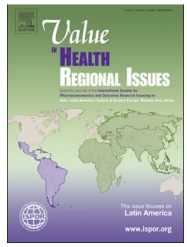
VALUE IN HEALTH REGIONAL ISSUES 11C (2016) 24–34

Available online at www.sciencedirect.com

ScienceDirect

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



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

Agustín Ciapponi, MD, MSc[1,], Alison Lee, MD[2], Ariel Bardach, MD, MSc, PhD[1], Demián Glujovsky, MD, MSc[1], Lucila Rey-Ares, MD[1], María Luisa Cafferata, MD[1], Pilar Valanzasca, MD[1], Sebastián García Martí, MD, MSc[1]*

[1]*Institute for Clinical Effectiveness and Health Policy (IECS), Buenos Aires, Argentina;* [2]*Southern Cone American Center for Cardiovascular Health (CESCAS/SACECH), Institute for Clinical Effectiveness and Health Policy (IECS), Buenos Aires, Argentina*

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.

* *Address correspondence to*: Agustín Ciapponi, Institute for Clinical Effectiveness and Health Policy, Southern American Branch of the Iberoamerican Cochrane Centre, Dr. Emilio Ravignani 2024, Buenos Aires C1414CPV, Argentina.

E-mail: aciapponi@iecs.org.ar

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