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Comparing pneumococcal conjugate vaccine schedules based on 3 and 2 primary doses: A systematic review and meta-analysis

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ABSTRACT

Background: Pneumococcal conjugate vaccines (PCV) were first licensed for use with 3 primary doses in infancy and a booster dose. The evidence for the effects of different schedules was examined in this systematic review and meta-analysis.
Methods: We searched 12 databases and trial registers up to March 2010. We selected randomised controlled trials (RCTs), cohort and case–control studies making direct comparisons between PCV schedules with 2 or 3 primary doses, with or without a booster dose. We extracted data on clinical, nasopharyngeal carriage and immunological outcomes and used meta-analysis to combine results where appropriate.
Results: Seropositivity levels (antibody concentration $\geq$0.35 μg/ml) following 3p and 2p PCV schedules were high for most serotypes (5 RCTs). Differences between schedules were generally small and tended to favour 3p schedules, particularly for serotypes 6B and 23F; between-study heterogeneity was high. Seropositivity levels following 3p+1 and 2p+1 schedules were similar but small differences favouring 3p+1 schedules were seen for serotypes 6B and 23F. We did not identify any RCTs reporting clinical outcomes for these comparisons. In 2 RCTs there was weak evidence of a reduction in carriage of *S. pneumoniae* serotypes included in the vaccine when 3p+0 schedules were compared to 2p+0 at 6 months of age.
Conclusions: Most data about the relative effects of different PCV schedules relate to immunological outcomes. Both 3p and 2p schedules result in high levels of seropositivity. The clinical relevance of differences in immunological outcomes between schedules is not known. There is an absence of clinical outcome data from RCTs with direct comparisons of any 2p with any 3p PCV schedule.

1. Introduction

Streptococcus pneumoniae is estimated to cause over 500,000 deaths in children under 5 years every year and a further 13 million cases of severe disease, including meningitis, septicaemia, and pneumonia [1]. There are more than 90 identified serotypes of *S. pneumoniae*, but only 10 account for most paediatric infections [2]. The existing 23-valent pneumococcal polysaccharide vaccine (PPV), is not licensed for children under 2 years old and its efficacy against invasive pneumococcal disease (IPD) remains controversial [3,4].

Pneumococcal conjugate vaccines (PCVs) are based on the conjugation of selected capsular polysaccharides to a protein carrier. Unlike PPV, they elicit T-cell dependent antibody responses, which make them immunogenic in infants [5]. The first of these vaccines was licensed in the US in 2000 and contains polysaccharide from 7 serotypes conjugated to a mutant diphtheria protein, CRM197 [6]. Since introduction, this vaccine has reduced the burden of invasive disease in young children in the US and offers indirect protection against disease in adults [7]. The licensure application for this vaccine included 2 randomised controlled trials (RCT) that assessed clinical outcomes. Both used a vaccination schedule of 3 primary doses before 7 months of age and a fourth dose at 12–15 months (schedule abbreviated as 3p+1) [8,9]. Since then, vaccines containing 10 and 13 serotypes have been licensed, based mainly on immunological non-inferiority to the 7-valent vaccine and safety data [10–12].

The majority of high income countries have now implemented a variety of PCV schedules into their childhood vaccination

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programmes. The World Health Organization (WHO) recommends a schedule of 3 primary doses without a booster (3p+0) [13] based on the results of RCTs in South Africa and the Gambia [14,15]. However, since PCVs induce immunological memory, it has been suggested that a schedule of 2 primary doses with a third dose in the second year of life (2p+1) might improve the duration of the immune response and ensure a strong herd effect [16]. This schedule has been introduced in several countries including the United Kingdom and France [17].

Schedules with fewer doses would be preferred, particularly in resource poor settings and countries where the routine immunisation schedule does not include a visit in the second year of life. Many middle and low income countries are currently in the process of making decisions about which PCV and which schedule to use and additional research about the use of alternative PCV schedules has been recommended [13]. We systematically reviewed data from studies that compared schedules containing 3 primary doses (with or without a booster) with 2 primary doses (with or without a booster).

2. Materials and methods

We followed a study protocol, which was developed with advice from an international expert group (see supplementary online text file 1).

2.1. Study identification

We searched 12 databases and trial registries (see supplementary online text) from their earliest date. The searches were conducted on August 28th 2009 and the Embase.com search was repeated on March 17th 2010. We used thesaurus and free text search terms adapted to each database relating to pneumococcus, streptococcus, conjugated vaccine, immunisation, or names of licensed pneumococcal conjugate vaccines. There were no restrictions on language, study design, or date of publication (full details in supplementary online text). Additionally, we screened bibliographies of selected review articles and asked experts in the field and vaccine manufacturers for other studies that might fit our inclusion criteria.

2.2. Study selection

Two pairs of reviewers independently evaluated articles. Titles and abstracts were screened first and then full text articles of potentially eligible items were read. We included RCTs, quasi-RCTs, cohort and case–control studies that enrolled children up to 18 years. We included data on licensed 7-, 10- or 13-valent PCVs and on 9-valent PCV, which contains serotypes 1 and 5 in addition to those in the 7-valent vaccine and is also conjugated to CRM197 [2]. Studies were eligible if they directly compared the following PCV schedules: 3p+0 *vs.* 2p+0; 3p+0 *vs.* 2p+1; 3p+1 *vs.* 2p+1; 3p+1 *vs.* 3p+0. We also studied the effects of a PPV booster in 2 direct comparisons with a PCV booster: 3p+1 *vs.* 3p+PPV and 2p+1 *vs.* 2p+PPV (protocol, p4, study questions). Data about antibody concentrations after the administration of PPV are reported in these 2 comparisons only. Studies were not eligible for inclusion if they only compared schedules to a control group that did not receive PCV. Eligible studies reported clinical, nasopharyngeal carriage or immunological outcomes. Observational studies reporting data only from individuals with an outcome (case-only studies) were excluded, as were those where all vaccinated children were HIV-infected, and all unvaccinated children were HIV-uninfected.

2.3. Data abstraction

Data were extracted on to a structured piloted form and checked for accuracy and completeness by PS. Data about the following outcomes, using definitions provided by study authors, were extracted: clinical outcomes including IPD, bacteraemia, pneumonia, otitis media, nasopharyngeal *S. pneumoniae* carriage, and immunological outcomes including IgG and opsonophagocytic activity (OPA). We extracted data on the potential risk of bias in individual trials including information on concealment of allocation sequences and blinding of outcome assessors [18]. Authors of individual studies were contacted only if reports of outcome data differed between publications of the same study.

2.4. Analysis

RCTs were analysed separately from observational studies. The primary outcomes of interest were clinical, followed by carriage and immunological outcomes. RCTs with groups that received a booster could contribute to more than one comparison. For example, if antibody concentrations were assessed in both groups after the primary vaccination series, these data were included in comparisons of 3p+0 *vs.* 2p+0 and of 3p+1 *vs.* 2p+1. We planned to use data from intention to treat (ITT) analyses but included data from per protocol (PP) analyses when ITT data were not available. For nasopharyngeal carriage outcomes we calculated the ratio (with 95% confidence intervals, CI) of the odds of carriage in children receiving the 3-dose compared with the 2-dose schedule as the reference group [19]. For immunological outcomes we calculated the absolute difference (with 95% CI) between the proportions seropositive following the 3-dose and 2-dose schedules. We considered IgG antibody levels measured by any enzyme-linked immunoassay (ELISA) above a threshold of 0.35 μg/ml as seropositive for all serotypes, as recommend by WHO [20]. An ELISA incorporating a 22F adsorption step has been accepted for use in licensure applications with a threshold of 0.20 μg/ml [21]. However, the 0.35 μg/ml threshold was the most consistently reported, and the prevalence difference and between trial heterogeneity were consistent regardless of the threshold. We report geometric mean concentration (GMC) data where seropositivity data were not available. We examined the association between OPA and IgG across trials that measured both outcomes. For each trial group we plotted the proportion with OPA titre ≥1:8 against the proportion ELISA seropositive (≥0.35 μg/ml).

We combined data statistically, where appropriate, using DerSimonian and Laird random-effects meta-analysis [22] in STATA version 10 (StataCorp LP, College Station, TX, USA). We quantified between-trial heterogeneity using the I^2 statistic; the proportion of the total variation in estimated prevalence ratios due to between-trial heterogeneity rather than to chance [23]. I^2 values of 25%, 50% and 75% can be interpreted as low, moderate and high levels of heterogeneity, respectively.

3. Results

Initial database searches yielded 3121 items and another 96 came from reference lists, experts, or repeat database searches, giving a total of 3217 unique items. Of these, 3188 items were excluded (Fig. 1). The remaining 29 items referred to 8 trials, 1 cohort study and 1 case–control study reporting on eligible comparisons and outcomes. Six trials and the cohort study contributed to immunological outcome comparison and 2 trials to nasopharyngeal carriage

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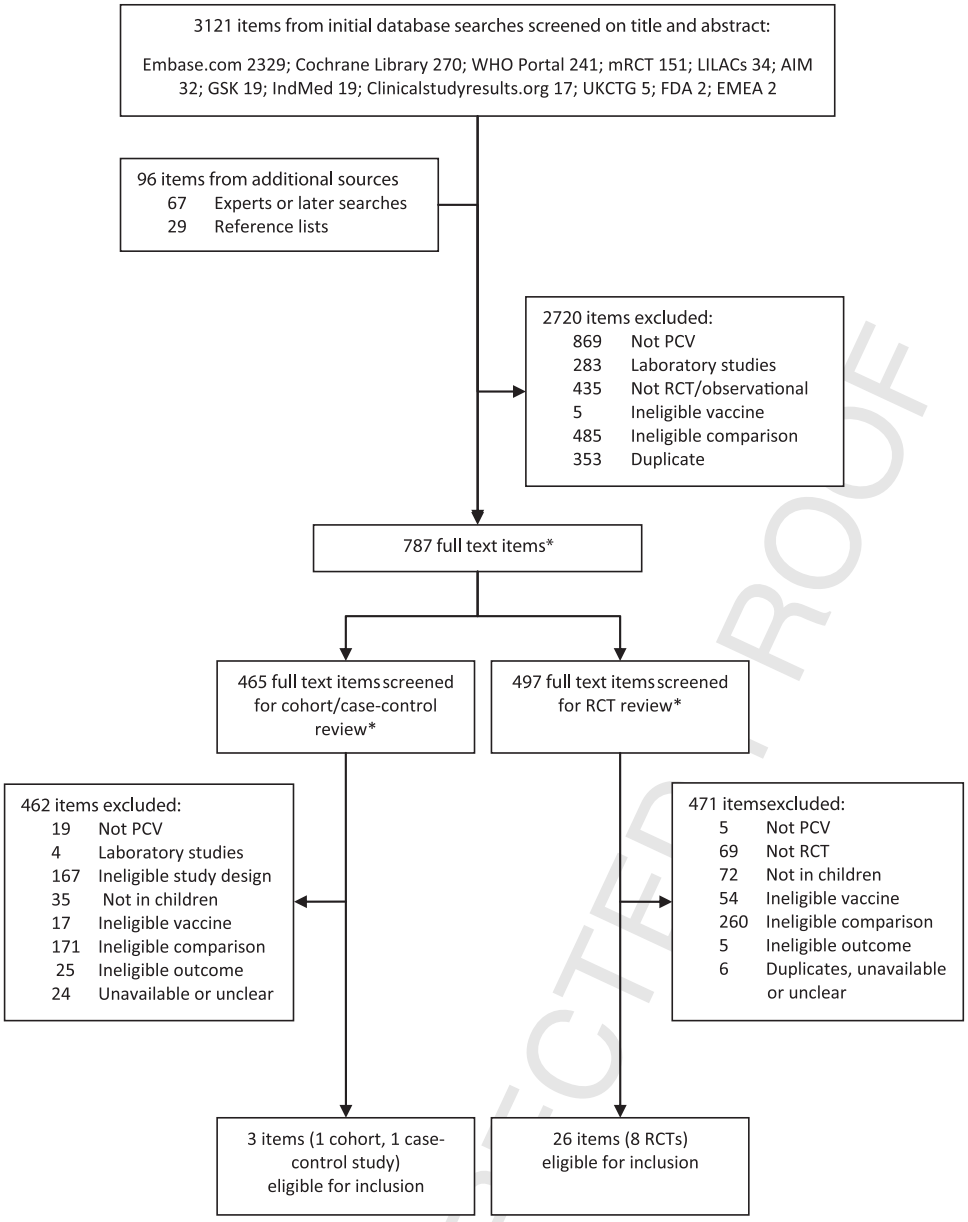

Fig. 1. Flow chart of studies. *175 full text items reviewed for eligibility in both RCT and cohort/case–control reviews as potential randomised and observational components. AIM, African Index Medicus; EMEA, European Medicines Agency; FDA, U.S. Food and Drug Administration; GSK, GlaxoSmithKline; IndMed, Indexing of Indian Medical Journals; LILACs, Latin American and Caribbean Health Sciences; mRCT, metaRegister of Controlled Trials; PCV; RCT, Randomised controlled trial; WHO Portal, World Health Organisation Clinical Trials Search Portal; UKCTG, UK Clinical Trials Gateway.

comparisons. Only the case–control study reported clinical outcomes.

3.1. Description of included studies

3.1.1. RCTs

The 8 RCTs were conducted in a total of 10 countries (Table 1). 1153 infants were randomised to schedules with 3 primary doses, and 948 to schedules with 2 primary doses. Three RCTs used 7-valent PCV (Fiji 7v [24], Gambia 7v [25], Israel 7v [26]), 4 used 9-valent PCV (Ghana 9v [27], Iceland 9v [28], UK1 9v [29], UK2 9v [29]) and 1 used 10-valent PCV (Europe 10v [30]). One RCT studied children with sickle-cell disease (Ghana 9v); the rest included children from the general population. Table 2 shows methodological features of the 8 RCTs, including adequacy of allocation concealment, the use of outcome assessor blinding and the type of analysis (intention to treat or per protocol). Analyses were intention to treat in 1 trial, per protocol in 2 and unclear in the remaining trials. It remained unclear whether the allocation concealment was adequate and whether outcome assessors were blinded for all trials, except Fiji 7v where laboratory staff were blinded.

3.1.2. Cohort and case–control studies

One cohort study (UKobs 9v [29]) compared groups from UK1 9v and UK2 9v RCTs which allowed comparisons that were not available from the randomised components of these studies (3p+0 *vs.* 2p+0; 3p+1 *vs.* 2p+1). This cohort study reported immunological outcomes only. The case–control study (USAobs 7v [31]) enrolled 782 cases of IPD and 2512 controls.

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Table 1
Summary of included RCTs with schedule-schedule comparisons, alphabetical order.

Study name, country and PCV valency [ref][a]	Schedule	Age at dose in months, mean		No. randomised	Outcomes reported	Time points for analysis, months
		Intended	Actual			
Europe (Denmark, Norway, Slovakia, Sweden) 10v [30]	3p+1	2, 3, 4, +b11m	1st: mean 2.8 2nd: mean 3.9 3rd: mean 5.0 Booster: mean 11.2	176	Seropositivity, GMC, OPA	6, 11, 12
	2p+1	2, 4, +b11m	1st: mean 2.8 2nd: mean 4.9 Booster: mean 11.1	175		
Fiji 7v [24]	3p+0	1.5, 2.5, 3.5	NR	136	Carriage, Seropositivity, GMC	4.5, 9, 12, 17[b]
	2p+0	1.5, 3.5		156		
Gambia 7v [25]	3p+PPV	2, 3, 4 + 10(PPV)	NR	228	Carriage, Seropositivity	5, 11, 15
	2p+PPV	2, 3 + 10(PPV)		228		
Ghana 9v (sickle-cell) [27]	3p+1	1.5, 2.5, 3.5 + 12	2.6, 3.9, 4.8, NR	21	GMC	13
	3p+PPV	1.5, 2.5, 3.5 + 12(PPV)	2.4, 3.5, 4.9, NR	21		
	3p+0	1.5, 2.5, 3.5	2.4, 3.9. 5.2	20		
Iceland 9v [28]	3p+1	3, 4, 5 + 12	NR	111[c]	Seropositivity, GMC	6, 12, 13
	3p+PPV	3, 4, 5 + 12(PPV)				
	2p+1	3, 5 + 12		112[c]		
	2p+PPV	3, 5 + 12(PPV)				
Israel 7v [26]	3p+1	2, 4, 6 + 12	NR	178	Seropositivity, GMC	7, 13, 19
	3p+0	2, 4, 6		178		
	2p+1	4, 6 + 12		189		
UK1 9v [29]	2p+1	2, 4 + 12	NR	88[c]	Seropositivity, GMC	13
	2p+PPV	2, 4 + 12(PPV)				
UK2 9v [29]	3p+1	2, 3, 4 + 12	NR	84[c]	Seropositivity, GMC	11
	3p+PPV	2, 3, 4 + 12(PPV)				

[a] Full list of references relating to each study given in supplementary online text.
[b] Approximately half of each group randomised to receive PPV at 12 m, 17 m data restricted to those not receiving PPV.
[c] The number undergoing the randomisation process. The number randomised to each group is unclear GMC, geometric mean concentration; NR, not reported; OPA, opsonophagocytic activity; PCV, pneumococcal conjugate vaccine; PPV, pneumococcal polysaccharide vaccine; 3p, 3 dose primary schedule, etc.; +1, booster dose.

Table 2
Reporting of methodological features of RCTs, alphabetical order.

Study, vaccine (manufacturer)	Intended interval between doses in primary series	Intended interval from last primary dose to sampling[a]	Adequate randomisation sequence generation	Adequate randomisation allocation concealment	Blinding of outcome assessors	Intention to treat or per protocol analyses
Europe 10v (GSK) [30]	2p: 2 mo 3p: 1 mo	Same in all groups	Unclear, 'randomised'	Unclear, 'randomised'	NR	PP
Fiji 7v (Wyeth) [24]	2p: 2 mo 3p: 1 mo	Same in all groups	Yes	Unclear (opaque envelopes but not clear if envelope linked to child before opening)	Laboratory staff blinded	NR
Gambia 7v (Wyeth) [25]	2p: 1 mo 3p: 1 mo	Differs between groups	Unclear, 'consecutively randomised'	Unclear, 'consecutively randomised'	NR	ITT
Ghana (sickle-cell) 9v (Wyeth) [27]	3p: 1 mo	Same in all groups	Yes	Unclear (envelopes used but not clear if envelope linked to child before opening)	NR	NR
Iceland 9v, (Wyeth) [28]	2p: 2 mo 3p: 1 mo	Same in all groups	Unclear, 'randomised'	Unclear, 'randomised'	NR	PP
Israel 7v, (Wyeth) [26]	2p: 2 mo 3p: 2 mo	Same in all groups	Yes	Unclear (opaque envelopes but not clear if envelope linked to child before opening)	NR	NR
UK1 infants 9v (Wyeth) [29]	2p: 2 mo	Same in all groups	Unclear, 'randomised'	Unclear, 'randomised'	NR	NR
UK2 infants 9v (Wyeth) [29]	3p: 1 mo	Same in all groups	Unclear, 'randomised'	Unclear, 'randomised'	NR	NR

All assessments based on information contained in published articles or pre-publication manuscripts. Authors of individual trials were not contacted for information on methodological features.
[a] Where one group receives booster PCV and another not, the classification of 'same in all groups' indicates that the time between last primary dose and sampling is the same in each group. ITT, intention to treat; NR, not reported; PP, per protocol.

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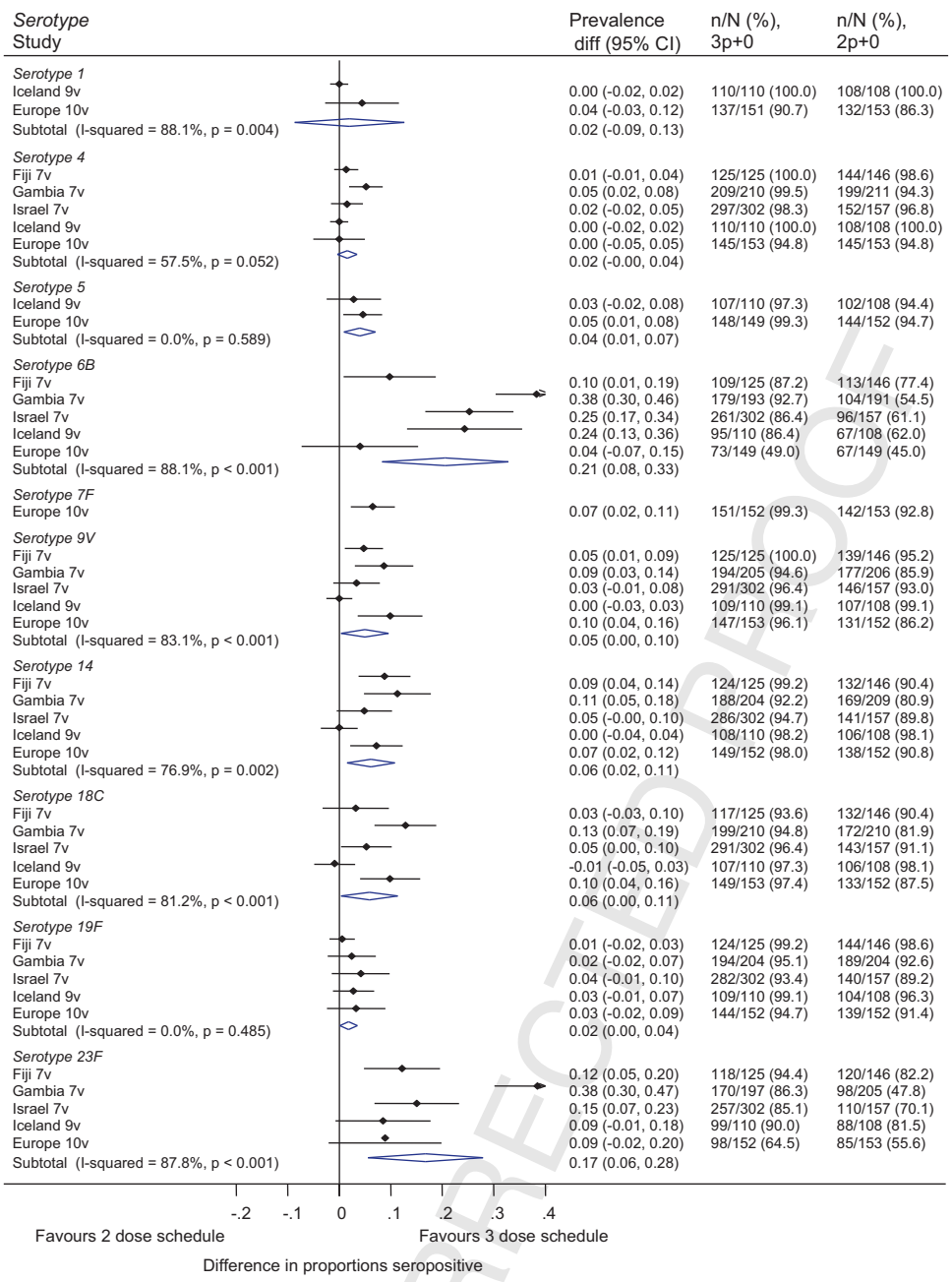

Fig. 2. 3p *vs.* 2p schedules, ELISA seropositivity at threshold 0.35 μg/ml, about age 6 months, by serotype (random-effects meta-analysis). n/N, number seropositive/total in group; prevalence diff, difference in seropositivity between groups shown as a proportion. Horizontal axis represents the difference, 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^2 value is the level of statistical heterogeneity between trials (<25% low heterogeneity).

3.2. Comparisons between 3 primary and 2 primary dose schedules

Immunological outcomes were reported most often so these are described first, followed by clinical outcomes and nasopharyngeal carriage.

3.2.1. Immunological outcomes

3.2.1.1. 3p+0 vs. 2p+0 schedules. Five RCTs (Fiji 7v, Gambia 7v, Israel 7v, Iceland 9v, Europe 10v) and 1 cohort study (UKobs 9v) reported on this comparison at approximately 6 months of age. In addition, 2 studies reported data at around 12 months of age (Fiji 7v, Iceland 9v), and 1 study in the second year of life (Fiji 7v). The percentage of children randomised who had blood drawn was high (above 80%) for all studies and time points.

At around 6 months of age, the proportion of children seropositive was generally high in both groups (Fig. 2). Differences varied between studies and serotypes but favoured the 3p+0 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 lev-

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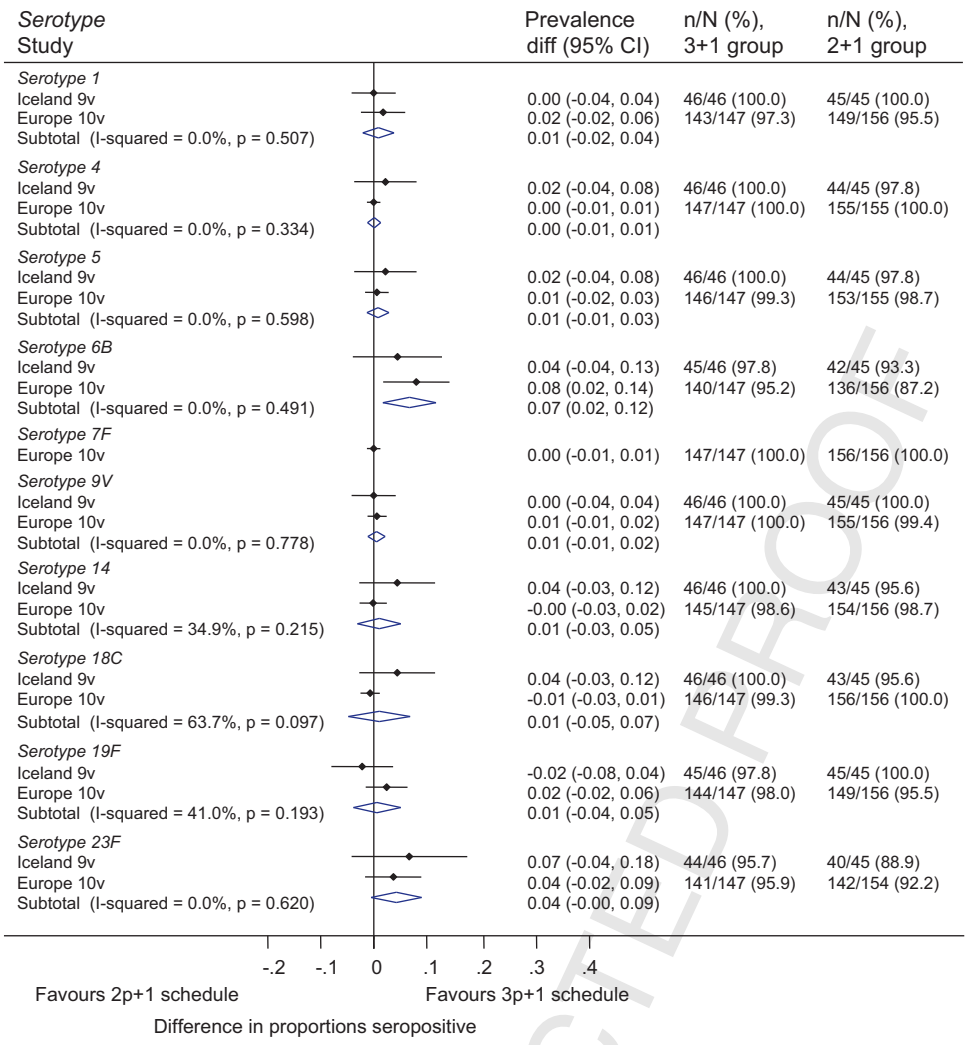

Fig. 3. 3p+1 *vs.* 2p+1, ELISA threshold 0.35 μg/ml, 1 month after booster dose, age about 12 months (random effects meta-analysis). n/N, number seropositive/total in group; prevalence diff, difference in seropositivity between groups shown as a proportion. Horizontal axis represents the difference, expressed as a proportion between groups receiving schedules of 3 primary and 1 booster dose *vs.* 2 primary and 1 booster 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^2 value is the level of statistical heterogeneity between trials (<25% low heterogeneity).

els were measured whilst 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, 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.

The cohort study (UKobs 9v) compared immunogenicity data following a 3p+0 schedule (2, 3 and 4 months) in one county with a 2p+0 schedule (2 and 4 months) in another, with broadly similar results 1 month after the last primary vaccination [29]. At 12 months of age (8 months after vaccination), there were more marked differences between the groups and overall levels of seropositivity had fallen for most serotypes (33–98% seropositive at a threshold of 0.35 μg/ml).

3.2.1.2. 3p+0 vs. 2p+1 schedules. There was 1 RCT (Israel 7v) that compared a 3p+0 (2, 4 and 6 months) with a 2p+1 (4, 6 and 12 months) schedule. Proportions seropositive at a threshold of 0.35 μg/ml were not reported for assessments after the booster dose. At 13 months, GMCs in the 3p+0 group (7 months after the last primary dose) were around one tenth of those in the 2p+1 group (1 month after the booster) for all serotypes. By 19 months of age GMCs were more similar with values in the 3p+0 group (13 months after the last primary dose) around half of those in the 2p+1 group (7 months after the booster) for all serotypes except 4 (GMC in the 3p+0 group around quarter of the 2p+1 group).

3.2.1.3. 3p+1 vs. 2p+1 schedules. Two RCTs reported on a 3p+1 *vs.* 2p+1 comparison and had seropositivity data at the 0.35 μg/ml level (Iceland 9v, Europe 10v) (Fig. 3). One month after a booster dose, the proportions seropositive were >90% for all serotypes except 6B in the Europe 10v study for the 2p+1 group, and 23F for the 2p+1 group in Iceland 9v. There were no data at this cut-off at older ages. In the UKobs 9v study, half the children in the 3p and 2p groups received a booster dose at 12 months. Only GMCs were

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reported at this time point. One month after the booster dose there was no statistical evidence of differences between groups.

3.2.1.4. 3p+1 vs. 3p+0. The 3p+1 *vs.* 3p+0 comparison was examined by 2 RCTs (Ghana 9v, Israel 7v), neither of which reported the proportions seropositive (≥0.35 μg/ml) after the booster dose. GMC ratios between intervention groups showed little heterogeneity between the two studies despite the Ghana children having sickle-cell disease. One month after the booster dose (7 months after the last primary dose in the 3p+0 group) pooled GMC values for all serotypes in 3p+1 groups were 5 to 15 times higher than in the 3p+0 groups. By 19 months of age (7 months after the booster) GMCs were more similar with values in the 3p+1 group around 1.5 to 3 times higher than those in the 3p+0 group.

3.2.1.5. 2p+1 vs. 2p+PPV and 3p+1 vs. 3p+PPV. One study reported seropositivity (at a cut-off of 0.35 μg/ml) data for the 2p+1 *vs.* 2p+PPV and 3p+1 *vs.* 3p+PPV comparisons (Iceland 9v). Results were almost identical in the PCV booster and PPV booster groups, with more than 85% seropositive in both groups for all serotypes after both 2- and 3-dose schedules. UK1 9v and UK2 9v reported only GMCs after the booster dose, with variable results for different serotypes and number of primary doses, when comparing groups which received PCV booster to those receiving PPV.

3.2.1.6. Opsonophagocytic antibody (OPA). Three RCTs reported results of OPA (Fiji 7v, Gambia 7v, Europe 10v). In general, the proportions at the group level with OPA titre ≥ 1:8 were very similar to the proportions with ELISA antibody levels ≥0.35 μg/ml at around 6 months of age (Fig. 4). For serotypes 6B and 23F, the proportions seropositive were higher by OPA than ELISA in the Europe 10v trial. Low OPA levels, relative to ELISA, were seen for serotype 14 in Fiji 7v and serotype 19F in Gambia 7v. The percentage of children randomised with results available for OPA analysis varied between studies. OPA data from the Gambia 7v trial appeared to relate to a subset of around 20%. Percentages assessed for OPA in Europe 10v ranged from 55 to 70% by serotype and time point. In Fiji 7v, 85% or more were sampled in each group at 6 months of age.

3.2.2. Clinical outcomes

There were no clinical outcome data from RCTs with eligible comparisons. In the case–control study of invasive pneumococcal disease (IPD), adjusted odds ratios (aOR) for disease caused by serotypes included in the vaccine were reported as: 3p+0 *vs.* 2p+0, aOR 1.5 (95%CI 0.54–4.35); 3p+0 *vs.* 2p+1, aOR 1.5 (95%CI 0.15–14.6); 3p+1 *vs.* 3p+0, aOR 0 (95%CI 0–0.87); 3p+1 *vs.* 2p+1, aOR 0 (95%CI 0–10.1). These comparisons were adjusted for underlying disorders only.

3.2.3. Nasopharyngeal S. pneumoniae carriage

3.2.3.1. 3p+0 vs. 2p+0 schedules. Two trials (Fiji 7v, Gambia 7v) contributed carriage data (Table 3). Serotypes were grouped as vaccine serotypes (VT) defined as carriage of any of the serotypes in the vaccine, i.e. 4, 6B, 9V, 14, 18C, 19F, 23F (reported in both studies), non-vaccine serotypes (NVT, Fiji 7v only), and carriage of any *S. pneumoniae* serotype (both studies). At about 6 months of age, the results from both trials were comparable and pooled odds ratios showed no evidence of a difference between 3p+0 and 2p+0 schedules in the prevalence of carriage of any pneumococcal serotype or of VT. Only one trial reported data beyond 6 months of age for this comparison (Fiji 7v, up to 17 months of age). Confidence intervals crossed 1 for all odds ratios except at 9 months in Fiji for VT.

4. Discussion

In this systematic review of immunisation schedules for PCV, immunological data showed that 3p schedules might result in slightly higher antibody levels than 2p schedules both before and after a booster dose, particularly for serotypes 6B and 23F. Results of OPA assessments were generally similar to those of seropositivity assessed by ELISA. There is an absence of clinical outcome data and limited data about nasopharyngeal carriage from direct comparisons of any 2p to any 3p schedule.

4.1. Strengths and limitations

This is, to our knowledge, the first systematic review to examine the evidence from direct comparisons of different PCV schedules. Other reviews have focused on the efficacy and/or effectiveness of PCV, comparing outcomes in vaccinated children with those receiving no vaccination or no PCV [33–36]. The strengths of this study include a wide search of databases encompassing published articles, manufacturer and regulatory authority databases and clinical trial registries so relevant RCTs are unlikely to have been missed. If the schedules compared were incompletely reported in abstracts, however, these studies might have been excluded early in the selection process. This is most likely for case–control studies. We also made a comprehensive assessment of potential sources of heterogeneity and bias between trials and compared serotype specific OPA data with ELISA seropositivity. To our knowledge data about OPA have not previously been compared across trials. A limitation identified by this review was the paucity of data on the outcomes and comparisons of interest. Furthermore, we found only 1 eligible study using 10-valent PCV and no studies using the 13-valent PCV were eligible so it is difficult to assess whether these vaccines behave differently to 7-valent vaccine for serotypes common to both vaccines. We explored the possibility of using network meta-analysis to make indirect comparisons whilst respecting the randomisation within trials, but found insufficient data. There is a risk of bias in making informal indirect comparisons between different PCV schedules in placebo (or non-pneumococcal vaccine) controlled trials, such as the large efficacy trials of 3p+0 or 3p+1 in South Africa, the Gambia and the USA.

4.2. Interpretation of findings

The assessment of the merits of different PCV schedules needs to be based on data about immunological and nasopharyngeal carriage outcomes, and data from observational study designs because of an absence of clinical outcome data from RCTs that directly compare different vaccination schedules. There was weak statistical evidence to suggest that the odds of pneumococcal carriage measured 1 month after the last dose were lower following a 3p compared with a 2p schedule; odds ratios are considered the best effect measure for estimating relative frequency of acquisition from cross-sectional data [19]. The evidence was insufficient to draw conclusions on the relative effect of 3p and 2p schedules on the carriage of vaccine type and non-vaccine type *S. pneumoniae*. Research is currently in progress to assess how carriage data relate to clinical disease [37]. Carriage could potentially be measured directly as the frequency of acquisition of colonisation, where new episodes of carriage are recorded in individuals who have never carried before, or who have carried but cleared the colonisation. These data require frequent collection of samples and are rarely reported.

Immunological data were most often reported but the clinical relevance of differences between schedules in seropositivity levels or GMCs is not known. The threshold IgG level of 0.35 μg/ml for all serotypes has been accepted as a benchmark for protection against IPD 4 weeks after a 3 dose primary series [20,21] but pro-

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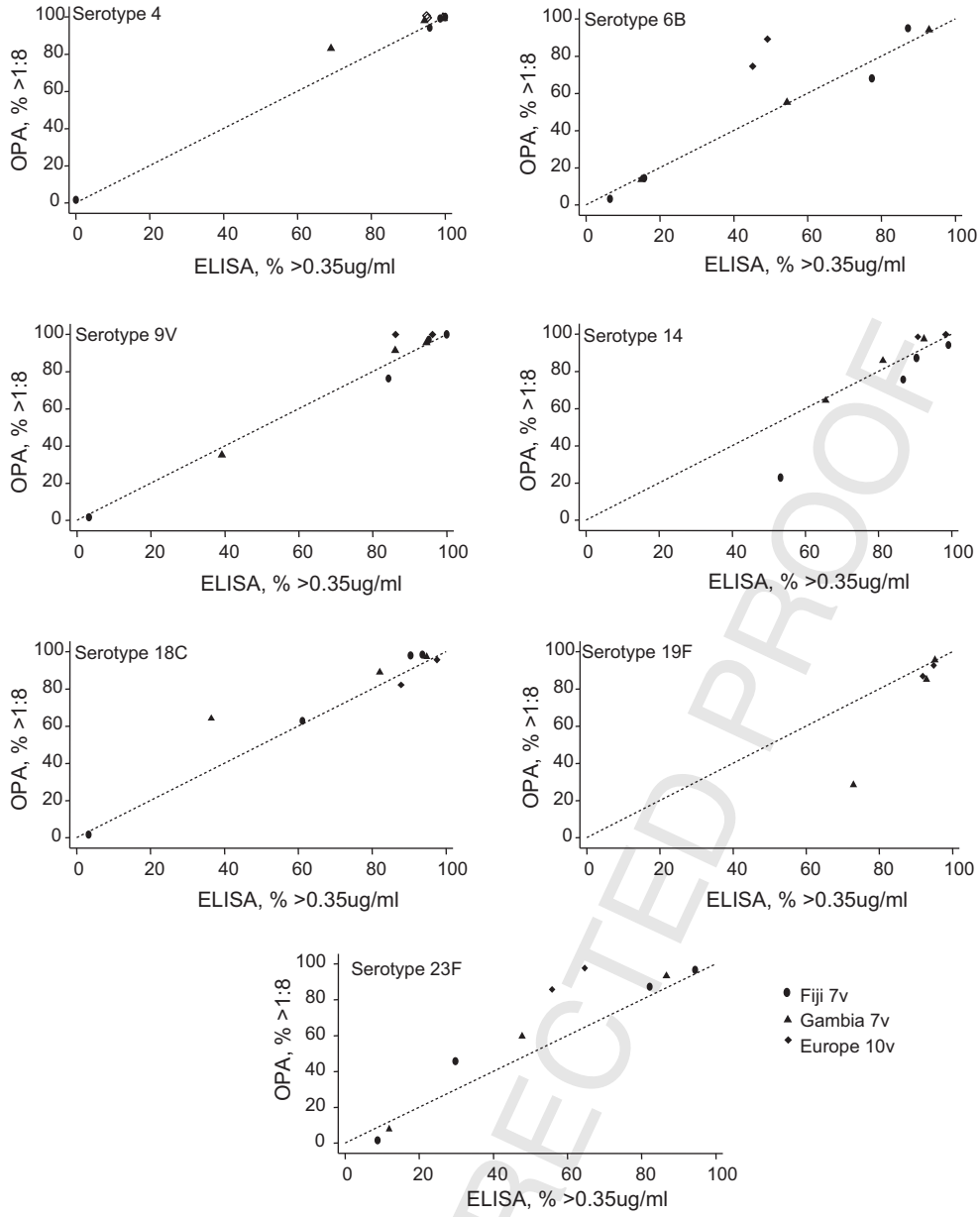

Fig. 4. Percentage of individuals with OPA > 1:8 compared to percentage of individuals with ELISA >0.35 μg/ml in each randomization group in the three trials reporting these data, about age 6 months, by serotype. Diagonal line represents equal percentages of individuals positive for each outcome. Data in this figure are from the three trials which report both OPA > 1:8 and ELISA > 0.35 μg/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.

tective levels of antibodies might differ between serotypes [38], for different clinical outcomes [39] and in different populations. The link between seropositivity and IPD was based on analyses of serotypes in the 7-valent vaccine only; there is no known immune correlate of protection against pneumococcal disease for serotypes in extended valency PCVs. It is also not known how immunological outcomes relate to carriage. Immunological outcome data need to be interpreted in conjunction with information about pneumococcal serotype distribution and age-specific incidence of disease. In this review, absolute differences in percentages seropositive following 3p and 2p schedules were mostly <10%. The largest differences were observed for serotypes 6B and 23F, which might suggest that a 3-dose primary schedule would be preferred if the burden of pneumococcal disease from these serotypes is high in the first year of life. A recent case–cohort study, matched using propensity scores, in the US found fewer hospitalisations and outpatient attendances for lower respiratory tract disease in the post-primary period in children who received 3 primary doses at median ages of 2.1, 4.2 and 6.2 months compared with 2 doses at median ages 2.2 and 5.7 months [39]. This study was not included in our review because the clinical outcome included conditions not specified in the protocol. Serotypes were not reported, but 6B is the second most common in North America [40] and breakthrough infections have been associated with serotype 6B [38].

Schedules with a booster dose at 12 months (2p+1 or 3p+1) resulted in markedly higher antibody levels than a 3p+0 schedule at 13 months of age (or 1 month after the booster was given) providing a rationale for the use of a schedule with a booster dose when there is a high burden of disease in the second year of life. However, surveillance data from Australia have shown a marked decline in invasive disease since a 3p+0 schedule was implemented in 2005 [41,42]. Comparison of the use of PCV and PPV as the booster

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Table 3
Odds ratios for carriage of *S. pneumoniae* at different ages, 3 primary doses *vs.* 2 primary doses.

Serotype, study	Odds ratio (95% CI)[a]			
	About 6 mo	About 9 mo	About 12 mo	About 17 mo
Any				
Fiji 7v [32]	1.10 (0.69–1.77)	0.73 (0.45–1.18)	0.90 (0.55–1.48)	0.96 (0.48–1.94)
Gambia 7v [25]	0.77 (0.46–1.29)	NR	NA[b]	NA[b]
Pooled,[c] I^2	0.94 (0.66–1.33), 0.0%	NA	NA	NA
Vaccine type				
Fiji 7v [32]	0.94 (0.43–2.04)	0.30 (0.10–0.92)	1.12 (0.42–3.01)	0.37 (0.04–3.63)
Gambia 7v [25]	0.69 (0.41–1.17)	NR	NA[b]	NA[b]
Pooled,[c] I^2	0.76 (0.50–1.17), 0.0%	NA	NA	NA
Non-vaccine type				
Fiji 7v [32]	1.20 (0.74–1.96)	0.95 (0.59–1.55)	0.86 (0.52–1.44)	NR
Gambia 7v [25]	1.02 (0.68–1.55)	NR	NA[b]	NA[b]
Pooled,[c] I^2	1.09 (0.80–1.50), 0.0%	NA	NA	NA

[a] An odds ratio greater than one indicates that the 3-dose group were more likely to carry than the 2-dose group.
[b] Children received PPV vaccination at 11 months of age and therefore no longer included in this schedule comparison.
[c] Random effects meta-analysis; mo, months; NA, not applicable; NR, not reported; I^2, measure of between trial heterogeneity.

dose was a pre-specified question in this review. There were few data available, however, and all were immunological. Interpretation of these data is further complicated by differences in how IgG antibody concentrations generated through PCV or PPV vaccination relate to antibody avidity and underlying immune responses [29,43].

There are several possible reasons for the marked heterogeneity between RCTs in differences between seropositivity following 3p and 2p schedules, including differing risk of bias between studies, timing of vaccinations and blood samples, differences in study populations and serotype distribution, vaccine valency and composition, or prevalence of carriage prior to vaccination. With only 5 RCTs, it was not possible to investigate heterogeneity in a meta-regression analysis. One source of heterogeneity resulting from study design would occur if the time between last vaccine dose and antibody measurement differed between groups. In this review, 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 trial than in the other 4 studies, suggests that these results were more likely to be due to the difference in sampling interval than to differences in immunological responses to the 2 schedules. Additionally, heterogeneity between studies might be less marked if a correlate of protection was known for each serotype, rather than using a uniform threshold. The assessment of functional antibody responses measured by OPA levels is being emphasised increasingly [2]. It has been shown that in individuals, OPA titres correlate well with ELISA antibody concentration for vaccine serotypes but not for vaccine-related serotypes [44]. In this review, the proportions seropositive by ELISA ($\geq$0.35 μg/ml) corresponded well to the proportion OPA positive (titre $\geq$ 1:8) for vaccine serotypes. At the study level, these findings support the correlation between ELISA antibody levels and functional antibody. Serotype-specific hyporesponsiveness to vaccination associated with pneumococcal carriage has been observed [45]. If this occurs, it may also account for some heterogeneity between studies, and would need to be taken in to account when making schedule-related decisions.

4.3. Implications for practice and research

There are now almost as many countries using 2p+1 PCV schedules as the licensed 3p+1 schedule [17]. The decisions to use such schedules are likely to have been based on immunogenicity data. For example, in the UK the Joint Committee on Vaccination and Immunisation cited the UK1 9v trial, 'as it has been shown to provide satisfactory primary immunogenicity and prime for memory responses to a booster dose in the second year of life' [46]. Post-marketing surveillance in individual countries has shown reductions in IPD caused by vaccine serotypes using a 2p+1 schedule [47] but the impact on pneumococcal pneumonia is not known. Additional information will be provided by an ongoing systematic review [48] and comparison of disease surveillance data in countries using 3p+1 schedules (e.g. USA, Canada and The Netherlands) to that in countries using reduced-dose schedules (UK, Israel and Mexico) [49]. Interpretation of findings of studies using the same schedule in different countries will need to take into consideration differences in aspects such as the pattern of circulating serotypes, contact patterns, co-morbidity, and co-administration of other vaccines and other potential confounders that can vary between countries.

There is a window of opportunity for new RCTs with clinical outcomes comparing 3p+1 to reduced dose schedules, especially in large countries or regions that are deciding on schedules for introducing extended valency vaccines. Pragmatic trials using randomised stepped-wedge introduction of different schedules in different areas, accompanied by enhanced surveillance for pneumococcal disease could provide valuable information. The sample sizes required would, however, be even larger than those of the original studies for licensure due to smaller expected differences between groups.

Standards of reporting of future RCTs of PCVs need to improve to assist both interpretation of individual trials and future systematic reviews. In the RCTs included in this review, the lack of reporting of methodological details that are essential for assessing the risk of bias was surprising, considering that the CONSORT statement was published well before most of these studies [50]. Although the risk of bias due to inadequate blinding is reduced when outcomes are objective rather than subjective [51], inadequate concealment of allocation remains a potential source of bias. Poor reporting of these aspects is a failing of many of the included studies. There is potential for biases to be introduced when there is marked loss to follow up. In the data reported here, high percentages of children randomised were available for analysis. However, there were exceptions, particularly for OPA data.

5. Conclusion

The introduction of PCV into routine childhood vaccination programmes in high income countries has reduced the incidence of IPD across all age groups. However, the progress of introducing PCV into several low income countries remains slow. The varying country specific burden of diseases as well as varying health infrastructures and resources add to the complexities in the decision making process in determining optimal vaccination programmes.

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Thus, information on the benefits on different vaccine schedules is essential if informed decisions are to be made. In this comprehensive systematic review, we highlight the paucity of data comparing 3 doses versus 2 doses of PCV before 1 year of age with or without a booster dose. Immunological data showed that both 3p and 2p schedules result in high levels of seropositivity. 3p schedules might result in slightly higher antibody levels than 2p schedules both before and after a booster dose particularly for serotypes 6B and 23F but the clinical relevance of these differences is not known.

Contributors

PS and NL designed the study, PS, AR, LB, NR, SS and TL extracted data, PS and TL analysed data, PS, AR, LB, NR, SS, TL, ME and NL interpreted data, drafted or revised the article. All authors approved the final version.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.vaccine.2011.07.042.

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