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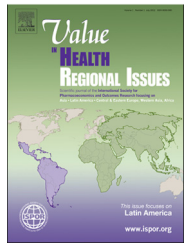

Interchangeability between Pneumococcal Conjugate Vaccines: A Systematic Review and Meta-Analysis

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ABSTRACT

Objectives: To assess the efficacy, cost-effectiveness, immunogenicity, and safety related to the interchangeability between pneumococcal conjugate vaccines (PCVs) and vaccination schedules in pediatric population. **Methods:** Systematic searches were conducted in December 2010 and April 2015 for economic evaluations in MEDLINE, EMBASE, LILACS, and Cochrane Central Register of Controlled Trials. Web sites and databases from medical societies, experts, and associations related to the topic, proceedings or congressional annals, and doctoral theses were also searched. No language or temporal restriction was applied. We included randomized controlled trials, economic evaluations, and systematic reviews evaluating antibody response, cost-effectiveness, and effectiveness of PCVs' interchangeability. A Strengthening the Reporting of Observational Studies in Epidemiology–based checklist was used to assess the risk of bias in observational studies and a Cochrane approach for experimental/quasi-experimental studies. Pairs of reviewers independently selected (through the Web-based Early Reviewer Organizer Software), assessed the quality, and extracted the data of the studies. Discrepancies were resolved by consensus. We planned to perform meta-analysis whenever appropriate. **Results:** Forty-six of 202 studies were included. There was no direct information available on the interchangeability between PCVs. The immunogenicity and safety between the 10-valent PCV (PCV10) and the 7-valent PCV were similar when both vaccines were coadministered with other routine pediatric vaccines. PCV10 and 13-valent PCV (PCV13) were consistently more cost-effective than 7-valent PCV. **Conclusions:** There was no direct comparative information available on the interchangeability among PCVs, but they have pretty similar immunogenicity and safety. PCV10 versus PCV13 cost-effectiveness varied according to price, indirect effects, and indirect costs. PCV10 gains more quality-adjusted life-years because of the prevention of more frequent yet less severe events such as otitis media, and PCV13 prevents less frequent but more costly events such as invasive diseases.

Keywords: conjugated pneumococcal vaccine, cost-effectiveness, efficacy, immunogenicity, interchangeability, safety.

Background

Streptococcus pneumoniae is a leading cause of childhood illness worldwide. Pneumococci vary widely in pathogenic potential. The most common disease results from strains that show a predilection for the respiratory tract and result in acute otitis media (AOM), sinusitis, or community-acquired pneumonia (CAP). Direct extension of infection from the middle ear or sinuses, or hematogenous spread from a pulmonary source, may result in meningitis [1]. Even after receiving appropriate treatment, patients with pneumococcal meningitis have a mortality rate of 20% to 30% [2,3].

The worldwide use of antibiotics has resulted in a dramatic decrease in morbidity and mortality from *S. pneumoniae* infection in the early 1940s. However, as the threat of resistance rises, primary prevention through vaccination is becoming more important [4,5]. There are more than 90 *S. pneumoniae* serotypes. The serotypes contained in various pneumococcal conjugate vaccines (PCVs) are described in Appendix 3 in Supplemental Materials found at http://dx.doi.org/10.1016/j.vhri.2015.12.001. Serotypes included in 7-valent PCV (PCV7) varied substantially by region from 49% to 82%, with highest serotype coverage in North America and Europe. 10-valent PCV (PCV10) has similar coverage as 13-valent PCV (PCV13), accounting for 70% or more of invasive pneumococcal disease (IPD) in every region and less regional variability than PCV7 [6]. PCVs are effective in preventing pneumonia among young children, and the impact is greater for IPD attributed to vaccine serotypes than for all serotypes-IPD [7]. The potential effectiveness of PCVs depends on the serotypes included, geographic context, and patients' demographic characteristics [8–14]. As a result, PCV recommendations may vary worldwide [14,15].

Conflict of interest: The authors have indicated that they have no conflicts of interest with regard to the content of this article.

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2212-1099$36.00 – see front matter

http://dx.doi.org/10.1016/j.vhri.2015.12.001

The pneumococcal immunization programs are changing given the fast introduction of different PCVs worldwide. There is uncertainty about the effects of interchanging PCVs with different valencies/conjugates (i.e., if you start a program with PCV7 what is known about switching to PCV10 or PCV13) or about the effects of different vaccination schedules on clinical or economic outcomes. This systematic review aimed to compare the immunogenicity, health economics, and safety of interchanging PCV7, PCV10, and PCV13 in pediatric population.

Methods

A systematic review was performed following Meta-analysis Of Observational Studies in Epidemiology guidelines for observational studies and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement for reporting systematic reviews and meta-analysis [16–18].

Eligibility Criteria

Studies were included if they were randomized controlled trials (RCTs), economic evaluations describing perspectives and decision models used, systematic reviews, or meta-analyses about interchangeability between at least two PCVs or vaccination schedules in subjects younger than 5 years (59 months). To be included the studies had to evaluate at least one outcome about efficacy, immunogenicity, cost-effectiveness, safety, or serotype distribution.

The primary outcome of interest was the serotype-specific pneumococcal antibody response considered as protective, specifically the percentage of subjects with immunoglobulin G concentration of 0.2 μg/ml or more, and opsonophagocytic activity (OPA) by a killing assay, with a cutoff opsonic titer of 8 Dil or more as OPA positivity [19–21]. Secondary outcomes evaluated were cost-effectiveness, including health service costs, cost per disability-adjusted life-year, quality-adjusted life-year, and total direct and indirect costs; *clinical effectiveness*, defined as the number of pneumococcal infections or total mortality due to invasive pneumococcal disease with *S. pneumoniae* isolates or mortality from infections with *S. pneumoniae* isolates; and the main adverse effects of each vaccine.

Studies about potential pneumococcal vaccine coverage and studies with information about only one PCV were exclusion criteria.

Search Strategy

A systematic search was conducted on December 27, 2010, using Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, and LILACS databases. An updated search for economic evaluations of PCVs, the most active research topic, was performed on April 19, 2015. Details of the searches are listed in Appendix 4 in Supplemental Materials found at http://dx.doi.org/10.1016/j.vhri.2015.12.001. Web sites and databases from medical societies, experts, and associations related to the topic, proceedings or congressional annals, and doctoral theses were also searched. An annotated search strategy for gray literature was included to retrieve information from relevant sources such as the World Health Organization Web site. No language or temporal restrictions were imposed.

Study Selection and Data Collection Process

We used Early Reviewer Organizer Software, a Web-based software, to facilitate the selection of studies during the systematic review [22]. Pairs of reviewers, randomly generated by Early Reviewer Organizer Software from all authors, independently evaluated the selected articles, and a separate pair of reviewers subsequently extracted data and assessed the studies' methodological quality using previously piloted spreadsheets. An algorithm developed by the research team was used to categorize the study designs and the methodological quality (see Appendix 5 in Supplemental Materials found at http://dx.doi.org/10.1016/j.vhri.2015.12.001). Discrepancies were resolved by consensus.

Risk of Bias Assessment

The risk of bias in observational studies was assessed using a checklist of essential items stated in Strengthening the Reporting of Observational studies in Epidemiology [23], and considering four methodological articles: Sanderson et al. [24], Fowkes and Fulton [25], Wong et al. [26], and Berra et al. [27]. We used an algorithm, programmed in an Excel spreadsheet, to estimate a summary risk of bias using four criteria (methods for selecting study participants, methods for measuring exposure and outcome variables, methods to control confounding, and comparability among control and intervention groups) and two minor criteria (statistical methods excluding confounding, and conflict of interest).

A simple approach was used to summarize the risk of bias drawn from the Cochrane "Risk of bias" tools for assessing RCTs and clinical controlled trials [28,29]. The Cochrane Effective Practice and Organisation of Care (EPOC) Quality criteria [30] were used to assess the risk of bias of the controlled before and after studies and interrupted time series (see Appendix 5 in Supplemental Materials). For health economic evaluations, we used the Users' Guides to the Medical Literature [31].

Synthesis of Results

A meta-analysis using Review Manager 5 software was planned (fixed-effects model). In cases of clinical, methodological, and statistically important heterogeneity ($I^2 > 50\%$), we planned not to present summary statistics.

Because this evidence was requested by the Pan-American Health Organization (PAHO) to be applied in the region, besides international studies, we used meta-analyses of unpublished and published data regarding the pneumococcal serotype prevalence among children in Latin America and the Caribbean (LAC) with AOM [32] and CAP [33] to determine the potential serotype coverage of PCVs.

Results

A systematic search of electronic databases retrieved 223 articles. Forty-five additional articles were included from gray literature search. Forty-nine studies were included in our analysis (Fig. 1). We found information about cost-effectiveness, immunogenicity, and safety related to the interchangeability between PCVs and vaccination schedules, but there were no data about efficacy. The data obtained were only sufficient to perform a meta-analysis for safety.

Immunogenicity

Four articles were included [34–37]. All RCTs were funded by GlaxoSmithKline. All compared a 10-valent pneumococcal nontypeable *Haemophilus influenzae* protein-D conjugate vaccine (PCV10) with a 7-valent pneumococcal nontoxic cross-reacting mutant of diptheria vaccine (PCV7) coadministered with other common childhood vaccines. Three studies determined immunogenicity following three-dose primary vaccination series, and

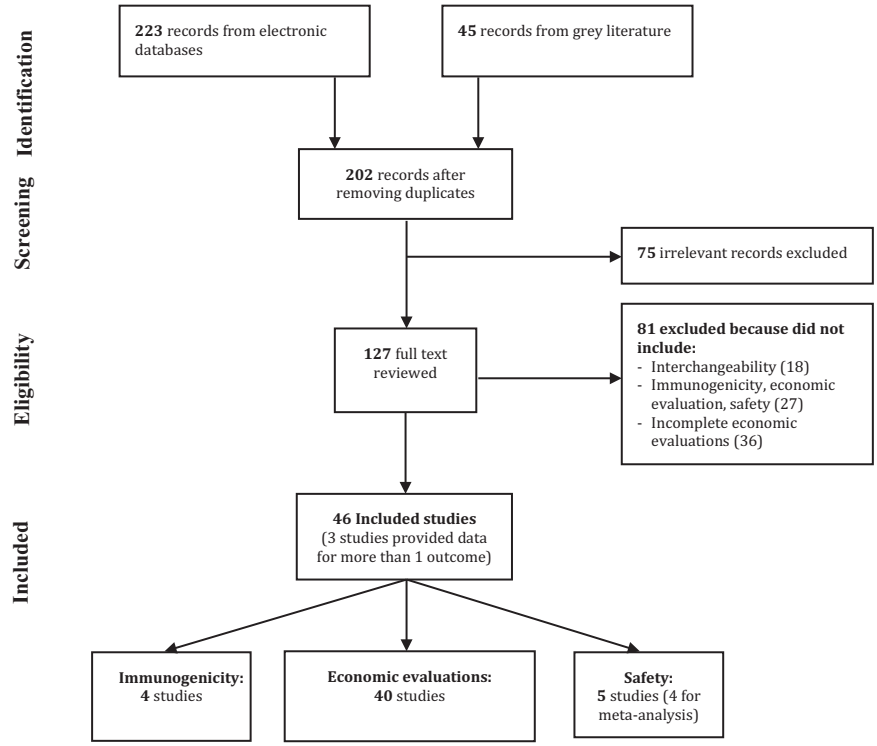

Fig. 1 – Flow of studies through the systematic review.

three studies, using the same populations and vaccines, determined immunogenicity following booster vaccination (Table 1) [34,36,37].

A three-dose primary vaccination showed a strong immune response for both PCV10 and PCV7 vaccines (Table 2 in Supplemental Materials found at http://dx.doi.org/10.1016/j.vhri.2015.12.001). Bermal et al. [34] found that excluding serotypes 1, 5, and 7F (present only in PCV10), the percentage of Filipino subjects with an antibody concentration of 0.2 μg/ml or more and OPA titers of 8 Dil or more for the seven common serotypes was similar for both vaccination groups. In Poland, they were within the same range for 5 of the 7 common serotypes, but PCV10 subjects had lower antibody percentages for serotypes 6B and 23 F, higher OPA positivity for serotype 19F, and lower OPA positivity for serotype 23F. Vesikari et al. [36] found that 95.4% or more of PCV10 subjects had antibody concentrations of 0.2 μg/ml or more for 8 of the 10 serotypes whereas 94.1% or more of PCV7 subjects had antibody concentrations of 0.2 μg/ml or more for only 3 of 7 serotypes. More than 90% of PCV10 subjects had OPA titers of 8 Dil or more for 8 of 10 serotypes, and more than 92.1% of PCV7 subjects had OPA titers of 8 Dil or more for 4 of 7 serotypes. Wysocki et al. [37] found that the percentage of subjects with antibody concentrations of 0.2 μg/ml or more was in the same range for all groups. OPA titers were 8 Dil or more in at least 90.4% of PCV10 subjects for 7 of 10 serotypes and at least 92.9% of PCV7 subjects for 4 of 7 serotypes.

Booster vaccination showed robust immune responses in all groups and in all studies (Table 2 in Supplemental Materials found at http://dx.doi.org/10.1016/j.vhri.2015.12.001). Following the booster dose in Bermal et al. [35], all groups had antibody concentrations and OPA seropositivity rates within the same ranges for the seven common serotypes. Vesikari et al. [36] showed a decline in antibody concentrations and OPA titers in both groups between the completion of the primary series and booster. However, 1 month after the booster dose, PCV10 antibodies increased by 6.0- to 16.7-fold, and PCV7 antibodies increased by 8.8- to 27.8-fold, compared with prebooster levels. More than 96% of all subjects had antibody concentrations of 0.2 μg/ml or more for the seven common serotypes and more than 99% of PCV10 subjects had antibody concentrations of 0.2 μg/ml or more against the three additional serotypes. More than 94.9% of PCV10 and 92.5% of PCV7 subjects had OPA titers of 8 Dil or more for the shared serotypes. Wysocki et al. [37] found that antibody concentrations of 0.2 μg/ml or more and OPA seropositivity were the same in all subjects for the common serotypes (98.8%). For serotypes 1, 5, and 7 F (covered only by PCV10), 90% of PCV10 subjects had antibody concentrations of 0.2 μg/ml or more and OPA titers of 8 Dil or more.

Health Economics

Forty economic evaluations [38–77] were included (10 of them were conference abstracts) (see Appendix 6 in Supplemental Materials found at http://dx.doi.org/10.1016/j.vhri.2015.12.001). Sixteen received financial support from GlaxoSmithKline (PCV10 manufacturer), 9 from Pfizer and 4 from Wyeth (PCV7 and PCV13 manufacturer), and 11 from other sources. Two studies were conducted in Africa, 14 in America, 6 in Asia, 15 in Europe, 1 in Oceania, and 2 in more than one continent.

Twenty-six studies analyzed the comparative cost-effectivenes of PCV10 and PCV13. Ten concluded that PCV10 was more cost-effective (all supported by GlaxoSmithKline), and 16 concluded that PCV13 was more cost-effective (8 from Pfizer, 3 from Wyeth, 2 from government agencies in South America, and 1 from GlaxoSmithKline). In general, the relationship between PCV10 and PCV13 depended on price setting and the importance that is assigned to outcome-related indirect costs. If AOM was the most important driver of related indirect costs, PCV10 was more cost-effective than PCV13; if IPD was the most important driver, PCV13 was more cost-effective than PCV10.

Table 1 – Description of immunogenicity and safety studies.

Study	Focus	Design	Quality	No. of subjects	Objectives	Study location	Study arms	Funding
Bermal et al. [34] Bermal et al. [35]	Immuno-genicity Safety	DB-RCT, 3:1 ratio CBA, open extension of an RCT	Met all criteria Met all criteria	761 in 1st vaccination cohort 756 in booster cohort	Reactogenicity after a primary vaccination series and booster dose of PCV10 or PCV7, coadministered with DTPw-HBV/Hib and poliovirus vaccines Noninferiority of PCV10 booster compared with PCV7 booster in terms of fever (temperature, >39°C)	The Philippines (age 6, 10, 14 wk)	PCV10 + DTPw-HBV/Hib + OPV → PCV10 booster PCV7 + DTPw-HBV/Hib + OPV → PCV7 booster	Glaxosmithkline Biologicals
						Poland (age 2, 4, 6 mo)	PCV10 + DTPw-HBV/Hib + IPV → PCV10 booster PCV7 + DTPw-HBV/Hib + IPV → PCV7 booster	
Vesikari et al. [36]	Immuno-genicity	RCT, noninferiority study	No loss in follow-up, per-protocol analysis, other criteria not reported. Comparable groups	1650 in 1° vaccination cohort 1112 in booster cohort	Evaluate noninferiority of immune response of PCV10 relative to PCV7 1 mo after three-dose primary vaccination course Evaluate the immunogenicity 1 mo after PCV10-primed patient boosted with PCV10, PCV7-primed patient boosted with PCV7, and PCV7-primed patient boosted with PCV10	Finland France* Poland (age 2, 3, 4 mo)	PCV10 + DTPa-HBV-IPV/Hib PCV10 booster PCV7 + DTPa-HBV-IPV/Hib PCV7 booster PCV7 + DTPa-HBV-IPV/Hib PCV10 booster	Glaxosmithkline Biologicals
Wysocki et al. [37]	Immuno-genicity	RCT (1:1:1:1), noninferiority study	No loss in follow-up, per-protocol analysis (phase I), ITT (phase II), other criteria not reported. Comparable groups	1499 in 1° vaccination cohort 1437 in booster cohort	Primary objective to assess noninferiority of safety (fever) of PCV10 relative to PCV7 Secondary objective to assess immunogenicity of PCV10 relative to PCV7 when coadministered with other routine vaccines after one vaccination series and after booster	Germany Poland Spain (age 2, 4, 6 mo)	PCV10 + MenC-CRM (2, 4 mo only) + DTPa-HBV-IPV/Hib (DTPa-IPV/Hib booster in Spain) → PCV10 booster PCV10 + MenC-TT (2, 4 mo only) + DTPa-HBV-IPV/Hib (DTPa-IPV/Hib booster in Spain) → PCV10 booster PCV10 + MenC-TT + DTPa-HBV-IPV (DTPa-IPV booster in Spain) → PCV10 booster PCV7 + Hib-MenC-TT + DTPa-HBV-IPV (DTPa-IPV booster in Spain) → PCV7 booster	Glaxosmithkline Biologicals

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Table 1 – *continued*

Study	Focus	Design	Quality	No. of subjects	Objectives	Study location	Study arms	Funding
Chevallier et al. [79]	Safety	Review of safety data from 5 RCTs, labeled Study A–E	-Search strategy not reported -Quality assessment not reported -Descriptive synthesis (similar results between studies) -Reliable primary outcome measure	4004 in 1° vaccination studies	Demonstrate that PCV10, compared with PCV7, when coadministered with other childhood vaccines did not induce more postimmunization febrile reactions	Study A (note: 1° vaccination subjects from Vesikari et al. study): Finland, France, Poland	See 1° vaccination schedule of Vesikari et al. [36]	Glaxosmithkline Biologicals
						Study B (note: 1° vaccination subjects from Wysocki et al. [37] study): Germany, Poland, Spain	See 1° vaccination schedule of Wysocki et al. [37]	
						Study C (note: 1° vaccination subjects from Bermal et al. [34]): The Philippines, Poland	See 1° vaccination schedule of Bermal et al. [34]	
				2549 in booster studies		Study D (note: booster subjects from Vesikari et al. [36] study): Finland, France, Poland	See booster schedule of Vesikari et al. [36]	
						Study E (note: booster subjects from Wysocki et al. [37] study): Germany, Poland, Spain	See booster schedule of Wysocki et al. [37]	
Ugpo et al. [78]	Safety	DB-RCT multicenter	Met all criteria	252 passive, 126 active, surveillance subjects	Assess adverse effects of PCV11 compared with placebo	The Philippines (age 6, 10, 14 wk)	PCV11 + DTwP-PRP-T + OPV Placebo	PATH

CBA, controlled before and after; CRM, cross-reacting mutant; DB, double-blinded; DTP, diphtheria pertussis tetanus; HBV, hepatitis B vaccine; Hib, *Haempphilus influenza* type b; IPV/OPV, inactivated/oral poliovirus vaccine; ITT, intention-to-treat; PCV, pneumococcal conjugate vaccine; MenC, meningitis C; RCT, randomized controlled trial; TT, tetanus toxoid.

* Second dose of one vaccine was DTPa-IPV/Hib.

Only Rozenbaum et al. [68] found that PCV vaccination, specifically with PCV7, was not cost-effective. Almost all studies found that PCV13 or PCV10 was more cost-effective compared with PCV7 or no vaccination (see Appendix 6 in Supplemental Materials).

Safety

Data from five RCTs were included for safety [34,36,37,78,79] (Table 1). Chevallier et al. [79] contained safety data from the primary vaccination cohorts of Bermal et al. [34], Vesikari et al. [36], and Wysocki et al. [37] and from the booster cohorts of Vesikari et al. [36] and Wysocki et al. [37] (see Immunogenicity section). Studies focused on the development of fever (temperature, >39C°) as a primary outcome; however, the studies also evaluated reports of pain, redness, swelling, drowsiness, irritability, and loss of appetite. In most studies, the intensity of symptoms was graded on size or a scale of 0 to 3, with grade 3 defined as preventing normal everyday activity.

Safety of primary vaccination is discussed in studies by Chevallier et al. [79] and Ugpo et al. [78] (Table 3 in Supplemental Materials found at http://dx.doi.org/10.1016/j.vhri.2015.12.001). In Chevallier et al. [79], 150 PCV10 and 44 PCV7 subjects reported adverse events, of which 6 were considered directly related to vaccination. General reactions, including drowsiness, irritability, loss of appetite, and fever, were within the same range in all PCV10 and PCV7 groups, except for drowsiness and irritability in study B (Wysocki et al. [37]) and irritability and loss of appetite in study C (Bermal et al. [34]). The incidence and intensity of local reactions in the PCV10 and PCV7 groups were within the same ranges in all studies. Ugpo et al. [78] compared reactions to PCV11 with those to placebo; pain was the most common symptom in both groups, followed by redness at injection site. The only significant difference between groups was that PCV11 subjects had more drowsiness than placebo groups following initial injection. The meta-analysis (four studies, 7526 participants) showed no difference between PCV10 and PCV7 for most severe adverse side effects (ASEs), but PCV10 was worse in two ASEs: risk ratio (Mantel-Haenszel methods, fixed, 95% confidence interval) = 1.37 (1.07–1.75) for irritability grade 3 and 1.34 (1.01–1.79) for fever (temperature, ≥39°C) (Table 3 in Supplemental Materials found at http://dx.doi.org/10.1016/j.vhri.2015.12.001; Fig. 2).

Safety of booster vaccination is discussed in studies by Bermal et al. [35] and Chevallier et al. [79] (Table 3 in Supplemental Materials found at http://dx.doi.org/10.1016/j.vhri.2015.12.001). Bermal et al. [35] showed that PCV10 was noninferior to PCV7 in terms of fever. The incidence of solicited side effects was within the same range for all groups. Overall, the incidence of

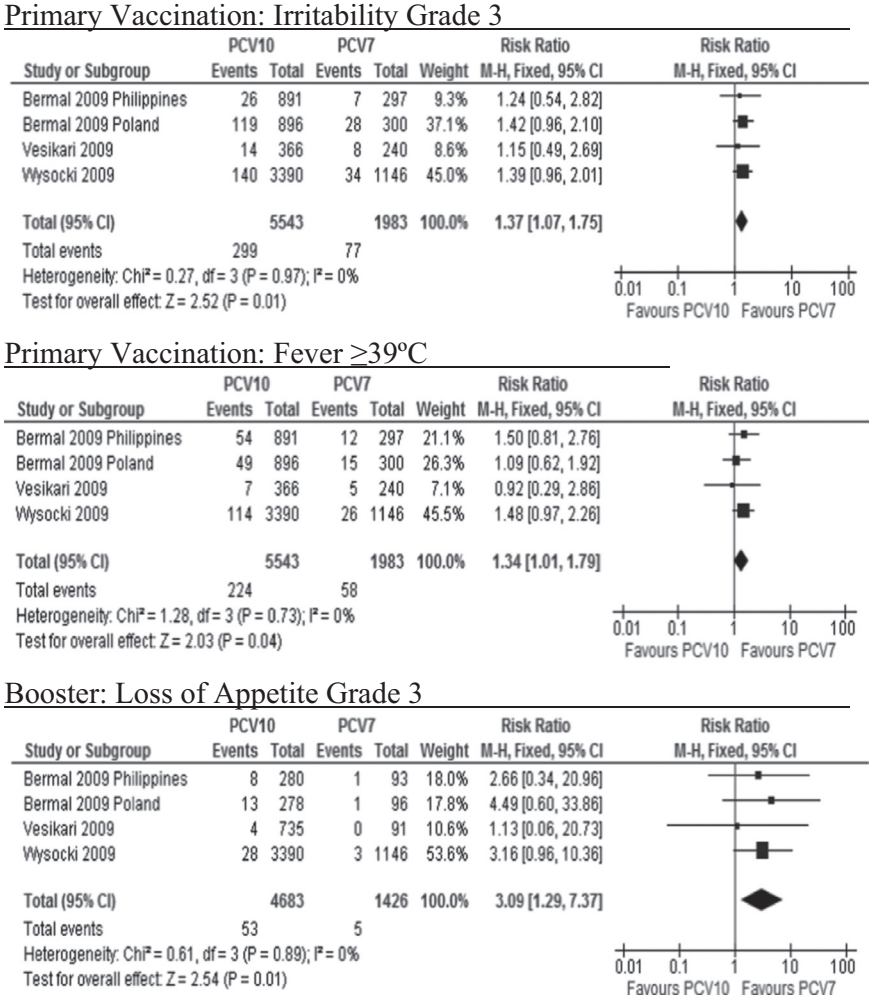

Fig. 2 – Safety of PCV10 vs. PCV7: Meta-analysis of the adverse side effect that showed statistically significant differences among arms. CI, confidence interval; PCV7, 7-valent pneumococcal conjugate vaccine; PCV10, 10-valent pneumococcal conjugate vaccine.

unsolicited side effects was higher in Poland than in the Philippines; however, the ranges between groups within each country were similar. Chevallier et al. [79] showed that there was no increase in the incidence or severity of general symptoms including fever after the booster dose, as compared to primary vaccination series. There was, however, an increase in the incidence of local symptoms. Pain and redness were the most common local symptoms. The meta-analysis (four studies, 6109 participants) showed no difference between PCV10 and PCV7 for most severe ASE, but PCV10 was worse for loss of appetite grade 3: risk ratio (M-H, fixed, 95% confidence interval) = 3.09 (1.29–7.37) (Table 3 in Supplemental Materials found at http://dx.doi.org/10.1016/j.vhri.2015.12.001; Fig. 2).

Only Vesikari et al. [36] analyzed PCV7 boosted with PCV10 and the frequency of ASEs was similar to the frequency of ASEs in groups boosted with the same vaccine (Table 3 in Supplemental Materials found at http://dx.doi.org/10.1016/j.vhri.2015.12.001).

Potential Serotype Coverage of PCV

A literature search using keywords acute otitis media, community-acquired pneumonia, streptococcus pneumoniae serotyping, or classification or distribution found five articles discussing pneumococcal serotype distribution [32,80–83]. Five studies discussed potential AOM coverage, and one of them discussed potential CAP coverage [33]. Data from these articles were used to calculate possible serotype coverage, assuming full protection for the serotypes included in the vaccines and without consideration of potential serogroup cross-protection.

The potential coverage of different pneumococcal conjugated vaccines in LAC was determined using data on the serotype distribution of CAP and AOM cases in LAC children younger than 5 years in Bardach et al. [32]. A total of 23,854 cases of CAP and 125,519 cases of AOM were found. A meta-analysis was performed for each serotype. The potential serotype coverage of pneumococcal vaccine for AOM was 52.8%, 73.6%, 77.1%, and 89.5% and for CAP was 52.2%, 65.2%, 65.2%, and 85.5% for PCV7, 9-valent PCV (PCV9), PCV10, and PCV13, respectively. *S. pneumoniae*, *H. influenzae*, and *Mycoplasma pneumoniae* were the most common CAP pathogens identified, whereas *S. pneumoniae* and *H. influenzae* were the most common AOM pathogens identified.

A study by Hausdorff et al. [80] analyzed nine AOM epidemiologic data sets from Argentina, Finland, France, Greece, Israel, and multicountry (a composite of subjects from Eastern and Central Europe) and three data sets from the United States [80]. Data from 3232 children and 3520 pneumococcal isolates were obtained. These data demonstrate that PCV7, PCV9, PCV10, and PCV13 would cover 67.4%, 69.7%, 69.7%, and 83.7% (Argentina); 60.8%, 60.8%, 61.4%, and 80% (Finland); 68.4%, 68.4%, 68.4%, and 73.5% (France); 53.3%, 54.6%, 58.4%, and 83.7% (Greece); 54.9%, 58.5%, 60.1%, and 77.9% (Israel); 53.6%, 63.6%, 66%, and 82.4% (multicountry); 70.2%, 70.9%, 71.7%, and 89.4% (United States data set 1); 68.3%, 68.8%, 69.3%, and 93.3% (United States data set 2); 65.3%, 65.3%, 65.3%, and 79.3% (United States data set 3); and 60.9%, 63.5%, 64.3%, and 82.2% (overall) of AOM isolates, respectively. In Japan, Hotomi et al. [81] described nationwide pneumococcal serotypes from 175 middle-ear fluid samples in children with AOM between February 2006 and June 2007. Using their data, PCV7, PCV9, PCV10, and PCV13 are projected to cover 60.5%, 61.1%, 61.7%, and 82.8% of AOM isolates, respectively. A study in Israel by Somech et al. [83] studied the distribution of pneumococcal serotypes over a 10-year period (1999–2008). A total of 9752 AOM culture-positive episodes were studied, with *S. pneumoniae* as the isolate in 5281 cases. PCV7, PCV9, PCV10, and PCV13 were projected to cover 53%, 58%, 59%, and 79% of the *S. pneumoniae* AOM isolates, respectively.

Potential PCV7, PCV9, PCV10, and PCV13 coverage is presented in Table 4.

Rodgers et al. [82] reviewed data on global serotype distribution of pneumococcal AOM in seven geographic regions. Original articles were not available for all data; therefore, the systematic review was included here. With data from North America, the coverage of PCV7, PCV10, and PCV13 was calculated to be 76.2%, 77.4%, and 82.8%, respectively. With data from Oceania, the coverage for PCV10 and PCV13 could not be calculated, but PCV7's coverage was calculated to be 69.8%. European findings included Greece, Finland, and the Czech Republic. In Greece, 50.9% to 70.5% of isolates were covered by PCV7 and PCV10 increased the coverage by 0% to 2.6% and PCV13 by 18.0% to 28.3%. In Finland and the Czech Republic, PCV13 would provide 17% to 20% more coverage than would PCV7. In Argentina, PCV10 and PCV13 increased 2.3% and 14%, respectively, against PCV7. Limited data were available from African countries, making it difficult to assess the impact of PCV10 and PCV13 while PCV7 was shown to cover 92% of the isolates.

Johnson et al. [6] systematically reviewed studies with IPD serotype data among children younger than 5 years from the published literature and unpublished data and 169 studies comprising 60,090 isolates from 70 countries. Globally, serotypes included in PCV7, PCV10, and PCV13 have a potential coverage of 51%, 71%, and 76%, respectively.

Discussion

Although the appropriate application of vaccines may change over time, given local serotype and age-specific pneumococcal epidemiology, PCV is effective in preventing childhood morbidity and mortality from various pneumococcal diseases. With growing antibiotic resistance, primary prevention is becoming increasingly important.

To our knowledge, this is the first systematic review and meta-analysis studying the interchangeability between PCVs. We evaluated PCV immunogenicity, health economics, and safety on PCV interchangeability. We used data from primary studies or systematic reviews, most of good quality (Table 1; see Appendix 6 in Supplemental Materials), estimating the potential serotype coverage of various PCV's schemes in various geographic locations.

The limitations of the evidence provided by our study are mainly related to the absence of primary data about the comparative clinical efficacy among PCVs and vaccination schedules. Because our search strategy required that at least two PCVs be present in the same study, we did not retrieve studies that evaluated only one PCV. Because this is a hot topic, much of the data on the newer vaccines PCV10 and PCV13 are not published yet. Besides, the available data only allow us to meta-analyze safety outcomes. It is also important to consider that PCVs' comparison across studies may be altered because coadministration of different vaccines affect the reactogenicity profile.

However, our sensitive search strategy, including gray literature, provide a comprehensive picture of all the available indirect evidence about PCVs' interchangeability and the methodological quality of the 18 included studies.

Primary vaccination by PCV10 was shown to be immunogenic by all included studies, and the immunogenicity profile of PCV10 and PCV7, for most of the common two serotypes, is similar. In Bermal et al. [34], two populations followed different vaccination schedules and higher immune responses were exhibited in The Philippines, which followed a less extended vaccination schedule, than in Poland. Vesikari et al. [36] found PCV10 to be noninferior to PCV7 for 8 of 10 pneumococcal serotypes (1, 4, 5,

Table 4 – Potential PCV7, PCV9, PCV10, PCV13 coverage (%) of total AOM and CAP cases.

Serotype	Bardach et al. [32]	Gentile et al. [33]	Hausdorff et al. [80]										Hotomi et al. [81]	Somech et al. [83]
	LAC (AOM)	LAC (CAP)	Overall (AOM)	ARG (AOM)	FIN (AOM)	FRA (AOM)	GRE (AOM)	ISR (AOM)	MUL (AOM)	US1 (AOM)	US2 (AOM)	US3 (AOM)	Japan (AOM)	Israel (AOM)
1	10	3.3	1.6	2.3	0	0	1.3	2	5.2	0.7	0	0	0.6	2
3	3.3	5.2	4	3.5	3.1	0	3.8	3.1	5.6	4.7	8.7	1	9.1	4
4	1.0	1.3	0.7	0	0.9	0	1.3	0.9	1.6	1	0	1	0.6	1
5	10.8	9.7	1	0		0	0	1.6	4.8	0	0.5	0	0	3
6 A	4.4	4	7.3	1.2	9.8	0	10.1	5.8	8.8	7	10.4	10.9	9.1	6
6B	7.4	12.4	10.1	5.8	12.7	13.9	3.8	6	4.4	15.8	11.5	18.7	11.4	7
7 F	3.5	0	0.8	0	0.6	0	3.8	1.6	2.4	0.8	0.5	0	0.6	1
9 V	3.6	7.2	4.6	2.3	2.2	5.1	7.6	4.9	10.4	4.5	5.2	0	1.1	4
11	0	0	1.3	0	5.1	0.6	1.3	0	0.8	1.6	0.5	2.6	1.1	0
14	33	5.9	13.1	53.5	6.3	18.4	8.9	13.4	12	10.2	16	11.9	11.4	14
15	0	0	2.1	1.2	5.1	0	2.5	2.6	1.6	1.5	0.2	2.6	2.3	0
18C	1.8	4.5	1.4	0	3.7	0.6	3.8	1.8	3.2	0	0	0	1.7	2
19 A	4.7	11.1	6.6	9.3	5.7	5.1	11.4	8.9	2	6	4.9	2.1	2.9	10
19 F	2.9	15.7	16.1	3.5	13.7	3.2	12.7	13.9	12.8	23.3	24.5	17.6	19.4	15
23 F	3.1	5.2	14.9	2.3	21.3	27.2	15.2	14	9.2	15.4	11.1	16.1	14.9	10
PCV7 coverage	52.8	52.2	60.9	67.4	60.8	68.4	53.3	54.9	53.6	70.2	68.3	65.3	60.5	53
PCV9 coverage	73.6	65.2	63.5	69.7	60.8	68.4	54.6	58.5	63.6	70.9	68.8	65.3	61.1	58
PCV10 coverage	77.1	65.2	64.3	69.7	61.4	68.4	58.4	60.1	66	71.7	69.3	65.3	61.7	59
PCV13 coverage	89.5	85.5	82.2	83.7	80	73.5	83.7	77.9	82.4	89.4	93.3	79.3	82.8	79

AOM, acute otitis media; ARG, Argentina; CAP, community-acquired pneumonia; FIN, Finland; FRA, France; GRE, Greece; ISR, Israel; LAC, Latin America and the Caribbean; MUL, multicountry from Eastern and Central Europe; PCV-7, 7-valent pneumococcal conjugate vaccine; PCV-9, 9-valent pneumococcal conjugate vaccine; PCV-10, 10-valent pneumococcal conjugate vaccine; PCV-13, 13-valent pneumococcal conjugate vaccine; US, United States.

7 F, 9 V, 14, 18C, and 19 F) using antibody concentrations and 10 of 10 pneumococcal serotypes using OPA seropositivity. These data suggest that concomitant application of pneumococcal primary vaccines and other common childhood vaccines does not affect immunogenicity and that differences in immune responses generated by PCV10 and PCV7 are small and likely clinically insignificant.

Booster vaccination resulted in a robust immune response against 7 and 10 pneumococcal serotypes for the PCV7 and PCV10 vaccines, respectively. All authors conclude that the reactogenicity profiles of PCV10 and PCV7 for the 7 common serotypes are comparable and it is unlikely that any differences are clinically significant. Unfortunately, there are no data yet about going from PCV10 to PCV13.

In general, PCV7, PCV10, and PCV13 were cost-effective when compared to no vaccination, using local cost-effectiveness thresholds. Only one study observed that PCV7 was not a cost-effective strategy compared with not vaccinating. All studies demonstrated that PCV10 and PCV13 were more cost-effective than PCV7 if the prices used for the analysis remained constant between the different vaccines. When PCV10 and PCV13 were compared against one another, in general PCV10 gained more quality-adjusted life-years because of its effectiveness against more frequent but less severe events such as otitis media. PCV13, however, prevents the less frequent but more severe and more costly effects of invasive disease. Our findings were consistent with a recent systematic review of economic evaluations reporting that combined uncertainty related to price differences, burden of disease, vaccine effectiveness, and herd and serotype replacement effects determine the preference base for either PCV10 or PCV13. The key assumptions, and results, depended on which manufacturer sponsored the study [84]. Another systematic review of the European studies concluded that they are mostly based on weak sources of data with great within-study and between-study variability generated by authors' assumptions [85].

Safety data show that PCV is safe. Primary vaccination with PCV11 has a similar safety profile to that of placebo injection. In addition, both primary and booster PCV10 and PCV7 vaccination series have similar reactogenicity and safety profiles (except for irritability and fever during primary vaccination and loss of appetite during booster, which were less frequent with PCV7) when administered to children from six countries, using a range of vaccination schedules and coadministering with various commonly used pediatric vaccines.

Data regarding the potential AOM and CAP coverage of PCV7, PCV9, PCV10, and PCV13 were found in LAC, Europe, Japan, and Israel. There were insufficient data to determine potential vaccine coverage in Africa. CAP coverage was discussed only in one study, which found that the percentage of potential CAP coverage rose as the number of serotypes included in the vaccine rose. Five studies worldwide showed a similar trend for AOM coverage. Overall, PCV13 had the potential to cover more cases of AOM than did PCV10, PCV9, and PCV7.

Two scientific recommendation statements regarding the interchangeability of PCV7 and PCV10 were retrieved. The Committee on Vaccine Preventable Diseases in Hong Kong stated that PCV 10 may be used as a direct replacement of PCV7 at any point during the course of immunization without altering the immunization schedule [86]. An Advisory Committee Statement of the National Advisory Committee on Immunization in Canada recommended changing the PCV7 to PCV13 at any point in the immunization schedule [87]. The Public Health Agency of Canada stated that infants who started a series with PCV7 or PCV10 can complete it with PCV13 [88].

PAHO asked us to perform a systematic review to make an evidence-based decision regarding PCVs' interchangeability. Considering the absence of direct evidence, the World Health Organization [89] recommended that vaccination schedules should be completed with the same vaccine (or containing the same carrier) and remained unchanged in the Recommended Routine Immunization (updated February 27, 2015). If this is not possible, and one begins a series with PCV7, one can complete the primary series with the vaccine available (PCV10 or PCV13). If the primary series is completed with PCV7, the child can receive a booster dose with PCV10 or PCV13.

Conclusions

There are currently no direct comparative data available on the interchangeability among PCVs; however, the indirect evidence found could assist policymakers about interchangeability decisions.

Our review showed mainly that PCV10 and PCV13 have similar safety profiles and immune responses as PCV7 for both primary vaccination and booster series for specific serotypes. In addition, PCV10 and PCV13 were found to be more cost-effective than PCV7. An analysis of potential serotype coverage found that worldwide PCV13 could cover more AOM and CAP cases than PCV10 whereas PCV10 could cover more AOM and CAP cases than PCV7.

PCV10 and PCV13 were more cost-effective than PCV7. PCV10 gained more quality-adjusted life-years because of its effectiveness against more frequent but less severe events such as otitis media. On the other side, PCV13 prevents invasive diseases, which are less frequent but more severe and costly

Our review showed that PCV10 or PCV13 vaccination programs could replace the less cost-effective PCV7 vaccination programs in most instances.

This study informed PAHO's 2011 technical advisory group's recommendations on immunization schedules. PAHO recommend that vaccination schedules should be completed with the same type of vaccine. If this is not possible, a primary series initiated with PCV7 could be completed or boostered with the vaccine available as PCV10 or PCV13, and the results assessed.

Acknowledgment

We thank our librarian Daniel Comandé for helping us in the searches.

Source of financial support: This study was supported by the Pan-American Health Organization and by the Institute for Clinical Effectiveness and Health Policy.

Supplemental Materials

Supplemental material accompanying this article can be found in the online version as a hyperlink at http://dx.doi.org/10.1016/j.vhri.2015.12.001 or, if a hard copy of article, at www.valueinhealthjournal.com/issues (select volume, issue, and article).

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