Vaccine 37 (2019) 1021–1029

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Review

Immunogenicity and safety of the 13-valent pneumococcal conjugate vaccine compared to 23-valent pneumococcal polysaccharide in immunocompetent adults: A systematic review and meta-analysis

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ARTICLE INFO

Article history:
Received 9 August 2018
Received in revised form 15 December 2018
Accepted 2 January 2019
Available online 23 January 2019

Keywords:
Streptococcus pneumoniae
Pneumococcal conjugate vaccines
PCV13
Adults
Meta-analysis
Systematic review
Immunogenicity
Pneumococcal disease
OPA

ABSTRACT

Background: Despite the use of 23-valent pneumococcal polysaccharide vaccine (PPV23) in adults there is substantial morbidity and mortality in the elderly due to pneumococcal infections. Since 2010, the 13-valent pneumococcal conjugate vaccine (PCV13) is in use for infant immunization programs to reduce rates of pneumococcal disease, but is not routinely used in adults. Recent literature suggests PCV13 may be used in adult vaccination programs as well.
Objective: To determine the immunogenicity and safety of PCV13 compared with the PPV23 in adults.
Design: Systematic review and meta-analysis.
Setting: Randomized controlled trials evaluating immunogenicity of a single dose of PCV13 and PPV23 in adults by the opsonophagocytic assay (OPA) geometric mean titer (GMT) response at 1-month post-vaccination were considered for inclusion.
Results: Five randomized trials were included with 4561 subjects ranging 50–95.5 years, consisting of 51% females. The pooled OPA GMT ratio (GMTR) in the PCV13 arm was significantly higher for 10 of 13 serotypes (1, 4, 5, 6A, 6B, 9V, 18C, 19A, 19F and 23F) compared with the PPV23 arm. Overall, pooled risk ratios (RR) for local and systemic reactions did not differ between PCV13 and PPV23. Pneumococcal naïve subjects experienced significantly higher local reactions in the PCV13 arm compared with the PPV23 arm (RR: 1.15, 95%CI: 1.05–1.26, p = 0.0025).
Conclusion: A single dose of PCV13 elicits a better immune response among adults compared with PPV23, while having a similar safety profile to PPV23.

Contents

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https://doi.org/10.1016/j.vaccine.2019.01.014
0264-410X/

1. Introduction

Streptococcus pneumoniae is a substantial cause of global morbidity and mortality with 1.6 million deaths annually [1]. Individuals with chronic conditions, lack of sanitation, living in crowded environments, homeless, and those aged below two and over 65 years are at increased risk of pneumococcal diseases [1,2]. Due to growing antibiotic resistance in *S. pneumoniae*, vaccination has become an important strategy to prevent and combat pneumococcal diseases [3].

There are two vaccines currently available for use in adults: 13-valent pneumococcal conjugate vaccine (PCV13) and 23-valent pneumococcal polysaccharide vaccine (PPV23) [4]. While PPV23 has been used for adults in many countries for over 3 decades, PCV13 was licensed in 2014 for use in an adult population. Subsequently, PCV13 was incorporated in the national immunization program for adults in very few countries for individuals 65 years of age and over [5–7]. PPV23 contains 23 serotypes wherein 11 serotypes are unique in comparison to PCV13 (2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, 33F) [5]. The United States of America, Canada, and several other high-income countries recommend PPV23 as a routine vaccination in adults 65 years of age and over or those 2–64 years with chronic medical conditions [5]. As a polysaccharide vaccine, it induces an immune response using B-cells in a time, and dose dependent manner [8]. However, studies show that PPV23 has 60–70% efficacy against invasive pneumococcal disease (IPD) in otherwise healthy adults [9], but the vaccine efficacy decreases in those who are immunocompromised; the protective effect of PPV23 against pneumococcal pneumonia and all-cause pneumonia is unclear, with some studies suggesting protection while others showing little vaccine effect [9,10].

PCV13 contains 13 pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7A, 9V, 14, 18C, 19A, 19F, 23F); 12 of which are common to PPV23 with the remaining 6A unique to the conjugate vaccine [4]. Contrary to the polysaccharide vaccine, PCV13 induces a T-cell dependent immune response that provides both a substantial initial response and immunological memory for future protection. A small number of western countries now recommend the routine use of PCV13 in select adults [5–7]. Although many studies have evaluated the immunogenicity of PCV13 in adults, a systematic review of its immunogenicity and safety considerations is lacking. The objective of this study was to perform a meta-analysis of head-to-head randomized controlled trials evaluating the immunogenicity and safety of a single dose of PCV13 and PPV23, in immunocompetent adults in order to provide decision makers with details for future policy changes.

2. Methods

2.1. Literature search strategy and study selection

The reporting of this systematic review and meta-analysis follows PRISMA guidelines [11]. The literature search included all publications until January 2018 from PubMed, Embase, MEDLINE, and CENTRAL. The following key words were used: *immunogenicity, PCV13, 13-valent pneumococcal conjugate vaccines, Streptococcus pneumoniae, pneumococcal conjugate vaccines, safety, adverse events, side effects,* and *adults.* Inclusion criteria were (i) randomized control trial, (ii) adult population 18 years of age and over, (iii) a single dose of PCV13 compared with PPV23. Studies were excluded if they used: (i) a placebo as a comparator, (ii) comparator other than PPV23, (iii) single arm with no comparator, (iv) had immunocompromised study populations, and (v) concomitant vaccinated populations. In the title and abstract screening phase different interventions, reviews, studies conducted in children, clinical guidelines, or non-randomized study designs were excluded. In the full text-screening phase two investigators (LM and KP) independently evaluated studies in detail using pre-determined inclusion and exclusion criteria. A manual review of the references of the final full text articles was also conducted.

2.2. Outcome assessment

All studies evaluated immunogenicity by measuring specific functional antibacterial opsonophagocytic activity (OPA) titers using 13 serotype-specific validated OPA assays. Although a specific level of OPA antibody has not been shown to correlate with protection against pneumococcal disease in adults, OPA antibody responses are generally accepted as a correlate of vaccine-induced protection [12].

For primary analyses, the pooled outcome included the standard definition used among all studies, that the non-inferiority criteria of PCV13, relative to PPV23, was met if the lower limit of the 2-sided 95% confidence interval (CI) for the geometric mean titer (GMT) ratio was greater than 0.5 (2-fold criterion), at 1 month post-vaccination. For each serotype, OPA GMTR in PCV13 arm was compared to the PPV23 arm and was considered significantly better compared to PPV23 when the 95% CI did not cross 1. Secondary outcome assessments included analyses of: (1) the 4-fold rise in 6A, the unique serotype that is only contained in the PCV13 vaccine; (2) any local reactions (pain, redness and swelling at injection site); (3) any systemic adverse events (muscle or joint pain, chills, fatigue, headache, vomiting, decreased appetite, rash) within 14 days post-vaccination; and (4) all-cause mortality up-to a year following vaccination.

2.3. Data synthesis and statistical analysis

Quality of each randomized control trial was assessed using Cochrane risk of bias tool [13]. Data extracted included the study year, author, study location, age groups, study population, receipt of previous pneumococcal vaccine, OPA GMT ratio, local and systemic safety events. For pooling reported GMTRs, we estimated the logarithm of the GMTR and corresponding standard errors using reported GMTR values and 95% CI for each study. OPA GMTRs pooled for each serotype are presented on a forest plot.

For safety and adverse effects outcomes, pooled risk ratios with 95% CI were calculated from the proportions of adverse events reported in each study using the restricted maximum likelihood method and a random-effects model. Pooled risk ratios (RR) were summarized for local reactions, systemic events and all-cause mortality. Publication bias was assessed using funnel plots [14]. Lastly, stratified analyses assessed the impact of prior pneumococcal vaccine experience or age on immunogenicity and safety outcomes.

The estimates of stratified analyses were assessed through a test of interaction [15]. The data analysis was conducted in R version 3.4.3 and Cochrane review manager version 5.3.

3. Results

3.1. Search results and trial characteristics

A systematic literature search generated 158 studies. After removing 79 duplicates, the titles and abstracts of the remaining 79 studies were evaluated by the inclusion criteria. Fifty-two studies were excluded based on age group, intervention, and clinical guidelines. The full-text of the remaining 27 studies were further evaluated using the inclusion criteria and 22 studies were excluded on basis of immunocompromised population, or interventions with concomitant dosing or placebo comparisons. The remaining five studies were found to be eligible for data extraction and meta-analysis (Fig. 1).

Five randomized trials were included with 4561 subjects ranging from 50–95.5 years, with 51% females [16–20] (Table 1). Two studies were conducted in the United States [16,18], one was conducted in both the United States and Sweden [17], with another in South Africa [19], and Japan [20]. Of the five studies selected, four were randomized, modified double-blind experiments [16–18,20], whereas Jeurgens et al., was a randomized, open-label experiment [19]. In addition, Jackson et al. added an additional arm to include adults aged 50–59 years old who received PCV13 [16]. Three out of five studies included pneumococcal vaccine-naive subjects [16,18,20] while the other two studies included populations who were previously vaccinated with PPV23 [17,19]. All five studies enrolled immunocompetent subjects who had stable chronic conditions (i.e. cardiovascular, diabetes mellitus or renal or urinary disorders) for at least 12 weeks [16–20]. Additional details on the study vaccines and subject characteristics are available in Supplementary eTables 1 and 2. All studies reported serotype specific the OPA GMTs [16–20] at 1 month, and only one study followed up and reported immunogenicity at 12 months [16]. Out of a total five studies [16–20], only three studies reported on mortality [16,17,19]; there were no deaths reported in two studies [18,20]. In these 3 studies, seventeen deaths were reported in the PCV13 arm and 4 deaths were reported in the PPV23.

Although four of five studies were considered low risk of bias in accordance with the Cochrane Risk of Bias Tool evaluation, Juergens et al was at risk for selection bias, performance bias and detection bias for being an open label study as seen in Supplementary, eFigure 1.

3.2. Description of the studies

Jackson et al. [16] evaluated immunogenicity in 1303 immunocompetent, pneumococcal vaccination naïve adults. Subjects (N = 828) aged 60–64, were randomized into the PCV13 or PPV23 arm in the double-blind portion of the study, and 406 subjects aged 50–59 years were enrolled in an open label study. In both age groups, patients in the PCV13 arm had statistically significant higher OPA titers in 9/13 serotypes compared with patients in the PPV23 at 1 month. Among the 60–64 year age group, local reactions associated with PCV13 (82.2%) were significantly higher compared with PPV23 (75.9%), particularly pain at the injection site. Systemic adverse events were comparable between PCV13 (82.6%) and PPV23 (82.1%). Interestingly, the frequency of both local (89.6%) and systemic reactions (84.4%) were higher among the 50–59 year age group, compared with those aged 60–64 years with both types of vaccine. Although no vaccine related deaths were reported, one death in the PCV13 arm was noted at 1 year.

Jackson et al. [17] evaluated immunogenicity in 936 immunocompetent adults aged 70 years and older who had previously received PPV23 more than five years ago. Patients were either administered a single dose of PCV13 or PPV23. Statistically significant increases in OPA GMTs were observed for 11/13 serotypes (1, 4, 5, 6A, 6B, 7F, 9V, 18C, 19A, 19F, 23F) one month after PCV13 compared with PPV23. Local reactions associated with PPV23 (64.1%) were significantly higher compared with PCV13 (56.5%). In addition, more systemic adverse events were seen with PPV23 (68.2%) than PCV13 (60.3%); no serious adverse events were

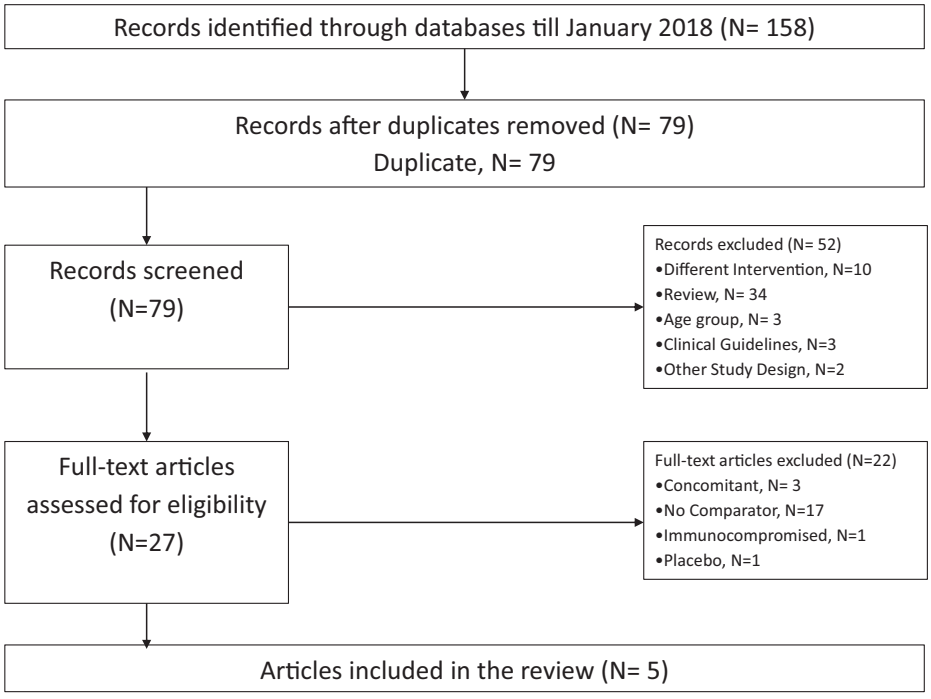

Fig. 1. Search strategy.

Table 1
Characteristics of the included studies.

Study	Country	Study Duration (months)	PPV23 Vaccine Naïve (Yes/No)	Age Groups (years)	Study Population (N = Consented)	Study Population (N = Safety Analysis)	Gender (%Female)	Chronic Diseases (%)	PCV13, N = randomized (N = evaluated)[a]	PPV23 N = randomized (N = evaluated)[a]	PCV13, Deaths (N)	PPV23, Deaths (N)	Study Quality[b]
Jackson 2013a [16]	USA	12.6	Yes	50–59	1303	1206	55.4	18.6	406	–			Good
				60–64					418(411)	417(407)	1	0	
Jackson 2013b [17]	USA/Sweden	13	No	>70	1008	936	48.7	42.7	464(431)	474(448)	4	4	Good
Greenberg 2014 [18]	USA	13	Yes	60–64	720	715	57.1	25.4[c]	482(470)	238(236)	0	0	Good
Juergens 2014 [19]	South Africa	24	No	>65	930	889	56.9	N.S.	309(299)	301(295)	12	0	Good
Shiramoto 2015 [20]	Japan	4	Yes	>65	764	737	50.4	N.S.	382(366)	382(367)	0	0	Good

Abbreviations: PCV13 stands for 13-valent pneumococcal conjugate vaccine, PPV23 stands for 23-valent pneumococcal polysaccharide vaccine, OPA GMTR: Opsonophagocytic assay geometric mean titer ratio. N.S. stands for not specified.

[a] Total number of individuals randomized (number of individuals evaluated for immunogenicity).

[b] Study quality was assessed based on Cochrane Risk of Bias tool.

[c] Derived based on the numbers indicated in the paper: 26.4% in PCV13 arm and 23.6% in PPV23arm.

reported. In this study, a total of 8 deaths were reported, 4 in each arm.

Greenberg et al. [18] evaluated immunogenicity in 706 immunocompetent healthy, pneumococcal vaccination naïve adults, aged 60–64 years. At one month post-vaccination, the PCV13 arm had statistical significantly higher OPA GMTRs in 11/13 serotypes (1, 4, 5, 6A, 6B, 7F, 9V, 18C, 19A, 19F, 23F) compared with PPV23 study arm. Local reactions associated with PCV13 (71.4%) were significantly higher compared with PPV23 (62.2%); higher frequency of systemic adverse events was seen with PPV23 (78.2%) compared with PCV13 (74.9%). No deaths were reported in this study.

Juergens et al. [19] evaluated immunogenicity in 915 immunocompetent adults aged ≥65 years who had previously received PPV23 more than five years prior. In this open-label study, subjects were randomized in to receive PCV13 (N = 309), PCV13 without aluminum phosphate (AlPO4) (N = 304) or PPV23 (N = 301). Only data regarding the PCV13 formulation with aluminum phosphate was included in the meta-analysis. The PCV13 arm had statistical significantly higher OPA GMTRs in 11/13 serotypes at one month following vaccination compared with PPV23 arm. For the first dose, local reactions, pain, redness and swelling were all significantly higher in PCV13 arm, when compared with PPV23. Systemic adverse events were comparable across groups (PCV13:60.5% and PPV23: 57.2%), except rash which was higher in PCV13 (16%) compared with PPV23 (6%). While no vaccine related deaths were reported in this study, there were 12 deaths in the PCV13 arm attributed to cardiovascular disease or cancer.

Shiramoto et al. [20] evaluated immunogenicity in 764 immunocompetent, pneumococcal vaccination naïve adults aged 65 years and older. OPA GMTs were statistically significantly higher for all 13 serotypes in PCV13 compared with PPV23 at one month post-vaccination. While local reactions associated with PCV13 were significantly higher compared with PPV23; systemic reactions were comparable in both study arms except rash which was significantly higher in the PCV13 (8.9%) arm, when compared to the PPV23 arm (3.6%). There were no deaths reported in this study.

3.3. Immunogenicity

Significantly higher GMTRs were observed for 10 of the 13 serotypes (1, 4, 5, 6A, 6B, 9V, 18C, 19A, 19F, and 23F) in the PCV13 arm, indicating a higher immunogenic response (Fig. 2 and Table 2). Serotype 6A, which is contained in PCV13 but not in PPV23, generated the highest GMTR of 7.58 (95% CI: 4.68–12.26). The serotypes which produced comparable GMTR values in both vaccines included: 3 (1.07, 95% CI: 0.78–1.48), 7F (1.68, 95% CI: 1.00–2.83), and 14 (0.95, 95% CI: 0.82–1.10).

When evaluating the effects of prior pneumococcal vaccination status, the ratio of OPA GMTR was found to be comparable across populations who had received a dose of PPV23 in the 5 years preceding, compared with a naive population, across all serotypes (Table 2). The age effect was evaluated by stratifying individuals in two age groups: less than 65 years or 65 years and over (Table 2). The ratio of OPA GMTR was comparable in both age groups for 9/13 serotypes (1, 3, 4, 6A, 6B, 9V, 14, 18C and 19A) in the PCV13 arm compared with PPV23. The younger age category demonstrated a better immune response for 2/13 serotypes (7F and 23F) in PCV13. Among subjects aged 65 years and older, a slightly higher immune response was observed for 2/13 serotypes (5 and 19F) in PCV13 compared with PPV23.

Serotypes which showed low heterogeneity among the studies included 9V, 14, 18C, and 19A (I^2 = 0.00%, p > 0.05). Serotypes that showed relatively high heterogeneity included 1, 3, 4, 5, 6A, 6B, 7F, 19F, and 23F with I^2 statistics greater than 50% and p < 0.05. Serotype 6A has notable variation amongst the results of the individual

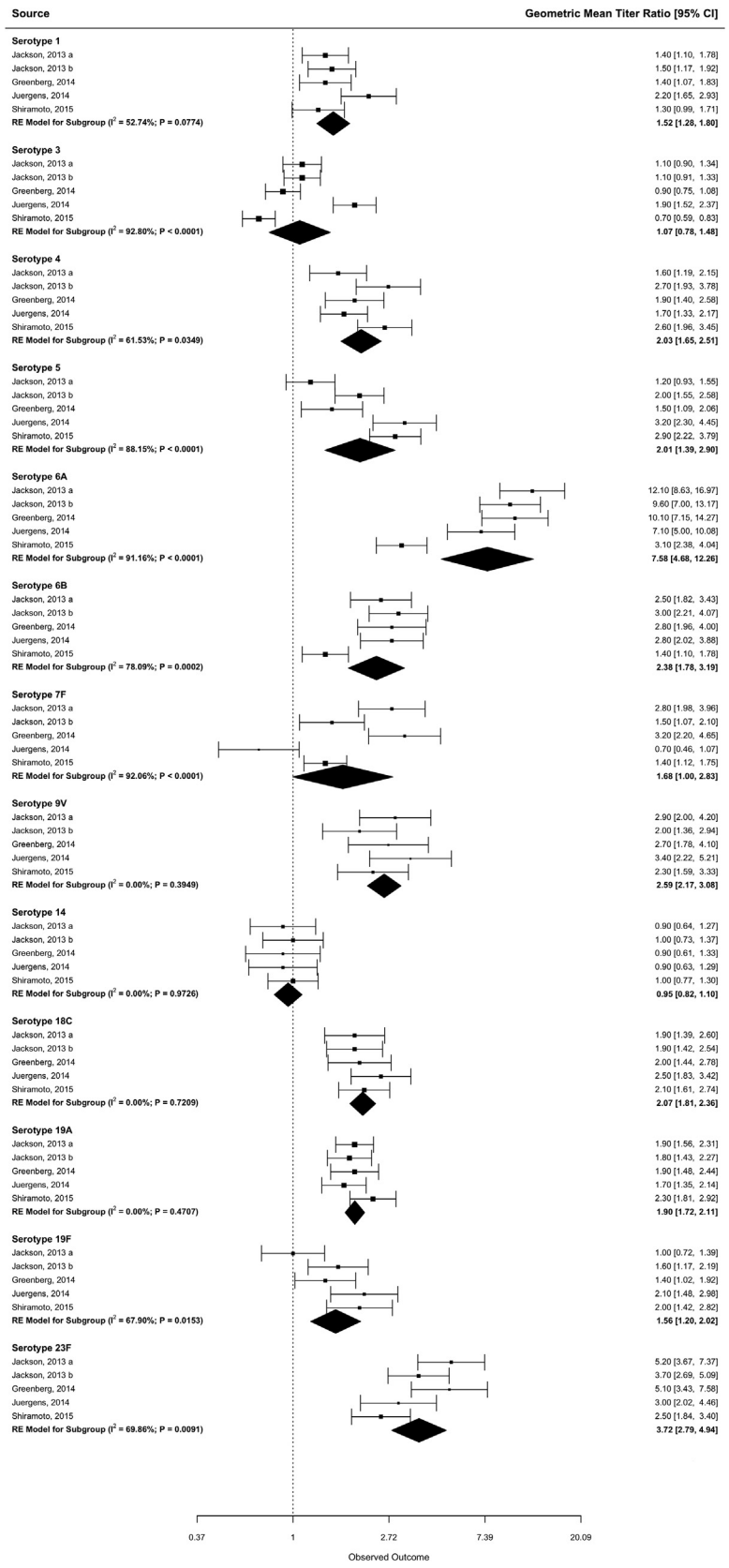

Fig. 2. Random effects model evaluating the pooled serotype-specific immunogenicity of 13-valent pneumococcal conjugate vaccine compared to 23-valent pneumococcal polysaccharide vaccine. [a] Jackson 2013 covers data of subjects under 65 year of age. [b] Jackson 2013 covers data of subjects aged 70 years and over.

Table 2
Overall summary of pooled serotype-specific immunogenicity reported at 1 month following vaccination for PCV13 compared with PPV23.

	Overall			Prior pneumococcal experience GMTR (95%CI)[a]			Age group GMTR (95%CI)[a]			
Serotype	GMTR (95% CI)[a]	p-value	I^2	Naïve	Experienced	Ratio of GMTR (95% CI)[b]	p-value	Under 65	65 and Above	Ratio of GMTR (95% CI)[b]	p-value
1	1.52 (1.28–1.80)	<0.0001	52.74	1.37 (1.18–1.59)	1.8 (1.24–2.62)	0.76 (0.51–1.14)	0.1826	1.4 (1.17–1.68)	1.62 (1.20–2.19)	0.86 (0.61–1.23)	0.4133
3	1.07 (0.78–1.48)	0.6694	92.8	0.88 (0.68–1.14)	1.44 (0.84–2.46)	0.61 (0.34–1.11)	0.1062	0.99 (0.81–1.21)	1.13 (0.64–1.99)	0.88 (0.48–1.6)	0.6672
4	2.03 (1.65–2.51)	<0.0001	61.53	2 (1.51–2.65)	2.11 (1.34–3.32)	0.95 (0.56–1.62)	0.8442	1.74 (1.41–2.15)	2.25 (1.67–3.05)	0.77 (0.54–1.11)	0.1673
5	2.01 (1.39–2.90)	0.0002	88.15	1.74 (1.03–2.93)	2.5 (1.58–3.96)	0.7 (0.35–1.4)	0.308	1.31 (1.06–1.63)	2.62 (1.97–3.48)	0.5 (0.35–0.71)	0.0001
6A	7.58 (4.68–12.26)	<0.0001	91.16	7.19 (3.10–16.71)	8.34 (6.21–11.20)	0.86 (0.35–2.1)	0.7443	11.08 (8.70–14.10)	5.92 (3.03–11.57)	1.87 (0.92–3.81)	0.0845
6B	2.38 (1.78–3.19)	<0.0001	78.09	2.11 (1.37–3.25)	2.9 (2.32–3.63)	0.73 (0.45–1.18)	0.1998	2.63 (2.07–3.33)	2.25 (1.38–3.66)	1.17 (0.68–2.01)	0.5742
7F	1.68 (1.00–2.83)	0.0515	92.06	2.28 (1.36–3.83)	1.04 (0.49–2.18)	2.19 (0.88–5.46)	0.0919	2.98 (2.31–3.84)	1.16 (0.74–1.82)	2.57 (1.53–4.31)	0.0003
9V	2.59 (2.17–3.08	<0.0001	0	2.61 (2.09–3.26)	2.59 (1.54–4.35)	1.01 (0.57–1.77)	0.9787	2.81 (2.13–3.71)	2.47 (1.84–3.32)	1.14 (0.76–1.7)	0.5318
14	0.95 (0.82–1.10)	0.4907	0	0.95 (0.79–1.14)	0.95 (0.75–1.21)	1 (0.74–1.35)	1	0.9 (0.70–1.16)	0.97 (0.82–1.16)	0.93 (0.69–1.26)	0.6272
18C	2.07 (1.81–2.36)	<0.0001	0	2.01 (1.69–2.39)	2.17 (1.66–2.83)	0.93 (0.67–1.27)	0.6381	1.95 (1.55–2.44)	2.14 (1.81–2.52)	0.91 (0.69–1.21)	0.5213
19A	1.9 (1.72–2.11)	<0.0001	0	2.01 (1.76–2.29)	1.75 (1.49–2.06)	1.15 (0.93–1.41)	0.1931	1.90 (1.63–2.22)	1.91 (1.60–2.29)	0.99 (0.79–1.26)	0.965
19F	1.56 (1.20–2.02)	0.0008	67.9	1.41 (0.95–2.07)	1.81 (1.39–2.36)	0.78 (0.48–1.25)	0.3028	1.19 (0.85–1.65)	1.87 (1.54–2.26)	0.64 (0.43–0.94)	0.0226
23F	3.72 (2.79–4.94)	<0.0001	69.86	4.01 (2.47–6.49)	3.41 (2.66–4.37)	1.18 (0.68–2.03)	0.5596	5.16 (3.97–6.70)	3.02 (2.37–3.86)	1.71 (1.2–2.44)	0.0033

Abbreviations: PCV13 stands for 13-valent pneumococcal conjugate vaccine, PPV23 stands for 23-valent pneumococcal polysaccharide vaccine, OPA GMTR: Opsonophagocytic assay geometric mean titer ratio. N.S. stands for not specified.
[a] Opsonophagocytic assay geometric mean titer ratio (OPA GMTR) estimated using random effects model.
[b] Test of interaction for stratified analyses.

studies (I^2 = 91.16%; p < 0.0001). No publication bias was found (Supplementary, eFigure 2 and eFigure 3).

3.4. Safety

A risk ratio for the overall rate of local reactions was found to be 1.08 (95% CI: 0.95–1.24), while the RR for overall systemic reactions was 0.97 (95% CI: 0.91–1.04), suggesting that the risk for experiencing adverse effects is comparable between the two vaccines (Table 3). Those with PCV13 were less likely to observe severe limitation of arm (RR: 0.51, 95%CI: 0.29–0.90, p = 0.0193) and aggravated generalized muscle pain compared to PPV23 (RR: 0.79, 95%CI: 0.71–0.89, p = 0.0001), but systemic reactions were comparable. Among pneumococcal naïve subjects local reactions were significantly higher in the PCV13 arm compared with PPV23 arm (RR: 1.15, 95%CI: 1.05–1.26, p = 0.0025). Overall local and systemic events were comparable when assessed by age (i.e., under and 65 years of age versus over 65 years of age), except fever and fatigue, which were significantly higher in those under 65 years of age (p < 0.05). Although there were no vaccine-related mortality reported in any of the studies, there were deaths from other reasons reported in 3 studies, and pooled all-cause mortality was 3.13 (95%CI: 0.45–21.70) [16,17,19]. Significant heterogeneity was observed between studies for local reactions (I^2 = 85.5%; p = 0.0001) but not for systemic reactions (I^2 = 49.2%; p = 0.16) or all-cause mortality (I^2 = 49.8%; p = 0.25).

4. Discussion

This is the first systematic review and meta-analysis to compare the immunogenicity and safety of PCV13 and PPV23 administered to immunocompetent adults. Our findings suggest PCV13 is highly immunogenic when compared with PPV23 with respect to 10 of the 13 individual serotypes. Immune response to PCV13 in individuals with prior pneumococcal vaccination (over five years ago) were comparable to naïve individuals. Age at vaccination only influenced immunogenicity for 2 serotypes, with the younger age group demonstrating a significantly better immune response for serotypes 7F and 23F compared with individuals who were 65 years of age or older who responded better for serotypes 5 and 19F. Finally, when measuring both local and systemic reactions, our findings demonstrate PCV13 has a comparable safety profile to PPV23.

While PPV23 has been used in the elderly, and adults with underlying comorbidities for over three decades, it has failed to significantly reduce the pneumococcal disease burden in adults [21]. In light of the better immune response conferred by PCV13 in 9/12 common serotypes, compared with PPV23, PCV13 presents itself as a useful contender for adults to fill the gaps left behind by PPV23 and remaining vaccine type pneumococcal disease. Owing to the use of PCV13 in children's national immunization program close to a decade, it is estimated that PCV13 will reduce vaccine serotype burden in adults by 90% [22]. Therefore, the debate in the scientific community is whether using PCV13 in the adult population will result in further reduction of pneumococcal disease.

PCV13 was found to increase antibody titers more effectively when compared to PPV23, while maintaining a similar safety profile. Previously, a few studies evaluating PCV7 and PPV23 in adults found immune responses to PCV7 to be slightly better than PPV23 [23,24]. As no direct comparison of PCV7 and PCV13 exists in adults, many paedriatic studies indicate immunogenicity and safety of PCV7 is comparable to PCV13 [25–27]. We were not able to find any other meta-analysis evaluating immunogenicity of PCVs to PPV23 in adults.

Table 3
Overall summary of pooled local reactions and systemic events reported up to day 14 after vaccination for 13-valent pneumococcal conjugate vaccine compared to 23-valent pneumococcal polysaccharide vaccine.

		Overall			Prior pneumococcal experience RR (95%CI)[a]				Age group RR (95%CI)[a]			
		RR (95% CI)[a]	p-value	I^2	Naïve	Experienced	Ratio of RR (95% CI)[b]	p-value	Under 65	65 and Above	Ratio of RR (95% CI)[b]	p-value
Local reactions												
Redness	Any	1.20 (0.57, 2.52)	0.6371	94.7%	1.63 (0.95, 2.81)	0.49 (0.36, 0.66)	3.33(1.79–6.19)	0.0002	1.28 (0.98, 1.67)	1.17 (0.21, 6.50)	1.09(0.19–6.22)	0.9193
	Mild	1.53 (0.83, 2.80)	0.1700	91.0%	1.58 (0.79, 3.16)	1.47 (0.34, 6.26)	1.07(0.21–5.43)	0.9304	1.14 (0.70, 1.86)	1.89 (0.68, 5.26)	0.6(0.19–1.87)	0.3817
	Moderate	1.68 (0.72, 3.90)	0.2276	91.1%	2.38 (1.32, 4.30)	1.03 (0.17, 6.21)	2.31(0.35–15.38)	0.3865	1.76 (1.15, 2.70)	1.64 (0.39, 7.00)	1.07(0.24–4.8)	0.9264
	Severe	1.12 (0.38, 3.31)	0.8328	72.8%	2.53 (1.02, 6.29)	0.59 (0.19, 1.89)	4.29(1–18.32)	0.0494	1.49 (0.30, 7.31)	1.06 (0.27, 4.10)	1.41(0.17–11.56)	0.7514
Swelling	Any	1.23 (0.52, 2.91)	0.6390	95.2%	1.73 (0.85, 3.52)	0.45 (0.33, 0.62)	3.84(1.77–8.35)	0.0007	1.22 (0.80, 1.86)	1.28 (0.16, 10.16)	0.95(0.11–7.96)	0.9646
	Mild	1.53 (0.89, 2.67)	0.1273	87.3%	1.88 (1.16, 3.06)	1.16 (0.35, 3.82)	1.62(0.45–5.9)	0.4638	1.49 (1.09, 2.03)	1.60 (0.60, 4.32)	0.93(0.33–2.61)	0.8921
	Moderate	1.11(0.45, 2.72)	0.8233	91.5%	1.19 (0.53, 2.67)	1.03 (0.09, 11.85)	1.16(0.09–15.07)	0.9123	0.97 (0.26, 3.58)	1.22 (0.28, 5.30)	0.8(0.11–5.73)	0.82
	Severe	1.09 (0.38, 3.15)	0.8676	22.3%	1.09 (0.38, 3.15)	–	–	–	0.59 (0.14, 2.47)	1.76 (0.52, 5.98)	0.34(0.05–2.21)	0.2559
Pain	Any	1.08 (0.95, 1.23)	0.2643	80.9%	1.13 (1.06, 1.20)	0.88 (0.79, 0.99)	1.28(1.13–1.46)	0.0001	1.12 (1.04, 1.22)	1.03 (0.75, 1.40)	1.09(0.79–1.51)	0.6143
	Mild	1.15 (1.02, 1.29)	0.0205	72.7%	1.18 (1.11, 1.26)	1.07 (0.79, 1.45)	1.1(0.81–1.5)	0.5354	1.18 (1.09, 1.28)	1.12 (0.90, 1.40)	1.05(0.83–1.33)	0.6602
	Moderate	0.72 (0.44, 1.16)	0.1793	89.4%	0.80 (0.64, 1.00)	0.69 (0.15, 3.15)	1.16(0.25–5.42)	0.8509	0.83 (0.69, 1.00)	0.63 (0.21, 1.84)	1.32(0.43–4.01)	0.6276
	Severe	0.73(0.24, 2.31)	0.6014	79.3%	0.67 (0.05, 8.94)	0.89 (0.35, 2.30)	0.75(0.05–11.87)	0.8401	0.67 (0.05, 8.94)	0.89 (0.35, 2.30)	0.75(0.05–11.87)	0.8401
Limitation of arm movement	Any	0.74 (0.50, 1.10)	0.1394	88.6%	0.91 (0.78, 1.05)	0.38 (0.28, 0.52)	2.39(1.7–3.37)	0	0.88 (0.75, 1.04)	0.62 (0.24, 1.60)	1.42(0.54–3.72)	0.4757
	Mild	0.74 (0.50, 1.10)	0.0541	82.2%	0.92 (0.79, 1.07)	0.46 (0.34, 0.60)	2(1.43–2.81)	0.0001	0.90 (0.76, 1.07)	0.62 (0.35, 1.09)	1.45(0.8–2.64)	0.2206
	Moderate	0.52 (0.33, 0.82)	0.0046	0.0%	0.55 (0.32, 0.93)	0.29 (0.04, 2.02)	1.9(0.24–14.79)	0.5413	0.51 (0.27, 0.97)	0.47 (0.187, 1.16)	1.09(0.35–3.32)	0.8863
	Severe	0.51 (0.29, 0.90)	0.0193	24.4%	0.45 (0.25, 0.84)	0.55 (0.10, 3.15)	0.82(0.13–4.97)	0.8273	0.42 (0.21, 0.85)	0.57 (0.21, 1.59)	0.74(0.22–2.48)	0.6224
Any local reaction		1.08 (0.95, 1.24)	0.2455	85.5%	1.15 (1.05, 1.26)	0.88 (0.80, 0.98)	1.31(1.15–1.49)	0.0001	1.10 (1.04, 1.17)	1.06 (0.74, 1.53)	1.04(0.72–1.49)	0.8418
Systemic events												
Any (≥38 °C)		1.01 (0.54, 1.89)	0.9737	42.7%	2.02 (0.85, 4.79)	0.76 (0.45, 1.27)	2.66(0.97–7.31)	0.0583	2.48 (0.86, 7.17)	0.81 (0.53, 1.26)	3.06(0.98–9.58)	0.0546
Mild (≥38 °C but <38.5 °C)		1.29 (0.59, 2.88)	0.5174	45.1%	3.18 (1.06, 9.59)	0.87 (0.48, 1.58)	3.66(1.05–12.75)	0.042	4.46 (1.04, 19.07)	0.95 (0.54, 1.67)	4.69(0.98–22.38)	0.0523
Moderate (≥38.5 °C but <39 °C)		0.98 (0.32, 3.01)	0.9714	0.0%	1.01 (0.06, 16.06)	0.97 (0.29, 3.33)	1.04(0.05–22.45)	0.9794	–	0.98 (0.32, 3.01)	–	–
Severe (≥39 °C but ≤40 °C)		0.80 (0.36, 1.78)	0.5784	0.0%	0.50 (0.07, 3.50)	0.88 (0.36, 2.13)	0.57(0.07–4.93)	0.6079	0.50 (0.07, 3.50)	0.88 (0.36, 2.13)	0.57(0.07–4.93)	0.6079
≥40 °C		0.32(0.1, 7.94)	0.4904	–	–	0.33 (0.01, 7.94)	–	–	–	0.33 (0.01, 7.94)	–	–
Fatigue		0.98 (0.87, 1.10)	0.3201	63.4%	1.03 (0.95, 1.12)	0.79 (0.69, 0.90)	1.3(1.11–1.53)	0.001	1.03 (0.94, 1.12)	0.84 (0.72, 0.99)	1.23(1.02–1.47)	0.0258
Headache		1.0 (0.92, 1.08)	0.935	0.0%	1.01 (0.92, 1.11)	0.96 (0.81, 1.13)	1.05(0.87–1.28)	0.6077	1.02 (0.93, 1.13)	0.93 (0.80, 1.09)	1.1(0.92–1.31)	0.3054
Chills		0.86 (0.68, 1.09)	0.2169	44.0%	0.95 (0.65, 1.40)	0.75 (0.54, 1.05)	1.27(0.77–2.09)	0.356	0.85 (0.65, 1.12)	0.97 (0.54, 1.74)	0.88(0.46–1.67)	0.6879
Rash		1.05 (0.60, 1.87)	0.8533	89.1%	1.23 (0.63, 2.44)	0.84 (0.24, 2.92)	1.46(0.35–6.06)	0.5987	0.91 (0.46, 1.79)	1.20 (0.42, 3.41)	0.76(0.22–2.65)	0.665
Vomiting		0.96 (0.66, 1.41)	0.8421	0.0%	0.89 (0.54, 1.45)	1.09 (0.59, 2.01)	0.82(0.37–1.8)	0.6157	0.82 (0.49, 1.37)	1.17 (0.66, 2.08)	0.7(0.32–1.51)	0.3656
Decreased appetite		0.86 (0.70, 1.06)	0.1546	34.2%	0.79 (0.57, 1.09)	0.98 (0.75, 1.29)	0.81(0.53–1.23)	0.3168	0.79 (0.52, 1.23)	0.94 (0.73, 1.21)	0.84(0.52–1.37)	0.4856
New generalized muscle pain		0.87 (0.75, 1.01)	0.0661	68.8%	0.96 (0.88, 1.05)	0.69 (0.45, 1.03)	1.39(0.9–2.15)	0.1378	0.95 (0.86, 1.04)	0.79 (0.57, 1.09)	1.2(0.85–1.69)	0.2894
Aggravated generalized muscle pain		0.79 (0.71, 0.89)	0.0001	0.0%	0.80 (0.64, 1.01)	0.76 (0.63, 0.93)	1.05(0.79–1.41)	0.7302	0.78 (0.61, 1.01)	0.78 (0.65, 0.95)	1(0.74–1.36)	1
New generalized joint pain		0.80 (0.69, 0.92)	0.0023	0.0%	0.79 (0.65, 0.95)	0.84 (0.65, 1.09)	0.94(0.68–1.3)	0.7089	0.75 (0.61, 0.92)	0.88 (0.70, 1.11)	0.85(0.63–1.16)	0.3095
Aggravated generalized joint pain		0.85 (0.66, 1.11)	0.2391	57.4%	0.91 (0.61, 1.37)	0.76 (0.58, 0.99)	1.2(0.74–1.94)	0.4646	0.89 (0.51, 1.53)	0.78 (0.60, 1.00)	1.14(0.62–2.11)	0.6744
Any systemic event		0.97 (0.91, 1.04)	0.4003	49.2%	0.99 (0.94, 1.04)	0.96 (0.81, 1.15)	1.03(0.86–1.23)	0.7342	0.99 (0.94, 1.04)	0.96 (0.81, 1.15)	1.03(0.86–1.23)	0.7342
All-cause mortality		3.13(0.45, 21.70)	0.2481	49.8%	2.98(0.12, 72.90)	3.89(0.18, 83.74)	0.77(0.01–65.3)	0.9065	2.98(0.12, 72.90)	3.89(0.18, 83.74)	0.77(0.01–65.3)	0.9065

[a] Risk Ratio estimated using random effects model.
[b] Test of interaction for stratified analyses.

Although we saw a total of 17 deaths in the PCV13 arm, compared to only 4 in PPV23, this result was not statistically significant, with the 95% CI broadly crossing 1. Upon further evaluation of the all-cause mortality data in PCV13 arm, the majority of deaths came from the open-labelled study by Juergens et al who reported 12 deaths related to cardiovascular disease and cancer; the open-labelled component may have led to the conjugate vaccine being administered to the sicker patients. In contrast, Ewald and colleagues, in their meta-analysis of 21 studies with 361,612 subjects, evaluating all PCV vaccines and PPV23/placebo found that all-cause mortality was comparable in PCV13 and control arms [28].

With aging, individuals become more susceptible to infection and their ability to mount an immune response is blunted as a result of immunosenescence [29–31]. As multiple doses of PPV23 are not found to be beneficial for boosting the response [21], the use of a conjugate vaccine, which allows for a better immune response, may be an advantageous option.

This meta-analysis is not without limitations. Firstly, all five RCTs included in the meta-analysis have high risk of bias in allocation concealment, as staff administering the study vaccines were unblinded to the allocation. However, the design of four studies ensured modified double blinding, which would mitigate this concern, as both measures of outcomes and patients were blinded to the vaccines, except Juergens et al. which was open-label. Secondly, the studies were all industry funded. Despite this potential bias, the studies were generally robust, and reported data and outcomes in a standardized manner, which facilitated a fair comparison. Third, all the trials included in the meta-analysis were conducted at different locations. This attributed to the high heterogeneity due to geographic differences, assays conducted in different laboratories, varied age groups and co-morbidities. Despite high heterogeneity, a robust immune response was observed in this population, which indicates generalizability of the results. Heterogeneity was carefully assessed using random effects modelling when stratifying for safety outcomes with prior pneumococcal vaccination to increase the findings application to the general population, and rule out possible confounding variables. In addition, patients included were from various high-income countries, such as the USA, Netherlands, Japan, and Sweden, which suggests these findings, may be generalizable to at least that population. Due to limited sequential dosing data, we were unable to meta-analyze the impact of multiple dosing.

5. Conclusion

A single dose of PCV13 generates a significant immune response among adults when compared with PPV23. Immune response to PCV13 was comparable among pneumococcal naïve individuals, and those with prior PPV23 vaccine. PCV13 was well tolerated and safe with overall comparable local reactions and systemic reactions as PPV23.

Author contributions

NKV conceived the study, conducted literature review; reviewed papers, adjudicated data discrepancy, conducted analysis and wrote the manuscript. KP and LM contributed to the review of abstracts and papers, data extraction, and manuscript writing and editing. AK contributed to data analysis and manuscript writing and editing. FM conceived the study, supervised literature review, and provided critical feedback for the manuscript. All five authors have read and approved the final manuscript.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors. NKV, KP, LM and AK did not have any financial support for this study; FM has received a grant from Pfizer within the last 5 years.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.01.014.

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