Pneumococcal conjugate vaccine dose-ranging studies in humans: A systematic review

R.K. Lucinde\textsuperscript{a,}\textdagger, G. Ong’ayo\textsuperscript{a}, C. Houlihan\textsuperscript{b}, C. Bottomley\textsuperscript{c}, D Goldblatt\textsuperscript{d}, J.A.G. Scott\textsuperscript{a,c}, K.E. Gallagher\textsuperscript{a,c}

\textsuperscript{a}KEMRI-Wellcome Trust Research Programme (KWTRP), Centre for Geographic Medical Research - Coast (CGMRC), Kilifi, Kenya

\textsuperscript{b}Division of Infection and Immunity, University College London, London, UK

\textsuperscript{c}Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, UK

\textsuperscript{d}Great Ormond Street Institute of Child Health, University College London, UK

Abstract

**Background**—*Streptococcus pneumoniae* is one of the most common bacterial pathogens of infants and young children. Antibody responses against the pneumococcal polysaccharide capsule are the basis of vaccine-mediated protection. We examined the relationship between the dose of polysaccharide in pneumococcal conjugate vaccines (PCVs) and immunogenicity.

**Methods**—A systematic search of English publications that evaluated the immunogenicity of varying doses of pneumococcal conjugate vaccines was performed in Medline and Embase (Ovid Sp) databases in August 2019. We included only articles that involved administration of pneumococcal conjugate vaccine in humans and assessed the immunogenicity of more than one serotype-specific saccharide dose. Results were synthesised descriptively due to the heterogeneity of product valency, product content and vaccine schedule.

**Results**—We identified 1691 articles after de-duplication; 9 studies met our inclusion criteria; 2 in adults, 6 in children and 1 in both. Doses of polysaccharide evaluated ranged from 0.44 mcg to 17.6 mcg. In infants, all doses tested elicited IgG geometric mean concentrations (GMCs) above the established correlate of protection (COP; 0.35 mcg/ml). A month after completion of the administered vaccine schedule, 95% confidence intervals of only three out of all the doses evaluated had GMCs that crossed below the COP. In the adult studies, all adults achieved GMCs that would be considered protective in children who have received 3 standard vaccine doses.

**Conclusion**—For some products, the mean antibody concentrations induced against some pneumococcal serotypes increased with increasing doses of the polysaccharide conjugate, but
for other serotypes, there were no clear dose–response relationships or the dose response curves were negative. Fractional doses of polysaccharide which contain less than is included in currently distributed formulations may be useful in the development of higher valency vaccines, or dose-sparing delivery for paediatric use.

Keywords
Pneumococcal conjugate vaccines; Dose-range; Systematic review; Immunogenicity

1 Background

The polysaccharide capsule of *Streptococcus pneumoniae* is the principal target of the mature human response to pneumococcal infection and the reason initial vaccine development focused on pneumococcal polysaccharide vaccines [1]. However, polysaccharides are poor immunogens, especially in infants and the elderly [1,2]. Conjugation of serotype-specific capsule polysaccharides to a carrier protein improves immunogenicity by stimulating T-cell dependent responses [3].

Early conjugate vaccine candidates differed in the dose of saccharide conjugated to the carrier protein, the saccharide chain length, the carrier protein used, the ratio of carrier protein to saccharide, the conjugation method, the adjuvant used and the vaccination schedule [4–27] (Table 1).

Some of the evidence that led to the vaccine formulations in use today has been summarised previously [3]. In brief, polysaccharides were found to be more immunogenic than oligosaccharides [2,28]. Proteins used in other conjugate vaccines, like Tetanus Toxoid (TT) or *Neisseria meningitidis* outer membrane protein (OMPC) generated lower immune responses when used in PCVs compared to other carrier proteins such as Diphtheria Toxoid (DT) and Diphtheria Toxoid mutant (Dip. CRM197) [3]. PCVs using TT, OMPC or protein D seemed to elicit a peaked response (immunogenicity increased with dose until a threshold and then decreased thereafter) or no dose-dependent response. However, candidates using DT or Dip. CRM197 as the carrier protein elicited a linear dose–response relationship and were less likely to induce epitopic B-cell suppression (CIES) than vaccines using TT or OMPC carrier proteins. Additionally, higher valency PCVs using Dip. CRM197 benefit from coadministration with other infant vaccines using DT protein [3].

The need to keep the total saccharide and carrier protein doses low to avoid interference and/or hypo responsiveness, while incorporating multiple serotypes into the vaccine, led to the development of candidates with lower saccharide doses and lower carrier protein load than the Hib conjugate vaccines previously developed [3]. Doses of saccharide in current conjugate vaccines were determined before the correlate of protection was known. Immunogenicity was measured in fold-rises of IgG titres compared to baseline. Relatively low concentrations of serotype-specific IgG (0.35 mcg/ml) in response to vaccine have since been shown to correlate with protection against invasive pneumococcal disease in infants [29], while protection against acquisition of carriage of pneumococci in the nasopharynx may require higher concentrations (2–5 mcg/ml) [30].
As of March 2019, 75% of countries globally had introduced PCV. Since 2010, Gavi, the Vaccine Alliance, has supported PCV introduction in 60 low and middle-income countries (LMICs) [31]. PCV alone represents the largest proportion of the Gavi budget when compared to all other vaccines [32] and, at approximately US$10 per fully immunized child, the most expensive vaccine in the routine vaccination schedule for many LMICs [33]. One approach to reducing the financial cost of PCV programmes is to use a fractional dose at each vaccination but this is only possible if lower doses are sufficiently immunogenic to indicate strong protection. We examined previous literature on the relationship between the dose of polysaccharide in pneumococcal conjugate vaccines (PCVs) and immunogenicity in a systematic review.

2 Methods

2.1 Search strategy

The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines were followed [34]. Medline and Embase databases (Ovid SP) were searched in April 2018 and the search was updated in August 2019. Search terms were built around (1) pneumococcal vaccination/immunisation (2) immunogenicity (3) dose/dosage/dose–response/dose-ranging. The search had no restrictions based on publication date. We included only English-language publications that involved administration of pneumococcal conjugate vaccine in humans and assessed the immunogenicity of more than one serotype-specific saccharide dose (Fig. 1, Supplementary Table 1).

2.2 Screening of articles

All articles retrieved from the two databases were exported into Endnote X8 (Clarivate Analytics, PA, USA) and duplicates were automatically and manually removed.

The title and/or abstracts were screened by two reviewers (RKL and KEG) independently (Fig. 1). Full texts were screened by two of three reviewers (KEG, CH and RKL). Articles were excluded if they did not assess >1 dose of polysaccharide conjugate and/or did not report serum IgG concentrations.

2.3 Data extraction & synthesis

Data from included articles were extracted into a template in Microsoft Excel 2013. Data on the study population, setting, vaccine formulation, comparison arms/cohorts, schedule, outcome measure(s) and timepoint of outcome measurement were noted alongside any analyses. The qualities of the included studies were evaluated using the Cochrane GRADE system [35].

The studies were not combined in a meta-analysis because of the heterogeneity in the vaccine valency, carrier protein, adjuvant, adjuvant dose, manufacturer and conjugation methods, the vaccination schedule and the population of analysis (children, adults with or without prior vaccination). Instead, serotype-specific dose response curves were estimated using data from studies with the same vaccination schedule and immunogenicity endpoints.
We requested the corresponding authors to provide access to the raw data. Where data was not provided, the proportion of infants and adults with IgG GMCs below the established correlate of protection (0.35 mcg/mL [36]) was estimated from the reported estimates of the geometric mean concentrations to each dose and log-scale standard deviation by assuming a normal distribution. To evaluate whether the assumption of normality was reasonable, the estimated proportions for one of the included studies which provided raw data, Rupp et al.’s formulation B, were compared with the reported proportions. The estimated proportions were found to be similar to those reported. Since Rupp et al. reported the proportion of responders (rather than proportion non-responders), the proportion of non-responders for their study was calculated as 1-proportion responders.

3 Results

The search identified 3791 articles; 1691 remained after deduplication (Fig. 1). A total of 360 full texts were reviewed; 9 studies were included in the review [2,28,37–43] (Table 2). Of the nine, two studies involved adult populations [41,43], six involved paediatric populations [2,28,38–40,42] and one involved adult and paediatric populations [37].

3.1 Quality of included studies

All the included studies were individually randomised controlled trials. The included studies were graded to have high to moderate quality of evidence (Supplementary Table 2). The blinding procedures for four of the nine studies [38–40,42] were not reported. Only five of the nine included studies, [37–39,41,43], mentioned the number of participants withdrawn or lost to follow up prior to the primary endpoint.

3.2 Immunogenicity in adult studies

Three studies involved adult populations [37,41,43] (Table 2). Lode et al. and Jackson et al. studied the immunogenicity of PCV7 (Prevnar®, Wyeth Vaccines, NY) in healthy adults > 70 years old with no history of PPV [43] and in adults 70–79 years old with a previous history of PPV exposure [41,44] respectively. The vaccines were administered as a single dose with polysaccharide doses ranging from 0.44 to 8.8 mcg for serotypes 4, 9V, 14, 18C, 19F, 23F and 0.88 to 17.6 mcg for serotype 6B. Rupp et al. evaluated the safety and immunogenicity of two formulations of PCV15 (Merck Sharp & Dohme Corp) in healthy adults aged 18 to 49 years with no history of either PPV or PCV exposure. The vaccines were administered as a single dose in each group at polysaccharide doses of 2 and 4 mcg. All PCV7 doses evaluated by Lode et al. and Jackson et al. were also evaluated by Rupp et al.

A dose dependent increase in serum IgG GMCs which then plateaued was apparent for serotype 4 for all three adult studies [37,41,43], serotype 6B for two out of three studies [41,43] and for serotype 23F in one of the three studies [41]. The overall IgG GMCs reported for Jackson et al. were lower than those reported for Lode et al. for all serotypes. IgG GMCs for serotype 9 and 23F reduced at higher doses in Lode et al. [43] and for both formulations in Rupp et al. [37], while those for serotype 19F, 18C, 9V and 23F for Lode et al. [43] increased with higher doses (Supplementary Fig. 1).
Estimated proportions of adults with IgG GMCs below the infant correlate of protection were calculated for the studies which reported IgG GMCs and the confidence intervals around these means, assuming a normal distribution (Supplementary Fig. 2). These proportions ranged between 0.1% (95% confidence interval (CI): 0–17.0%) (Lode et al., serotype 18C, dose: 4.4 mcg/mL) and 22.3% (95% CI: 12.4–36.8%) (Jackson et al., serotype 4, dose: 0.44 mcg/mL).

### 3.3 Immunogenicity in paediatric studies

A total of 7 studies involved paediatric populations ranging from 2 to 30 months of age [2,28,37–40,42] (Table 2). Daum et al. [28], Ahman et al. (1998 and 1999) [39,40] and Zangwill et al. [42] evaluated varying doses of experimental PCVs in 3-dose schedules at 2, 4 and 6 months of age. Steinhoff et al. [2] evaluated the immunogenicity of varying doses of PCV2 after a single dose administered at 18–30 months. Anderson et al. [38] evaluated varying doses of an experimental PCV3 with two different carrier proteins (Dip. CRM197 and Tetanus Toxoid) after two doses administered at 24 and 26 months. Rupp et al. [37] evaluated varying doses of two PCV15 formulations (Merck Sharp & Dohme Corp) after administration of a 4-dose schedule at 2, 4, 6 and 12–15 months of age. Concomitant vaccinations as per national vaccination schedules were allowed for all the studies. As immunogenicity varies with age, the two studies in toddlers [2,38] were not included in the descriptive synthesis as toddlers are not the target population for current routine immunization programmes. The common serotype evaluated by the toddler studies [2,38] was 23F. The proportion of toddlers with > 4-fold increase in IgG GMCs from baseline after a single dose for serotype 23F in these two studies ranged between 20% (group that received 5.1 mcg of PCV) [38] and 94% (group that received 2 mcg of PCV) [2].

Serotype specific IgG GMCs post final dose in comparable infant populations were plotted against each other for the common serotypes 6B, 14, 19F and 23F using data from Daum et al. [28], Ahman et al. (1998 and 1999) [39,40] and Rupp et al.’s formulation A with 250 mcg of aluminium phosphate [37]. Zangwill et al.’s [42] IgG GMCs were included for serotype 6B (Fig. 2). A dose–response effect was apparent for STs 14, 19F and 23F for the Daum et al. [28] and Ahman (1998) et al. [39] studies.

Confidence intervals around the IgG GMC for serotype 6B and 23F’s highest dose in the Ahman (1999) et al. [40] study crossed the correlate of protection as well as those for Ahman (1998) et al.’s [39] lowest dose for serotype 23F (Fig. 2).

Estimated proportions of infants with IgG GMCs below the correlate of protection (0.35 mcg/mL) were calculated for comparable infant studies which reported IgG GMCs and the confidence intervals around these means. Serotype 6B had the highest proportion of infants below the correlate of protection compared to other serotypes (Fig. 3). Increasing doses for STs 6B, 14 and 23F seemed to correspond to a decrease in the proportion of infants below the correlate of protection in the Ahman (1998) et al. trial [39].

### 3.4 Follow-up post primary endpoint in children

The longest follow up reported was 36 months after enrolment [39,40]. A booster dose was administered to children in three studies. All booster doses elicited a strong memory
response. Two studies reported that after a polysaccharide vaccine booster, antibody responses post-boost were higher in those who received the lowest vaccine dose in infancy (Table 3).

4 Discussion

This review aimed to collate evidence on the immunogenicity of varying doses of serotype specific polysaccharide within PCVs. Nine studies were included after a literature search that was limited to studies in humans that reported immunogenicity outcomes for varying doses. It is likely that more information on dose–response exists but lies unpublished by vaccine manufacturers as part of their research and development data. The studies included were all RCTs and graded to be of moderate to high quality evidence. Some of the studies had small sample sizes per trial arm but the effect of this on the statistical power of the results could not be calculated due to limitations in the data reported e.g. no information on loss to follow up and the IgG GMC variance. The included studies were published between 1994 and 2018. Most studies were published before there was an established immune correlate of protection in children, to inform the study results. The most recent study was of a PCV15 [37] which is currently undergoing adult and paediatric clinical development.

Of the seven paediatric studies included, five administered the study vaccine in a schedule of 3 primary doses (3p + 0) or a schedule of 3 primary doses plus a booster (3p + 1) to infants, starting at 2 months of age i.e. findings may be relevant to current routine infant immunisation schedules. The PCV doses tested ranged between 0.5 and 10 mcg. Only two of these five paediatric studies showed a dose–response where higher ST-specific doses correlated with higher GMCs after the prime vaccinations [37,39]. Paradoxically a clear dose response was not seen for ST6B; however, this serotype is consistently included at higher doses in licensed products than other serotypes, the data supporting this is decision is unclear from the available literature.

When the proportion of children with antibody titres above the established correlate of protection was estimated from the reported GMCs, the confidence intervals around the estimates are wide. Only one of the five studies showed a consistent favourable trend with dose, where the proportion of infants below the correlate of protection (i.e. “unprotected”) decreased with higher doses [39]. The limitations of this approach are acknowledged, the assumption of a normal distribution could be incorrect, despite it being supported by the data visually. Assuming alternative distributions could result in greater or lesser proportions above the correlate of protection. The performance of the assays used by the older studies [2,28,39,40] were not standardised. Because of this, it is unclear how their antibody results relate to the 0.35 mcg/ml threshold and they may not be accurate at the lower limits.

Additionally, the established correlate of protection is thought to overestimate the IgG concentrations needed to protect against invasive pneumococcal disease (IPD) caused by serotypes 6A, 6B, 18C and 23F and underestimate the concentration needed to protect against IPD caused by serotypes 1, 3, 7F, 19A and 19F [45,46]. Future PCVs may benefit from being evaluated against ST-specific thresholds rather than a common correlate of protection. However, this review provides some evidence that smaller doses than those included in currently distributed PCVs are immunogenic and could be protective in children.
In all three adult studies, there was a dose response where the highest dose induced the highest immune response [43]. History of pneumococcal polysaccharide vaccine prior to PCV administration could have contributed to the consistently lower IgG GMCs (hyporesponsiveness) in otherwise comparable participants enrolled in the Jackson et al. study, compared to the Lode et al. study [1,43]. There is no established correlate of protection for adult populations and therefore the clinical implications of the observed dose–response are unclear.

Lower priming doses were reported to give a higher GMCs post-boost, regardless of the vaccination schedule, in two paediatric and two adult studies that assessed this [37,39,40,42]. There are some data from studies of other vaccines that indicate smaller prime doses may elicit better memory responses to a booster dose [48,49]. Although the mechanisms for this are unclear, it is a reminder that measures of immunogenicity one month after the final dose in the series should not be seen in isolation and future studies should assess the impact of dose on immune memory.

This review is limited by the fact that the observed relationships between dose and immunogenicity are heterogenous and much of this variation may be attributable to factors other than the saccharide dose e.g. the carrier protein, the ratio of polysaccharide to carrier protein, the method of conjugation and the adjuvant of choice [3]. The two Ahman et al. studies provide a comparison of two carrier protein conjugates across three saccharide doses. In these studies, the TT conjugates [40] show a varied pattern, whereas the DT conjugates showed a dose–response relationship for some STs [39]. Other important factors are the conjugation technique and dose of adjuvant. For example, the Rupp et al. studies evaluated varying doses of PCV15 in two formulations that differed in their conjugation method and amount of aluminium hydroxide. One formulation performed better than the other across all serotypes in adults and infants and was selected for further clinical investigation [37]. Interaction with concurrently administered vaccines can also influence immune responses [47]. Despite reporting a satisfactory immune response to a primary series with OMPC as a carrier protein, Zangwill et al. [42], reported a negative effect of concurrent immunization with a homologous carrier protein (Hib conjugate vaccine) on the immune response to PCV. In addition to these factors, development of higher valency PCVs will also need to consider the total polysaccharide and carrier protein content to avoid hypo-responsiveness and immune interference e.g., PCV13 has been shown to induce a lower individual immune response compared to PCV7 and this may be due to the increase in total polysaccharide and carrier protein content [3,47].

5 Conclusion

In conclusion, for some products, the mean antibody concentrations induced against some pneumococcal serotypes increased with increasing doses of the polysaccharide conjugate, but for other serotypes and other products there was no clear dose–response relationship or the dose response curves were negative. Overall, in children, evidence suggests smaller doses of polysaccharide than those in currently distributed formulations are immunogenic and may be protective. However, the carrier protein content, conjugation technique and adjuvant also determine the quality and quantity of the immune response.
Since development of higher valency PCVs relies on optimization of the polysaccharide dose while minimizing the total polysaccharide and carrier protein content and adjuvant volume [3], evidence of the immunogenicity of these small doses of polysaccharide may be useful in the development of higher valency vaccines, or dose-sparing delivery.

References

[1]. Poolman J, Borrow R. Hyporesponsiveness and its clinical implications after vaccination with polysaccharide or glycoconjugate vaccines. Expert Rev Vaccines. 2011; 10 (3) 307–22. [PubMed: 21434799]

[2]. Steinhoff MC, Edwards K, Keyserling H, Thomas ML, Johnson C, Madore D, et al. A randomized comparison of three bivalent Streptococcus pneumoniae glycoprotein conjugate vaccines in young children: effect of polysaccharide size and linkage characteristics. Pediatr Infect Dis J. 1994; 13 (5) 368–72. [PubMed: 8072818]

[3]. Poolman JT, Peeters CCAM, van den Dobbelsteen GPJM. The history of pneumococcal conjugate vaccine development: dose selection. Expert Rev Vaccines. 2013; 12 (12) 1379–94. [PubMed: 24195479]

[4]. Kayhty H, Ahman H, Ronnberg P-R, Tillikainen R, Eskola J. Pneumococcal polysaccharide-meninococcal outer membrane protein complex conjugate vaccine is immunogenic in infants and children. J Infect Dis. 1995; 172 (5) 1273–8. [PubMed: 7594664]

[5]. Molrine DC, George S, Tarbell N, Mauch P, Diller L, Neuberg D, et al. Antibody responses to polysaccharide and polysaccharide-conjugate vaccines after treatment of Hodgkin disease. Ann Intern Med. 1995; 123: 828–34. [PubMed: 7486464]

[6]. Chan CY, Molrine DC, George S, Tarbell NJ, Mauch P, Diller L, et al. Pneumococcal conjugate vaccine primes for antibody responses to polysaccharide pneumococcal vaccine after treatment of Hodgkin’s disease. J Infect Dis. 1996; 173: 256–8. [PubMed: 8537671]

[7]. Anderson EL, Kennedy DJ, Geldmacher KM, Donnelly J, Mendelman PM. Immunogenicity of heptavalent pneumococcal conjugate vaccine in infants. J Pediatr. 1996; 128 (5) 649–53. [PubMed: 8627437]

[8]. Miernyk KM, Parkinson AJ, Rudolph KM, Petersen KM, Bulkow LR, Greenberg DP, et al. Immunogenicity of a heptavalent pneumococcal conjugate vaccine in Apache and Navajo Indian, Alaska native, and non-native American children aged <2 years. Clin Infect Dis. 2000; 31: 34–41. [PubMed: 10913393]

[9]. Åhman H, Käyhty H, Tamminen P, Vuorela A, Malinoski F, Eskola J. Pentavalent pneumococcal oligosaccharide conjugate vaccine PncCRM is well-tolerated and able to induce an antibody response in infants. Pediatr Infect Dis J. 1996; 15 (2) 134–9. [PubMed: 8822286]

[10]. Powers DC, Anderson EL, Lattenbach K, Mink CM. Reactogenicity and immunogenicity of a protein-conjugated pneumococcal oligosaccharide vaccine in older children. J Infect Dis. 1996; 173 (4) 1014–8. [PubMed: 8603942]

[11]. King JC Jr, Vink PE, Chang I, Kimura A, Parks M, Smilie M, et al. Antibody titers eight months after three doses of a five-valent pneumococcal conjugate vaccine in HIV and non-HIV-infected children less than two years of age. Vaccine. 1998; 16: 361–5. [PubMed: 9607056]

[12]. Soininen A, Seppala I, Nieminen T, Eskola J, Kayhty H. IgG subclass distribution of antibodies after vaccination of adults with pneumococcal conjugate vaccines. Vaccine. 1999; 17: 1889–97. [PubMed: 10217586]

[13]. Leach A, Ceesay SJ, Banya WAS, Greenwood BM. Pilot trial of a pentavalent pneumococcal polysaccharide/protein conjugate vaccine in Gambian infants. Pediatr Infect Dis J. 1996; 15 (4) 333–9. [PubMed: 866803]

[14]. Dagan R, Melamed R, Zamir O, Leroy O. Safety and immunogenicity of tetravalent pneumococcal vaccines containing 6B, 14, 19F and 23F polysaccharides conjugated to either tetanus toxoid or diphtheria toxoid in young infants and their boosterability by native polysaccharide antigens. Pediatr Infect Dis J. 1997; 16 (11) 1053–9. [PubMed: 9384339]
[15]. Rennels MB, Edwards KM, Keyserling HL, Reisinger KS, Hoberman DA, Madore DV, et al. Safety and immunogenicity of heptavalent pneumococcal vaccine conjugated to CRM197 in United States infants. Pediatrics. 1998; 101 (4) 604–11. [PubMed: 9521941]

[16]. Shinefield HR, Black S, Ray P, Chang IH, Lewis N, Fireman B, et al. Safety and immunogenicity of heptavalent pneumococcal CRM197 conjugate vaccine in infants and toddlers. Pediatr Infect Dis J. 1999; 18 (9) 757–63. [PubMed: 10493334]

[17]. Mbelle N, Huebner R, Wasas A, Kimura A, Chang Ih, Klugman K. Immunogenicity and impact on nasopharyngeal carriage of a nonavalent pneumococcal conjugate vaccine. J Infect Dis. 1999; 180 (4) 1171–6. [PubMed: 10479145]

[18]. Huebner RE, Mbelle N, Forrest B, Madore DV, Klugman KP. Immunogenicity after one, two or three doses and impact on the antibody response to coadministered antigens of a nonavalent pneumococcal conjugate vaccine in infants of Soweto, South Africa. Pediatr Infect Dis J. 2002; 21 (11) 1004–7. [PubMed: 12442020]

[19]. Madhi SA, Kuwanda L, Cutland C, Holm A, Kayhty H, Klugman KP. Quantitative and qualitative antibody response to pneumococcal conjugate vaccine among African human immunodeficiency virus-infected and uninfected children. Pediatr Infect Dis J. 2005; 24: 410–6. [PubMed: 15876939]

[20]. Puumalainen T, Zeta-Capeding MR, Käyhty H, Lucero MG, Auranen K, Leroy O, et al. Antibody response to an eleven valent diphtheria- and tetanus-conjugated pneumococcal conjugate vaccine in Filipino infants. Pediatr Infect Dis J. 2002; 21 (4) 309–14. [PubMed: 12075672]

[21]. Dagan R, Käyhty H, Wuorimaa T, Yaich M, Bailleux F, Zamir O, et al. Tolerability and immunogenicity of an eleven valent mixed carrier Streptococcus pneumoniae capsular polysaccharide-diphtheria toxoid or tetanus protein conjugate vaccine in Finnish and Israeli infants. Pediatr Infect Dis J. 2004; 23 (2) 91–8. [PubMed: 14872172]

[22]. Soininen A, Nohynek H, Lucero M, Jousimies K, Ugpo J, Williams G, et al. IgG antibody concentrations after immunization with 11-valent mixed-carrier pneumococcal conjugate vaccine in efficacy trial against pneumonia among Filipino infants. Vaccine. 2009; 27 (20) 2680–8. [PubMed: 19428879]

[23]. Eick A, Croll J, Weatherholtz R, Croll L, Santosham M. Safety and immunogenicity of two octavalent pneumococcal conjugate vaccines in American Indian infants. Vaccine. 2004; 22 (9-10) 1260–4. [PubMed: 15003655]

[24]. Prymula R, Chlibek R, Splino M, Kaliskova E, Kohl I, Lommel P, et al. Safety of the 11-valent pneumococcal vaccine conjugated to non-typeable Haemophilus influenzae-derived protein D in the first 2 years of life and immunogenicity of the co-administered hexavalent diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated polio virus, Haemophilus influenzae type b and control hepatitis A vaccines. Vaccine. 2008; 26 (35) 4563–70. [PubMed: 18602724]

[25]. Dotres CP, Puga R, Ricardo Y, Broño CR, Paredes B, Echemendia V, et al. Safety and preliminary immunogenicity of Cuban pneumococcal conjugate vaccine candidate in healthy children: a randomized phase I clinical trial. Vaccine. 2014; 32 (41) 5266–70. [PubMed: 25068497]

[26]. McFetridge R, Meulen A-T, Folkersd SD, Hoecka JA, Dallas M, Hoover PA, et al. Safety, tolerability, and immunogenicity of 15-valent pneumococcal conjugate vaccine in healthy adults. Vaccine. 2015; 33 (24) 2793–9. [PubMed: 25913828]

[27]. Sobanjo-ter Meulen A, Vesikari T, Malacanan EA, Shapiro SA, Dallas MJ, Hoover PA, et al. Safety, tolerability and immunogenicity of 15-valent pneumococcal conjugate vaccine in toddlers previously vaccinated with 7-valent pneumococcal conjugate vaccine. Pediatr Infect Dis J. 2015; 34: 186–94. [PubMed: 25741971]

[28]. Daum RS, Hoberman D, Rennels MB, Bewley K, Malinoski F, Rothstein E, et al. Infant immunization with pneumococcal CRM197 vaccines: effect of saccharide size on immunogenicity and interactions with simultaneously administered vaccines. J Infect Dis. 1997; 176: 445–55. [PubMed: 9237711]

[29]. Jódar L, Butler J, Carlone G, Dagan R, Godblatt D, Käyhty H, et al. Serological criteria for evaluation and licensure of new pneumococcal conjugate vaccine formulations for use in infants. Vaccine. 2003; 21 (23) 3265–72. [PubMed: 12804857]
[30]. Voysey M, Fanshawe TR, O’Brien KL, Kandasamy R, Shrestha S, et al. Serotype-specific correlates of protection for pneumococcal carriage: an analysis of immunity in 19 countries. Clin Infect Dis. 2018; 66: 913–20. [PubMed: 29069415]

[31]. Center IV A. VIEW-hub report: Global vaccine introduction and implementation. Johns Hopkins Bloomberg School of Public Health; 2019.

[32]. Gavi Secretariat. Alternative Dosing Schedules for PCV: Gavi eligible and transitioning country perspectives; Vaccine Implementation presentation 9–10 Feb 2016; 2016.

[33]. Gavi. Gavi’s pneumococcal support. 2016. http://www.gavi.org/support/nvs/pneumococcal/

[34]. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med. 2009; 151: 264–9. [PubMed: 19622511]

[35]. Ryan R, Hill S. How to GRADE the quality of the evidence Cochrane Consumers and Communication Group. Version 3.0 2016.

[36]. Siber GR, Chang Ih, Baker S, Fernsten P, O’Brien KL, Santosham M, et al. Estimating the protective concentration of anti-pneumococcal capsular polysaccharide antibodies. Vaccine. 2007; 25 (19) 3816–26. [PubMed: 17368878]

[37]. Rupp R, Hurley D, Grayson S, Li J, Nolan K, McFetridge RD, et al. A dose ranging study of 2 different formulations of 15-valent pneumococcal conjugate vaccine (PCV15) in healthy infants. Human Vaccines Immunother. 2019; 15 (3) 549–59.

[38]. Anderson P, Treanor J, Porcelli S, Pichichero M. Non-interference between two protein carriers when used with the same polysaccharide for pneumococcal conjugate vaccines in 2-year-old children. Vaccine. 2003; 21 (13-14) 1554–9. [PubMed: 12615453]

[39]. Åhman H, Käyhty H, Lehtonen H, Leroy O, Froeschle J, Eskola J. Streptococcus pneumoniae capsular polysaccharide-diphtheria toxoid conjugate vaccine is immunogenic in early infancy and able to induce immunologic memory. Pediatr Infect Dis J. 1998; 17 (3) 211–6. [PubMed: 9535248]

[40]. Åhman H, Käyhty H, Vuorela A, Leroy O, Eskola J. Dose dependency of antibody response in infants and children to pneumococcal polysaccharides conjugated to tetanus toxoid. Vaccine. 1999; 17: 2726–32. [PubMed: 10418924]

[41]. Jackson LA, Neuzil KM, Nahm MH, Whitney CG, Yu O, Nelson JC, et al. Immunogenicity of varying dosages of 7-valent pneumococcal polysaccharide-protein conjugate vaccine in seniors previously vaccinated with 23-valent pneumococcal polysaccharide vaccine. Vaccine. 2007; 25 (20) 4029–37. [PubMed: 17391816]

[42]. Zangwill KM, Greenberg DP, Chiu C-Y, Mendelman P, Wong VK, Chang S-J, et al. Safety and immunogenicity of a heptavalent pneumococcal conjugate vaccine in infants. Vaccine. 2003; 21: 1894–900. [PubMed: 12706674]

[43]. Lode H, Schmoele-Thoma B, Gruber W, Ahlers N, Fernsten P, Baker S, et al. Dose-ranging study of a single injection of pneumococcal conjugate vaccine (1x, 2x, or 4x) in healthy subjects aged 70 years or older. Vaccine. 2011; 29 (31) 4940–6. [PubMed: 21596077]

[44]. Jackson L, Neuzil K, Whitney C, Starkovich P, Dunstan M, Yu O, et al. Safety of varying dosages of 7-valent pneumococcal protein conjugate vaccine in seniors previously vaccinated with 23-valent pneumococcal polysaccharide vaccine. Vaccine. 2005; 23 (28) 3697–703. [PubMed: 15882530]

[45]. Andrews NJ, Wright PA, Burbidge P, Pearce E, Roalfe L, Zancolli M, et al. Serotype-specific effectiveness and correlates of protection for the 13-valent pneumococcal conjugate vaccine: a postlicensure indirect cohort study. Lancet Infect Dis. 2014; 14 (9) 839–46. [PubMed: 25042756]

[46]. Principi N, Esposito S. Serological criteria and carriage measurement for evaluation of new pneumococcal vaccines. Hum Vaccin Immunother. 2015; 11 (6) 1494–500. [PubMed: 25970715]

[47]. Dagan R, Poolman J, Siegrist C-A. Glycoconjugate vaccines and immune interference: a review. Vaccine. 2010; 28 (34) 5513–23. [PubMed: 20600514]

[48]. Borrow R, Goldblatt D, Finn A, Southern J, Ashton L, Andrews N, et al. Immunogenicity of, and immunologic memory to, a reduced primary schedule of meningococcal C-tetanus toxoid conjugate vaccine in infants in the United Kingdom. Infect Immun. 2003; 71 (10) 5549–55. [PubMed: 14500473]
[49]. Asante KP, Abdulla S, Agnandji S, Lyimo J, Vekemans J, Soulanourdjingar S, et al. Safety and efficacy of the RTS, S/AS01E candidate malaria vaccine given with expanded-programme-on-immunisation vaccines: 19 month follow-up of a randomised, open-label, phase 2 trial. Lancet Infect Dis. 2011; 11 (10) 741–9. [PubMed: 21782519]
Fig. 1. PRISMA flow diagram.
This diagram describes the literature search process and inclusion/exclusion criteria used to identify the studies included in this review.
(a) Immunogenicity outcome for serotype 19F

(b) Immunogenicity outcome for serotype 14
Fig. 2. Immunogenicity outcome in paediatric studies.

These figures illustrate the various immunogenicity outcomes for some of the included paediatric studies. The round dots represent point estimates i.e. the IgG GMCs reported for each polysaccharide dose evaluated. The limits plotted about the point estimates are margins of error calculated from the point estimates and their 95% confidence intervals.

Note: the scale of the axes for 6B and 23F differ from the scale for 19F and 14 due to the difference in range of GMCs. Legend: Publication (vaccine carrier protein) (a) Immunogenicity outcome for serotype 19F. (b) Immunogenicity outcome for serotype 14.
(c) Immunogenicity outcome for serotype 6B. (d) Immunogenicity outcome for serotype 23F.
Fig. 3. Estimated proportion of infants below correlate of protection (COP).
These figures illustrate the proportion of infants below the established COP as estimated from the data extracted. The round dots represent point estimates i.e. The estimated proportion below COP. The limits plotted about the point estimates are margins of error obtained from the difference between the 95% confidence intervals and the respective point estimates on either side. Legend: Publication (vaccine carrier protein) (a) Proportions

Vaccine. Author manuscript; available in PMC 2022 September 06.
for serotype 6B. (b) Proportions for serotype 14. (c) Proportions for serotype 19F. (d) Proportions for serotype 23F.
Table 1
Candidate Pneumococcal Conjugate Vaccine formulation (pre- and post-licensure).

| Licensure status | Licensed as PCV7 | Licensed in PCV10 | Licensed in PCV13 | Not licensed | Conjugate protein | Adjuvant |
|------------------|------------------|------------------|------------------|--------------|------------------|----------|
| Pneumococcal serotype saccharide, dose (μg) | 4                   | 6B               | 9V               | 14C          | 19F              | 23F      | 1       | 5       | 7F       | 3       | 6A       | 19A       | 22F       | 33F       |
| Licensed as PCV7 | 1                 | 1                 | 1                 | 1            |                  |          |         |         |          |         |          |          |          |          |          |
| Licensed as PCV8 | 1                 | 1                 | 1                 | 1            |                  |          |         |         |          |         |          |          |          |          |          |
| Licensed as PCV9 | 1                 | 1                 | 1                 | 1            |                  |          |         |         |          |         |          |          |          |          |          |
| Licensed as PCV10| 1                 | 1                 | 1                 | 1            |                  |          |         |         |          |         |          |          |          |          |          |
| Licensed as PCV11| 1                 | 1                 | 1                 | 1            |                  |          |         |         |          |         |          |          |          |          |          |
| Licensed as PCV12| 1                 | 1                 | 1                 | 1            |                  |          |         |         |          |         |          |          |          |          |          |
| Licensed as PCV13| 1                 | 1                 | 1                 | 1            |                  |          |         |         |          |         |          |          |          |          |          |
| Licensed as PCV14| 1                 | 1                 | 1                 | 1            |                  |          |         |         |          |         |          |          |          |          |          |
| Licensed as PCV15| 1                 | 1                 | 1                 | 1            |                  |          |         |         |          |         |          |          |          |          |          |
| Licensed as PCV16| 1                 | 1                 | 1                 | 1            |                  |          |         |         |          |         |          |          |          |          |          |
| Licensed as PCV17| 1                 | 1                 | 1                 | 1            |                  |          |         |         |          |         |          |          |          |          |          |
| Licensed as PCV18| 1                 | 1                 | 1                 | 1            |                  |          |         |         |          |         |          |          |          |          |          |
| Licensed as PCV19| 1                 | 1                 | 1                 | 1            |                  |          |         |         |          |         |          |          |          |          |          |
| Licensed as PCV20| 1                 | 1                 | 1                 | 1            |                  |          |         |         |          |         |          |          |          |          |          |
| Licensed as PCV21| 1                 | 1                 | 1                 | 1            |                  |          |         |         |          |         |          |          |          |          |          |
| Licensed as PCV22| 1                 | 1                 | 1                 | 1            |                  |          |         |         |          |         |          |          |          |          |          |
| Licensed as PCV23| 1                 | 1                 | 1                 | 1            |                  |          |         |         |          |         |          |          |          |          |          |
| Licensed as PCV24| 1                 | 1                 | 1                 | 1            |                  |          |         |         |          |         |          |          |          |          |          |
| Licensed as PCV25| 1                 | 1                 | 1                 | 1            |                  |          |         |         |          |         |          |          |          |          |          |
| Licensed as PCV26| 1                 | 1                 | 1                 | 1            |                  |          |         |         |          |         |          |          |          |          |          |
| Licensed as PCV27| 1                 | 1                 | 1                 | 1            |                  |          |         |         |          |         |          |          |          |          |          |

Pre-licensure vaccine candidates [Manufacturer, year of earliest appearance in publication]

- PCV4 [4] [Merck, 1995]
- PCV7 [5,6] [Merck, 1995]
- PCV7 [7,8] [Merck, 1996]
- PCV5 [9–12] [Lederle, 1996]
- PCV5 [13] [Lederle, 1996]
- PCV4 [14] [Pasteur Mérieux, 1997]
- PCV7 [15,16] [Wyeth, 1998]
- PCV9 [17–19] [Wyeth-Lederle, 1999]
- PCV11 [20–22] [Aventis Pasteur, 2001]
- PCV8 [23] [Aventis Pasteur, 2004]
- PCV8 [23] [Aventis Pasteur, 2004]
- PCV11 [24] [GSK, 2008]
- PCV7 [25] [Centre for Bimolecular Chemistry Cuba, 2014]
- PCV15 [26,27] [Merck Sharpe & Dohme, 2015]

Licensed products [year of licensure]:

- PCV7 (Pfizer/Wyeth; 2000)

Vaccine. Author manuscript; available in PMC 2022 September 06.
| Licensure status | Licensed as PCV7 | Licensed in PCV10 | Licensed in PCV13 | Not licensed | Conjugate protein | Adjuvant |
|-----------------|-----------------|------------------|------------------|-------------|------------------|---------|
| Pneumococcal serotype saccharide, dose (μg) |  |  |  |  |  |
| PCV10 (GSK, 2009) | 4 6B 9V 14 18C 19F 23F 1 5 7F 3 6A 19A 22F 33F | 3.0 1.0 1.0 1.0 3.0 1.0 1.0 1.0 |  |  | D (NTHib), Dip, TT | Aluminium phosphate |
| PCV13 (Pfizer/Wyeth; 2010) | 2.2 4.4 2.2 2.2 2.2 2.2 2.2 2.2 2.2 2.2 2.2 2.2 2.2 2.2 |  |  |  | Dip, CRM197 | Aluminium phosphate |

Abbreviations: CRM197: non-toxic mutant of Diphtheria toxin; D(NTHib): Protein D of non-typeable Haemophilus influenzae type b; DT: Diphtheria Toxin; OMPC: outer membrane protein complex of Neisseria meningitidis serotype B; TT: Tetanus Toxin.

\(^1\)PCV10 (GSK) product.
### Table 2

**Summary of included studies.**

| Reference                  | Population (age at enrolment) | Vaccine schedule | Arms | Total Sample Size | PCV valency (targeted serotypes) | Manufacturing company | Carrier protein | Adjuvant | Doses tested (mcg) | Timepoint of primary outcome |
|---------------------------|-------------------------------|------------------|------|------------------|----------------------------------|------------------------|-----------------|----------|------------------|-------------------------------|
| Steinhoff (1994) [2]      | American children (18 – 30 months) | Single dose      | 118  | 7                | PCV 2 (6B, 23F)                  | Lederle               | DT              | Aluminium Phosphate | 2, 10                        | 1-month post dose             |
| Daum (1997) [28]          | American infants (2–3 months) | 2, 4, 6 months   | 400  | 7                | PCV 5 (6B, 14, 18C, 19F, 23F)    | Wyeth-Lederle         | DT              | Aluminium Phosphate | 0.5, 2, 5                  | 1-month post dose             |
| Ahman (1998) [39]         | Finnish infants (9–13 weeks)  | 2, 4, 6 months   | 125  | 4                | PCV 4 (6B, 14, 19F, 23F)         | Pasteur Merieux       | DT              | Not stated          | 1, 3, 10                    | 1-month post dose             |
| Ahman (1999) [40]         | Finnish infants (9-13 weeks)  | 2, 4, 6 months   | 75   | 3                | PCV 4 (6B, 14, 19F, 23F)         | Pasteur Merieux       | TT              | Not stated          | 1, 3, 10                    | 1-month post dose             |
| Zangwill (2003) [42]      | American infants (2 months)   | 2, 4, 6, 12 months | 240 | 3                | PCV 7 (4, 6B, 9V, 14, 18C, 23F)  | Merck & Co            | OMPC (123 vs 110 mcg) | Aluminium Phosphate | 6B: 5, 8, 14, 18C, 23F | 1-month post dose             |
| Anderson (2003) [38]      | American children (2 years)   | 24, 26 months    | 112  | 5                | PCV 3 (6A, 14, 19F)              | Eli Lilly &Co         | CRM197          | None                | 6A: 6, 7, 14, 18C, 23F | 1-month post dose             |
| Rupp (2019) [37]          | American infants (6–12 weeks) | 2, 4, 6, 12-15 months | 404 | 8                | PCV 15 Formulation A2 (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, 33F) | Merck & Co            | CRM197          | Aluminium Phosphate (125 vs 250 mcg) | 2, 4, 6B: 2, 4, 8 | 1-month post dose             |
|                           | American infants (6 – 12 weeks) | 2, 4, 6, 12-15 months | 404 | 8                | PCV 15 Formulation B2 (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, 33F) | Merck & Co            | CRM197          | Aluminium Phosphate (125 vs 250 mcg) | 2, 4, 6B: 4, 8 | 1-month post dose             |
| American adults (18–49 years) with no history of PPV or PCV | Single dose | 80 | 4 | | | | | | | |
| American adults (18–49 years) with no history of PCV | | | | | | | | | | |

*Vaccine. Author manuscript; available in PMC 2022 September 06.*
| Reference  | Population (age at enrolment) | Vaccine schedule | Total Sample Size | Arms | PCV valency (targeted serotypes) | Manufacturing company | Carrier protein | Adjuvant Doses tested (mcg) | Timepoint of primary outcome |
|------------|-------------------------------|------------------|-------------------|------|---------------------------------|-----------------------|----------------|-----------------------------|-----------------------------|
| Lode (2011) [43] | German adults (>70 years) with no history of PPV or PCV | Single dose | 443 | 4 | PCV 7 (4, 6B, 9V, 14, 18C, 19F, 23F) | Wyeth Vaccines CRM197 | Aluminium Phosphate (125 vs 250 mcg) | 0.44, 2.2, 4.4, 8.8, 6B: 0.88, 4.4, 8.8, 17.6 | 1-month post dose |
| Jackson (2007) [41,44] | Adults (70–79 years) with history of PPV at least 5 years prior | Single dose | 220 | 5 | PCV 7 (4, 6B, 9V, 14, 18C, 19F, 23F) | Wyeth Vaccines CRM197 | Aluminium Phosphate (125 vs 250 mcg) | 0.44, 2.2, 4.4, 8.8, 6B: 0.88, 4.4, 8.8, 17.6 | 1-month post dose |

Abbreviations: CRM 197: non-toxic mutant of Diphtheria toxin; DT: Diphtheria Toxin; OMPC: outer membrane protein complex of Neisseria meningitidis serotype B; TT: Tetanus Toxin.

1 Doses stated are for all serotypes unless named serotypes are specified.

2 The two Rupp et al. formulations were conjugated differently. However, each formulation evaluated either 125 or 250 mcg aluminium phosphate adjuvant.
### Table 3
Follow-up post primary series paediatric studies.

| Study                        | Longest follow-up | Booster dose administered | Antibody levels pre-boost                                                                 | Response to booster dose                                                                 |
|------------------------------|-------------------|---------------------------|-------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|
| Ahman et al. [39]            | 36 months         | PncPS at 14 months       | At 14 months significant waning of IgG GMCs against STs 6B, 14 and 19F but not against 23F. No significant difference in titres by original dose of PCV. | 3–24-fold increase in IgG GMCs. Booster response was highest in those who received the lowest doses in infancy. |
| Ahman et al. [40]            | 36 months         | PncPS at 14 months       | At 14 months significant waning of IgG GMCs No significant difference in titres by original dose of PCV. | 2.15–12-fold increase in IgG GMCs Booster response was highest in those who received the lowest doses in infancy |
| Zangwill et al. [42]         | 13 months         | PCV at 12 months         | Antibody decline was substantial but comparable in all groups                               | 4.3–6.5-fold rise, comparable in all groups                                               |

Abbreviations: DT: Diphtheria toxoid; GMC: geometric mean concentration; IgG: immunoglobulin; OMPC: outer membrane protein complex of Neisseria meningitidis serotype B; PCV: pneumococcal conjugate vaccine; PncPS: Pneumococcal Polysaccharide Vaccine; ST: serotype; TT: tetanus toxoid.

1 Boost dose was administered to all infants who received PCV in infancy (not placebo).