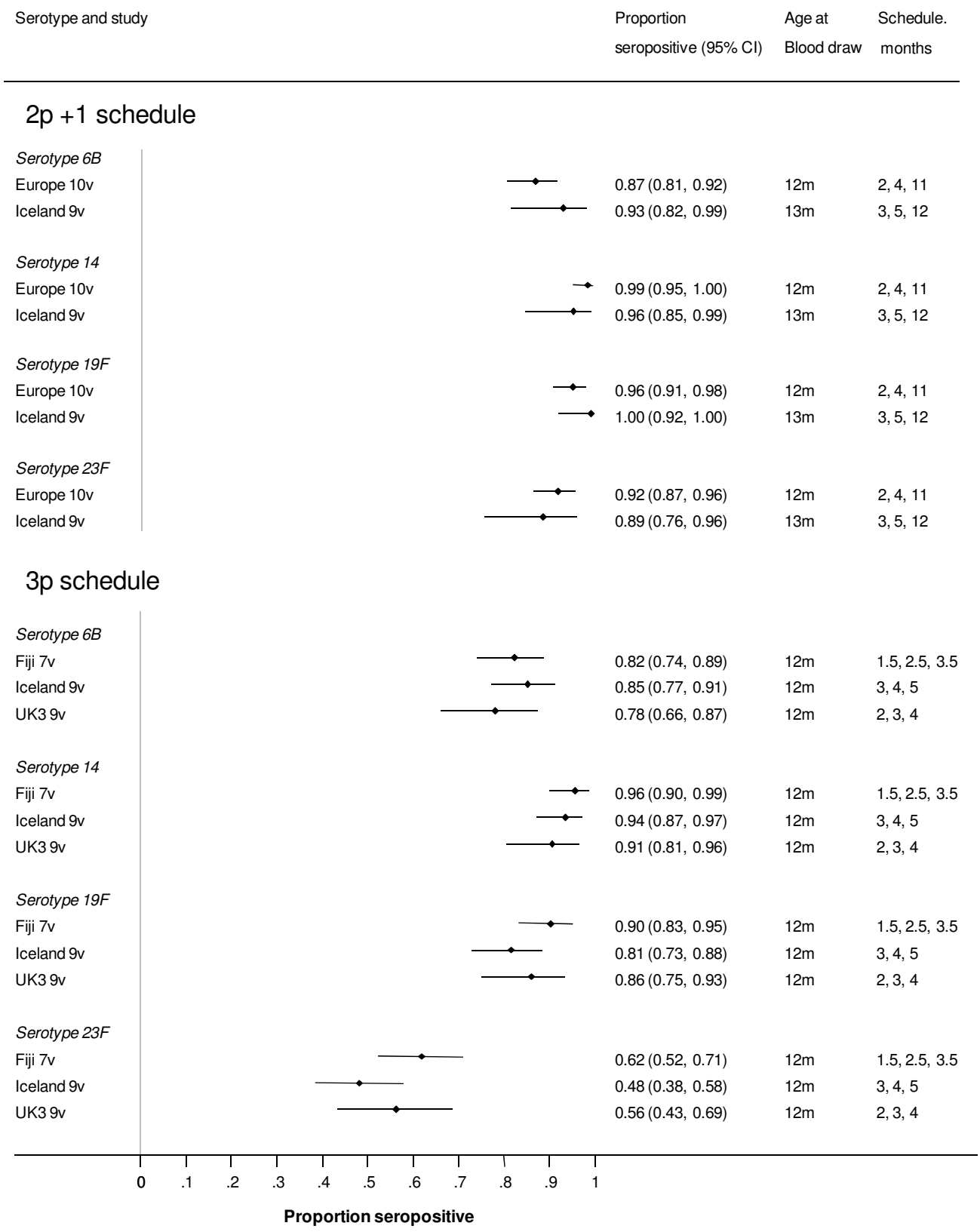


Legend:

n/N - number OPA >1:8/total in group. Prevalence diff - difference in seropositivity between groups shown as a proportion.

Horizontal axis represents the difference, expressed as a proportion between groups receiving schedules of 3 primary doses vs. 2primary doses. Vertical line through risk difference of 0 shows no difference in levels of seropositivity between groups. Solid black diamonds represent point estimate of prevalence difference; horizontal black line represents 95% confidence interval. Open diamond represents the pooled estimate, combined using random effects meta-analysis; vertical points of diamond represent point estimate and horizontal points represent 95% confidence interval; I2 value is the level of statistical heterogeneity between trials (<25% low heterogeneity).

Figure 3.22: Comparison G (3p vs. 2p+1). Absolute seropositivity at ~12 months, ELISA threshold 0.35ug/mL, by schedule, serotype and study

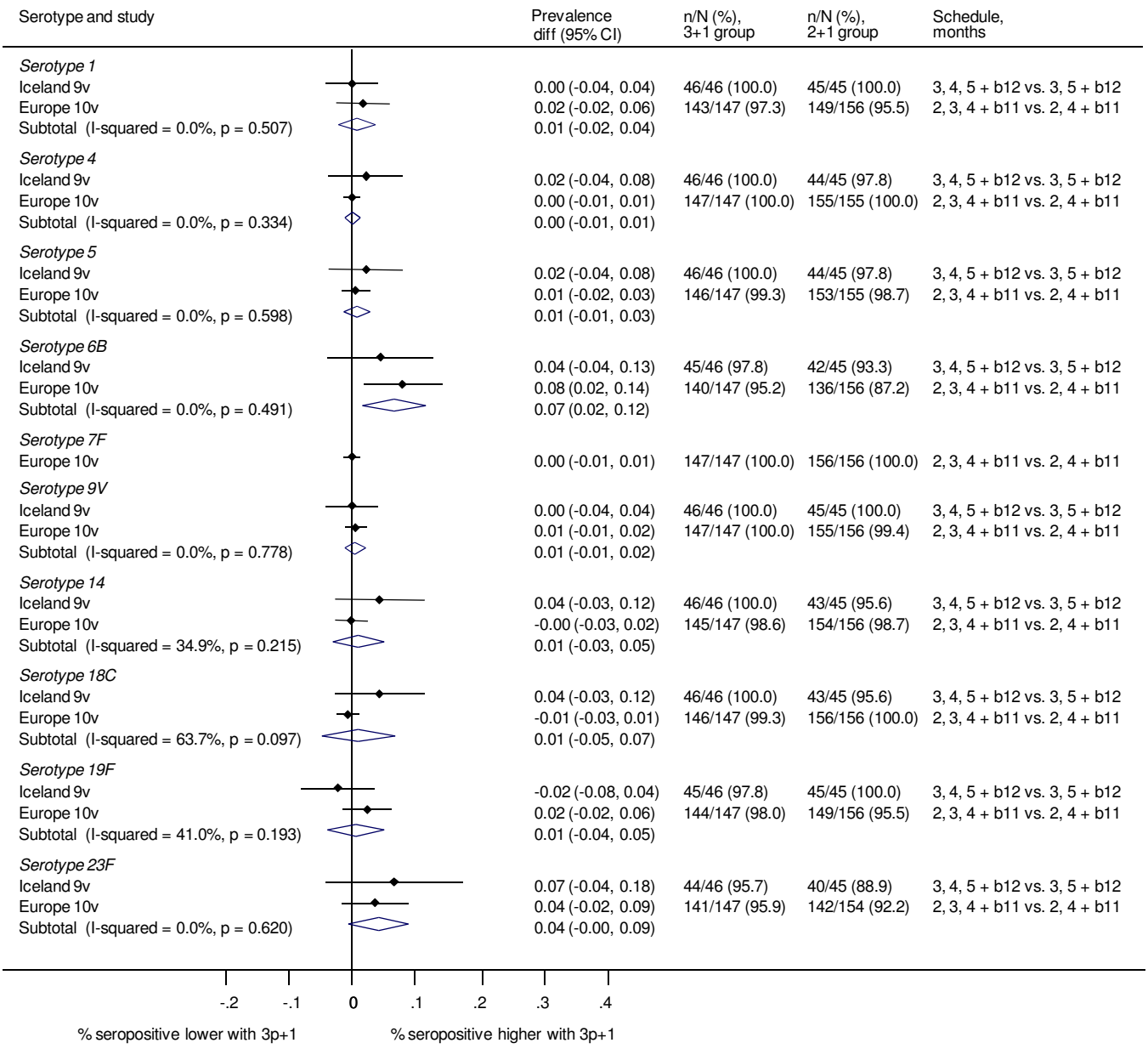


Legend:

Schedules reported as intended age in months for each dose.

Solid black diamonds represent point estimate of prevalence; horizontal black line represents 95% confidence interval.

Figure 3.23: Comparison L (3p+1 *vs.* 2p+1). Seropositivity 1 month after the booster dose, ELISA threshold 0.35ug/mL, by serotype and study

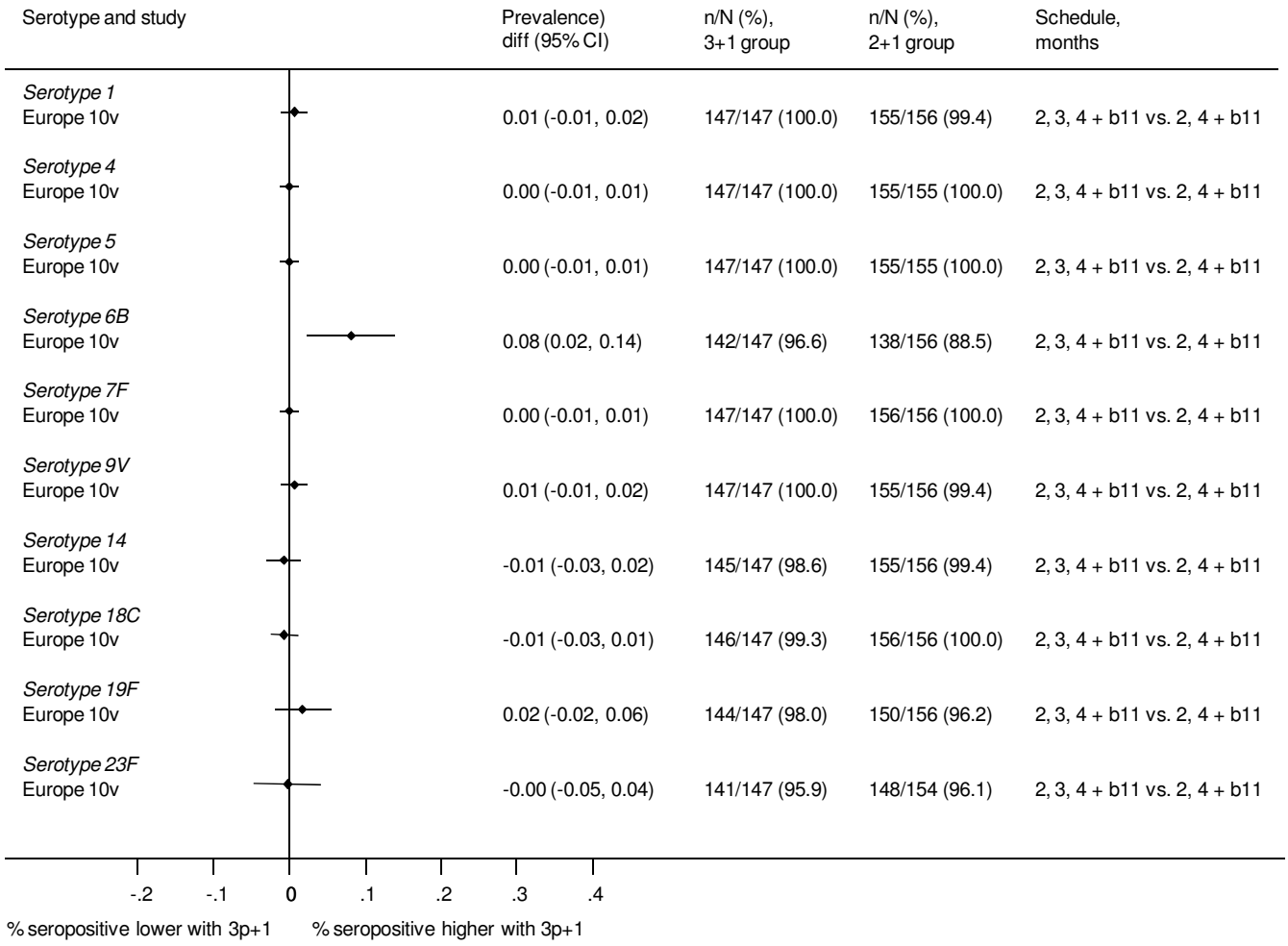


Legend:

n/N - number seropositive/total in group. Prevalence diff - difference in seropositivity between groups shown as a proportion. Horizontal axis represents the difference, expressed as a proportion between groups receiving schedules of 3 primary doses and a PCV booster vs. 2 primary doses and a PCV booster. Vertical line through risk difference of 0 shows no difference in levels of seropositivity between groups. Solid black diamonds represent point estimate of prevalence difference; horizontal black line represents 95% confidence interval. Open diamond represents the pooled estimate, combined using random effects meta-analysis; vertical points of diamond represent point estimate and horizontal points represent 95% confidence interval; I2 value is the level of statistical heterogeneity between trials (<25% low heterogeneity).

Iceland data read from graphs using PlotDigitizer software. Due to resolution of graphs in the original publication, readings are prone to a degree of error.

Figure 3.24: Comparison L (3p+1 vs. 2p+1). Seropositivity at 1 month after the booster dose, ELISA threshold 0.20ug/mL, by serotype and study

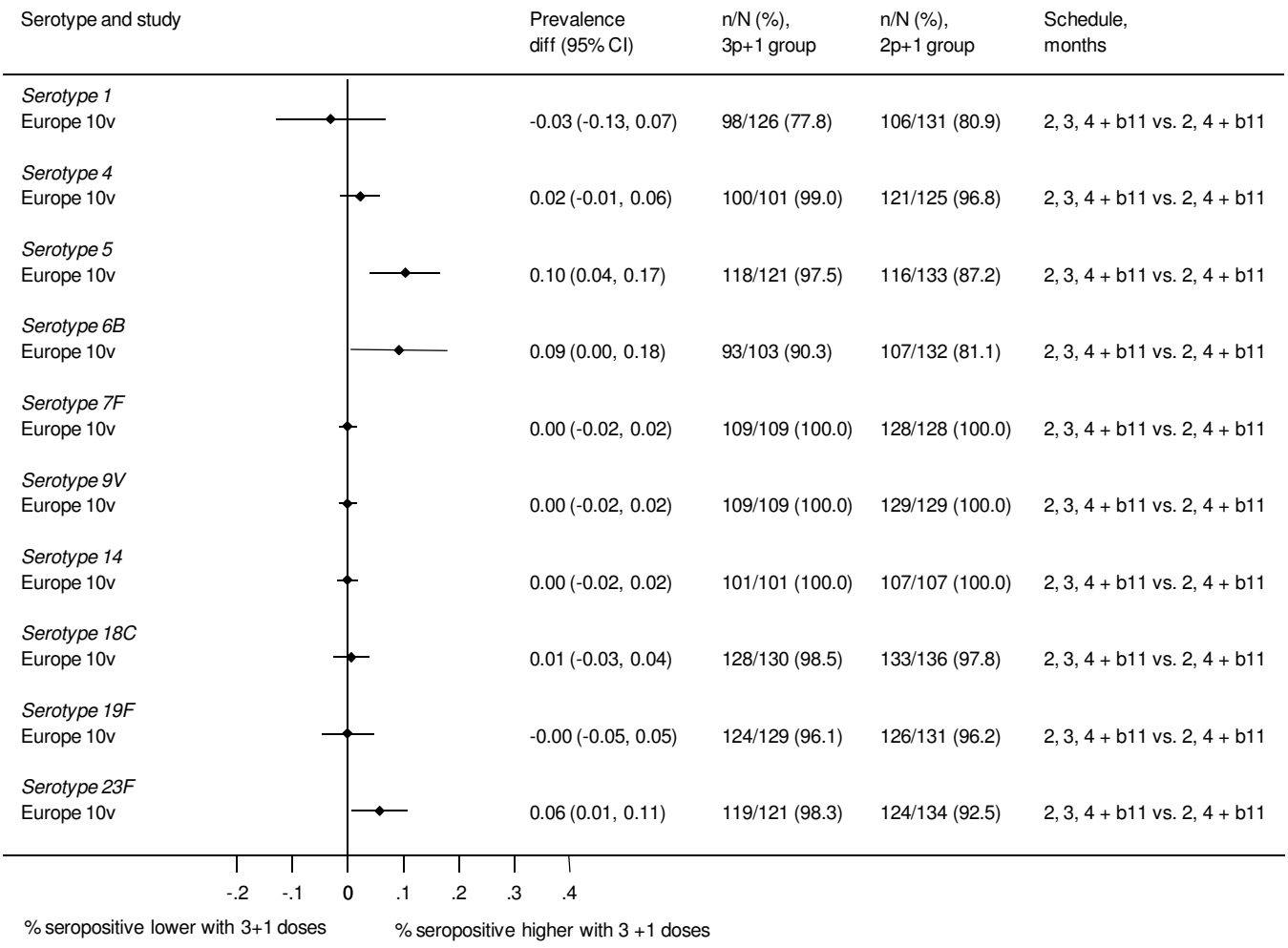


Legend:

n/N - number seropositive/total in group. Prevalence diff - difference in seropositivity between groups shown as a proportion.

Horizontal axis represents the difference, expressed as a proportion between groups receiving schedules of 3 primary doses vs. 2 primary doses. Vertical line through risk difference of 0 shows no difference in levels of seropositivity between groups. Solid black diamonds represent point estimate of prevalence difference; horizontal black line represents 95% confidence interval. Open diamond represents the pooled estimate, combined using random effects meta-analysis; vertical points of diamond represent point estimate and horizontal points represent 95% confidence interval; I2 value is the level of statistical heterogeneity between trials (<25% low heterogeneity).

Figure 3.25: Comparison L. 3p+1 vs. 2p+1 schedules, OPA seropositivity one month after booster dose, OPA threshold 1:8, by serotype and study

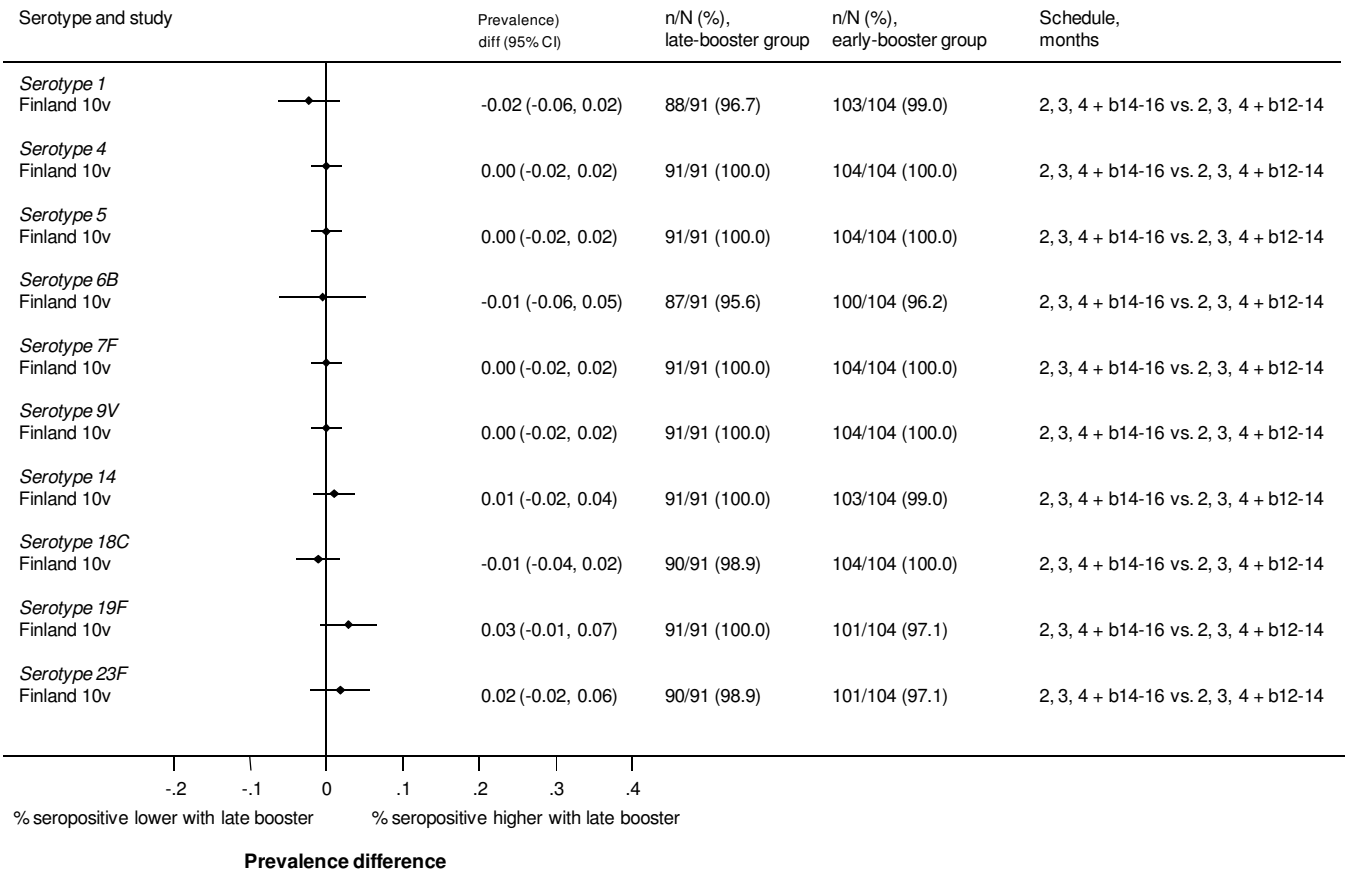


Legend:

n/N - number OPA >1:8/total in group. Prevalence diff - difference in seropositivity between groups shown as a proportion.

Horizontal axis represents the difference, expressed as a proportion between groups receiving schedules of 3 primary doses and a booster vs. 2primary doses. And a booster Vertical line through risk difference of 0 shows no difference in levels of seropositivity between groups. Solid black diamonds represent point estimate of prevalence difference; horizontal black line represents 95% confidence interval. Open diamond represents the pooled estimate, combined using random effects meta-analysis; vertical points of diamond represent point estimate and horizontal points represent 95% confidence interval; I2 value is the level of statistical heterogeneity between trials (<25% low heterogeneity).

Figure 3.26: Comparison Q (Longer interval between primary and booster vs. shorter interval between primary and booster). Seropositivity at 1.5 month after the booster dose, ELISA threshold 0.20ug/mL, by serotype and study

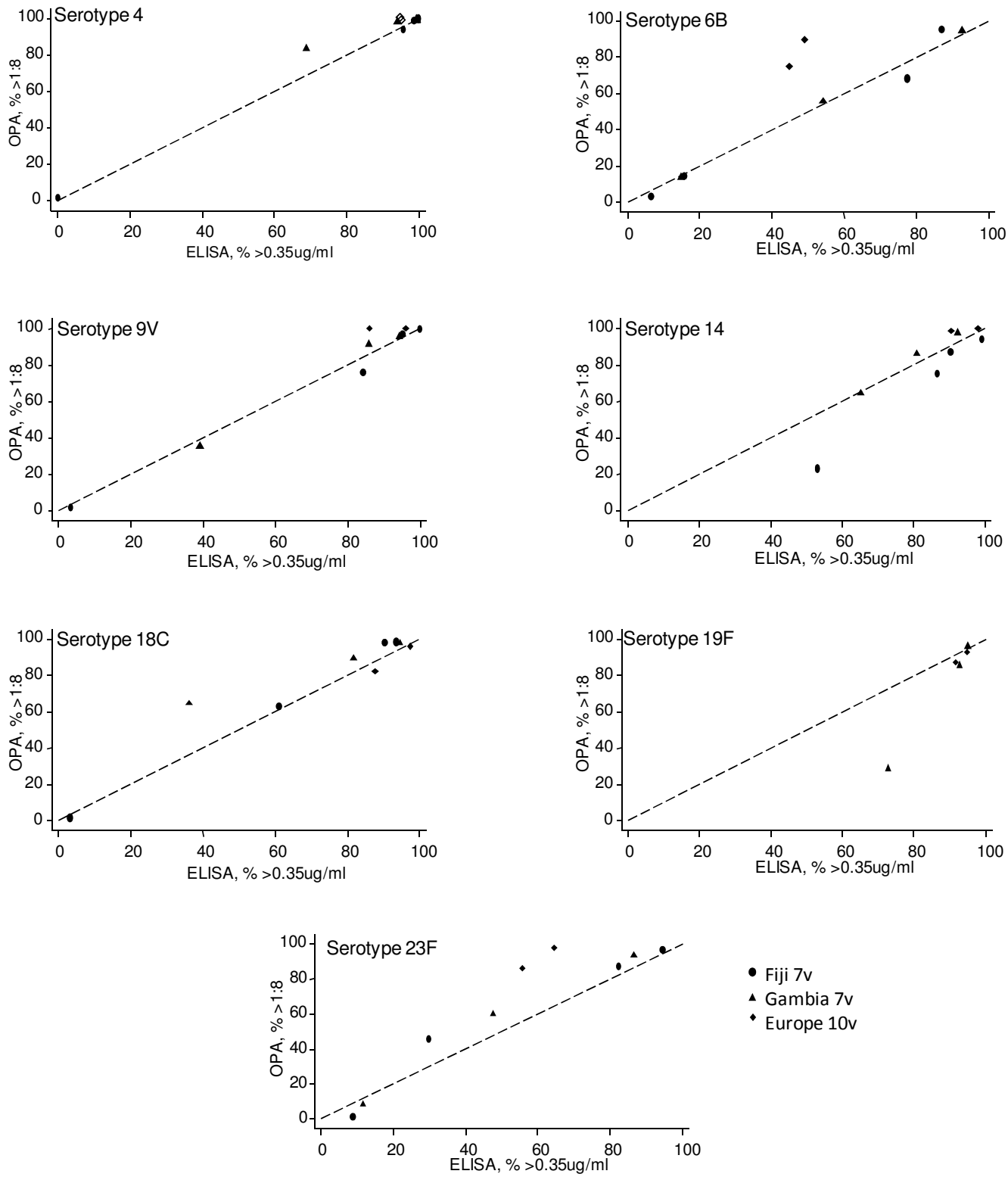


Legend:

n/N - number seropositive/total in group. Prevalence diff - difference in seropositivity between groups shown as a proportion.

Horizontal axis represents the difference, expressed as a proportion between groups receiving schedules of 3 primary doses vs. 2 primary doses. Vertical line through risk difference of 0 shows no difference in levels of seropositivity between groups. Solid black diamonds represent point estimate of prevalence difference; horizontal black line represents 95% confidence interval. Open diamond represents the pooled estimate, combined using random effects meta-analysis; vertical points of diamond represent point estimate and horizontal points represent 95% confidence interval; I2 value is the level of statistical heterogeneity between trials (<25% low heterogeneity).

Figure 3.27: Percentage of individuals with OPA >1:8 compared to percentage of individuals with ELISA >0.35µg/ml in each randomization group in the three trials reporting these data, about age 6 months, by serotype



Diagonal line represents equal percentages of individuals positive for each outcome. Data in this figure are from the three trials which report both OPA >1:8 and ELISA >0.35µg/ml. Each point represents one trial arm from these trials: Fiji 7v 0-, 1-, 2-, 3-dose arms; Gambia 7v 1-, 2-, 3- dose arms; Europe 10v 2-, 3- dose arms. OPA data not available for Fiji 7v for serotype 19F.These data are at the group level and associations at the individual level between the two outcomes may differ to those seen here.

Table 3.1: Summary of included RCTs with schedule-schedule comparisons reporting immunological outcomes, alphabetical order

Study name and PCV valency	Country	Schedules, age at dose in months		Number of participants randomized	Outcomes reported
		Intended	Actual age at administration		
Canada1 7v primary [10] [1]	Canada	3, 5, 7	Not reported	124	Seropositivity, GMC
		2, 4, 6	1st: mean 2.2	126	
Canada1 7v booster [11] [1]	Canada	3p + b18	18.5	167	Seropositivity, GMC
		3p + b15	15.5	168	
Chile 10v [12]	Chile	2, 4, 6, + b>18	Not reported	119	Seropositivity, GMC, OPA
		2 catch-up >18		121	
Europe 10v [13]	Denmark, Norway, Slovakia, Sweden	2, 3, 4, +b11m	2.8, 3.9 ,5.0, 11.2	176	Seropositivity, GMC, OPA
		2, 4, +b11m	2.8, 4.9, 11.1	175	
Fiji 7v [14]	Fiji	1.5, 2.5, 3.5 +/- b12(PPV)	Not reported	136	Seropositivity, GMC, OPA
		1.5, 3.5 +/- b12(PPV)		156	
		3.5 +/- b12(PPV)		128	
Finland 10v [15]	Finland	2, 3, 4, + b14-16m	Not reported	101	Seropositivity, GMC
		2, 3, 4, + b12-14m		110	
Gambia 7v [16]	The Gambia	2, 3, 4 + b10(PPV)	median 1.7, 3.0, 4.2, 10.5	228	Seropositivity, GMC, OPA
		2, 3 + b10(PPV)	median 1.8, 3.0, 10.5	228	
		2 + b10(PPV)	median 1.8, 10.4	228	
Germany 7v [17]	Germany	6, 7, 8 + b11-15	Not reported	113	GMC[2]
		2, 3, 4 + b11-15		118	
Ghana infants 9v [18]	Ghana	1.5, 2.5, 3.5 + b12	2.6, 3.9, 4.8, NR	21	GMC
		1.5, 2.5, 3.5 + b12(PPV)	2.4, 3.5, 4.9, NR	21	
		1.5, 2.5, 3.5	2.4, 3.9. 5.2	20	
Ghana toddlers 9v [19]	Ghana	2 doses PCV (2 months apart)	14.9, 17.1	46	GMC
		1 dose PCV + PPV(2 months apart)	14.9, 17.5	46	
Iceland 9v [20]	Iceland	3, 4, 5 + b12	Not reported	111[3]	Seropositivity, GMC
		3, 4, 5 + b12(PPV)			
		3, 5 + b12		112[3]	
		3, 5 + b12(PPV)			
Israel 7v [21]	Israel	2, 4, 6 + b12	2.1, 4.0, 5.8, 12.5[4]	178	Seropositivity, GMC
		2, 4, 6	NR[4]	178	
		4, 6 + b12	3.9, 5.7, 12.4	189	
UK1 7v [22]	United Kingdom	5, 6, 7 + b13(PPV)	Not reported	120	GMC
		2, 3, 4 + b13(PPV)		124	
UK2 9v [23]	United Kingdom	2, 4 + b12	Not reported	88[3]	Seropositivity, GMC
		2, 4 + b12(PPV)			
UK3 9v [23]	United Kingdom	2, 3, 4 + b12	Not reported	84[3]	Seropositivity, GMC
		2, 3, 4 + b12(PPV)			
UK4 9v [23]	United Kingdom	12, 14+18 (PPV)	Not reported	45	Seropositivity, GMC
		12+18 (PPV)		47	
USA3 7v [24]	United States	2-3.5, 4.5, 6.5	1st :median 2.1	188	Seropositivity, GMC
		1.5-3, 4, 6		188	

Legend:

b – booster; GMC – geometric mean concentration of IgG antibodies; OPA – opsonophagocytic activity; NR – not reported; PCV – pneumococcal conjugate vaccine; PPV – pneumococcal polysaccharide vaccine; Seropositivity 3p – 3 dose primary schedule, etc.; +1 – booster dose.

1 Canada1 7v primary and Canada1 7v booster include the same children, but individuals were randomized for a second time after the primary course. Each intervention group for the booster study therefore contains individuals who receives 2, 4, 6m and 3, 5, 7m primary schedules.

Results after the booster dose are not reported in a way that allows examination of the original intervention groups. These 2 phases of the study are therefore reported separately, and do not occur in the same analysis. In Canada1 7v primary, there was an additional comparison group for which PCV related outcome data were not reported. This group was therefore not included in the reporting of Canada1 7v primary, but is included in Canada1 7v booster, which accounts for the difference in number of participants in the 2 phases of the study.

2 Results not reported in enough detail to include in analyses (no confidence intervals reported)

3 The number undergoing the randomization process. The numbers randomized to each group are unclear

4 The ages at administration given for the 3p+1 group appear to relate to both the 3p+1 and the 3p group, but not clearly stated in original publication

Table 3.2: ELISA assays used and antibody concentration thresholds reported

Study	Assay	GMC only	Threshold for EIA seropositivity, µg/mL[1]						
			0.05	0.15	0.20	0.35	0.50	1.0	5.0
Canada1 7v primary	'standardized ELISA'			✓			✓		
Canada1 7v booster	'published ELISA'			✓			✓		
Chile 10v	"22F-ELISA"		✓		✓				
Europe 10v	ELISA, with 22F pre-adsorption		✓		✓	✓			
Fiji 7v	'modified WHO ELISA' against reference serum 89SF					✓		✓	
Finland 10v	"22F-ELISA"		✓		✓				
Gambia 7v	'ELISA…adapted WHO'					✓			
Germany 7v	"standard ELISA methods"	Yes							
Ghana infants 9v	"ELISA ...based on an original assay described by Quataert"	Yes							
Ghana toddler 9v	"ELISA ...based on an original assay described by Quataert"	Yes							
Iceland 9v	ELISA, no 22F pre-adsorption					✓			
Israel 7v	ELISA, 22F and C pre-adsorption					✓		✓	✓
UK1 7v	'standard ELISA' against reference serum 89SF	Yes							
UK2-4 9v[2]	ELISA, with 22F pre-adsorption				✓	✓		✓	
USA3 7v	'standardized ELISA'		✓						

Legend:

1 In published articles, not all thresholds are reported for all possible comparisons;

2 Three trials reported separately

Table 3.3: Order of description and presentation of comparisons of vaccination schedules in RCTs reporting immunological outcomes

Comparison	Study	Schedules, months	Age at which samples taken[1], months	Age at which 0.35µg/ml available, months	Age at which 0.20µg/ml available, months	Age at which GMC available, months	Age at which OPA available, months
Comparison A 2p vs. 1p	Fiji 7v	1.5, 3.5 3.5	4.5, 9, 12, 17	4.5, 9, 12, 17	NR	4.5, 9, 12, 17	4.5, 9, 12, 17
	Gambia 7v[2]	2, 3 2	5.5	5.5	NR	5.5	5.5
Comparison B 3p vs. 1p	Fiji 7v	1.5, 2.5, 3.5 3.5	4.5, 9, 12, 17	4.5, 9, 12, 17	NR	4.5, 9, 12, 17	4.5, 9, 12, 17
	Gambia 7v[2]	2, 3, 4 2	5.5	5.5	NR	5.5	5.5
Comparison C 3p vs. 2p	Fiji 7v	1.5, 2.5, 3.5 1.5, 3.5	4.5, 9, 12, 17	4.5, 9, 12, 17	NR	4.5, 9, 12, 17	4.5, 9, 12, 17
	Gambia 7v[2]	2, 3, 4 2, 3	5.5	5.5	NR	5.5	5.5
	Israel 7v[2]	2, 4, 6 4, 6	7	7	NR	NR[3]	NR
	Iceland 9v[2]	3, 4, 5 3, 5	6, 12	6, 12	NR	6	NR
	Europe 10v[2]	2, 3, 4 2, 4	6, 11	6	6, 11	6, 11	6, 11
Comparison D 2p + PPV vs. 1p +PPV	Fiji 7v	1.5, 3.5 + b12(PPV) 3.5+ b12(PPV)	17	17	NR	17	17
	Gambia 7v	2, 3, 4 + b10(PPV) 2 , 3 + b10(PPV)	11, 15	11, 15	NR	11, 15	11, 15
Comparison F 2p + 1 vs. 2p + PPV	Iceland 9v	3, 5 + b12 3, 4, 5 + b12(PPV)	13	13	NR	13	NR
	UK2 9v	2, 4 + b12 2, 4 + b12(PPV)	13	NR	NR	13	NR
Comparison G 3p vs. 2p + 1	Israel 7v	2, 4, 6 4, 6 + b12	13, 19 (and 1 month post completion: 13 vs. 7m)	NR	NR	13, 19 (and 1 month post completion: 13 vs. 7m)	NR
Comparison H 3p + PPV vs. 1p+ PPV	Fiji 7v	1.5, 2.5, 3.5+ b12(PPV) 3.5+ b12(PPV)	17	17	NR	17	17
	Gambia 7v	2, 3, 4 + b10(PPV) 2 + b10(PPV)	11, 15	11, 15	NR	11, 15	11, 15
Comparison I 3p + PPV vs. 2p +PPV	Fiji 7v	1.5, 2.5, 3.5+ b12(PPV) 1.5, 3.5+ b12(PPV)	17	17	NR	17	17
	Gambia 7v	2, 3, 4 + b10(PPV) 2 , 3 + b10(PPV)	11, 15	11, 15	NR	11, 15	11, 15
	Iceland 9v	3, 4, 5 +b12(PPV) 3, 5 + b12 (PPV)	13	13	NR	13	NR
Comparison J 3p + PPV vs. 2p + 1	Iceland 9v	3, 4, 5 +b12(PPV) 3, 5 + b12	13	13	NR	13	NR

Comparison	Study	Schedules, months	Age at which samples taken[1], months	Age at which 0.35µg/ml available, months	Age at which 0.20µg/ml available, months	Age at which GMC available, months	Age at which OPA available, months
Comparison K 3p + 1 vs. 2p + PPV	Iceland 9v	3, 4, 5 +b12 3, 5 + b12(PPV)	13	13	NR	13	NR
Comparison L 3p + 1 vs. 2p + 1	Israel 7v	2, 4, 6 + b 12 4, 6 + b12	13, 19	NR	NR	13, 19	NR
	Iceland 9v	3, 5 + b 12 3, 4, 5 +b 12	13	13	NR	13	NR
	Europe 10v	2, 3, 4 + b 11 2, 4 + b 11	12	12	12	12	12
Comparison M 3p + 1 vs. 3p	Israel 7v	2, 4, 6 + b12 2, 4, 6	13, 19 (and 1 month post completion: 13 vs. 7m)	NR	NR	13, 19 (and 1 month post completion: 13 vs. 7m)	NR
	Ghana infants 9v	1.5, 2.5, 3.5 + 12 1.5, 2.5, 3.5	13 (and 1 month post completion: 13 vs. 4.5m)	NR	NR	13 (and 1 month post completion: 13 vs. 4.5m)	NR
Comparison N 3p +1 vs. 3p + PPV	Ghana infants 9v	1.5, 2.5, 3.5 + 12 1.5, 2.5, 3.5 + 12(PPV)	13	NR	NR	13	NR
	Iceland 9v	3, 4, 5 +b12 3, 4, 5 + b12(PPV)	13	13	NR	13	NR
	UK3 9v	2, 3, 4 + b12 2, 3, 4 +b12 (PPV)	13	NR	NR	13	NR
Comparison O Late start vs. early start	Canada1 7v primary [4]	3, 5, 7 2, 4, 6	1 month post completion: 8 vs. 7m	NR	NR	1 month post completion: 8 vs. 7m	NR
	Germany 7v	6, 7, 8 +b11-15 2, 3, 4 +b11-15	11-15, 12-16	NR	NR	NR	NR
	UK1 7v	5, 6, 7 2, 3, 4	13	NR	NR	13	NR
	UK1 7v	5, 6, 7 + b13(PPV) 2, 3, 4 + b13(PPV)	14	NR	NR	14	NR
	USA3 7v	1.5-3, 4, 6 2-3.5, 4.5, 6.5	7	NR	NR	7	NR
Comparison Q longer interval between primary and booster vs. shorter interval between primary and booster	Finland 10v	2, 3, 4 + b 14-16 2, 3, 4 + b 12-14	1.5 months post completion: 15.5 vs.13.5m	NR	1.5 months post completion: 15.5 vs.13.5m	1.5 months post completion: 15.5 vs.13.5m	NR
	Canada1 7v booster [4]	3p + b18 3p + b15	1 month post completion: 19 vs.16m	NR	NR	1 month post completion: 19 vs.16m	NR
Comparison R Catch up vs. catch up	Ghana toddlers 9v	2 doses PCV (2 months apart) 1 dose PCV + PPV (2 months apart)	1 month post completion	NR	NR	1 month post completion	NR
	UK4 9v	12, 14 12	1 month post completion: 15 vs.13m	1 month post completion: 15 vs.13m	1 month post completion: 15 vs.13m	1 month post completion: 15 vs.13m	NR

Comparison	Study	Schedules, months	Age at which samples taken[1], months	Age at which 0.35µg/ml available, months	Age at which 0.20µg/ml available, months	Age at which GMC available, months	Age at which OPA available, months
Comparison S	UK4 9v	12, 14 + b18(PPV)	19	NR	NR	19	NR
2 + PPV vs.		12 + b18(PPV)					
1 + PPV							
Comparison T	Chile 10v	2, 4, 6, + b>18	1 month post completion:	NR	1 month post completion:	1 month post completion:	1 month post completion:
Primary (+/- booster) vs. catch-up		2 catch-up >18	>19		>19	>19	>19

Legend:

Shaded grey rows are those reported in main text;

1 Time point at which blood samples taken for assessment;

2 Samples taken before booster dose so comparison of primary schedule also possible;

3 At 7 months of age, 2 intervention groups have received 3 primary doses of PCV. GMCs are reported separately for each 3p group and were not combined for this analysis

4 Canada1 7v primary and Canada1 7v booster include the same children, but individuals were randomized for a second time after the primary course. Each intervention group for the booster study therefore contain individuals who receives 2, 4, 6m and 3, 5, 7m primary schedules. Results after the booster dose are not reported in a way which allows examination of the original intervention groups. These 2 phases of the study are therefore reported separately, and never both occur in the same analysis.

b – booster; p – primary schedule; NR – not reported; OPA- opsonophagocytic activity; PPV – pneumococcal polysaccharide vaccine; v – valent

Table 3.4: Reporting of methodological features of RCTs reporting immunological outcomes, alphabetical order

Study, vaccine (manufacturer)	Intended interval between doses in primary series	Intended interval from last dose PCV/PPV to blood sampling[1]	Adequate randomization sequence generation	Adequate randomization allocation concealment	Blinding of outcome assessors	Intention to treat or per protocol analyses[2]
Canada1 7v primary [10] [3]	2m	Same in all groups	Unclear, 'randomized'	Unclear, 'randomized'	"With evaluator blinding"	ITT
Canada1 7v booster [11] [3]	2m	Same in all groups	Unclear, 'randomized'	Unclear, 'randomized'	"evaluator-blinded"	NR
Chile 10v [12]	2m	Same in all groups	Unclear, 'randomized'	Unclear, 'randomized'	NR	PP
Europe 10v [13]	2p: 2m 3p: 1m	Same in all groups	Unclear, 'randomized'	Unclear, 'randomized'	NR	PP
Fiji 7v [14]	2p: 2m 3p: 1m	Same in all groups	Yes	Unclear (opaque envelopes but not clear if envelope linked to child before opening)	Laboratory staff blinded	NR
Finland 10v [15]	1m	Same in all groups	Unclear, 'randomized'	Unclear, 'randomized'	NR	PP
Gambia 7v [16]	1m	Differs by either 1 or 2 months between groups, until PPV booster	Unclear, 'consecutively randomized'	Unclear, 'consecutively randomized'	NR	ITT
Ghana infants (sickle-cell) 9v [18]	1m	Possible to compare same in all groups, or with differences in intervals of up to 8.5m (after booster)	Yes	Unclear (envelopes used but not clear if envelope linked to child before opening)	NR	NR
Ghana toddlers (sickle-cell) 9v [18]	NA	Same in all groups	Yes	Unclear (envelopes used but not clear if envelope linked to child before opening)	NR	NR
Iceland 9v [20]	2p: 2m 3p: 1m	Same in all groups	Unclear, 'randomized'	Unclear, 'randomized'	NR	PP
Israel 7v [21]	2m	Possible to compare same in all groups, or with differences in intervals of up to 6m (after booster)	Yes	Unclear (opaque envelopes but not clear if envelope linked to child before opening)	NR	NR
UK1 7v [22]	1m	Differs by 3m	Yes	Unclear, not well described	NR	ITT
UK2 infants 9v [23]	2m	Same in all groups	Unclear, 'randomized'	Unclear, 'randomized'	NR	NR
UK3 infants 9v [23]	1m	Same in all groups	Unclear, 'randomized'	Unclear, 'randomized'	NR	NR

UK4 toddlers 9v [23]	NA	Same in all groups	Unclear, 'randomized'	Unclear, 'randomized'	NR	NR
USA3 7v [24]	Approx 2m	Same in all groups	Not fully randomized, "10% randomness and the center as minimization factor"	Unclear, internet randomization (not clear if child data entered prior to allocation being given)	Laboratory staff blinded	PP

Germany 7v not included in table as no data analyzed in this review

1 Where intended interval is categorized as 'same', this applies to all time points. Where one group receives booster PCV and another not, this is listed as 'same' if time between last primary dose and sampling is the same in each group.

2 As reported by authors of included articles.

3 Canada1 7v primary and Canada1 7v booster include the same children, but individuals were randomized for a second time after the primary course. Each intervention group for the booster study therefore contain individuals who receives 2, 4, 6m and 3, 5, 7m primary schedules. Results after the booster dose are not reported in a way which allows examination of the original intervention groups. These 2 phases of the study are therefore reported separately, and never both occur in the same analysis.

ITT – intention to treat; NA – not applicable; NR – not reported; PP – per protocol

Table 3.5: Comparison A (2p vs. 1p) Geometric mean antibody concentrations at ~6, ~9 , ~12 and ~17 months, by serotype.

Age	Serotype	Study	GMC, µg/ml (95% CI		Studies in meta-analysis, N	Combined ratio of GMCs from meta-analysis (95% CI)	I^2, %
			2p	1p			
6 months	4	Fiji 7v	5.23 (4.46, 6.13)	2.20 (1.80, 2.70)	2	5.58 (1.01, 30.81)	96.7
		Gambia 7v	2.04 (1.54, 2.70)	0.15 (0.09, 0.24)			
	6B	Fiji 7v	0.86 (0.70, 1.07)	0.19 (0.16, 0.22)	1*	4.53 (3.47, 5.90)	NA
		Gambia 7v	0.05 (0.03, 0.08)	0.00 (0.00, 0.01)			
	9V	Fiji 7v	4.71 (3.88, 5.71)	0.90 (0.74, 1.09)	2	12.10 (2.22, 65.82)	95.6
		Gambia 7v	0.59 (0.41, 0.84)	0.02 (0.01, 0.03)			
	14	Fiji 7v	3.12 (2.42, 4.03)	1.07 (0.89, 1.27)	2	4.05 (1.89, 8.70)	75
		Gambia 7v	1.03 (0.64, 1.65)	0.16 (0.09, 0.26)			
	18C	Fiji 7v	2.67 (2.16, 3.31)	0.58 (0.45, 0.74)	2	14.09 (1.54, 128.76)	98
		Gambia 7v	0.44 (0.30, 0.66)	0.01 (0.01, 0.02)			
	19F	Fiji 7v	7.99 (6.62, 9.64)	0.84 (0.70, 1.00)	2	10.04 (7.95, 12.68)	0
		Gambia 7v	2.16 (1.56, 2.99)	0.17 (0.11, 0.26)			
	23F	Fiji 7v	1.65 (1.29, 2.11)	0.23 (0.20, 0.27)	1*	7.17 (5.38, 9.57)	NA
		Gambia 7v	0.07 (0.04, 0.11)	0.00 (0.00, 0.00)			
9 months	4	Fiji 7v	0.86 (0.67, 1.12)	0.60 (0.42, 0.85)	1	1.43 (0.93, 2.22)	NA
	6B	Fiji 7v	0.81 (0.59, 1.12)	0.39 (0.29, 0.52)	1	2.08 (1.35, 3.20)	NA
	9V	Fiji 7v	0.72 (1.38, 0.56)	0.56 (0.40, 0.77)	1	1.79 (1.14, 2.79)	NA
	14	Fiji 7v	1.93 (1.20, 3.09)	1.11 (0.79, 1.57)	1	1.74 (0.97, 3.12)	NA
	18C	Fiji 7v	0.41 (0.33, 0.53)	0.18 (0.14, 0.24)	1	2.28 (1.59, 3.26)	NA
	19F	Fiji 7v	1.40 (1.05, 1.86)	0.89 (0.61, 1.29)	1	1.57 (0.98, 2.52)	NA
	23F	Fiji 7v	0.44 (0.33, 0.60)	0.24 (0.18, 0.32)	1	1.83 (1.21, 2.78)	NA
12	4	Fiji 7v	0.47 (0.40, 0.54)	0.63 (0.50, 0.81)	1	0.75 (0.56, 0.99)	NA
months	6B	Fiji 7v	0.76 (0.63, 0.92)	0.57 (0.46, 0.71)	1	1.33 (1.00, 1.78)	NA
	9V	Fiji 7v	0.62 (0.54, 0.71)	0.50 (0.41, 0.62)	1	1.24 (0.97, 1.59)	NA
	14	Fiji 7v	1.52 (1.26, 1.84)	1.16 (0.94, 1.44)	1	1.31 (0.99, 1.74)	NA
	18C	Fiji 7v	0.24 (0.21, 0.28)	0.17 (0.15, 0.20)	1	1.41 (1.15, 1.73)	NA
	19F	Fiji 7v	1.14 (0.95, 1.36)	0.93 (0.76, 1.15)	1	1.23 (0.93, 1.61)	NA
	23F	Fiji 7v	0.42 (0.35, 0.50)	0.26 (0.21, 0.31)	1	1.62 (1.24, 2.10)	NA
17	4	Fiji 7v	0.43 (0.33, 0.56)	0.56 (0.39, 0.80)	1	0.77 (0.49, 1.20)	NA
months	6B	Fiji 7v	0.78 (0.58, 1.04)	0.62 (0.47, 0.83)	1	1.26 (0.84, 1.89)	NA
	9V	Fiji 7v	0.49 (0.39, 0.62)	0.51 (0.36, 0.71)	1	0.96 (0.64, 1.45)	NA
	14	Fiji 7v	1.12 (0.86, 1.46)	0.93 (0.66, 1.32)	1	1.20 (0.78, 1.86)	NA
	18C	Fiji 7v	0.20 (0.16, 0.25)	0.15 (0.12, 0.19)	1	1.33 (0.97, 1.84)	NA
	19F	Fiji 7v	1.06 (0.82, 1.38)	0.92 (0.66, 1.26)	1	1.15 (0.76, 1.74)	NA
	23F	Fiji 7v	0.43 (0.32, 0.58)	0.32 (0.22, 0.48)	1	1.34 (0.82, 2.19)	NA

Legend:

I^2 value is the level of statistical heterogeneity between trials (<25% low heterogeneity); NA – not applicable

* Gambia 7v data not included in meta-analysis as zero value in 1 or more groups

Table 3.6: Comparison B (3p vs. 1p). Geometric mean antibody concentrations at ~6, ~9 , ~12 and ~17 months, by serotype

Age	Serotype	Study	GMC, µg/ml (95% CI		Studies in meta-analysis, N	Combined ratio of GMCs from meta-analysis (95% CI)	I^2, %
			3p	1p			
6 months	4	Fiji 7v	5.47 (4.84, 6.19)	2.20 (1.80, 2.70)	2	8.21 (0.77, 87.28)	98.6
		Gambia 7v	4.16 (3.61, 4.79)	0.15 (0.09, 0.24)			
	6B	Fiji 7v	1.66 (1.33, 2.07)	0.19 (0.16, 0.22)	1*	8.74 (6.65, 11.47)	NA
		Gambia 7v	3.47 (2.41, 4.98)	0.00 (0.00, 0.01)			
	9V	Fiji 7v	4.76 (4.19, 5.40)	0.90 (0.74, 1.09)	2	21.32 (1.35, 337.16)	98.6
		Gambia 7v	1.77 (1.36, 2.29)	0.02 (0.01, 0.03)			
	14	Fiji 7v	5.51 (4.50, 6.76)	1.07 (0.89, 1.27)	2	11.92 (2.19, 64.93)	95.7
		Gambia 7v	4.65 (3.21, 6.72)	0.16 (0.09, 0.26)			
	18C	Fiji 7v	3.20 (2.66, 3.86)	0.58 (0.45, 0.74)	2	33.18 (0.98, 1124.99)	99.4
		Gambia 7v	2.01 (1.53, 2.63)	0.01 (0.01, 0.02)			
	19F	Fiji 7v	5.52 (4.79, 6.36)	0.84 (0.70, 1.00)	2	12.98 (3.29, 51.25)	95.7
		Gambia 7v	4.54 (3.37, 6.10)	0.17 (0.11, 0.26)			
	23F	Fiji 7v	2.93 (2.39, 3.59)	0.23 (0.20, 0.27)	1*	12.74 (9.89, 16.40)	NA
		Gambia 7v	1.50 (1.04, 2.18)	0.00 (0.00, 0.00)			
9 months	4	Fiji 7v	0.79 (0.55, 1.14)	0.60 (0.42, 0.85)	1	1.32 (0.79, 2.19)	NA
	6B	Fiji 7v	0.82 (0.58, 1.17)	0.39 (0.29, 0.52)	1	2.10 (1.33, 3.32)	NA
	9V	Fiji 7v	0.91 (0.71, 1.16)	0.56 (0.40, 0.77)	1	1.63 (1.08, 2.45)	NA
	14	Fiji 7v	3.99 (2.86, 5.57)	1.11 (0.79, 1.57)	1	3.59 (2.23, 5.80)	NA
	18C	Fiji 7v	0.49 (0.37, 0.65)	0.18 (0.14, 0.24)	1	2.72 (1.84, 4.02)	NA
	19F	Fiji 7v	1.04 (0.70, 1.54)	0.89 (0.61, 1.29)	1	1.17 (0.68, 2.01)	NA
	23F	Fiji 7v	0.65 (0.46, 0.94)	0.24 (0.18, 0.32)	1	2.71 (1.71, 4.28)	NA
12	4	Fiji 7v	0.48 (0.41, 0.57)	0.63 (0.50, 0.81)	1	0.76 (0.57, 1.02)	NA
months	6B	Fiji 7v	0.86 (0.72, 1.03)	0.57 (0.46, 0.71)	1	1.51 (1.14, 2.00)	NA
	9V	Fiji 7v	0.59 (0.51, 0.67)	0.50 (0.41, 0.62)	1	1.18 (0.92, 1.51)	NA
	14	Fiji 7v	2.38 (1.98, 2.86)	1.16 (0.94, 1.44)	1	2.05 (1.55, 2.72)	NA
	18C	Fiji 7v	0.32 (0.27, 0.38)	0.17 (0.15, 0.20)	1	1.88 (1.51, 2.35)	NA
	19F	Fiji 7v	1.05 (0.83, 1.34)	0.93 (0.76, 1.15)	1	1.13 (0.82, 1.55)	NA
	23F	Fiji 7v	0.54 (0.44, 0.66)	0.26 (0.21, 0.31)	1	2.08 (1.57, 2.75)	NA
17	4	Fiji 7v	0.35 (0.29, 0.43)	0.56 (0.39, 0.80)	1	0.63 (0.41, 0.94)	NA
months	6B	Fiji 7v	0.91 (0.69, 1.21)	0.62 (0.47, 0.83)	1	1.47 (0.98, 2.19)	NA
	9V	Fiji 7v	0.41 (0.34, 0.49)	0.51 (0.36, 0.71)	1	0.80 (0.55, 1.18)	NA
	14	Fiji 7v	1.78 (1.42, 2.24)	0.93 (0.66, 1.32)	1	1.91 (1.26, 2.90)	NA
	18C	Fiji 7v	0.21 (0.18, 0.26)	0.15 (0.12, 0.19)	1	1.40 (1.04, 1.88)	NA
	19F	Fiji 7v	1.19 (0.84, 1.67)	0.92 (0.66, 1.26)	1	1.29 (0.81, 2.07)	NA
	23F	Fiji 7v	0.57 (0.43, 0.75)	0.32 (0.22, 0.48)	1	1.78 (1.10, 2.88)	NA

Legend:

I^2 value is the level of statistical heterogeneity between trials (<25% low heterogeneity); NA – not applicable;

* Gambia 7v data not included in meta-analysis as zero value in 1 or more groups.

Table 3.7: Comparison C (3p vs. 2p). Geometric mean antibody concentrations at at ~6, ~9 , ~12 and ~17 months, by serotype, study, and time point

Age	Serotype	Study	GMC, µg/ml (95% CI		Studies in meta-analysis, N*	Combined ratio of GMCs from meta-analysis (95% CI)	I^2, %
			3p	2p			
6 months	1	Iceland 9v	3.34 (2.93, 3.80)	3.62 (3.13, 4.19)	2	1.05 (0.82, 1.35)	70.1
		Europe 10v	1.23 (1.07, 1.42)	1.03 (0.90, 1.18)			
	4	Fiji 7v	5.47 (4.84, 6.19)	5.23 (4.46, 6.13)	4	1.32 (1.06, 1.65)	75.7
		Gambia 7v	4.16 (3.61, 4.79)	2.04 (1.54, 2.70)			
		Iceland 9v	2.97 (2.62, 3.38)	2.34 (2.01, 2.74)			
		Europe 10v	1.71 (1.47, 1.99)	1.37 (1.21, 1.55)			
	5	Iceland 9v	1.52 (1.33, 1.74)	1.20 (1.02, 1.41)	2	1.34 (1.16, 1.54)	0
		Europe 10v	1.85 (1.63, 2.10)	1.32 (1.14, 1.52)			
	6B	Fiji 7v	1.66 (1.33, 2.07)	0.86 (0.70, 1.07)	4	4.83 (1.45, 16.14)	97.6
		Gambia 7v	3.47 (2.41, 4.98)	0.05 (0.03, 0.08)			
		Iceland 9v	1.94 (1.48, 2.53)	0.69 (0.52, 0.90)			
		Europe 10v	0.31 (0.25, 0.38)	0.19 (0.15, 0.24)			
	7F	Europe 10v	2.14 (1.90, 2.40)	1.28 (1.13, 1.46)	1	1.67 (1.41, 1.99)	NA
	9V	Fiji 7v	4.76 (4.19, 5.40)	4.71 (3.88, 5.71)	4	1.47 (1.04, 2.07)	87.5
		Gambia 7v	1.77 (1.36, 2.29)	0.59 (0.41, 0.84)			
		Iceland 9v	1.99 (1.74, 2.27)	1.73 (1.47, 2.02)			
		Europe 10v	1.47 (1.29, 1.68)	0.92 (0.81, 1.05)			
	14	Fiji 7v	5.51 (4.50, 6.76)	3.12 (2.42, 4.03)	4	1.87 (1.34, 2.61)	75.3
		Gambia 7v	4.65 (3.21, 6.72)	1.03 (0.64, 1.65)			
		Iceland 9v	6.95 (5.82, 8.29)	4.69 (3.66, 6.02)			
		Europe 10v	2.57 (2.22, 2.97)	1.72 (1.45, 2.05)			
	18C	Fiji 7v	3.20 (2.66, 3.86)	2.67 (2.16, 3.31)	4	2.00 (1.16, 3.47)	93.8
		Gambia 7v	2.01 (1.53, 2.63)	0.44 (0.30, 0.66)			
		Iceland 9v	1.83 (1.60, 2.09)	1.52 (1.33, 1.75)			
		Europe 10v	3.42 (2.87, 4.07)	1.26 (1.06, 1.51)			
	19F	Fiji 7v	5.52 (4.79, 6.36)	7.99 (6.62, 9.64)	4	1.34 (0.82, 2.20)	91.6
		Gambia 7v	4.54 (3.37, 6.10)	2.16 (1.56, 2.99)			
		Iceland 9v	4.19 (3.62, 4.84)	3.20 (2.65, 3.87)			
		Europe 10v	4.43 (3.60, 5.45)	2.43 (1.97, 2.98)			
	23F	Fiji 7v	2.93 (2.39, 3.59)	1.65 (1.29, 2.11)	4	3.03 (1.31, 6.99)	95.1
		Gambia 7v	1.50 (1.04, 2.18)	0.07 (0.04, 0.11)			
		Iceland 9v	1.77 (1.36, 2.31)	0.91 (0.72, 1.14)			
		Europe 10v	0.52 (0.42, 0.63)	0.38 (0.30, 0.47)			

9 months	4	Fiji 7v	0.79 (0.55, 1.14)	0.86 (0.67, 1.12)	1	0.92 (0.59, 1.43)	NA
	6B	Fiji 7v	0.82 (0.58, 1.17)	0.81 (0.59, 1.12)	1	1.01 (0.63, 1.63)	NA
	9V	Fiji 7v	0.91 (0.71, 1.16)	1.00 (0.72, 1.38)	1	0.91 (0.62, 1.34)	NA
	14	Fiji 7v	3.99 (2.86, 5.57)	1.93 (1.20, 3.09)	1	2.07 (1.16, 3.69)	NA
	18C	Fiji 7v	0.49 (0.37, 0.65)	0.41 (0.33, 0.53)	1	1.20 (0.83, 1.73)	NA
	19F	Fiji 7v	1.04 (0.70, 1.54)	1.40 (1.05, 1.86)	1	0.74 (0.46, 1.21)	NA
	23F	Fiji 7v	0.65 (0.46, 0.94)	0.44 (0.33, 0.60)	1	1.48 (0.93, 2.35)	NA
12	1	Europe 10v	0.30 (0.26, 0.34)	0.21 (0.19, 0.24)	1	1.43 (1.20, 1.71)	NA
months	4	Fiji 7v	0.48 (0.41, 0.57)	0.47 (0.40, 0.54)	2	1.28 (0.83, 1.99)	88.9
		Europe 10v	0.64 (0.56, 0.73)	0.40 (0.35, 0.46)			
	5	Europe 10v	0.59 (0.51, 0.68)	0.43 (0.37, 0.50)	1	1.37 (1.11, 1.69)	NA
	6B	Fiji 7v	0.86 (0.72, 1.03)	0.76 (0.63, 0.92)	2	1.32 (0.96, 1.83)	63
		Europe 10v	0.44 (0.36, 0.54)	0.28 (0.23, 0.35)			
	7F	Europe 10v	0.92 (0.81, 1.05)	0.55 (0.49, 0.63)	1	1.67 (1.40, 2.00)	NA
	9V	Fiji 7v	0.59 (0.51, 0.67)	0.62 (0.54, 0.71)	2	1.26 (0.73, 2.20)	94.2
		Europe 10v	0.87 (0.77, 0.99)	0.52 (0.46, 0.60)			
	14	Fiji 7v	2.38 (1.98, 2.86)	1.52 (1.26, 1.84)	2	1.76 (1.40, 2.23)	35.8
		Europe 10v	1.53 (1.27, 1.85)	0.77 (0.64, 0.93)			
	18C	Fiji 7v	0.32 (0.27, 0.38)	0.24 (0.21, 0.28)	2	1.60 (1.11, 2.30)	80.2
		Europe 10v	1.14 (0.96, 1.35)	0.59 (0.50, 0.69)			
	19F	Fiji 7v	1.05 (0.83, 1.34)	1.14 (0.95, 1.36)	2	1.23 (0.70, 2.16)	87.6
		Europe 10v	1.70 (1.41, 2.04)	1.04 (0.87, 1.25)			
	23F	Fiji 7v	0.54 (0.44, 0.66)	0.42 (0.35, 0.50)	2	1.33 (1.09, 1.62)	0
		Europe 10v	0.44 (0.36, 0.54)	0.32 (0.26, 0.40)			
17	4	Fiji 7v	0.35 (0.29, 0.43)	0.43 (0.33, 0.56)	1	0.81 (0.59, 1.13)	NA
months	6B	Fiji 7v	0.91 (0.69, 1.21)	0.78 (0.58, 1.04)	1	1.17 (0.78, 1.75)	NA
	9V	Fiji 7v	0.41 (0.34, 0.49)	0.49 (0.39, 0.62)	1	0.84 (0.62, 1.12)	NA
	14	Fiji 7v	1.78 (1.42, 2.24)	1.12 (0.86, 1.46)	1	1.59 (1.12, 2.25)	NA
	18C	Fiji 7v	0.21 (0.18, 0.26)	0.20 (0.16, 0.25)	1	1.05 (0.79, 1.40)	NA
	19F	Fiji 7v	1.19 (0.84, 1.67)	1.06 (0.82, 1.38)	1	1.12 (0.73, 1.73)	NA
	23F	Fiji 7v	0.57 (0.43, 0.75)	0.43 (0.32, 0.58)	1	1.33 (0.88, 1.99)	NA

Legend:

I^2 value is the level of statistical heterogeneity between trials (<25% low heterogeneity); NA – not applicable;

* Israel 7v data not included in this analysis; prior to booster there are 2 groups that received a 3p schedule and GMC data cannot be combined.

Table 3.8: Comparison G (3p vs. 2p + 1). Geometric mean antibody concentrations and seropositivity at 13 and 19 months, by serotype

Age	Serotype	Study	GMC, µg/ml (95% CI		Studies in meta-analysis, N	Combined ratio of GMCs from meta-analysis (95% CI)	I^2, %
			3p	2p+1			
13	4	Israel 7v	0.32 (0.28, 0.37)	4.78 (4.60, 5.50)	1	0.07 (0.06, 0.08)	NA
months	6B	Israel 7v	0.80 (0.65, 0.99)	6.93 (5.36, 8.95)	1	0.12 (0.08, 0.16)	NA
	9V	Israel 7v	0.48 (0.43, 0.54)	3.45 (3.05, 3.91)	1	0.14 (0.12, 0.16)	NA
	14	Israel 7v	1.37 (1.11, 1.69)	12.16 (10.39, 14.22)	1	0.11 (0.09, 0.15)	NA
	18C	Israel 7v	0.32 (0.28, 0.36)	2.80 (2.45, 3.20)	1	0.11 (0.10, 0.14)	NA
	19F	Israel 7v	0.55 (0.44, 0.67)	4.90 (4.08, 5.88)	1	0.11 (0.08, 0.15)	NA
	23F	Israel 7v	0.40 (0.33, 0.48)	3.87 (3.32, 4.52)	1	0.10 (0.08, 0.13)	NA
19	4	Israel 7v	0.14 (0.12, 0.17)	0.48 (0.40, 0.56)	1	0.29 (0.23, 0.37)	NA
months	6B	Israel 7v	0.76 (0.63, 0.93)	1.46 (1.22, 1.76)	1	0.52 (0.40, 0.68)	NA
	9V	Israel 7v	0.35 (0.30, 0.40)	0.55 (0.49, 0.62)	1	0.64 (0.53, 0.77)	NA
	14	Israel 7v	0.90 (0.71, 1.15)	2.00 (1.71, 2.35)	1	0.45 (0.34, 0.60)	NA
	18C	Israel 7v	0.20 (0.17, 0.23)	0.38 (0.33, 0.44)	1	0.53 (0.43, 0.65)	NA
	19F	Israel 7v	0.63 (0.49, 0.82)	1.45 (1.12, 1.87)	1	0.43 (0.30, 0.62)	NA
	23F	Israel 7v	0.29 (0.24, 0.34)	0.65 (0.55, 0.78)	1	0.45 (0.35, 0.57)	NA

Legend:

I^2 value is the level of statistical heterogeneity between trials (<25% low heterogeneity); NA – not applicable.

Table 3.9: Comparison L (3p+1 vs. 2p+1). Geometric mean antibody concentrations at 1 and 7 month after booster dose, by serotype

Age	Serotype	Study	GMC, µg/ml (95% CI		Studies in meta-analysis, N	Combined ratio of GMCs from meta-analysis (95% CI)	I^2, %
			3p+1	2p+1			
1 month	1	Iceland 9v	4.48 (3.48, 5.78)	4.48 (3.56, 5.65)	2	1.01 (0.85, 1.21)	0
after		Europe 10v	1.88 (1.62, 2.17)	1.85 (1.59, 2.15)			
booster	4	Israel 7v	3.98 (3.40, 4.67)	4.78 (4.60, 5.50)	3	1.00 (0.80, 1.25)	66.1
dose		Iceland 9v	4.30 (3.43, 5.40)	3.87 (3.04, 4.92)			
		Europe 10v	3.47 (3.03, 3.98)	3.06 (2.68, 3.49)			
	5	Iceland 9v	3.18 (2.60, 3.90)	3.28 (2.65, 4.04)	2	1.12 (0.90, 1.38)	36.1
		Europe 10v	3.21 (2.81, 3.67)	2.65 (2.31, 3.03)			
	6B	Israel 7v	10.99 (8.78, 13.77)	6.93 (5.36, 8.95)	3	1.60 (1.30, 1.98)	0
		Iceland 9v	14.01 (9.41, 20.86)	9.42 (6.34, 14.00)			
		Europe 10v	1.85 (1.54, 2.22)	1.12 (0.88, 1.41)			
	7F	Europe 10v	3.88 (3.45, 4.37)	2.81 (2.51, 3.15)	1	1.38 (1.17, 1.63)	NA
	9V	Israel 7v	3.49 (3.03, 4.01)	3.45 (3.05, 3.91)	3	1.14 (0.94, 1.39)	59
		Iceland 9v	2.55 (2.06, 3.16)	2.39 (1.94, 2.95)			
		Europe 10v	3.97 (3.49, 4.50)	2.95 (2.59, 3.37)			
	14	Israel 7v	12.92 (10.96, 15.22)	12.16 (10.39, 14.22)	3	1.18 (1.02, 1.36)	0
		Iceland 9v	10.15 (8.20, 12.55)	8.75 (6.37, 12.02)			
		Europe 10v	5.47 (4.68, 6.40)	4.19 (3.62, 4.85)			
	18C	Israel 7v	3.70 (3.17, 4.30)	2.80 (2.45, 3.20)	3	1.26 (1.10, 1.44)	0
		Iceland 9v	2.37 (1.92, 2.92)	1.79 (1.43, 2.24)			
		Europe 10v	7.20 (6.08, 8.52)	6.24 (5.43, 7.18)			
	19F	Israel 7v	4.07 (3.37, 4.91)	4.90 (4.08, 5.88)	3	1.10 (0.82, 1.47)	68.3
		Iceland 9v	4.48 (3.38, 5.93)	3.38 (2.98, 4.93)			
		Europe 10v	6.95 (5.92, 8.17)	5.58 (4.65, 6.69)			
	23F	Israel 7v	5.64 (4.72, 6.72)	3.87 (3.32, 4.52)	3	1.34 (1.14, 1.59)	0.6
		Iceland 9v	4.42 (3.23, 6.06)	2.83 (1.90, 4.23)			
		Europe 10v	2.78 (2.31, 3.35)	2.41 (1.98, 2.94)			
7 months	4	Israel 7v	0.42 (0.35, 0.50)	0.48 (0.40, 0.56)	1	0.88 (0.68, 1.12)	NA
after	6B	Israel 7v	1.97 (1.65, 2.36)	1.46 (1.22, 1.76)	1	1.35 (1.04, 1.74)	NA
booster	9V	Israel 7v	0.67 (0.58, 0.77)	0.55 (0.49, 0.62)	1	1.22 (1.01, 1.46)	NA
dose	14	Israel 7v	2.38 (2.00, 2.83)	2.00 (1.71, 2.35)	1	1.19 (0.94, 1.51)	NA
	18C	Israel 7v	0.49 (0.42, 0.57)	0.38 (0.33, 0.44)	1	1.29 (1.05, 1.59)	NA
	19F	Israel 7v	1.00 (0.80, 1.25)	1.45 (1.12, 1.87)	1	0.69 (0.49, 0.97)	NA
	23F	Israel 7v	0.88 (0.73, 1.06)	0.65 (0.55, 0.78)	1	1.35 (1.05, 1.75)	NA

Legend:

I^2 value is the level of statistical heterogeneity between trials (<25% low heterogeneity); NA – not applicable.

Table 3.10: Comparison L (3p+1 vs. 3p). Geometric mean antibody concentrations at 13 and 19 months of age, by serotype

Age	Serotype	Study	GMC, µg/ml (95% CI)		Studies in meta-analysis, N	Combined ratio of GMCs from meta-analysis (95% CI)	I^2, %
			3p+1	3p			
13 months	1	Ghana infants 9v	4.98 (1.63, 15.20)	0.69 (0.32, 1.50)	1	7.22 (1.86, 28.05)	NA
	4	Israel 7v	3.98 (3.40, 4.67)	0.32 (0.28, 0.37)	2	12.70 (10.32, 15.62)	0
		Ghana infants 9v	8.61 (4.59, 16.17)	0.40 (0.17, 0.96)			
	5	Ghana infants 9v	4.64 (1.32, 16.31)	0.86 (0.36, 2.03)	1	5.40 (1.17, 24.81)	NA
	6B	Israel 7v	10.99 (8.78, 13.77)	0.80 (0.65, 0.99)	2	13.32 (9.86, 18.00)	0
		Ghana infants 9v	9.23 (2.83, 30.03)	1.35 (0.60, 3.06)			
	9V	Israel 7v	3.49 (3.03, 4.01)	0.48 (0.43, 0.54)	2	7.25 (6.06, 8.67)	0
		Ghana infants 9v	3.51 (1.23, 10.06)	0.57 (0.23, 1.39)			
	14	Israel 7v	12.92 (10.96, 15.22)	1.37 (1.11, 1.69)	2	8.10 (4.24, 15.48)	30.2
		Ghana infants 9v	8.15 (2.14, 31.12)	2.06 (1.38, 3.07)			
	18C	Israel 7v	3.70 (3.17, 4.30)	0.32 (0.28, 0.36)	2	11.50 (9.45, 13.98)	0
		Ghana infants 9v	5.17 (1.73, 15.48)	0.61 (0.24, 1.60)			
	19F	Israel 7v	4.07 (3.37, 4.91)	0.55 (0.44, 0.67)	2	7.35 (5.56, 9.74)	0
		Ghana infants 9v	1.91 (0.23, 15.86)	0.43 (0.10, 1.75)			
	23F	Israel 7v	5.64 (4.72, 6.72)	0.40 (0.33, 0.48)	2	14.13 (10.95, 18.22)	0
		Ghana infants 9v	6.56 (2.78, 15.49)	0.43 (0.10, 1.75)			
19	4	Israel 7v	0.42 (0.35, 0.50)	0.14 (0.12, 0.17)	1	3.00 (2.34, 3.85)	NA
months	6B	Israel 7v	1.97 (1.65, 2.36)	0.76 (0.63, 0.93)	1	2.59 (1.99, 3.38)	NA
	9V	Israel 7v	0.67 (0.58, 0.77)	0.35 (0.30, 0.40)	1	1.91 (1.56, 2.34)	NA
	14	Israel 7v	2.38 (2.00, 2.83)	0.90 (0.71, 1.15)	1	2.64 (1.96, 3.56)	NA
	18C	Israel 7v	0.49 (0.42, 0.57)	0.20 (0.17, 0.23)	1	2.45 (1.98, 3.04)	NA
	19F	Israel 7v	1.00 (0.80, 1.25)	0.63 (0.49, 0.82)	1	1.59 (1.13, 2.23)	NA
	23F	Israel 7v	0.88 (0.73, 1.06)	0.29 (0.24, 0.34)	1	3.03 (2.35, 3.92)	NA

Legend:

I^2 value is the level of statistical heterogeneity between trials (<25% low heterogeneity); NA – not applicable.

Table 3.11: Comparison O (Later vs. earlier age at start of primary schedule). Geometric mean antibody concentrations after vaccination, by serotype

Age	Serotype	Study	GMC, µg/ml (95% CI		Studies in meta-analysis, N	Combined ratio of GMCs from meta-analysis (95% CI)	I^2, %
			Late start	Early start			
1 month post-	4	Canada1 7v, primary	3.51 (3.06, 4.02)	3.84 (3.33, 4.42)	1	0.91 (0.75, 1.11)	NA
PCV	6B	Canada1 7v, primary	5.39 (4.25, 6.85)	3.35 (2.56, 4.40)	1	1.61 (1.12, 2.31)	NA
	9V	Canada1 7v, primary	2.02 (1.75, 2.33)	2.07 (1.76, 2.43)	1	0.98 (0.79, 1.21)	NA
	14	Canada1 7v, primary	5.84 (4.92, 6.94)	6.37 (5.26, 7.71)	1	0.92 (0.71, 1.19)	NA
	18C	Canada1 7v, primary	3.75 (3.22, 4.36)	3.01 (2.50, 3.64)	1	1.25 (0.98, 1.59)	NA
	19F	Canada1 7v, primary	3.52 (2.95, 4.21)	3.30 (2.78, 3.92)	1	1.07 (0.83, 1.37)	NA
	23F	Canada1 7v, primary	2.50 (2.01, 3.11)	1.83 (1.48, 2.27)	1	1.37 (1.01, 1.85)	NA
7 months	4	USA3 7v	1.62 (1.44, 1.83)	2.07 (1.81, 2.37)	1	0.78 (0.65, 0.94)	NA
of age	6B	USA3 7v	0.59 (0.49, 0.72)	0.67 (0.52, 0.87)	1	0.88 (0.64, 1.21)	NA
	9V	USA3 7v	1.11 (0.97, 1.28)	1.60 (1.39, 1.85)	1	0.69 (0.57, 0.85)	NA
	14	USA3 7v	4.51 (3.91, 5.19)	6.32 (5.39, 7.41)	1	0.71 (0.58, 0.88)	NA
	18C	USA3 7v	2.37 (2.06, 2.72)	2.96 (2.53, 3.47)	1	0.80 (0.65, 0.99)	NA
	19F	USA3 7v	0.75 (0.66, 0.86)	1.05 (0.91, 1.22)	1	0.71 (0.59, 0.87)	NA
	23F	USA3 7v	1.29 (1.09, 1.53)	1.81 (1.45, 2.25)	1	0.71 (0.54, 0.94)	NA
13	4	UK1 7v*	0.70 (0.60, 0.88)	0.27 (0.23, 0.31)	1	2.59 (2.03, 3.31)	NA
Months	6B	UK1 7v*	1.53 (1.27, 1.84)	0.96 (0.78, 1.24)	1	1.59 (1.18, 2.14)	NA
of age	9V	UK1 7v*	0.66 (0.57, 0.77)	0.33 (0.28, 0.39)	1	2.00 (1.60, 2.50)	NA
	14	UK1 7v*	2.68 (2.29, 3.13)	1.02 (0.79, 1.31)	1	2.63 (1.95, 3.54)	NA
	18C	UK1 7v*	0.66 (0.56, 0.78)	0.29 (0.24, 0.34)	1	2.28 (1.79, 2.89)	NA
	19F	UK1 7v*	0.90 (0.72, 1.12)	0.63 (0.48, 0.82)	1	1.43 (1.01, 2.02)	NA
	23F	UK1 7v*	0.54 (0.44, 0.68)	0.27 (0.22, 0.34)	1	2.00 (1.47, 2.72)	NA

Legend:

I^2 value is the level of statistical heterogeneity between trials (<25% low heterogeneity); NA – not applicable;

*Data in UK1 7v tables of low resolution. Small errors possible in extraction.

Table 3.12: Comparison Q (Longer vs. shorter interval between primary and booster). Geometric mean antibody concentrations 1 month after booster dose, by serotype

Serotype	Study	GMC, µg/ml (95% CI		Studies in meta-analysis, N	Combined ratio of GMCs from meta-analysis (95% CI)	I^2, %
		Longer interval	Shorter interval			
1	Finland 10v	1.24 (1.04, 1.49)	1.11 (0.96, 1.28)	1	1.12 (0.89, 1.41)	NA
4	Canada1 7v, booster	5.39 (4.62, 6.30)	4.42 (3.77, 5.18)	2	1.21 (1.04, 1.41)	0
	Finland 10v	2.54 (2.16, 2.98)	2.11 (1.83, 2.42)			
5	Finland 10v	1.93 (1.61, 2.32)	1.61 (1.36, 1.89)	1	1.20 (0.94, 1.53)	NA
6B	Canada1 7v, booster	12.26 (10.17, 14.79)	11.10 (9.16, 13.45)	2	1.12 (0.92, 1.37)	0
	Finland 10v	1.63 (1.31, 2.01)	1.42 (1.17, 1.73)			
7F	Finland 10v	2.93 (2.55, 3.36)	2.94 (2.62, 3.30)	1	1.00 (0.83, 1.19)	NA
9V	Canada1 7v, booster	3.49 (3.04, 4.01)	3.16 (2.78, 3.60)	2	1.11 (0.96, 1.28)	0
	Finland 10v	2.60 (2.21, 3.06)	2.33 (2.05, 2.65)			
14	Canada1 7v, booster	11.12 (9.67, 12.79)	11.22 (9.89, 12.74)	2	1.00 (0.86, 1.16)	0
	Finland 10v	4.19 (3.50, 5.01)	4.18 (3.53, 4.97)			
18C	Canada1 7v, booster	2.33 (2.00, 2.72)	2.28 (1.97, 2.63)	2	0.82 (0.54, 1.26)	87.6
	Finland 10v	2.74 (2.30, 3.26)	4.14 (3.66, 4.68)			
19F	Canada1 7v, booster	5.04 (4.36, 5.82)	4.38 (3.79, 5.08)	2	1.06 (0.86, 1.30)	30.7
	Finland 10v	3.94 (3.33, 4.67)	4.23 (3.40, 5.27)			
23F	Canada1 7v, booster	5.74 (4.81, 6.85)	4.81 (3.95, 5.86)	2	1.31 (1.08, 1.58)	0
	Finland 10v	2.41 (2.03, 2.85)	1.68 (1.36, 2.08)			

Legend:

I^2 value is the level of statistical heterogeneity between trials (<25% low heterogeneity); NA – not applicable.

Annex 3.2
Description of RCTs comparing PCV schedules and reporting immunological outcomes

Study details	Participant characteristics	Schedule A / schedule B / schedule C	Schedule A population characteristics	Schedule B population characteristics	Schedule C population characteristics	Immunological outcomes assessed GMC ✓ ; Seropositivity ◊ ; OPA ●										
						1	4	5	6A	6B	7F	9V	14	18C	19A	19F	23F
Canada1 7v primary [1, 2]																	
Location: Canada **Recruitment dates:** In 2002 **Vaccine used:** 7v PCV; Prevnar **Funding:** Wyeth **Assay used:** "Standardized ELISA" assays.	**Inclusion criteria:** Healthy infants at 2 months of age, informed consent. **Exclusion criteria:** children with severe chronic disease; impairment of the immune system; bleeding disorder or prior blood component infusion; prior pneumococcal infection; or hypersensitivity to any component of trial vaccines; infants born to women with hepatitis B.	**A:** 3, 5, 7 m **B:** 2, 4, 6 m **C:** 2, 4, 6 m **Additional information:** Group A: At 2, 4, 6 m DTaP-IPV/Hib + Hepatitis B given in different thighs. Groups B & C: DTaP-IPV/Hib + Hepatitis B given at the same time in the opposite thigh to PCV.	**N**=124 **Mean age at randomization:** NR **Mean age at first study dose:** 67.1 days **Gender (M/F):** 74/50 **Blood sample strategy:** 1 month after last dose i.e. 8m.	**N**=126 **Mean age at randomization:** NR **Mean age at first study dose:** 67.1 days **Gender (M/F):** 80/46 **Blood sample strategy:** 1 month after last dose i.e.7m.	**N**= 126 **Mean age at randomization:** NR **Mean age at first study dose:** 66.8 days **Gender (M/F):** 69/57 **Blood sample strategy:** 2 months after last dose i.e. 8m.		✓ ◊			✓ ◊		✓ ◊	✓ ◊	✓ ◊		✓ ◊	✓ ◊
Canada1 7v booster [1, 2, 16]																	
Location: Canada **Recruitment dates:** In 2003 **Vaccine used:** 7v PCV; Prevnar **Funding:** Wyeth **Assay used:** "published ELISA methods".	**Inclusion criteria:** completed a study of 3-dose primary PCV schedule; with a final blood sample obtained at 7-8 months age. Subjects in good health. **Exclusion criteria:** see Canada1 7v primary.	**A:** (2, 4, 6 or 3, 5, 7) + b18m **B:** (2, 4, 6 or 3, 5, 7) + b15m **Additional information:** DTaP-IPV/Hib also given at 15 or 18m. It is unclear which patients from the primary immunization got the different schedule, as they were not reported separately.	**N**=167 **Mean age at randomization:** NR **Mean age at first study dose:** 555 ± 8d **Gender (M/F):** 98/69 **Blood sample strategy:** 1 month after the booster immunization.	**N**= 168 **Mean age at randomization:** NR **Mean age at first study dose:** 465 ± 8d **Gender (M/F):** 100/68 **Blood sample strategy:** 1 month after the booster immunization.		✓ ◊			✓ ◊		✓ ◊	✓ ◊	✓ ◊		✓ ◊	✓ ◊

Study details	Participant characteristics	Schedule A / schedule B / schedule C	Schedule A population characteristics	Schedule B population characteristics	Schedule C population characteristics	Immunological outcomes assessed GMC ✓ ; Seropositivity ◊ ; OPA •											
						1	4	5	6A	6B	7F	9V	14	18C	19A	19F	23F
Chile 10v [3, 17-21]																	
Location: Chile **Recruitment dates:** Aug 2007-Mar 2008 **Vaccine used:** 10v PCV; Synflorix **Funding:** GSK **Assay used:** not reported.	**Inclusion criteria:** Healthy infants aged 8-16 weeks; informed consent; free of obvious health problems. **Exclusion criteria:** investigational or non-registered drug or non-study vaccine use; history of diseases covered by study vaccines immune deficiency.	**A:** 2, 4, 6 + b>18m **B:** 2 "catch up" at >18m **Additional information:** Group A: HAV co-administered with DTaP-HBV-IPV/Hib followed by PCV . Group B: PCV co-administered with DTaP-HBV-IPV/Hib followed by HAV. (Also had HAV at 2, 4, 6m). DTaP-HBV-IPV/Hib at 2,4,6m, HAV at 12m for all.	**N**= 84 **Mean age at randomization:** 18.3 ± 0.44m **Mean age at first study dose:** NR **Gender (M/F):** 45/39 **Blood sample strategy:** 1m after booster vaccination.	**N**= 79 **Mean age at randomization:** 18.3 ± 0.50m **Mean age at first study dose:** NR **Gender (M/F):** 35/44 **Blood sample strategy:** 1m after booster vaccination.		✓ ◊ •	✓ ◊ •	✓ ◊ •	✓ ◊ •	✓ ◊ •	✓ ◊ •	✓ ◊ •	✓ ◊ •	✓ ◊ •	✓ ◊ •	✓ ◊ •	✓ ◊ •
Europe 10v [4, 20, 22-24]																	
Location: Denmark; Norway; Slovakia; Sweden **Recruitment dates:** Jan 2006-Jan 2007 **Vaccine used:** 10v PCV; Synflorix **Funding:** GSK **Assay used:** Using "22F-ELISA" [25].	**Inclusion criteria:** Healthy infants aged 8-16w; informed consent; free of obvious health problems; gestation 36-42w. **Exclusion criteria:** investigational or non-registered drug or non-study vaccine use; previous pneumococcal vaccine; history of diseases covered by study vaccines immune deficiency.	**A:** 2,3,4 + b11m **B:** 2,4 + b11m **Additional information:** DTaP-HepB-IPV/Hib or DTaP-IPV/Hib at 2, 3, 4 m according to country.	**N**= 176 **Mean age at randomization:** NR **Mean age at first study dose:** 12.1 ± 1.90 w **Gender (M/F):** 91/85 **Blood sample strategy:** 5, 11, 12m	**N**= 175 **Mean age at randomization:** NR **Mean age at first study dose:** 12.0 ± 1.91w **Gender (M/F):** 89/86 **Blood sample strategy:** 5, 11, 12m		✓ ◊ •	✓ ◊ •	✓ ◊ •		✓ ◊ •	✓ ◊ •	✓ ◊ •	✓ ◊ •	✓ ◊ •			✓ ◊ •	✓ ◊ •

Study details	Participant characteristics	Schedule A / schedule B / schedule C	Schedule A population characteristics	Schedule B population characteristics	Schedule C population characteristics	Immunological outcomes assessed GMC ✓ ; Seropositivity ◊ ; OPA •											
						1	4	5	6A	6B	7F	9V	14	18C	19A	19F	23F
Fiji 7v [5, 26-31] and pre-publication manuscript																	
Location: Fiji **Recruitment dates:** not reported **Vaccine used:** 7v PCV; Prevnar **Funding:** NIAID + NHMRC; other vaccines donated by GSK and CSL Biotherapies; unclear if vaccine donated by Wyeth **Assay used:** "Modified WHO ELISA method" against reference serum 89SF [32].	**Inclusion criteria:** Healthy infants aged 6-8w; no significant maternal or perinatal disease history, residing in health centre area; family anticipated lived in study area for 2 years. **Exclusion criteria:** allergy to vaccine components; allergic reaction to previous vaccine; HIV positive mother; immuno-deficiency; thrombocytopenia or coagulation disorder; immunosuppressive drugs; received blood product since birth; any diseases.	**A:** 1.5, 2.5, 3.5 m **B:** 1.5, 3.5 m **C:** 3.5 m **Additional information:** DTwP, HepB Hib + OPV given at 1.5, 2.5, 3.5 months; MMR at 12 months, PPV to half children in each group at 12m.	**N**= 136 **Median age at randomization:** 6.7w **Mean age at first study dose:** NR **Gender (M/F):** 71/65 **Blood sample strategy:** 18w, 9m ,12m, 17m	**N**= 156 **Median age at randomization:** 6.4w **Mean age at first study dose:** NR **Gender (M/F):** 70/86 **Blood sample strategy:** 18w, 9m ,12m, 17m	**N**= 128 **Median age at randomization:** 6.5w **Mean age at first study dose:** NR **Gender (M/F):** 59/69 **Blood sample strategy:** 18w, 9m ,12m, 17m		✓ ◊ •			✓ ◊ •		✓ ◊ •	✓ ◊ •	✓ ◊ •		✓ ◊	✓ ◊ •
Finland 10v [6, 20, 33, 34]																	
Location: Finland **Recruitment dates:** Oct 2006-Dec 2007 **Vaccine used:** 10v PCV; Synflorix **Funding:** GSK **Assay used:** not reported.	**Inclusion criteria:** healthy; 12-14m at time of first vaccine; received ≥1 dose 10val PCV in study; informed consent. **Exclusion criteria:** investigational or non-registered drug or non-study vaccine use; any extra PCV after primary study; immune-suppressed; exposure to or infection with vaccine diseases history of neurological disease.	**A:** (2, 3, 4) + b14-16m **B:** (2, 3, 4) + b12-14m **Additional information:** Group A: PCV co-administered with MMRV at 12-14m, MMRV and at 14-16 m DTaP-HepB-IPV/Hib. Group B: MMRV co-administered with DTaP-HepB-IPV/Hib at 12-14m, and PCV + MMRV at 14-16m Group C: Not analyzed.	**N**= 101 **Mean age at randomization:** 12.3 ± 0.50 m **Mean age at first study dose:** NR **Gender (M/F):** 49/52 **Blood sample strategy:** 1m after 3rd primary vaccination, 42-56d after booster.	**N**= 110 **Mean age at randomization:** 12.3 ± 0.48 m **Mean age at first study dose:** NR **Gender (M/F):** 61/49 **Blood sample strategy:** 1m after 3rd primary vaccination, 42-56d after booster.		✓ ◊	✓ ◊	✓ ◊		✓ ◊	✓ ◊	✓ ◊	✓ ◊	✓ ◊		✓ ◊	✓ ◊

Study details	Participant characteristics	Schedule A / schedule B / schedule C	Schedule A population characteristics	Schedule B population characteristics	Schedule C population characteristics	Immunological outcomes assessed GMC ✓ ; Seropositivity ◊ ; OPA •											
						1	4	5	6A	6B	7F	9V	14	18C	19A	19F	23F
Gambia 7v [7, 35] and pre-publication manuscript																	
Location: Gambia **Recruitment dates:** NR **Vaccine used:** 7v PCV; Prevnar **Funding:** WHO (funding); MRC sponsor **Assay used:** "adapted WHO ELISA method" [36].	**Inclusion criteria:** Infants presenting for first routine DTP/Hib vaccination; informed consent. **Exclusion criteria:** Known HIV infected mother ; neurological abnormality; no consent; established pneumococcal disease .	**A:** 2, 3, 4 m **B:** 2, 3 m **C:** 2 m **Additional information:** Routine EPI vaccinations including DTP, Hib, OPV and HepB given at 2, 3, 4m; PPV booster given at 10m.	**N**= 227 **Mean age at randomization:** NR **Mean age at first study dose:** NR **Gender (M/F):** 107/120 **Blood sample strategy:** 18w, 11, 15 m	**N**= 228 **Mean age at randomization:** NR **Mean age at first study dose:** NR **Gender (M/F):** 105/123 **Blood sample strategy:** 18w, 11, 15 m	**N**= 228 **Mean age at randomization:** NR **Mean age at first study dose:** NR **Gender (M/F):** 113/115 **Blood sample strategy:** 18w, 11, 15 m		✓ ◊ •			✓ ◊ •		✓ ◊ •	✓ ◊ •	✓ ◊ •		✓ ◊ •	✓ ◊ •
Germany 7v [8]																	
Location: Germany **Recruitment dates:** Not reported **Vaccine used:** 7v PCV; Prevnar **Funding:** Wyeth Pharma GmbH **Assay used:** "Standard ELISA methods" [37, 38].	**Inclusion criteria:** Healthy infants aged 2m, informed consent **Exclusion criteria:** diphtheria; tetanus; pertussis; invasive Hib or pneumococcal disease; prior immunization against these diseases; allergic reactions against vaccine components; BW<2000g; impairment immune system; neurological disease or chronic disorders.	**A:** 6, 7, 8 + b11-15m **B:** 2, 3, 4 + b11-15m **Additional information:** DTaP-IPV-Hib at 2, 3, 4, 11-15m.	**N**= 113 **Mean age at randomization:** NR by group, range 57-112d for all groups **Mean age at first study dose:** NR **Gender (M/F):** NR **Blood sample strategy:** 1 m after last primary dose, at booster and 1m after.	**N**= 118 **Mean age at randomization:** NR by group, range 57-112d for all groups. **Mean age at first study dose:** NR **Gender (M/F):** NR **Blood sample strategy:** 1 m after last primary dose, at booster and 1m after.			✓			✓		✓	✓	✓		✓	✓

Study details	Participant characteristics	Schedule A / schedule B / schedule C	Schedule A population characteristics	Schedule B population characteristics	Schedule C population characteristics	Immunological outcomes assessed GMC ✓ ; Seropositivity ◊ ; OPA •											
						1	4	5	6A	6B	7F	9V	14	18C	19A	19F	23F
Ghana infants 9v [9] and pre-publication manuscript																	
Location: Ghana **Recruitment dates:** 1997-2000 **Vaccine used:** 9v PCV (Wyeth) **Funding:** United Kingdom Department for International Development **Assay used:** "ELISA ..based on an original assay described by Quataert".	**Inclusion criteria:** Infants with sickle-cell disease **Exclusion criteria:** an acute febrile illness; under-nutrition (weight for age,<80%); a severe chronic illness; a congenital malformation or defect; non-resident in the Kumasi metropolis, fever of >38°C.	**A:** 1.5, 2.5, 3.5 + b12 **B:** 1.5, 2.5, 3.5 + PPV(12) **C:** 1.5, 2.5, 3.5 + Hib **Additional information:** All groups received PCV co-administered with their EPI vaccines.	**N**= 21 **Mean age at randomization:** 2.2m (all groups) **Mean age at first study dose:** 2.6m **Gender (M/F):** 14/7 **Blood sample strategy:** 1m after last primary dose, before and after boosting.	**N**= 21 **Mean age at randomization:** 2.2m (all groups) **Mean age at first study dose:** 2.4m **Gender (M/F):** **13**/8 **Blood sample strategy:** 1m after last primary dose, before and after boosting.	**N**= 20 **Mean age at randomization:** 2.2m (all groups) **Mean age at first study dose:** 2.4m **Gender (M/F):** 11/9 **Blood sample strategy:** 1m after last primary dose, before and after boosting.	✓	✓	✓		✓		✓	✓	✓		✓	✓
Ghana toddlers 9v [10] and pre-publication manuscript																	
Location: Ghana **Recruitment dates:** 1997-2000 **Vaccine used:** 9v PCV (Wyeth) **Funding:** United Kingdom Department for International Development **Assay used:** "ELISA ...based on an original assay described by Quataert".	**Inclusion criteria:** Toddlers with sickle-cell disease **Exclusion criteria:** an acute febrile illness; undernutrition (weight for age,<80%); a severe chronic illness; a congenital malformation or defect; non-resident in the Kumasi metropolis, fever of >38°C.	**A:** 2 doses 2m apart **B:** 1 dose and PPV 2 m apart **C:** 1 dose PPV **Additional information:**	**N**= 46 **Mean age at randomization:** 13.7m (all groups) **Mean age at first study dose:** 14.9m **Gender (M/F):** **17**/29 **Blood sample strategy:** 1m after each vaccination.	**N**= 46 **Mean age at randomization:** 13.7m (all groups) **Mean age at first study dose:** 14.9m **Gender (M/F):** 24/22 **Blood sample strategy:** 1m after each vaccination.	**N**= 46 **Mean age at randomization:** 13.7m (all groups) **Mean age at first study dose:** 14.7m **Gender (M/F):** **20**/26 **Blood sample strategy:** 1m after each vaccination.	✓	✓	✓		✓		✓	✓	✓		✓	✓

Study details	Participant characteristics	Schedule A / schedule B / schedule C	Schedule A population characteristics	Schedule B population characteristics	Schedule C population characteristics	Immunological outcomes assessed GMC ✓ ; Seropositivity ◊ ; OPA •											
						1	4	5	6A	6B	7F	9V	14	18C	19A	19F	23F
Iceland 9v [11, 39] [40]																	
Location: Iceland **Recruitment dates:** not reported **Vaccine used:** 9vPnC-MnCC (Wyeth) **Funding:** Wyeth **Assay used:** ELISA using cell wall polysaccharide neutralization but not serotype 22-F pre-adsorption. [37, 41, 42].	**Inclusion criteria:** healthy term infants **Exclusion criteria:** NR	**A:** 3,4,5 + b12m (PCV/PPV) **B:** 3, 5 + b12m (PCV/PPV) **Additional information:** Children boosted with either PCV or PPV. PPV boosted children also got MnCC booster (CRM197). DTaP-IPV/Hib at 3, 5, 12m for all infants.	**N**= 111 **Mean age at randomization:** NR **Mean age at first study dose:** NR **Gender (M/F):** NR **Blood sample strategy:** 3, 6, 12, 13m and 12.25m in a subgroup.	**N**= 112 **Mean age at randomization:** NR **Mean age at first study dose:** NR **Gender (M/F):** NR **Blood sample strategy:** 3, 6, 12, 13m and 12.25m in a subgroup.		✓ ◊	✓ ◊	✓ ◊		✓ ◊		✓ ◊	✓ ◊	✓ ◊		✓ ◊	✓ ◊
Israel 7v [12, 43-50]																	
Location: Israel **Recruitment dates:** Aug 2005-Mar 2008 **Vaccine used:** 7v PCV; Prevnar **Funding:** Wyeth **Assay used:** ELISA after double absorption with C- and serotype 22F polysaccharide as in Quataert et al.1995 [37], 2004 [51], Concepcion and Frasch 2001 [25].	**Inclusion criteria:** Healthy infants , 2m ± 3w; informed consent **Exclusion criteria:** Born at <35w; acute disease; metabolic disorder or congenital abnormality of clinical importance; previous serious reaction to a vaccine; HIV infected; fever >38.0 ˚C.	**A:** 2,4,6 + b12m **B:** 2,4,6 **C:** 4,6 + b12m **Additional information:** DTaP-IPV/Hib at 2, 4, 6, 12m; MMR at 12m.	**N**= 178 **Mean age at randomization:** NR **Mean age at first study dose:** 2.1 ± 0.2m **Gender (M/F):** 93/85 **Blood sample strategy:** 7, 13m	**N**= 178 **Mean age at randomization:** NR **Mean age at first study dose:** 2.1 ± 0.2m **Gender (M/F):** 93/85 **Blood sample strategy:** 7, 13m	**N**= 189 **Mean age at randomization:** NR **Mean age at first study dose:** 3.9 ± 0.3m **Gender (M/F):** 88/101 **Blood sample strategy:** 7, 13m		✓ ◊			✓ ◊		✓ ◊	✓ ◊	✓ ◊		✓ ◊	✓ ◊
UK1 7v [13, 52, 53]																	

Study details	Participant characteristics	Schedule A / schedule B / schedule C	Schedule A population characteristics	Schedule B population characteristics	Schedule C population characteristics	Immunological outcomes assessed GMC ✓ ; Seropositivity ◊ ; OPA •											
						1	4	5	6A	6B	7F	9V	14	18C	19A	19F	23F
Location: UK **Recruitment dates:** 1997 to 1998 **Vaccine used:** 7v PCV**;** Prevnar **Funding:** Wyeth **Assay used:** "Standard ELISA" against reference serum 89SF [37].	**Inclusion criteria:** Health infants aged 6-10w; informed consent. **Exclusion criteria:** birth weight <2000g; any severe or chronic illness.	**A:** 5, 6, 7 + b13 m **B:** 2, 3, 4 + b13 m **C:** 2, 3, 4 + b13 m **Additional information:** Group B received PCV in separate syringes from DTwP/Hib. Group C received PCV combined in syringes with Hib and separate with DTwP. All groups received DTwP, Hib and OPV at 2,4,6m, MMR and PPV at 13-16m.	**N**= 120 **Mean age at randomization:** NR **Mean age at first study dose:** NR **Gender (M/F):** NR **Blood sample strategy:** 2,5,13,14 m	**N**= 124 **Mean age at randomization:** NR **Mean age at first study dose:** NR **Gender (M/F):** NR **Blood sample strategy:** 2,5,13,14 m	**N**= 124 **Mean age at randomization:** NR **Mean age at first study dose:** NR **Gender (M/F):** NR **Blood sample strategy:** 2,5,13,14 m		✓			✓		✓	✓	✓		✓	✓
UK2 9v [14, 54]																	
Location: UK **Recruitment dates:** Jan 2000-Oct 2001 **Vaccine used:** 9v PCV (Wyeth) **Funding:** Health Protection Agency, Wyeth provided PCV vaccine **Assay used:** ELISA after adsorption with cell wall and 22F polysaccharides as in Wernette et al. 2003 [25] and WHO protocol [55].	**Inclusion criteria:** Healthy infants aged 7-11 w; informed consent. **Exclusion criteria:** Previous confirmed pneumococcal or meningococcal disease; systemic disease or fever; contraindications for vaccination; in other trial; language problems; immuno-compromised.	**A:** 2,4 + b12m **B:** 2,4 + b12m (PPV) **Additional information:** DTaP-Hib; OPV and Men C at 2, 3, 4 m. 1 dose MMR given to some toddlers (not clear if 100%).	**N**= unclear (88 randomized to 1 of the 2 groups) **Mean age at randomization:** 2.0 m **Mean age at first study dose:** NR **Gender (M/F):** NR **Blood sample strategy:** 1m after last primary dose, at booster and 1m after.	**N**= unclear (88 randomized to 1 of the 2 groups) **Mean age at randomization:** 2.0 m **Mean age at first study dose:** NR **Gender (M/F):** NR **Blood sample strategy:** 1m after last primary dose, at booster and 1m after.		✓ ◊	✓ ◊	✓ ◊		✓ ◊		✓ ◊	✓ ◊	✓ ◊		✓ ◊	✓ ◊
UK3 9v [14, 54]																	

Study details	Participant characteristics	Schedule A / schedule B / schedule C	Schedule A population characteristics	Schedule B population characteristics	Schedule C population characteristics	Immunological outcomes assessed GMC ✓ ; Seropositivity ◊ ; OPA •											
						1	4	5	6A	6B	7F	9V	14	18C	19A	19F	23F
Location: UK **Recruitment dates:** Sep 2001-Jan 2003 **Vaccine used:** 9v PCV (Wyeth) **Funding:** Health Protection Agency, Wyeth provided PCV vaccine **Assay used:** See UK2 9v.	**Inclusion criteria:** See above **Exclusion criteria:** See UK2 9v.	**A:** 2,3,4 + b12m **B:** 2,3,4 + b12m (PPV) **Additional information:** See UK2 9v.	**N**= unclear (84 randomized to 1 of the 2 groups) **Mean age at randomization:** 2.0 m **Mean age at first study dose:** NR **Gender (M/F):** NR **Blood sample strategy:** 1m after last primary dose, at booster, and 1m after.	**N**= unclear (84 randomized to 1 of the 2 groups) **Mean age at randomization:** 2.0 m **Mean age at first study dose:** NR **Gender (M/F):** NR **Blood sample strategy:** 1m after last primary dose, at booster, and 1m after.		✓ ◊	✓ ◊	✓ ◊		✓ ◊		✓ ◊	✓ ◊	✓ ◊		✓ ◊	✓ ◊
UK4 9v [14, 54]																	
Location: UK **Recruitment dates:** Jan 2000-Oct 2001 **Vaccine used:** 9v PCV (Wyeth) **Funding:** Health Protection Agency, Wyeth provided PCV vaccine **Assay used:** See UK2 9v.	**Inclusion criteria:** Healthy toddlers aged 12-18m; informed consent. **Exclusion criteria:** See UK2 9v.	**A:** 12, 14 + b18m (PPV) **B:** 12 + b18m (PPV) **Additional information:** See UK2 9v.	**N**= 45 **Mean age at randomization:** 12.4 m **Mean age at first study dose:** NR **Gender (M/F):** NR **Blood sample strategy:** 1m after 14m dose, at booster, and 1m after.	**N**= 47 **Mean age at randomization:** 12.4 m **Mean age at first study dose:** NR **Gender (M/F):** NR **Blood sample strategy:** 1m after 12m dose, at booster, and 1m after.		✓ ◊	✓ ◊	✓ ◊		✓ ◊		✓ ◊	✓ ◊	✓ ◊		✓ ◊	✓ ◊
USA3 7v [15]																	

Study details	Participant characteristics	Schedule A / schedule B / schedule C	Schedule A population characteristics	Schedule B population characteristics	Schedule C population characteristics	Immunological outcomes assessed GMC ✓ ; Seropositivity ◊ ; OPA ●											
						1	4	5	6A	6B	7F	9V	14	18C	19A	19F	23F
Location: USA **Recruitment dates:** not reported **Vaccine used:** 7v PCV; Prevnar **Funding:** GSK **Assay used:** "standardized ELISA" performed in a blinded fashion at GSK with (unnamed) reference serum.	**Inclusion criteria:** Healthy infants 6-12 weeks at time of first vaccination; informed consent. **Exclusion criteria:** Born at <36w; immune dysfunction; use of immune modifying or immunosuppressive drugs; chronic disease, history of vaccine hypersensitivity.	**A**: 2-3.5, 4.5, 6.5m **B:** 1.5-3, 4, 6m (separate) **C:** 1.5-3, 4, 6m (combination) **Additional information:** Group A: DTaP-Hep-B-IPV + Hib + 7v PCV Group B: DTaP; HepB; IPV; Hib; 7v PCV Group C: DTaP-HepB-IPV + Hib then 7v PCV 0.5 months later.	**N**= 188 **Mean age at randomization:** NR **Mean age at first study dose:** Median 9 weeks for all infants **Gender (M/F):** NR **Blood sample strategy:** 1m after last DTaP vaccination.	**N**= 188 **Mean age at randomization:** NR **Mean age at first study dose:** Median 9 weeks for all infants **Gender (M/F):** NR **Blood sample strategy:** 1m after last DTaP vaccination.	**N**= 199 **Mean age at randomization:** NR **Mean age at first study dose:** Median 9 weeks for all infants **Gender (M/F):** NR **Blood sample strategy:** 1m after last DTaP vaccination.		✓ ◊			✓ ◊		✓ ◊	✓ ◊	✓ ◊		✓ ◊	✓ ◊

DTP - diphtheria, tetanus and pertussis vaccine; DTaP- diphtheria, tetanus and acellular pertussis vaccine; DTwP- diphtheria, tetanus and whole-cell pertussis vaccine; EPI - Expanded Program on Immunization; HAV - hepatitis A vaccine; HepB - hepatitis B vaccine; Hib - Haemophilus influenae vaccine; IPV - inactivated polio vaccine; MenC - meningococcal group C vaccine; MMR - measles mumps rublella vaccine; OPV- oral polio vaccine; PCV - pneumococcal conjugate vaccine; PPV - pneumococcal polysaccharide vaccine.

References

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Annex 4.1: Tables

Table 4.1: Summary of included cohort studies, alphabetical order

Study name and PCV valency	Country	Schedules, age at dose in months		Number of participants	Outcomes reported		
		Intended	Actual age at administration (median)		Clinical	Carriage	Immunogenicity
Finland obs 7v [1]	Finland	2, 4, 6 + b15	Not reported	30	-	-	SP, GMC
		2, 4, 6 + b15(PPV)		29			
Finland obs 10v [2]	Finland	3, 4, 5 +b12-15	Not reported	150	Adverse events[1] Mortality	-	SP, GMC, OPA
		7, 11, b12-15		150			
		12, 23		150			
		> 24 (1 dose)		150			
Germany obs 7v [3]	Germany	2, 3, 4 + b12–15	3.1, 4.3, 5.7, 14.6 (both groups)	5609	IPD Pneumonia Otitis media Mortality	-	-
		no PCV and no PPV		1802			
International obs 7v [4]	Poland/Philippines	2, 4, 6, + b12-18	1.9, 3.8, 5.3[2]	103	Adverse events[1] Mortality	-	SP, GMC, OPA
		1.5, 2.5, 3.5 + b12-18	1.8, 2.9, 4.1[2]	100			
International obs 10v [4]	Poland/Philippines	2, 4, 6 + b12-18	1.9, 3.8, 5.3[2]	303	Adverse events[1] Mortality	-	SP, GMC, OPA
		1.5, 2.5, 3.5 + b12-18	1.8, 2.9, 4.1[2]	300			
Italy obs 7v [5]	Italy	3, 5, + b11	2.7, 4.6, 11.3	819	IPD Pneumonia Otitis media	-	-
		no PCV and no PPV	NA	752			
Korea obs 7v [6]	Korea	3p+1 (schedule not reported)	Not reported	200	-	Carriage	-
		no PCV and no PPV		200			
Norway obs 7v [7]	Norway	1 dose (>24m) or 2 doses (12-24m)	Not reported	56	-	Carriage	-
		no PCV and no PPV		38			
Spain1 obs 7v [8]	Spain	2p or 3p + b12-15[3]	Not reported	1	-	Carriage	-
		12, 14[3]		52			
		24[3]		2			
		no PCV and no PPV		60			
UK1 obs 7v [9]	UK	2, 3, 4 + b13(PPV)	Not reported	267	-	Carriage	-
		no PCV and no PPV		~300			
UK2 obs 7v[4] [10]	UK	Schedule not reported	Not reported	61	IPD	-	-
		PPV or no PPV		191			
UK3 obs 7v[5] [11]	UK	2,4 + b12	2.0, 4.1	239	-	-	SP, GMC, OPA
		2,3 + b12	2.0, 3.1	154			
UK obs 9v [12]	UK	2, 3, 4 + b12	Not reported	≥ 36	-	-	SP, GMC
		2, 4 + b12		≥ 39			
		2, 3, 4 + b12(PPV)		≥ 46			
		2, 4 + b12(PPV)		≥ 39			

Study name and PCV valency	Country	Schedules, age at dose in months		Number of participants	Outcomes reported		
		Intended	Actual age at administration (median)		Clinical	Carriage	Immunogenicity
USA1 obs 7v[4] [13]	USA	2, 4, 6[6]	2.1, 4.0, 5.5[2]	11	-	-	SP, GMC
		2, 4, 6, + b24(PPV)[6]	2.3, 3.9, 5.7, 24.8[2]	34			
		12[6]	13.4[2]	3			
		12, 24(PPV)[6]	12.3, 24.2[2]	13			
USA obs 7/13V [14]	USA	≥3 doses PCV7 + 2 doses PCV13 >55d apart (15m-24m)	13v doses: 18.0, 20.0[2]	126	-	-	SP, GMC
		≥3 doses PCV7 + 1 dose PCV13 (24m-5y)	13v dose: 3.1y[2]	181			

Legend:

b – booster; GMC – geometric mean concentration (ELISA); IPD - invasive pneumococcal disease; NA - not applicable; obs – denotes an observational study; OPA – opsonophagocytic activity; PCV – pneumococcal conjugate vaccine; PPV – pneumococcal polysaccharide vaccine; SP - seropositivity (ELISA); 3p – 3 dose primary schedule, etc.; +1 – booster dose; ~ approximate number;

1 Adverse events reported include clinical outcomes which are eligible for this review. However, data were not specifically collected for these outcomes, and no case definitions were applied. These data were therefore not considered to reflect the effect of vaccine and are not analyzed as such in this review

2 Means

3 Schedule might commence later but with same number of doses and same intervals in primary schedule, PPV also given in some/all groups (unclear)

4 Some or all participants had sickle cell disease

5 Randomized controlled trial where randomization pattern was amended during trial. Separate data from before and after protocol amendment not currently available, so included classed as observational. Boosters given at 12 or 13 months but post-booster data not currently available.

6 Groups with PPV contain on children with sickle cell disease, those groups without PPV contain only children without sickle cell disease

Table excludes 1 study which reports only outcomes in adults [15], and 2 studies which report carriage only as the percentage of samples and not of children [16, 17]

Table 4.2: Summary of included case-control studies, alphabetical order

Study name	Country	Comparisons	Number of participants		Outcome
			Cases	controls	
Spain2 obs 7v [18]	Spain	1 or more doses vs. 0 "Complete" vaccination[1] vs. 0 "Incomplete" vaccination[1] vs. 0	85	425	IPD
USA2 obs 7v [19]	USA	**Infant schedules examined in case-control study:** no PCV; 2 doses ≤ 7m; 3 doses ≤ 7m; 2 doses ≤ 7m, 1 dose 12-16m 1 dose ≤ 7m: ♦ - - - 2 doses ≤ 7m: ♦ - ♦ ♦ 3 doses ≤ 7m: ♦ ♦ - ♦ 2 doses ≤ 7m, 1 dose 12-16m: ♦ ♦ ♦ - 1 dose ≤ 7m, 1 dose 8-11m, 1 dose 12-16m: ♦ - - - 3 doses ≤ 7m, 1 dose 12-16m: ♦ ♦ ♦ ♦ 1 dose 7-11m, 2 doses 12-16m: ♦ - - - **Toddler schedules**: 1 dose 12-23m: ♦ - - - 2 doses 12-23m: ♦ - - - 1 dose ≥ 24 m: ♦ - - -	782	2512	IPD

1 Complete vaccination defined as 3 doses if the first dose was given at 2-6 months, or 2 doses if the first dose occurred at 7-23 months, or 1 dose if the first dose occurred at 24 or more months
obs – denotes an observational study

♦ Case-control study reports a comparison of the schedules described in column and row
- Case-control study does not report the comparison of the schedules described in column and row

Table 4.3: Detailed description of included cohort studies

Study details	Participant characteristics	Schedule A / schedule B / schedule C	Schedule A population characteristics	Schedule B population characteristics	Schedule C population characteristics	Schedule D population characteristics	Assignment to schedule	Statistical analysis
Finland obs 7v	[1]							
Location: Finland **Recruitment dates:** NR **Vaccine used:** 7v PCV, Prevnar **Funding:** Wyeth-Lederle Pediatrics and Vaccines. **Assay used:** EIA, using pneumococcal C polysaccharide to neutralize anti-pneumococcal C polysaccharide antibodies	**Inclusion criteria:** NR **Exclusion criteria:** NR	**A:** 2, 4, 6 + b15 **B:** 2, 4, 6 + b15(PPV) **Additional information:** All subjects received DTP and Hib conjugate vaccine at 2, 4, 6 and 24 months, IPV at 7 and 12 months; and MMR at 16 months.	**N= 30** **Mean age at first study dose:** NR **Gender (M/F, %male):** NR **Blood sample strategy:** At each dose, 1 month after final primary dose, 1 month after booster and 9 months after booster.	**N= 29** **Mean age at first study dose:** NR **Gender (M/F, %male):** NR **Blood sample strategy:** At each dose, 1 month after final primary dose, 1 month after booster and 9 months after booster.			NR	**Method of analysis:** Log transformed and ANOVA used to compare antibody concentrations between groups. Proportions with detectable antibody compared using Yates-corrected chi square test or with Fisher's two tailed exact test. **Adjustment for potential confounders:** None **VE calculation:** None
Finland obs 10v	[2, 20]							
Location: Finland **Recruitment dates:** from Sept. 2006 **Vaccine used:** 10v PCV; Synflorix **Funding:** GSK **Assay used:** NR	**Inclusion criteria:** healthy male or female who, at the time for first vaccination, were 9-12w or 7-11mo, 12-23mo, ≥24mo **Exclusion criteria:** NR	**A:** 3, 4, 5 + b12-15 **B:** 7, 11, + b12-15 **C:** 12, 23 **D:** > 24 (1 dose) **Additional information:** Subjects in schedule A received co-administered DTaP-IPV/Hib	**N= 150** **Mean age at first study dose:** NR **Gender (M/F, %male):** 84/66 , 56.0% **Blood sample strategy:** 1 month after dose 3, before booster, 1 month post booster **Assessment of clinical outcomes:** NR	**N= 150** **Mean age at first study dose:** NR **Gender (M/F, %male):** 82/68, 54.7% **Blood sample strategy:** 1 month after dose 2, before dose 3, 1 month after dose 3 **Assessment of clinical outcomes:** NR	**N= 150** **Mean age at first study dose:** NR **Gender (M/F, %male):** 74/76, 49.3% **Blood sample strategy:** 1 month after dose 2 **Assessment of clinical outcomes:** NR	**N= 150** **Mean age at first study dose:** NR **Gender (M/F, %male):** 78/72, 52.0% **Blood sample strategy:** 1 month after the single dose **Assessment of clinical outcomes:** NR	Age at recruitment determined the group allocation	**Method of analysis:** Specific methods not reported **Adjustment for potential confounders:** None **VE calculation:** None
Germany obs 7v	[3]							

Study details	Participant characteristics	Schedule A / schedule B / schedule C	Schedule A population characteristics	Schedule B population characteristics	Schedule C population characteristics	Schedule D population characteristics	Assignment to schedule	Statistical analysis
Location: Germany **Recruitment dates:** Aug. 2001 - Dec. 2002 **Vaccine used: 7v** PCV; Prevnar **Funding:** Wyeth	**Inclusion criteria:** healthy infants 2-6 months of age who received standard vaccination with or without PCV. One control child selected after 3 included in vaccine group **Exclusion criteria:** Thrombocytopenia, coagulation disorders, moderate or severe fever, hypersensitivity to vaccine components	**A:** 2, 3, 4 + b12–15 **B:** no PCV and no PPV **Additional information:** DtaP-HBV-IPV/Hib or „other common routine childhood vaccine" given at 2, 3, 4, 12-15m in both groups Children with underlying condition were preferentially given PCV	**N= 5609** **Mean age at first study dose:** 3.1, 4.3, 5.7, 14.6 (both groups combined) **Gender (M/F, %male):** 2317/2171 , 51.7% **Assessment of clinical outcomes:** Unclear, possibly parental report with confirmation by treating physician. Follow up until 1 year after last PCV vaccination.	**N= 1802** **Mean age at first study dose:** 3.1, 4.3, 5.7, 14.6 (both groups combined) **Gender (M/F, %male):** 793/703 , 53.0% **Assessment of clinical outcomes:** Unclear, possibly parental report with confirmation by treating physician. Follow up until 1 year after last vaccination.			Parental choice. One child selected for schedule B after 3 included in schedule A	**Method of analysis:** Crude risks based on first event data, compared with Fisher's exact test. **Adjustment for potential confounders:** propensity score matched pair analysis. **VE calculation:** (1-Risk Ratio) x 100
International obs 7v **Location**: Poland/Philippines **Recruitment dates:** Aug. 2006- Apr. 2007 **Vaccine used:** 7v PCV; Prevenar **Funding:** GSK **Assay used:** 22F-inhibition ELISA	[4, 20-25] **Inclusion criteria:** Healthy infants 6-12w of age, gestation period 36-42w **Exclusion criteria:** Previous vaccination with antigens given in study (except for HBV within the first 2 weeks of life), history of diphtheria, tetanus, pertussis, hepatitis B, polio or Hib disease, history of seizure or neurologic disease, immunosuppressive therapy or disease, major congenital defects, serious chronic illness, receipt of immunoglobulins or blood products	**A:** 2, 4, 6 + b12-18 **B:**1.5, 2.5, 3.5 + b12-18 **Additional information:** DTwP-HBV/Hib given to each group with the same schedule as PCV. Schedule A received IPV, and schedule B received OPV with the same schedule as PCV	**N= 103** **Mean age at first study dose:** 1.9m **Gender (M/F, %male):** 57/46, 55.3% **Blood sample strategy:** 1 month after last primary dose, pre-booster, 1 month post-booster **Assessment of clinical outcomes:** Diary cards, other methods not reported. from first vaccination until 6m post-booster	**N=100** **Mean age at first study dose:** 1.8 **Gender (M/F, %male):** 52/48, 52.0% **Blood sample strategy:** 1 month after last primary dose, pre-booster, 1 month post-booster **Assessment of clinical outcomes:** Diary cards, other methods not reported. from first vaccination until 6m post-booster			Geographical location: Those in Poland received the 2, 4, 6m primary schedule and those in the Philippines received the 1.5, 2.5, 3.5m primary schedule	**Method of analysis:** Specific methods not reported **Adjustment for potential confounders:** None **VE calculation:** None
International obs 10v	[4, 20-25]							

Study details	Participant characteristics	Schedule A / schedule B / schedule C	Schedule A population characteristics	Schedule B population characteristics	Schedule C population characteristics	Schedule D population characteristics	Assignment to schedule	Statistical analysis
Location: Poland/Philippines **Recruitment dates:** Aug. 2006- Apr. 2007 **Vaccine used:** 10v PCV; Synflorix **Funding:** GSK **Assay used:** 22F-inhibition ELISA	**Inclusion criteria:** Healthy infants 6-12w of age, gestation period 36-42w **Exclusion criteria:** Previous vaccination with antigens given in study (except for HBV within the first 2 weeks of life), history of diphtheria, tetanus, pertussis, hepatitis B, polio or Hib disease, history of seizure or neurologic disease, immunosuppressive therapy or disease, major congenital defects, serious chronic illness, receipt of immunoglobulins or blood products	**A:** 2, 4, 6 + b12-18 **B:**1.5, 2.5, 3.5 + b12-18 **Additional information:** Schedule A was conducted in Poland, Schedule B in the Philippines DTwP-HBV/Hib given to each group with the same schedule as PCV. Schedule A received IPV, and schedule B received OPV with the same schedule as PCV	**N= 303** **Mean age at first study dose:** 1.8m **Gender (M/F, %male):** 162/141, 53.5% **Blood sample strategy:** 1 month after last primary dose, pre-booster, 1 month post-booster **Assessment of clinical outcomes:** Diary cards, other methods not reported. from first vaccination until 6m post-booster	**N= 300** **Mean age at first study dose:** 1.9m **Gender (M/F, %male):** 154/146, 51.3% **Blood sample strategy:** 1 month after last primary dose, pre-booster, 1 month post-booster **Assessment of clinical outcomes:** Diary cards, other methods not reported. from first vaccination until 6m post-booster			Geographical location: Those in Poland received the 2, 4, 6m primary schedule and those in the Philippines received the 1.5, 2.5, 3.5m primary schedule	**Method of analysis:** Specific methods not reported **Adjustment for potential confounders:** None **VE calculation:** None
Italy obs 7v **Location**: Italy **Recruitment dates:** Sept. - Dec. 2002 **Vaccine used:** 7v PCV; Prevnar **Funding:** In part by University of Milan. Remainder not reported	**[5]** **Inclusion criteria:** Healthy children presenting to 1 of 11 vaccination centres **Exclusion criteria:** **i**mmunodeficiency, serious chronic or progressive disease, history of seizures, born to HbsAg- or HCV-positive mothers, allergy to vaccine components, received treatment altering immune response, history of pneumococcal disease, antipyretic within 4h before vaccine	**A:** 3, 5, + b11 **B:** no PCV and no PPV **Additional information:** DTaP/IPV/Hib administered as 3, 5 and 11m in both groups	**N= 819** **Median age at first study dose:** 2.7m **Gender (M/F, %male):** 476/335, 58.7% **Assessment of clinical outcomes:** Monthly telephone interviews with parents, confirmation through paediatrician. Follow up continued for 24 months after the second dose	**N= 752** **Median age at first study dose:** 2.7m **Gender (M/F, %male):** 413/331, 55.5% **Assessment of clinical outcomes:** Monthly telephone interviews with parents, confirmation through paediatrician. Follow up continued for 24 months after the second dose			Parental choice	**Method of analysis:** Unclear. States that relative risks calculated but rates presented. States all episodes included but not clear if multiple events in 1 child taken in to account in analyses. **Adjustment for potential confounders:** None **VE calculation:** None
Korea obs 7v	[6]							

Study details	Participant characteristics	Schedule A / schedule B / schedule C	Schedule A population characteristics	Schedule B population characteristics	Schedule C population characteristics	Schedule D population characteristics	Assignment to schedule	Statistical analysis
Location: Korea **Recruitment dates:** NR **Vaccine used:** 7v PCV; Prevnar **Funding:** NR	**Inclusion criteria:** NR **Exclusion criteria:** NR	**A:** 3p+1 (Schedule not reported) **B:** no PCV and no PPV **Additional information:** Abstract only, minimal information provided	**N= 200** **Mean age at first study dose:** NR **Gender (M/F):** NR **Sampling strategy:** NR	**N= 200** **Mean age at first study dose:** NR **Gender (M/F):** NR **Sampling strategy:** NR			Not reported	**Method of analysis:** Only percentages reported **Adjustment for potential confounders:** None **VE calculation:** None
Norway 7v	[7]							
Location: Norway **Recruitment dates:** May 2003 **Vaccine used:** 7v PCV; Prevnar **Funding:** Norwegian Research Council	**Inclusion criteria:** NR **Exclusion criteria:** NR	**A:** 1 dose (>24m) or 2 doses (12-24m, 3 months apart) **B:** no PCV and no PPV **Additional information:** NR	**N= 56** **Mean age at first study dose:** approx 25.4m **Gender (M/F):** NR **Sampling strategy:** pre-vaccination, 3 months after first vaccination, 9 months after first vaccination (May 2003, Aug.2003 Feb. 2004)	**N= 38** **Mean age at first study dose:** approx 40.7m **Gender (M/F):** NR **Sampling strategy:** May 2003, Aug.2003 Feb. 2004			Vaccinated if attending a day-care centre where there were 2 cases of pneumococcal meningitis in April 2003, not vaccinated if at 1 of 3 control day-care centres	**Method of analysis:** χ^2 test, "odds ratios calculated" **Adjustment for potential confounders:** None **VE calculation:** None
Spain1 obs 7v	[8]							
Location: Canary Islands, Spain (likely, but not confirmed) **Recruitment dates:** 2005-2006 **Vaccine used:** 7v PCV; Prevnar **Funding:** Canary Island Foundation for health and Research	**Inclusion criteria:** Schedules A, B and C: cochlear implant. Schedule D: unvaccinated, healthy children without otorhinolaryngeal illness in previous 6 months **Exclusion criteria:** NR	**A:** 2-6mo: 3p 2montha apart + b12-15*; 7-11mo: 2p 2montha apart + b12-15* **B:** 12-23m: 2 doses 2 months apart* **C:** 2-5yo: 1 dose 8+PPV)* **D:** no PCV and no PPV **Additional information:** Schedules A, B and C have cochlear implants, D do not	**N= 1** **Mean age at first study dose:** NR **Gender (M/F, %male):** NR **Sampling strategy:** NR	**N= 52** **Mean age at first study dose:** NR **Gender (M/F, %male):** NR **Sampling strategy:** NR	**N= 2** **Mean age at first study dose:** NR **Gender (M/F, %male):** NR **Sampling strategy:** NR	**N= 60** **Mean age at first study dose:** NR **Gender (M/F, %male):** NR **Sampling strategy:** NR	Age at enrolment, Schedule D only if no cochlear implant	**Method of analysis:** Descriptive analysis only **Adjustment for potential confounders:** None **VE calculation:** None
UK1 obs 7v	[9, 26]							

Study details	Participant characteristics	Schedule A / schedule B / schedule C	Schedule A population characteristics	Schedule B population characteristics	Schedule C population characteristics	Schedule D population characteristics	Assignment to schedule	Statistical analysis
Location: UK **Recruitment dates:** June - Aug 2000 **Vaccine used:** 7v PCV; Prevnar **Funding:** Wyeth Lederle	**Inclusion criteria:** NR **Exclusion criteria:** NR	**A:** 2, 3, 4 + b13(PPV) **B:** no PCV and no PPV **Additional information:** NR	**N= 267** **Mean age at first study dose:** NR **Gender (M/F):** NR **Sampling strategy:** Sampled in summer and winter	**N= ~300** **Mean age at first study dose:** NR **Gender (M/F):** NR **Sampling strategy:** Sampled in summer and winter			Vaccinated children were included in a previous study, unvaccinated children recruited through nurseries and doctors of vaccinated children	**Method of analysis:** Percentages compared using χ^2 test. **Adjustment for potential confounders:** None **VE calculation:** None
UK2 obs 7v (sickle cell disease)	[10]							
Location: UK **Recruitment dates:** 1982-2005 **Vaccine used:** 7v PCV; Prevnar **Funding:** NHS executive, Wellcome trust. National Heart Lung and Blood Institute	**Inclusion criteria:** Major haemoglobinopathy **Exclusion criteria:** NR	**A:** PCV (schedule NR) **B:** PPV or no PPV **Additional information:** Penicillin V starting at 3m, PPV from 1993, Hib vaccine from 2000 PCV from 2002	**N=61** **Mean age at first study dose:** NR **Gender (M/F):** NR **Assessment of clinical outcomes:** NR	**N= 191** **Mean age at first study dose:** NR **Gender (M/F):** NR **Assessment of clinical outcomes:** NR			Vaccinated if born after Jan. 2002	**Method of analysis:** NR **Adjustment for potential confounders:** None **VE calculation:** None
UK3 obs 7v	**[11]**							
Location: UK **Recruitment dates:** approx. 2006 **Vaccine used:** 7v PCV; Prevnar **Funding:** Department of Health, UK **Assay used:** ELISA after adsorption with cell wall and 22F polysaccharides as in Wernette et al. 2003 [27] and WHO protocol [28].	**Inclusion criteria:** eligible for routine vaccination, no contraindication to vaccination **Exclusion criteria:** NR	**A:** 2, 4 + b12 **B:** 2, 3 + b12 **Additional information:** Co-administered with Meningitec Menjugate, NeisVac-C. Pediacel given at 2, 3, 4m	**N= 239** **Mean age at first study dose:** Median 2.0m **Gender (M/F):NR** **Blood sample strategy:** 1 month after primary schedule (5m) and before booster (12m)	**N= 154** **Mean age at first study dose:** Median 2.0m **Gender (M/F): NR** **Blood sample strategy:** 1 month after primary schedule (4m) and before booster (12m)			Randomization until late 2006, then assigned to schedule A exclusively	**Method of analysis:** "For comparing the study groups the rule of non-overlapping confidence intervals was used" **Adjustment for potential confounders:** None **VE calculation:** None
UK obs 9v	[12, 29]							

Study details	Participant characteristics	Schedule A / schedule B / schedule C	Schedule A population characteristics	Schedule B population characteristics	Schedule C population characteristics	Schedule D population characteristics	Assignment to schedule	Statistical analysis
Location: UK **Recruitment dates:** **Sched A:** Sep 2001-Jan 2003 **Sched B**: Jan 2000-Oct 2001 **Vaccine used:** 9v PCV (Wyeth) **Funding:** Health Protection Agency, Wyeth provided PCV **Assay used:** ELISA after adsorption with cell wall and 22F polysaccharides as in Wernette et al. 2003 [27] and WHO protocol [28].	**Inclusion criteria:** Healthy infants aged 7-11 w; informed consent **Exclusion criteria:** Previous confirmed pneumococcal or meningococcal disease; systemic disease or fever; contraindications for vaccination; in other trial; language problems; immuno-compromised.	**A:** 2, 3, 4 + b12 **B:** 2, 4 + b12 **C:** 2, 3, 4 + b12(PPV) **D**: 2, 4 + b12(PPV) **Additional information:** DTaP-Hib; OPV and Men C (CRM197) at 2, 3, 4 m. Randomized to A or C (Gloucestershire), or B or D (Hertfordshire). These comparisons reported in RCT Immunogenicity section of review	**N= 36 (booster phase)** **Mean age at first study dose:** NR **Gender (M/F):** NR **Blood sample strategy:** 1 m after last primary dose, at booster and 1m after	**N= 39 (booster phase** **Mean age at first study dose:** NR **Gender (M/F):** NR **Blood sample strategy:** 1m after last primary dose, at booster and 1m after	**N= 46 (booster phase)** **Mean age at first study dose:** NR **Gender (M/F):** NR **Blood sample strategy:** 1m after last primary dose, at booster and 1m after	**N= 39 (booster phase)** **Mean age at first study dose:** NR **Gender (M/F):** NR **Blood sample strategy:** 1 m after last primary dose, at booster and 1m after	Geographical location: Those in Hertfordshire received a 2-dose primary schedule, and those in Gloucestershire received a 3-dose primary schedule	**Method of analysis:** t test, χ^2 test, Fisher's exact test **Adjustment for potential confounders:** None **VE calculation:** None
USA1 obs 7v (some participants have sickle cell disease)	[13, 30]							
Location: USA **Recruitment dates:** Jan. 1995 - July 1997 **Vaccine used:** 7v PCV; Prevnar **Funding:** Thrasher Fund, Wyeth Lederle Vaccines, Thomas Wilson Sanatorium **Assay used:** ELISA (Koskela method), premixed with C-polysaccharide	**Inclusion criteria:** NR except that age and race matched children without sickle cell disease were recruited from primary care practices **Exclusion criteria:** NR	**A:** (non sickle cell) 2, 4, 6 **B:** (sickle cell) 2, 4, 6, + b24(PPV) **C:** (non sickle cell) 12 **D:** (sickle cell) 12, 24(PPV) **Additional information:** NR	**N=** 11 **Mean age at first study dose:** 2.1m **Gender (M/F, %male):** 5/6 , 45.5% **Blood sample strategy:** month after last PCV dose (7m), 12m, 24m	**N=** 34 **Mean age at first study dose:** 2.3m **Gender (M/F, %male):** 13/ 21 , 38.2% **Blood sample strategy:** 1 month after last PCV dose, 12m, before and after PPV (7m, 12m, 24m, 25m)	**N=** 3 **Mean age at first study dose:** 13.4m **Gender (M/F, %male):** 1/2, 33.3% **Blood sample strategy:** 1 month after last PCV dose (13m), 24m	**N=** 13 **Mean age at first study dose:** 12.3m **Gender (M/F, %male):** 5/8, 38.5% **Blood sample strategy:** 1 month after last PCV dose, before and after PPV (13m, 24m, 25m)	Age at enrolment and sickle cell status: enrolled before 2m received 3 dose primary schedule, enrolled after 2m received 12m dose; Sickle cell additionally received PPV at 24m	**Method of analysis:** paired and non-paired t-tests on log antibody concentrations, χ^2 test, Fisher's exact test **Adjustment for potential confounders:** None **VE calculation:** None
USA obs 7/13v	**[14, 31]**							

Study details	Participant characteristics	Schedule A / schedule B / schedule C	Schedule A population characteristics	Schedule B population characteristics	Schedule C population characteristics	Schedule D population characteristics	Assignment to schedule	Statistical analysis
Location: US **Recruitment dates:** Nov 2008-NR **Vaccine used:** 13v PCV, Prevnar 13 **Funding:** Wyeth **Assay used:** NR	**Inclusion criteria:** healthy, ≥ 3 doses PCV7 previously, 15m - 5yo **Exclusion criteria:** NR	**A:** ≥3 doses PCV7 + 2 doses PCV13 >55d apart (15m-24m) **B**: ≥3 doses PCV7 + dose PCV13 (24m-5y) **Additional information:** Children received a variety of non-study vaccinations which varied for each child	**N=**126 **Mean age at first study dose:** 18.0m **Gender (M/F, %male):** 51/58 46.8% **Blood sample strategy:** 1 month after last vaccination	**N=** 181 **Mean age at first study dose:** 37.2m **Gender (M/F, %male):** 104/71 59.4% **Blood sample strategy:** 1 month after last vaccination			Age at enrolment	**Method of analysis:** NR **Adjustment for potential confounders:** None **VE calculation:** None

* PPV also given in some/all groups (unclear).

DTP - diphtheria, tetanus and pertussis vaccine; DTaP- diphtheria, tetanus and acellular pertussis vaccine; DTwP- diphtheria, tetanus and whole-cell pertussis vaccine; EPI - Expanded Program on Immunization; GSK – GlaxoSmthKline; HAV/HepA - hepatitis A vaccine; HepB - hepatitis B vaccine; Hib - Haemophilus influenzae vaccine; IPV - inactivated polio vaccine; m - months; MenC - meningococcal group C vaccine; MMR - measles mumps rubella vaccine; NR – not reported; OPV- oral polio vaccine; PCV - pneumococcal conjugate vaccine; PPV - pneumococcal polysaccharide vaccine

Table 4.4: Detailed description of included case-control studies

Study name	Country	Comparisons	Number of participants		Outcomes reported	Outcomes description		Statistics used
			Cases	controls		Cases	Controls	
Spain2 7v (case control) 563 [18]								
	Spain	1 or more doses vs. 0 "Complete" vaccination* vs. 0 "Incomplete" vaccination* vs. 0	85	425	IPD	**Source:** surveillance system in Navarra detecting all cases of IPD in hospital microbiology labs **Inclusion criteria:** <5 years of age, born and residing in Navarra, who received microbiologically confirmed diagnosis of IPD between week 41 of 2001 and week 40 of 2005 **Characteristics:** pneumonia with bacteraemia 32 (38%) Meningitis 5 (6%) Received MnCC vaccine 83 (98%) Residents of metropolitan areas of capital 54 (63%)	**Source:** hospitals in Navarra, same hospital as matching cases were born **Inclusion criteria::** born in same hospital and on same date as cases subjects **Matching:** Individually matched by birth date and birth hospital. **Characteristics:** case patients and controls did not differ with regard to sex, age, Spanish nationality, or metropolitan residence.	Matched analysis. ORs for vaccination, with their 95%Cis were calculated using conditional logistic regression. VE was calculated as 1 minus the matched OR. Unmatched dichotomous variables were compared using x2 or Fishers exact tests.
USA2 obs 7v (case control) 704 [19]								
	USA	**Infant schedules:** / no PCV / 2 doses ≤ 7m / 3 doses ≤ 7m / 2 doses ≤ 7m, 1 dose 12-16m	782	2512	IPD	**Source:** Active Bacterial Core Surveillance (ABCS)- all clinical microbiology labs in surveillance areas **Inclusion criteria:** children younger than 2years with onset of IPD between Jan 1, 2001 and June 30, 2003 and children aged 2-4 years with onset between. Jan 1, 2001, and May 31, 2004. **Characteristics:** Day care attendance 396 (51%), Breastfeeding 528 (68%), Birth weight <2500g 75 (10%), >=3 doses Haemophilus influenza type b vaccine 269 (73%), >=3 doses DTaP vaccine 640 (82%), chronic illness 88 (11%), Immunocompromising disorder 85 (11%)	**Source:** birth certificate registries, all children from ABCS areas born within 2 weeks of enrolled case child **Inclusion criteria:** for every enrolled child, a list of 15 ctrl was generated from birth-certificate registries. **Matching:** post code (then the closest in age) **Characteristics:** Day care attendance 955 (38%), Breastfeeding 1850 (74%), Birth weight <2500g 63 (3%), >=3 doses Haemophilus influenza type b vaccine 1914 (76%), >=3 doses DTaP vaccine 2163 (86%), Chronic illness 105 (4%), Immunocompromising disorder 63 (3%)	Matched analysis, conditional logistic regression to compare vaccination schedules to no vaccination.
		1 dose ≤ 7m / x / - / - / -						
		2 doses ≤ 7m / x / - / x / x						
		3 doses ≤ 7m / x / x / - / x						
		2 doses ≤ 7m, 1 dose 12-16m / x / x / x / -						
		- / x / - / - / -						
		3 doses ≤ 7m, 1 dose 12-16m / x / x / x / x						
		1 dose 7-11m, 2 doses 12-16m / x / - / -						
		Toddler schedules:						
		1 dose 12-23m / x / - / - / -						
		2 doses 12-23m / x / - / - / -						
		1 dose ≥ 24 m / x / - / - / -						

*Complete vaccination defined as 3 doses if the first dose was given at 2-6 months, or 2 doses if the first dose occurred at 7-23 months, or 1 dose if the first dose occurred at 24 or more months

Table 4.5: Order of description and presentation of comparisons of vaccination schedules in cohort studies

Comparison	Study	Schedules, months	Time		
			Clinical	Carriage, months	Immunogenicity, months
Schedule vs. schedule (comparisons A-T)					
Comparison C	UK obs 9v [12]	2, 3, 4	-	-	5, 12
3p vs. 2p		2, 4			5, 12
Comparison I	UK obs 9v [12]	2, 3, 4 + b12(PPV)	-	-	13
3p + PPV vs. 2p +PPV		2, 4 + b12(PPV)			13
Comparison L	UK obs 9v [12]	2, 3, 4 + b12	-	-	13
3p + 1 vs. 2p +1		2, 4 + b12			13
Comparison N	Finland obs 7v [1]	2, 4, 6 + b15	-	-	16, 24
3p + 1 vs. 3p + PPV		2, 4, 6 + b15(PPV)			
Comparison P	International obs 7v [4]	2, 4, 6 + b12-18	2-12m, from booster until 6m post-booster	-	7, 12-18, 13-19
2m interval vs. 1m interval		1.5, 2.5, 3.5 + b12-18	1.5-9.5m, from booster until 6m post-booster		4.5, 12-18, 13-19
	International obs 10v [4]	2, 4, 6 + b12-18	2-12m, from booster until 6m post-booster	-	7, 12-18, 13-19
		1.5, 2.5, 3.5 + b12-18	1.5-9.5m, from booster until 6m post-booster		4.5, 12-18, 13-19
	UK3 obs 7v [11]	2,4	-	-	5, 12
		2,3			4, 12
Comparison R	Finland obs 10v [2]	7, 11	Entire study period	-	12, pre-booster (12-15)
Catch up vs. catch up		> 24 (1 dose)	Entire study period		>25m
	Finland obs 10v [2]	7, 11	Entire study period	-	12, pre-booster (12-15)
		12, 23	Entire study period		24
	Finland obs 10v [2]	7, 11, b12-15	Entire study period	-	13-16m
		> 24 (1 dose)	Entire study period		>25
	Finland obs 10v [2]	7, 11, b12-15	Entire study period	-	13-16m
		12, 23	Entire study period		24
	Finland obs 10v [2]	12, 23	Entire study period	-	24
		> 24 (1 dose)	Entire study period		>25
	Spain1 obs 7v [8]	12, 14[1]	-	Unclear	-
		24[1]		Unclear	
Comparison T	USA1 obs 7v [13]	2, 4, 6[2]	-	-	7, 12, 24
Primary (+/- booster) vs. catch-up		12[2]			13, 24
	Finland obs 10v [2]	3, 4, 5	-	-	6, pre-booster (12-15)
		> 24 (1 dose)			>25
	Finland obs 10v [2]	3, 4, 5	-	-	6, pre-booster (12-15)
		7, 11			12, pre-booster (12-15)
	Finland obs 10v [2]	3, 4, 5	-	-	6, pre-booster (12-15)
		12, 23			24
	USA1 obs 7v[3] [13]	2, 4, 6, + b24(PPV) [2]	-	-	7, 12, 24, 25
		12 + 24(PPV) [2]			13, 24, 25
	Finland obs 10v [2]	3, 4, 5 +b12-15	Entire study period	-	13-16m
		> 24 (1 dose)	Entire study period		>25
	Finland obs 10v [2]	3, 4, 5 +b12-15	Entire study period	-	13-16m
		12, 23	Entire study period		24
	Finland obs 10v [2]	3, 4, 5 +b12-15	Entire study period	-	13-16m
		7, 11, 12-15	Entire study period		13-16m
Schedule vs. no PCV					

Comparison	Study	Schedules, months	Time		
			Clinical	Carriage, months	Immunogenicity, months
(comparisons U-Z)					
Comparison V3	UK1 obs 7v [9]	2, 3, 4 + b13(PPV)	-	mean 33, 40.3	-
3p + PPV vs. 0		no PCV and no PPV		mean 36.4, 39.9	
Comparison W2	Italy obs 7v [5]	3, 5, + b11	6-30m	-	-
2p + 1 vs. 0		no PCV and no PPV	6-30m		
Comparison W3	Germany obs 7v [3]	2, 3, 4 + b12–15	2-27m	-	-
3p + 1 vs. 0		no PCV and no PPV	2-27m		
	Korea obs 7v [6]	3p+1	-	18-59m	-
		(Schedule not reported)			
		no PCV and no PPV		18-59m	
Comparison W4	Spain1 obs 7v [8]	2p or 3p + b12-15[1] / 12, 14[1] / 24[1]	-	mean 44.4	-
1, 2, 3, or 4 doses vs. 0				mean 38.4	
		no PCV and no PPV			
Comparison X1	Norway 7v [7]	1 dose (12m - >24m))	-	mean approx. 28.4	-
1 catch up dose vs. 0		no PCV and no PPV		mean approx 43.7	
Comparison Y	Norway 7v [7]	1 dose (>24m) or 2 doses (12-24m)	-	mean approx. 34.4	-
1 or 2 catch up doses vs. 0		no PCV and no PPV		mean approx 49.7	
Comparison Z	UK2 obs 7v[3] [10]	Schedule not reported	Unclear	-	-
Unknown schedule vs. 0		PPV or no PPV			
Comparison other	USA obs 7/13V [14]	≥3 doses PCV7 + 2 doses PCV13 >55d apart (15m-24m)	-	-	18-27m
		≥3 doses PCV7 + dose PCV13 (24m-5y)			25m-5y

Legend:

Shaded grey rows are those reported in main text;

1 Schedule might commence later but with same number of doses and same intervals in primary schedule, PPV also given in some/all groups (unclear)

2 Children with sickle cell disease received PPV in addition to the PCV schedule, Children without sickle cell disease did not

3 Some or all participants had sickle cell disease

b – booster; p – primary schedule; obs – denotes an observational study; PCV – pneumococcal conjugate vaccine; PPV – pneumococcal polysaccharide vaccine; v – valent

Table 4.6: Order of description and presentation of comparisons of vaccination schedules in Case-control studies

Comparison	Study	Schedules, months
Comparison C	USA2 obs 7v [19]	3 doses ≤ 7m
3p vs. 2p		2 doses ≤ 7m
Comparison E	USA2 obs 7v [19]	2 doses ≤ 7m, 1 dose 12-16m
2p+1 vs. 2p		2 doses ≤ 7m
Comparison G	USA2 obs 7v [19]	3 doses ≤ 7m
3p vs. 2p+1		2 doses ≤ 7m, 1 dose 12-16m
Comparison L	USA2 obs 7v [19]	3 doses ≤ 7m, 1 dose 12-16m
3p + 1 vs. 2p +1		2 doses ≤ 7m, 1 dose 12-16m
Comparison M	USA2 obs 7v [19]	3 doses ≤ 7m, 1 dose 12-16m
3p + 1 vs. 3p		3 doses ≤ 7m
Comparison U1	USA2 obs 7v [19]	1 dose ≤ 7m
1p vs. 0		No PCV
Comparison U2	USA2 obs 7v [19]	2 doses ≤ 7m
2p vs. 0		No PCV
Comparison U3	USA2 obs 7v [19]	3 doses ≤ 7m
3p vs. 0		No PCV
Comparison W2	USA2 obs 7v [19]	2 doses ≤ 7m, 1 dose 12-16m
2p + 1 vs. 0		No PCV
Comparison W3	USA2 obs 7v [19]	3 doses ≤ 7m, 1 dose 12-16m
3p + 1 vs. 0		No PCV
Comparison W4	Spain2 obs 7v [18]	1 or more doses
1, 2, 3, or 4 doses vs. 0		"Complete" vaccination[1]
		"Incomplete" vaccination[1]
		No PCV

1 Complete vaccination defined as 3 doses if the first dose was given at 2-6 months, or 2 doses if the first dose occurred at 7-23 months, or 1 dose if the first dose occurred at 24 or more months
PCV – pneumococcal conjugate vaccine

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