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ORIGINAL RESEARCH

Indirect Comparison of PCV20 Immunogenicity with PCV10 in Pediatric 3+1 and 2+1 Schedules

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ABSTRACT

***Introduction*:** The 20-valent pneumococcal conjugate vaccine (PCV20) was licensed for prevention of pneumococcal disease in infants and children on the basis of immunogenicity compared with PCV13. We aimed to evaluate PCV20 immunogenicity compared with PCV10 (Synflorix; PhiD-CV) because both vaccines demonstrated lower immunogenicity than PCV13. Nevertheless, PCV10 was highly effective against vaccine-serotype pneumococcal disease in post-licensure studies. Since no study has directly compared PCV20 versus PCV10, we conducted an indirect comparison.

***Methods*:** We conducted indirect comparisons for PCV20 versus PCV10 using data from published randomized control trials that directly compared these vaccines with PCV13 in 3+1 or 2+1 schedules. Serotype-specific immunoglobulin (Ig)G concentrations and opsonophagocytic activity (OPA) were assessed post-booster dose and post-primary series. First, geometric mean ratios (GMRs) were obtained for shared serotypes for each direct comparison against PCV13; we conducted a meta-analysis to generate pooled GMRs if data from multiple trials were available. Next, we indirectly compared relative GMRs of PCV20 versus PCV10 using PCV13 as the common comparator. In this descriptive analysis, GMRs > 1 favored PCV20 and GMR < 1 favored PCV10.

***Results*:** Meta-analyses of PCV10 versus PCV13 data found that PCV10 was less immunogenic for most of the ten shared serotypes. When indirectly compared via PCV13, the relative immunogenicity of PCV20 versus PCV10 varied by serotype. Overall, IgG responses for the ten shared serotypes were similar for both 3+1 and 2+1 schedules, both post-primary series and post-booster dose. GMRs for both IgG and OPA

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were close to the line of equivalence, or spread between favoring PCV20 or PCV10.
Conclusions: The comparable immunogenicity of PCV20 versus PCV10 in 2+1 and 3+1 schedules suggests that PCV20 will have similar effectiveness for the ten serotypes included in both vaccines, including for direct protection during infancy and toddler age, while also expanding serotype coverage. Effectiveness for PCV20 needs to be confirmed in post-marketing studies.

Keywords: Antibodies; Immunogenicity; Indirect comparison; Pediatrics; Pneumococcal conjugate vaccine (PCV); *Streptococcus pneumoniae*; Vaccine schedules

Key Summary Points

Why carry out this study?
The 20-valent pneumococcal conjugate vaccine (PCV20) was licensed for the prevention of pneumococcal disease in infants and children on the basis of safety and immunogenicity, however, its effectiveness is not known.
The main objective of this study was to evaluate the relative immunogenicity of PCV20 versus PCV10, a vaccine with well-documented effectiveness, in commonly used pediatric schedules (3+1 and 2+1).
What was learned from the study?
Indirect comparison found that PCV20 immunogenicity was generally similar to PCV10 for shared serotypes, in either 2+1 or 3+1 schedules, post-infant and booster doses.
Because PCV10 was highly effective at preventing vaccine-type invasive pneumococcal disease at the individual and population levels, these findings support that PCV20 will have similar effectiveness for the ten common serotypes while expanding serotype coverage.
PCV20 effectiveness should be confirmed with real-world studies.

INTRODUCTION

Pneumococcal conjugate vaccines (PCVs) have led to substantial reductions in the global burden of pneumococcal disease and associated deaths in children since their introduction in 2000 [1]. However, a significant burden of pneumococcal disease remains. In settings where the 10- and 13-valent PCVs (PCV10 and PCV13) have been widely used, much of the remaining disease burden is due to non-vaccine serotypes [2]. The 20-valent pneumococcal conjugate vaccine (PCV20) was developed to provide expanded protection against pneumococcal disease by adding seven medically important serotypes (8, 10A, 11A, 12F, 15B, 22F, 33F) beyond those included in PCV13 [3]. A systematic review of invasive pneumococcal disease (IPD) data published during 2010–2020 reported that 27.8% of cases in children were due to the seven additional serotypes included in PCV20 [4].

As efficacy trials for expanded-valency PCVs are no longer feasible nor ethical to conduct in children, evaluation and licensure of novel PCVs have been based upon safety and immunogenicity trials when compared with PCV13, in line with World Health Organization (WHO) recommendations [5]. Two pivotal, phase 3 non-inferiority trials directly compared the immunogenicity of PCV20 with PCV13 when administered as either two or three priming doses in infancy followed by a booster dose (2+1 or 3+1 schedules, respectively). The results supported inferring clinical protection by immunobridging of real-world effectiveness and impact data from PCV13 [6–10]. For the 13 serotypes included in both vaccines (shared serotypes), serotype-specific IgG levels were moderately lower for PCV20 compared with PCV13, particularly after the primary series, an expected finding as higher valency PCVs typically result in lower immunogenicity to individual antigens due to immune interference [11, 12]. After the booster dose, IgG concentrations after PCV20 vaccination became more similar to the PCV13 comparator arm in both schedules.

Previously, PCV13 licensure trials found that immune responses were generally lower than

those induced by PCV7 for the seven shared serotypes, with serotypes 6B and 9V missing a non-inferiority criterion after the primary series in the 3 + 1 pivotal study [13]. However, post-licensure studies confirmed that PCV13 provided substantial clinical protection including for serotypes that missed non-inferiority criteria [8, 9, 14]. Similar observations were made for the 10-valent PCV (PCV10 [Synflorix; PhiD-CV]) when compared with PCV7 [15]. In randomized controlled trials (RCTs), PCV10 induced lower serotype-specific IgG concentrations compared with PCV13 for several shared serotypes [16]. However, real-world evidence confirmed that PCV10 was highly effective in preventing IPD due to serotypes included in the vaccine [17, 18]. The SpIDnet multicountry European surveillance study found that effectiveness of ≥ 1 dose of PCV10 was 84.8% (95% CI 69.4–92.5%) against vaccine-type IPD, remarkably similar to the effectiveness of ≥ 1 dose of PCV13 (84.2% [95% CI 79.0–88.1%]) [9].

In the absence of head-to-head RCTs that directly compare vaccine immunogenicity, indirect comparisons can assess the relative immunogenicity of different vaccines when evaluated against a common comparator. Indirect comparisons have been used for a variety of vaccines for which multiple products and formulations are available, including PCVs [19–21]. Evaluating PCV20 against another PCV with well-established effectiveness, such as PCV10, could help address uncertainties regarding PCV20's clinical protection, particularly for the 2 + 1 schedule. In the pivotal phase 3 trial that compared PCV20 with PCV13, four serotypes (6A, 6B, 9V, and 23F), which are also included in PCV10, failed to meet both non-inferiority criteria, indicating lower immunogenicity, when assessed after the two-dose primary series [7]. While no RCTs have directly compared immunogenicity of PCV20 versus PCV10, an indirect comparison could help to infer clinical protection for PCV20 if the relative immunogenicity of the two vaccines were found to be similar. Currently, no efficacy or effectiveness data are available for PCV20.

The main objective of this study was to evaluate the relative immunogenicity of PCV20 versus PCV10 in commonly used pediatric schedules (3 + 1 and 2 + 1) when compared with PCV13. Indirect comparisons were conducted for serotype-specific IgG concentrations as well as opsonophagocytic activity (OPA) titers, which measure antibody functional activity. We also conducted an indirect comparison of PCV20 versus the 15-valent PCV (PCV15) using IgG and OPA data from all available phase 3 trial data to augment indirect comparisons previously conducted by others [20, 21].

METHODS

PCV20 versus PCV10 Indirect Comparison

This study indirectly compared PCV20 and PCV10 (Synflorix; PhiD-CV) for the common serotypes (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F) in pediatric populations, for both 2 + 1 and 3 + 1 schedules (Fig. 1A). For PCV20 versus PCV13, two studies were selected a priori (Table 1). These were two phase 3 randomized controlled trials (RCTs) that directly compared PCV20 versus PCV13: Korbal et al. [7], which evaluated a 2 + 1 schedule, and Senders et al.[6], which used a 3 + 1 schedule. IgG and OPA GMRs from the two phase RCTs that compared PCV20 versus PCV13 are presented in Supplementary Tables 1 and 2.

To identify RCTs that directly compared PCV10 with PCV13, our main data source was Feng et al., who conducted a systematic literature review to identify studies that compared the immunogenicity of licensed PCVs for infants or children in head-to-head randomized trials, as of 17 February 2023 [16]. We screened the studies identified by Feng et al. to identify relevant studies that compared PCV10 with PCV13 using a 2 + 1 or 3 + 1 schedule. We also conducted a hand search to identify any additional relevant studies not included in the Feng publication. The seven studies of PCV10 versus PCV13 included in the indirect comparison are described in Table 1. A flow chart of study selection (Supplementary Fig. 1) and further details are provided in the Supplementary Information.

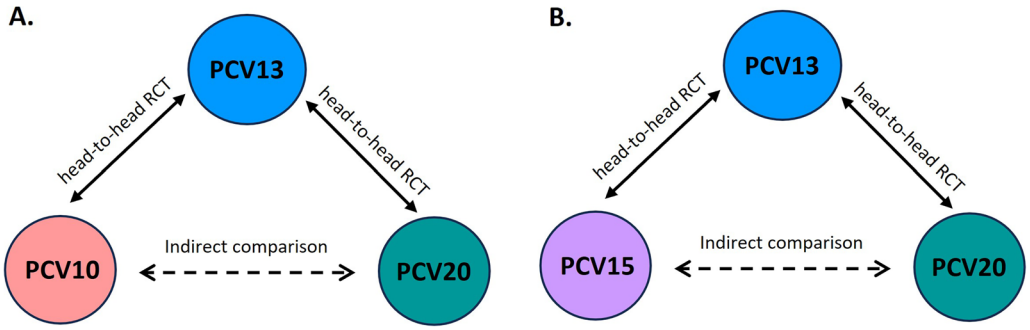

Fig. 1 Indirect comparison diagram for the 20-valent pneumococcal conjugate vaccine (PCV20) versus 10-valent pneumococcal conjugate vaccine (PCV10) (**A**) and PCV20 versus 15-valent pneumococcal conjugate vaccine (PCV15) (**B**). *PCV13* 13-valent pneumococcal conjugate vaccine, *RCT* randomized controlled trial

Table 1 Summary of included studies

Author and year	Country	Regimen	Vaccination timing
PCV20 versus PCV13			
Senders [6]	USA	3 + 1	2, 4, 6, and 12–15 months
Korbal [7]	Denmark, Poland, Norway, Finland, Czech Republic, Netherlands, Italy, Australia	2 + 1	2–3, 4–5, and 11–12 months
PCV10 versus PCV13			
Carmona Martinez 2019 [22]	Czech Republic, Germany, Poland, Spain	3 + 1	2, 3, 4, and 12–15 months
Prymula 2017 [23]	Czech Republic, Germany, Poland, Sweden	3 + 1	2, 3, 4, and 12–15 months
Wijmenga-Mansuur 2015 [24]	Netherlands	3 + 1	2, 3, 4, and 11 months[a]
Temple 2019 [30]	Vietnam	2 + 1	2, 4, and 9.5 months
Kawade 2023 [31]	India	2 + 1	6 weeks, 14 weeks, and 9 months
Madhi 2020 [32]	South Africa	2 + 1	6, 14, and 40 weeks
Adigweme 2023 [29]	The Gambia	2 + 1	6–8 weeks, 14–16 weeks, and 9–18 months
PCV15 versus PCV13			
Lupinacci [26]	USA, Puerto Rico, Thailand, Türkiye	3 + 1	2, 4, 6, and 12–15 months
Martinon-Torres [28]	Australia, Belgium, Czech Republic, Estonia, Germany, Greece, Poland, Russian Federation, Spain	2 + 1	2, 4, and 11–15 months
Benfield [27]	Denmark, Finland, Italy, Norway	2 + 1	3, 5, and 12 months

[a]Included immunogenicity data after booster dose only

Indirect comparisons were conducted for two outcomes: IgG concentrations (IgG geometric mean ratios [GMRs]) and OPA titers (OPA GMRs). The indirect comparison of PCV20 versus PCV10 used aggregate-level data from direct comparisons (PCV20 versus PCV13 and PCV10 versus PCV13) (see Supplementary information). When there was only a single RCT used in the analysis, for example, Senders et al. [6] for PCV20 versus PCV13 in 3 + 1 schedule, serotype-specific direct GMRs and 95% confidence intervals (CIs) were used. If more than one direct comparison study was included (for example, three RCTs for PCV10 versus PCV13 in the 2 + 1 schedule [22–24]), the meta-analysis software Revman 5.3 was used to generate pooled results of the GMRs and 95% CIs of the included studies for each serotype (see Supplementary information). To account for heterogeneity among studies, we used random methods analysis models in pooling (meta-analyzing) studies to calculate the direct estimates. Next, the Bucher et al. method was used to perform indirect comparisons, generating a ratio of the direct comparisons (see Supplementary information for details) [25]. Results were reported as serotype-specific indirect GMR and 95% CIs between PCV20 and PCV10 at two timepoints: approximately 1 month after the booster dose (post-booster) and approximately 1 month after the two- or three-dose primary series (post-primary series). Analysis was descriptive, with indirect GMRs < 1 favoring PCV15 and indirect GMRs > 1 favoring PCV20. In general, wide confidence intervals are inherent in indirect comparisons, as the uncertainty, or variance, of the indirect estimate is the sum of uncertainties from the two direct estimates.

PCV20 versus PCV15 Indirect Comparison

We indirectly compared PCV20 and PCV15 for the common serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 22F, and 33F) in pediatric populations, for both 2 + 1 and 3 + 1 schedules (Fig. 1B). Included studies were selected a priori and consisted of pivotal phase 3 trials that compared PCV20 versus PCV13 ($n = 2$) or PCV15 versus PCV13 ($n = 3$) (Table 1). The same statistical methods as described for the PCV20 versus PCV10 indirect comparison were used to generate indirect IgG and OPA GMRs for PCV20 versus PCV15. For the 3 + 1 schedule, direct PCV15 versus PCV13 IgG and OPA GMR data were from a single phase 3 RCT [26] (Supplementary Tables 3 and 4). For the 2 + 1 schedule, data from two phase 3 RCTs that compared PCV15 with PCV13 [27, 28] were used in a meta-analysis to generate pooled direct IgG GMRs (Supplementary Figs. 2 and 3) and pooled direct OPA GMRs (Supplementary Figs. 4 and 5).

This study used data from previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors; as such, ethical approval was not required.

RESULTS

Primary Analysis: PCV20 versus PCV10

For the 3 + 1 schedule, a meta-analysis of IgG GMRs from three RCTs comparing PCV10 versus PCV13 (Table 1) [22–24] found that PCV13 was more immunogenic that PCV10 for most shared serotypes both post-booster and post-primary series (Supplementary Figs. 6 and 7). In the indirect comparison, PCV20 versus PCV10 IgG responses after the booster dose were similar, with GMRs close to 1, the line of equivalence, for serotypes 1, 6B, 7F, and 9V (Fig. 2A). IgG GMRs favored PCV10 for serotypes 4 and 18C and favored PCV20 for serotypes 5, 14, and 23F. Results for 19F were inconclusive due to wide 95% CIs, which were due to contrasting results from one of the three RCTs that directly compared PCV10 versus PCV13 (Supplementary Fig. 6). After the three-dose primary series, IgG responses were similar for serotypes 1, 4, 5, 7F, 9V, 18C; GMRs favored PCV10 for serotypes 6B, 14, and 19F, and favored PCV20 for serotype 23F (Fig. 2B).

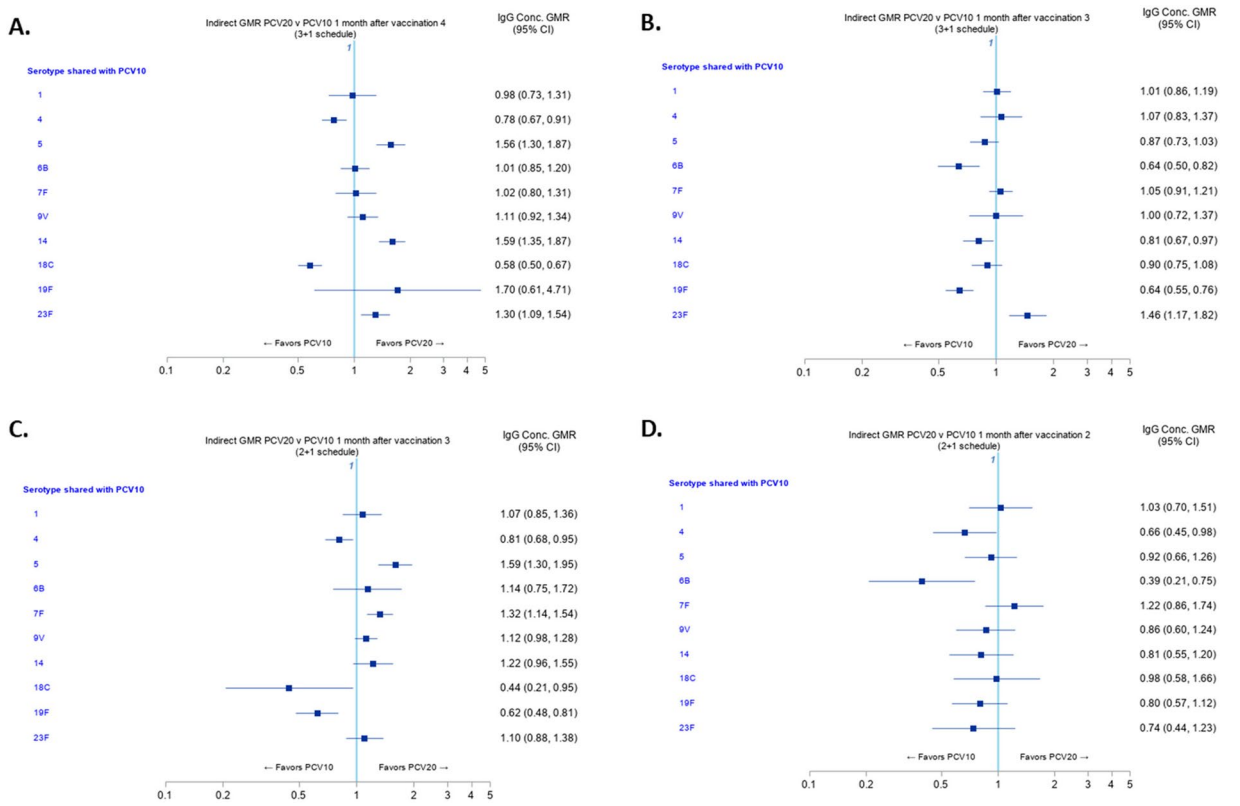

Fig. 2 Indirect comparison of PCV20 versus PCV10 IgG geometric mean ratios (GMR) for the ten shared serotypes for 3 + 1 (**A** and **B**) and 2 + 1 schedules (**C** and **D**) after the booster dose (**A** and **C**) and primary infant series (**B** and **D**)

For the 2 + 1 schedule, meta-analysis of four RCTs that directly compared PCV10 versus PCV13 (Table 1) [29–32] also found that direct IgG GMRs favored PCV13 for most of the ten shared serotypes (Supplementary Figs. 8 and 9). In the 2 + 1 indirect comparison of PCV20 versus PCV10 post booster, IgG responses were similar for serotypes 1, 6B, 9V, 14, and 23F; GMRs favored PCV10 for serotypes 4, 18C, and 19F; and GMRs favored PCV20 for serotypes 5 and 7F (Fig. 2C). After the two-dose primary series, IgG responses were similar for serotypes 1, 5, 7F, 9V, 14, 18C, 19F, and 23F, while GMRs favored PCV10 for serotypes 4 and 6B (Fig. 2D).

For examination of OPA responses in the 3 + 1 schedule, a meta-analysis was conducted to generate pooled direct OPA GMRs post-booster (Supplementary Fig. 10) and post-primary series (Supplementary Fig. 11) from two RCTs that evaluated PCV10 versus PCV13 [20, 21] (Table 1). Direct OPA GMRs favored PCV13 for most shared serotypes. For the indirect comparison of PCV20 versus PCV10 after the booster dose, OPA GMRs showed similarity for serotypes 4 and 6B; marginally favored PCV10 for serotypes 1 and 18C and favored PCV20 for serotype 14; and showed more pronounced differences favoring PCV10 for serotype 19F and PCV20 for serotypes 5, 7F, 9V, and 23F (Fig. 3A). After the primary three-dose series, OPA responses were similar for serotypes 4, 5, 6B, 9V, and 14; favored PCV10 for serotype 19F and favored PCV20 for serotypes 7F, 18C, and 23F, with borderline results for serotype 1 (Fig. 3B).

For the 2 + 1 schedule, a meta-analysis was conducted to generate pooled direct OPA GMRs post-booster dose (Supplementary Fig. 12) and post-primary series (Supplementary Fig. 13) from the four RCTs that directly compared PCV10 versus PCV13 [27–30], however, only Adigweme et al. and Temple et al. reported OPA results post-primary series [29, 30]. Pooled

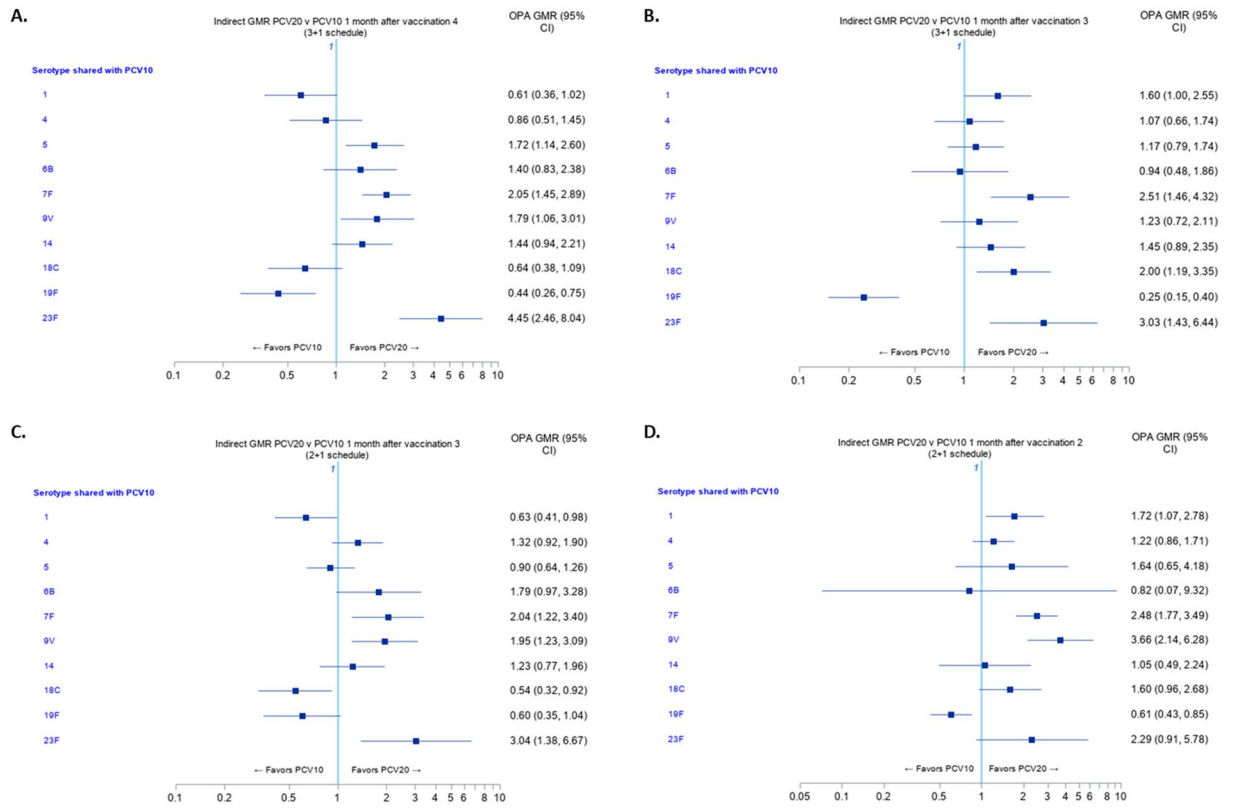

Fig. 3 Indirect comparison of PCV20 versus PCV10 opsonophagocytic activity (OPA) geometric mean ratios (GMR) for the ten shared serotypes for 3 + 1 (**A** and **B**) and 2 + 1 schedules (**C** and **D**) after the booster dose (**A** and **C**) and primary series (**B** and **D**)

direct OPA GMRs favored PCV13 for most shared serotypes. In the indirect comparison of PCV20 versus PCV10 after the booster dose, relative OPA responses were similar for serotypes 4, 5, and 14; OPA GMRs marginally favored PCV10 for serotypes 19F and PCV20 for serotype 6B (with wide 95% CIs that included 1) and showed more pronounced differences favoring PCV10 for serotypes 1 and 18C and PCV20 for serotypes 7F, 9V, and 23F (Fig. 3C). After the two-dose primary series, OPA responses were similar for serotypes 4 and 14; OPA GMRs favored PCV10 for serotype 19F and PCV20 for serotypes 1, 7F, and 9V, with borderline results for serotypes 5, 18C, and 23F (Fig. 3D). Results for serotype 6B were inconclusive, with wide 95% CI likely due to the contrasting results from the two RCTs that directly compared PCV10 versus PCV13 (Supplementary Fig. 13).

Secondary Analysis: PCV20 versus PCV15

In the indirect comparison of PCV20 versus PCV15, IgG responses following the booster dose were similar for most serotypes for both the 3 + 1 and 2 + 1 schedules, indicated by GMRs clustering around 1, the line of equivalence (Figs. 4A and C). In both 3 + 1 and 2 + 1 schedules, IgG GMRs favored PCV15 for serotype 3 and PCV20 for serotypes 22F and 33F, which are included in PCV15 and PCV20 but not the PCV13 comparator vaccine (Fig. 4). There were some differences in relative IgG responses after the primary series, particularly for the 2 + 1 schedule, where GMRs favored PCV15 for eight shared serotypes (Fig. 4D). The indirect comparison of PCV20 versus PCV15 OPA responses found that immunogenicity was similar across schedules and timepoints,

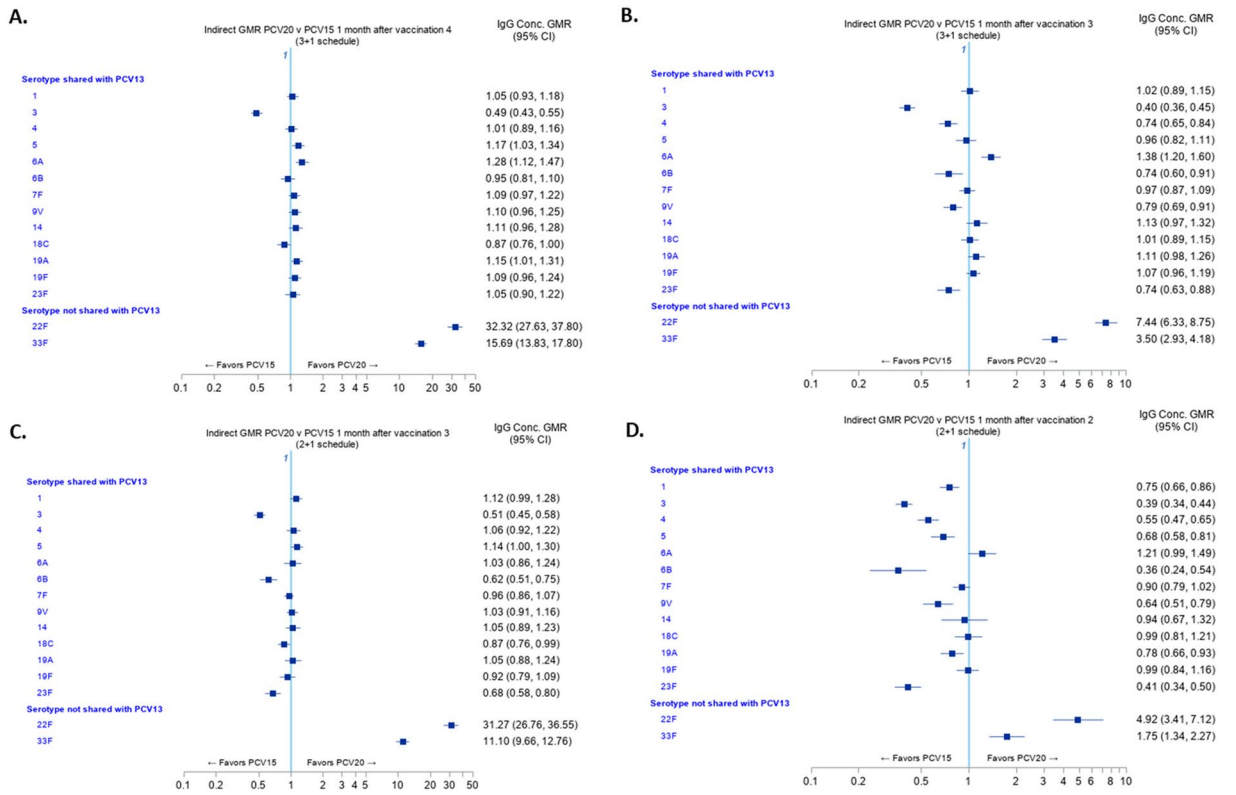

Fig. 4 Indirect comparison of PCV20 versus PCV15 IgG geometric mean ratios (GMR) for the 15 share serotypes for 3 + 1 (**A** and **B**) and 2 + 1 schedules (**C** and **D**) after the booster dose (**A** and **C**) and primary infant schedule (**B** and **D**)

with OPA GMRs clustering around the line of equivalence for most serotypes (Fig. 5). The indirect OPA GMR 95% CIs were generally wider than those observed for indirect IgG GMRs.

DISCUSSION

Our primary study question was to indirectly compare PCV20 immune responses to PCV10, a licensed vaccine with well-proven clinical protection. IgG and OPA responses induced by PCV20 vaccination in 3 + 1 and 2 + 1 schedules were overall similar to PCV10.

While PCV20 expands protection to five serotypes not included in other licensed PCVs, minor decrements in immunogenicity against the shared PCV13 serotypes in phase 3 RCTs raised some concerns about its clinical effectiveness, particularly in the 2 + 1 schedule. Our meta-analysis of PCV10 RCT data found that, like PCV20, its immunogenicity was lower than PCV13 for most of the shared serotypes, consistent with findings from a systematic review and network analysis conducted by Feng et al. [16] In the PCV20 versus PCV10 indirect comparison, although results varied by individual serotype, overall immune responses for the ten shared serotypes were generally similar, including for the 2 + 1 schedule. GMRs for both IgG and OPA were close to the line of equivalence, or spread between favoring PCV20 or PCV10. These findings support that PCV20 is expected to provide similar protection for the ten common serotypes. PCV10 was highly effective against vaccine-type IPD, demonstrated by a large, cluster-randomized trial in Finland and in observational studies showing direct effectiveness against vaccine-type IPD and population-level reductions in disease

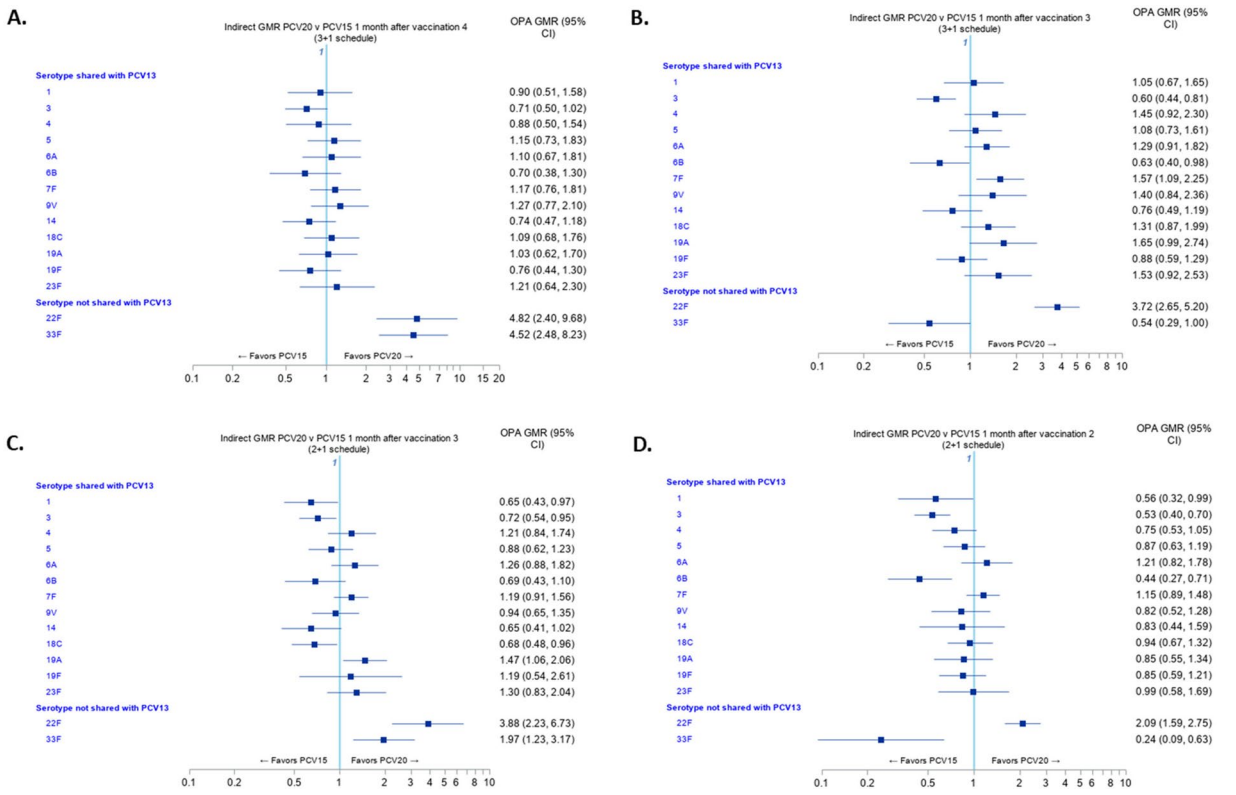

Fig. 5 Indirect comparison of PCV20 versus PCV15 opsonophagocytic activity (OPA) geometric mean ratios (GMR) for the 15 matched serotypes for 3 + 1 (**A** and **B**) and 2 + 1 schedules (**C** and **D**) after the booster dose (**A** and **C**) and primary infant series (**B** and **D**)

incidence [9, 18, 33, 34]. For example, following introduction of PCV10 in a 2 + 1 schedule in Finland, the incidence of vaccine-type IPD fell by 92% among vaccine-eligible children, and declined in older, unvaccinated children, indicating indirect protection [35]. The clinical implications of slight differences in relative immunogenicity, for example, for serotype 19F, for which the IgG GMR favored PCV10 post-booster in the 2 + 1 schedule, are not known, and highlight the need for real-world PCV20 effectiveness studies. Similarly, GMRs favored PCV10 serotypes 4 and 18C post-booster dose in both the 3 + 1 and 2 + 1 schedules, although IPD due to these serotypes rarely occurs in children in settings with mature PCV13 programs [2].

No data exist on PCV15 effectiveness to date, and thus comparison with this vaccine does not inform conclusions regarding PCV20 effectiveness. Nevertheless, this analysis was conducted for completeness. Post-booster immunogenicity, including OPA and IgG responses, was largely similar between PCV20 and PCV15 in both 3 + 1 and 2 + 1 schedules. However, IgG GMRs for serotype 3 favored PCV15, while 22F and 33F favored PCV20. As serotypes 22F and 33F are not contained within the PCV13 comparator, these results should be interpreted with caution. At the population level, the booster dose is considered most important, since it extends protection into the age of highest transmission and drives indirect protection [36–38]. The implications of differences in IgG levels post-infant series are less well understood, but likely will be small given that young, incompletely vaccinated infants are largely protected via indirect effects [39]. Where data overlapped, our analysis provided similar results as previous indirect comparisons of PCV20 versus PCV15 [20, 21]. Mt-Isa and colleagues indirectly compared PCV20 and PCV15 IgG GMRs in the 3 + 1

schedule (excluding serotypes 22F and 33F) and reported that PCV15 was non-inferior to PCV20 for all PCV13 serotypes and superior for serotype 3 [20]. Another study indirectly compared OPA responses between PCV20 and PCV15 post-booster dose using 3+1 PCV20 versus PCV13 data from a phase 2 RCT and a single phase 3 2+1 PCV15 versus PCV13 RCT [3, 21]. For both schedules, PCV15/PCV20 ratios were close to one for most serotypes, and the conclusion that "two new vaccines induce a broadly similar response" is consistent with our findings. PCV20 also provides expanded serotype coverage. In an analysis of IPD surveillance data in children aged under 5 years in high-income countries, PCV20 would cover an additional 38.2% of IPD beyond serotypes contained in PCV13, versus 10.6% for PCV15 [2]. Recent national surveillance data from Spain showed that in 2023, PCV20 would cover 19% more IPD in children aged under 5 years than PCV15 and 30% more IPD than PCV13 [40]. In Japan in 2022, 20.0% of IPD in children aged under 5 years was due to the five PCV20-unique serotypes not included in PCV15 [41].

Serotype 3 remains an important cause of pediatric IPD in children and has unique biological features due to its capsule structure, thickness, and ability to shed that may enhance virulence and ability to escape immune responses [42–44]. While several studies have reported PCV13 protection against serotype 3 IPD in children, its characteristics may contribute to PCV13 delivering a shorter duration of protection, resulting in lower vaccine effectiveness compared with other serotypes in children [9, 44, 45]. PCV10 does not contain serotype 3 and thus our study can make no inferences regarding the effectiveness of PCV20 against this serotype. Currently, it is unknown whether the higher IgG levels following immunization with PCV15 will improve clinical protection against serotype 3. The degree to which either PCV15 or PCV20 prevent serotype 3 disease at an individual or population level is an important question and will need to be assessed with well-designed effectiveness studies.

The indirect comparisons presented here are subject to several limitations. Indirect comparisons assume transitivity, a requirement that the RCTs included are similar, on average, in all important factors other than the intervention comparison being made [46]. The trial populations included in our indirect comparisons differed geographically, particularly for PCV20 versus PCV10 in the 2+1 schedule, as all the PCV10 trials were conducted in low- or middle-income countries, whereas the PCV20 trial only included children from high-income countries. Additionally, the booster dose was given at an earlier age in some PCV10 2+1 RCTs. The distribution of pneumococcal serotypes in disease and carriage may have differed by study populations, potentially impacting baseline IgG levels and responses to vaccination. In addition, imbalances in the geographic location of PCV13 and PCV10 trials and participant characteristics such as race have the potential to bias immune responses [47, 48]. A systematic literature review found that IgG geometric mean concentration (GMC) responses to PCV tended to be higher in infants from the Western Pacific region and Africa compared with Europe and the Americas [47]. We did not adjust for geographic or demographic differences among study populations, as the number of studies was insufficient to conduct meta-regression to account for heterogeneity [49]. However, since the indirect comparison method uses the ratio of PCV20 or PCV10 responses relative to PCV13 from the included studies, rather than the absolute GMCs, we would not expect geographical differences to cause a directional bias, although differences across study populations do present a limitation. Trial populations also differed for the PCV20 versus PCV15 indirect comparisons. In the 3+1 analysis, 26.2% of participants in the PCV15 RCT were Asian compared with 1.6% in the PCV20 RCT study [6, 26]. Unlike the indirect comparison of PCV15 versus PCV20 performed by Mt-Isa et al. [20], we did not perform a matching-adjusted indirect comparison. However, Mt-Isa reported that unadjusted versus matched results (by age and race) were very similar [20]. Another limitation is that in the original RCTs, OPAs are typically conducted on a randomly selected subset of participants,

with the smaller sample sizes and higher assay variability resulting in wider 95% CIs that made interpretation of OPA results less certain compared with IgG GMR results. In the PCV20 phase 3 trials, OPA data were descriptive, and GMRs compared with PCV13 were calculated post hoc for this indirect comparison. Laboratory methods for quantifying serotype-specific IgG and OPA titers also varied across studies. Lastly, we were not able to conduct indirect comparisons for serotypes 8, 10A, 11A, 12F, and 15B, as these are unique to PCV20.

CONCLUSIONS

We found that PCV20 immunogenicity was similar to PCV10, which was highly effective at preventing vaccine-type IPD, in either 2+1 or 3+1 schedules, suggesting that PCV20 will likely be clinically effective despite lower immunogenicity compared with PCV13, at least for the common ten serotypes. Individual- and population-level effectiveness, including for serotype 3, should be confirmed in robust post-licensure studies for any new PCV. In the meantime, serotype coverage should remain a key factor in decision-making regarding PCV use.

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Data Availability. All data generated or analyzed during this study are included in this published article/as supplementary information files.

Declarations

Conflicts of Interest. Eileen M. Dunne, Valda A. Struwig, Wing Lowe, Claire H. Wilson, Johnna E. Perdrizet, Noor Tamimi, Kyla Hayford, Luis Jodar, Bradford D. Gessner, and Christian Theilacker are employed by Pfizer and may own Pfizer stock or stock options. Pfizer manufactures PCV13 and PCV20.

Ethical Approval. This study used data from previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors; as such, ethical approval was not required.

REFERENCES

1. Wahl B, O'Brien KL, Greenbaum A, Majumder A, Liu L, Chu Y, et al. Burden of *Streptococcus*

pneumoniae and *Haemophilus influenzae* type b disease in children in the era of conjugate vaccines: global, regional, and national estimates for 2000–2015. Lancet Glob Health. 2018;6(7):e744–57. https://doi.org/10.1016/S2214-109X(18)30247-X.

2. Grant LR, Slack MPE, Theilacker C, Vojicic J, Dion S, Reinert R-R, et al. Distribution of serotypes causing invasive pneumococcal disease in children from high-income countries and the impact of pediatric pneumococcal vaccination. Clin Infect Dis. 2023;76(3):e1062–70. https://doi.org/10.1093/cid/ciac475.

3. Senders S, Klein NP, Lamberth E, Thompson A, Drozd J, Trammel J, et al. Safety and immunogenicity of a 20-valent pneumococcal conjugate vaccine in healthy infants in the United States. Pediatr Infect Dis J. 2021;40(10):944–51. https://doi.org/10.1097/inf.0000000000003277.

4. Méroc E, Fletcher MA, Hanquet G, Slack MPE, Baay M, Hayford K, Gessner BD, Grant LR. Systematic literature review of the epidemiological characteristics of pneumococcal disease caused by the additional serotypes covered by the 20-valent pneumococcal conjugate vaccine. Microorganisms. 2023;11(7):1816. https://doi.org/10.3390/microorganisms11071816.

5. World Health Organization. Annex 3, Recommendations to assure the quality, safety and efficacy of pneumococcal conjugate vaccines. WHO Technical Report Series No 977, Sixtieth report, 2013. Geneva, Switzerland: World Health Organization; 2013. pp. 91–151.

6. Senders S, Klein NP, Tamimi N, Thompson A, Baugher G, Trammel J, et al. A phase three study of the safety and immunogenicity of a four-dose series of 20-valent pneumococcal conjugate vaccine in healthy infants. Pediatr Infect Dis J. 2024;43(6):596–603. https://doi.org/10.1097/INF.0000000000004334.

7. Korbal P, Wysocki J, Jackowska T, Kline M, Tamimi N, Drozd J, et al. Phase 3 safety and immunogenicity study of a three-dose series of twenty-valent pneumococcal conjugate vaccine in healthy infants and toddlers. Pediatr Infect Dis J. 2024;43(6):587–95. https://doi.org/10.1097/INF.0000000000004300.

8. Moore MR, Link-Gelles R, Schaffner W, Lynfield R, Lexau C, Bennett NM, et al. Effect of use of 13-valent pneumococcal conjugate vaccine in children on invasive pneumococcal disease in children and adults in the USA: analysis of multisite, population-based surveillance. Lancet Infect Dis. 2015;15(3):301–9. https://doi.org/10.1016/S1473-3099(14)71081-3.

9. Savulescu C, Krizova P, Valentiner-Branth P, Ladhani S, Rinta-Kokko H, Levy C, et al. Effectiveness of 10 and 13-valent pneumococcal conjugate vaccines against invasive pneumococcal disease in European children: SpIDnet observational multicentre study. Vaccine. 2022;40(29):3963–74. https://doi.org/10.1016/j.vaccine.2022.05.011.

10. Lepoutre A, Varon E, Georges S, Dorléans F, Janoir C, Gutmann L, et al. Impact of the pneumococcal conjugate vaccines on invasive pneumococcal disease in France, 2001–2012. Vaccine. 2015;33(2):359–66. https://doi.org/10.1016/j.vaccine.2014.11.011.

11. Dagan R, Poolman J, Siegrist C-A. Glycoconjugate vaccines and immune interference: a review. Vaccine. 2010;28(34):5513–23. https://doi.org/10.1016/j.vaccine.2010.06.026.

12. Temple B, Licciardi P. Is it time to reconsider how higher valency pneumococcal conjugate vaccines are evaluated? Lancet Infect Dis. 2024. https://doi.org/10.1016/S1473-3099(23)00634-5.

13. Yeh SH, Gurtman A, Hurley DC, Block SL, Schwartz RH, Patterson S, et al. immunogenicity and safety of 13-Valent pneumococcal conjugate vaccine in infants and toddlers. Pediatrics. 2010;126(3):e493–505. https://doi.org/10.1542/peds.2009-3027.

14. Andrews NJ, Waight 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. https://doi.org/10.1016/S1473-3099(14)70822-9.

15. Vesikari T, Wysocki J, Chevallier B, Karvonen A, Czajka H, Arsène J-P, et al. Immunogenicity of the 10-valent pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV) compared to the licensed 7vCRM vaccine. Pediatr Infect Dis J. 2009;28(4):S66–76. https://doi.org/10.1097/INF.0b013e318199f8ef.

16. Feng S, McLellan J, Pidduck N, Roberts N, Higgins JPT, Choi Y, et al. Immunogenicity and seroefficacy of 10-valent and 13-valent pneumococcal conjugate vaccines: a systematic review and network meta-analysis of individual participant data. eClinicalMedicine. 2023;61:102073. https://doi.org/10.1016/j.eclinm.2023.102073.

17. World Health Organization. Pneumococcal conjugate vaccines in infants and children under 5 years of age: WHO position paper—February 2019. Wkly Epidemiol Rec. 2019;94(08):85–103.

18. Berman-Rosa M, O'Donnell S, Barker M, Quach C. Efficacy and effectiveness of the PCV-10 and PCV-13 vaccines against invasive pneumococcal disease. Pediatrics. 2020. https://doi.org/10.1542/peds.2019-0377.

19. Hauser MI, Muscatello DJ, Soh ACY, Dwyer DE, Turner RM. An indirect comparison meta-analysis of AS03 and MF59 adjuvants in pandemic influenza A(H1N1)pdm09 vaccines. Vaccine. 2019;37(31):4246–55. https://doi.org/10.1016/j.vaccine.2019.06.039.

20. Mt-Isa S, Chumbley JR, Crawford EL, Banniettis N, Buchwald UK, Weaver J, et al. An indirect treatment comparison (ITC) and matching-adjusted indirect comparison (MAIC) between a 15-valent (V114) and a 20-valent (PCV20) pneumococcal conjugate vaccine among healthy infants. Expert Rev Vaccines. 2023;22(1):906–17. https://doi.org/10.1080/14760584.2023.2270039.

21. De Wals PJC. PCV13, PCV15 or PCV20: which vaccine is best for children in terms of immunogenicity. Can Commun Dis Rep. 2024;50(1–2):35–9.

22. Carmona Martinez A, Prymula R, Miranda Valdivieso M, Otero Reigada MDC, Merino Arribas JM, Brzostek J, et al. Immunogenicity and safety of 11- and 12-valent pneumococcal non-typeable *Haemophilus influenzae* protein D-conjugate vaccines (11vPHiD-CV, 12vPHiD-CV) in infants: results from a phase II, randomised, multicentre study. Vaccine. 2019;37(1):176–86. https://doi.org/10.1016/j.vaccine.2018.07.023.

23. Prymula R, Szenborn L, Silfverdal S-A, Wysocki J, Albrecht P, Traskine M, et al. Safety, reactogenicity and immunogenicity of two investigational pneumococcal protein-based vaccines: results from a randomized phase II study in infants. Vaccine. 2017;35(35, Part B):4603–11. https://doi.org/10.1016/j.vaccine.2017.07.008.

24. Wijmenga-Monsuur AJ, van Westen E, Knol MJ, Jongerius RMC, Zancolli M, Goldblatt D, et al. Direct comparison of immunogenicity induced by 10- or 13-valent pneumococcal conjugate vaccine around the 11-month booster in Dutch infants. PLoS ONE. 2015;10(12): e0144739. https://doi.org/10.1371/journal.pone.0144739.

25. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol. 1997;50(6):683–91. https://doi.org/10.1016/s0895-4356(97)00049-8.

26. Lupinacci R, Rupp R, Wittawatmongkol O, Jones J, Quinones J, Ulukol B, et al. A phase 3, multicenter, randomized, double-blind, active-comparator-controlled study to evaluate the safety, tolerability, and immunogenicity of a 4-dose regimen of V114, a 15-valent pneumococcal conjugate vaccine, in healthy infants (PNEU-PED). Vaccine. 2023;41(5):1142–52. https://doi.org/10.1016/j.vaccine.2022.12.054.

27. Benfield T, Rämet M, Valentini P, Seppä I, Dagan R, Richmond P, et al. Safety, tolerability, and immunogenicity of V114 pneumococcal vaccine compared with PCV13 in a 2+1 regimen in healthy infants: A phase III study (PNEU-PED-EU-2). Vaccine. 2023;41(15):2456–65. https://doi.org/10.1016/j.vaccine.2023.02.041.

28. Martinon-Torres F, Wysocki J, Szenborn L, Carmona-Martinez A, Poder A, Dagan R, et al. A phase III, multicenter, randomized, double-blind, active comparator-controlled study to evaluate the safety, tolerability, and immunogenicity of V114 compared with PCV13 in healthy infants (PNEU-PED-EU-1). Vaccine. 2023;41(21):3387–98. https://doi.org/10.1016/j.vaccine.2023.04.036.

29. Adigweme I, Futa A, Saidy-Jah E, Edem B, Akpalu E, Dibbasey T, et al. Immunogenicity and safety of a 10-valent pneumococcal conjugate vaccine administered as a 2 + 1 schedule to healthy infants in the Gambia: a single-centre, double-blind, active-controlled, randomised, phase 3 trial. Lancet Infect Dis. 2023;23(5):609–20. https://doi.org/10.1016/S1473-3099(22)00734-4.

30. Temple B, Toan NT, Dai VTT, Bright K, Licciardi PV, Marimla RA, et al. Immunogenicity and reactogenicity of ten-valent versus 13-valent pneumococcal conjugate vaccines among infants in Ho Chi Minh City, Vietnam: a randomised controlled trial. Lancet Infect Dis. 2019;19(5):497–509. https://doi.org/10.1016/S1473-3099(18)30734-5.

31. Kawade A, Dayma G, Apte A, Telang N, Satpute M, Pearce E, et al. Effect of reduced two-dose (1+1) schedule of 10 and 13-valent pneumococcal conjugate vaccines (Synflorix™ and Prevenar13™)) on nasopharyngeal carriage and serotype-specific immune response in the first two years of life: results from an open-labelled randomized controlled trial in Indian children. Vaccine. 2023;41(19):3066–79. https://doi.org/10.1016/j.vaccine.2023.04.008.

32. Madhi SA, Mutsaerts EAML, Izu A, Boyce W, Bhikha S, Ikulinda BT, et al. Immunogenicity of a single-dose compared with a two-dose primary series followed by a booster dose of ten-valent

or 13-valent pneumococcal conjugate vaccine in South African children: an open-label, randomised, non-inferiority trial. Lancet Infect Dis. 2020;20(12):1426–36. https://doi.org/10.1016/S1473-3099(20)30289-9.

33. Peckeu L, van der Ende A, de Melker HE, Sanders EAM, Knol MJ. Impact and effectiveness of the 10-valent pneumococcal conjugate vaccine on invasive pneumococcal disease among children under 5 years of age in the Netherlands. Vaccine. 2021;39(2):431–7. https://doi.org/10.1016/j.vaccine.2020.11.018.

34. Palmu AA, Jokinen J, Borys D, Nieminen H, Ruokokoski E, Siira L, et al. Effectiveness of the ten-valent pneumococcal *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV10) against invasive pneumococcal disease: a cluster randomised trial. Lancet. 2013;381(9862):214–22. https://doi.org/10.1016/S0140-6736(12)61854-6.

35. Jokinen J, Rinta-Kokko H, Siira L, Palmu AA, Virtanen MJ, Nohynek H, et al. Impact of ten-valent pneumococcal conjugate vaccination on invasive pneumococcal disease in Finnish children—A population-based study. PLoS ONE. 2015;10(3): e0120290. https://doi.org/10.1371/journal.pone.0120290.

36. Wiese AD, Grijalva CG. To boost or not to boost? Lessons from the Australian pneumococcal conjugate vaccination program. Clin Infect Dis. 2019;70(12):2616–8. https://doi.org/10.1093/cid/ciz735.

37. Rodgers GL, Whitney CG, Klugman KP. Triumph of pneumococcal conjugate vaccines: overcoming a common foe. J Infect Dis. 2021;224(Supplement_4):S352–9. https://doi.org/10.1093/infdis/jiaa535.

38. Weinberger DM, Grant LR, Weatherholtz RC, Warren JL, O'Brien KL, Hammitt LL. Relating pneumococcal carriage among children to disease rates among adults before and after the introduction of conjugate vaccines. Am J Epidemiol. 2016;183(11):1055–62. https://doi.org/10.1093/aje/kwv283.

39. BenShimol S, van der Beek BA, Mor M, Megged O, Dagan R. Dynamics of invasive pneumococcal disease in infants <2 years old following PCV7/13 implementation using two infant and a booster dose schedule: evidence for indirect protection of young infants, Israel, 2004 to 2019. Euro Surveill. 2023. https://doi.org/10.2807/1560-7917.Es.2023.28.25.2200765.

40. Pérez-García C, Sempere J, de Miguel S, Hita S, Úbeda A, Vidal EJ, Llorente J, Limia A, de Miguel AG, Sanz JC, Martinón-Torres F, Ardanuy C, Domenech M, Yuste J. Surveillance of invasive pneumococcal disease in Spain exploring the impact of the COVID-19 pandemic (2019–2023). J Infect. 2024;89(2): 106204.

41. Takeuchi N, Chang B, Ishiwada N, Cho Y, Nishi J, Okada K, Fujieda M, Oda M, Saitoh A, Hosoya M, Ishiguro N. Nationwide population-based surveillance of invasive pneumococcal disease in children in Japan (2014–2022): impact of 13-valent pneumococcal conjugate vaccine and Covid-19 pandemic. SSRN. https://ssrn.com/abstract=5077290.

42. Luck JN, Tettelin H, Orihuela CJ. Sugar-coated killer: serotype 3 pneumococcal disease. Front Cell Infect Microbiol. 2020;23(10): 613287. https://doi.org/10.3389/fcimb.2020.613287.

43. Sings HL, Gessner BD, Wasserman MD, Jodar L. Pneumococcal conjugate vaccine impact on serotype 3: a review of surveillance data. Infect Dis Ther. 2021;10(1):521–39. https://doi.org/10.1007/s40121-021-00406-w.

44. Sings HL, De Wals P, Gessner BD, Isturiz R, Laferriere C, McLaughlin JM, et al. Effectiveness of 13-valent pneumococcal conjugate vaccine against invasive disease caused by serotype 3 in children: a systematic review and meta-analysis of observational studies. Clin Infect Dis. 2018;68(12):2135–43. https://doi.org/10.1093/cid/ciy920.

45. Deceuninck G, Brousseau N, Lefebvre B, Quach C, Tapiero B, Bui Y-G, et al. Effectiveness of thirteen-valent pneumococcal conjugate vaccine to prevent serotype 3 invasive pneumococcal disease in Quebec in children. Canada Vaccine. 2023;41(38):5486–9. https://doi.org/10.1016/j.vaccine.2023.07.049.

46. Chaimani A, Caldwell DM, Li T, Higgins JP, Salanti G. Undertaking network meta-analyses. In: Cochrane handbook for systematic reviews of interventions. 2019. pp. 285–320.

47. Choe YJ, Blatt DB, Lee HJ, Choi EH. Associations between geographic region and immune response variations to pneumococcal conjugate vaccines in clinical trials: a systematic review and meta-analysis. Int J Infect Dis. 2020;92:261–8. https://doi.org/10.1016/j.ijid.2019.12.021.

48. Lindholm DE, Licciardi PV, Ratu FT, Kim Mulholland E, Nguyen CD, Russell FM. Predictors of antibody persistence to the 7-valent pneumococcal conjugate vaccine in healthy Fijian infants at 12 months of age. Vaccine.

2020;38(33):5095–9. https://doi.org/10.1016/j.vaccine.2020.06.02.

49. Deeks JJ, Higgins JPT, Altman DG, McKenzie JE, Veroniki AA (editors). Chapter 10: Analysing data and undertaking meta-analyses [last updated November 2024]. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane handbook for systematic reviews of interventions version 6.5. Cochrane, 2024. www.training.cochrane.org/handbook.