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Methods for a Systematic Review of Pneumococcal Conjugate Vaccine Dosing Schedules

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Background: *Streptococcus pneumoniae* causes a considerable amount of morbidity and mortality in children <5. However, pneumococcal conjugate vaccines (PCVs) can prevent much of this burden. Until recently, PCVs were mostly available only in developed countries using a variety of dosing schedules. As more lower income countries make decisions to introduce PCV into their national immunization programs, an optimal schedule with which to administer PCV has become a key policy question.

Methods: We performed a systematic review of English literature published from 1994 to 2010 on the effects of PCV dosing schedules on immunogenicity, nasopharyngeal carriage, invasive pneumococcal disease and pneumonia. Data were independently double abstracted and cleaned for analysis. Descriptive analyses were performed.

Results: We identified 12,980 citations from the literature search (12,976) and secondary means (44). Double review of titles and abstracts yielded 769 articles that underwent full data abstraction. Of these, 350 were further analyzed and are presented in separate reports in this supplement.

Conclusions: This article presents the methods utilized in our systematic review. Because of the heterogenity of the study methods of the reports identified by this review, we did not conduct formal meta-analyses. However, these methods allow us to present a full landscape of the literature on PCV dosing schedules.

Key Words: pneumococcal conjugate vaccine, immunization schedule, methods, systematic review

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Pneumococcal conjugate vaccines (PCVs) are being introduced into the routine immunization schedules of many countries, including those of developing countries. This unprecedented roll-out of vaccine is motivated by the recognized high burden of pneumococcal morbidity and mortality in young children. Annually, pneumococcus is estimated to cause more than 500,000 deaths and 14.5 million episodes of pneumonia in children under 5 years of age worldwide.[1,2] Until recently, PCVs were mostly available only in developed countries because of the high financial cost of the vaccine. Although originally licensed on a three primary dose regimen plus one booster (3+1), PCVs have now been licensed for use on a variety of dosing schedules.[3–5] In addition, the World Health Organization initially recommended PCV on a schedule of 3 primary doses without a booster, the schedule commonly used in lower income countries.[6] As a greater number of lower income countries make decisions to introduce PCV into their national immunization programs, an optimal schedule at which to administer PCV has become a key policy question. We conducted a systematic review of the literature on PCV dosing schedules. This article describes the methods used to review and analyze the data from this project. The results of the impact of PCV dosing schedules on immunogenicity, invasive pneumococccal disease (IPD), pneumonia, nasopharyngeal (NP) colonization and indirect effects are the subject of separate publications.[7–11]

METHODS

The methods and analyses for this study were developed by the core team of study investigators with ad hoc input from relevant experts in the pneumococcal field. The methods used in this review have been modeled from similar systematic reviews of this nature.

Literature Search Strategy

We performed a systematic literature review to identify all available data between January 1994 and September 2010 from published and selected unpublished sources on the immunogenicity and direct and indirect effects on NP carriage, IPD and pneumonia of various PCV schedules for healthy children as well as children with underlying medical conditions (eg, sickle cell disease and HIV). We reviewed all data from clinical trials (both randomized controlled trials and other designs), other clinical studies (eg, observational studies) and surveillance database analyses performed in the setting of PCV use. Only studies published in the English language were considered for review because of the low likelihood that such studies had been published in non-English journals.

Specific search terms and choice of databases were developed with the advice of a professional librarian from Johns Hopkins University and used to identify articles (Table 1). To be identified in the search, each article had to include a minimum of one "narrow vaccine term" and one "pneumococcal term." Terms were listed as Medical Subject Headings (MeSH) or other categories specific to

TABLE 1. Detailed Search Strategy Utilized in the Literature Search

Search Terms

Pneumococcal terms:
1. Pathogen terms
"*Streptococcus pneumoniae*"[mesh]
("Diplococcus"[all fields] AND "pneumoniae"[all fields])
("micrococcus"[all fields] AND "pneumoniae"[all fields])
"Pneumococcus"[all fields]
"pneumococcal"[all fields]
"s. pneumoniae"[all fields]
"pneumococci"[all fields]
Pneumococc*[all fields]
"Streptococcus"[mesh]
"Streptococcal"[mesh]

2. Outcome-related terms
"Pneumonia, Pneumococcal"[mesh]
"Meningitis, Pneumococcal"[mesh]
"Meningitis, Streptococcal"[mesh]
"Pneumococcal Infections"[mesh]
"Streptococcal Infections"[mesh]
"Otitis Media"[mesh]
("lobar"[all fields] AND "pneumonia"[all fields])
("Nasopharyngeal"[all fields] AND "carriage"[all fields])
("Nasopharyngeal"[all fields]AND "colonization"[all fields])
(" nasopharyngeal"[all fields] AND "colonisation"[all fields])
("Community acquired"[all fields] AND "pneumonia"[all fields])
("community acquired"[all fields] AND "pneumonias"[all fields])
("Bacteraemic"[all fields] AND "pneumonia"[all fields])
("bacteraemic"[all fields] AND "pneumonias"[all fields])
("Bacteremic"[all fields] AND "pneumonia"[all fields])
("bacteremic"[all fields] AND "pneumonias"[all fields])
"Anti-pneumococcal"[all fields]
"antipneumococcal"[all fields]
("lower respiratory tract infection"[all fields])
("lower respiratory tract infections"[all fields])
("Invasive disease"[all fields])
("invasive pneumococcal disease"[all fields])
("invasive bacterial disease"[all fields])
("Bacterial pneumonia"[all fields])
("Bacterial pneumonias"[all fields])
("Otitis Media"[all fields])
("inner ear infection"[all fields])
("inner ear infections"[all fields])

Narrow vaccine terms:
"Vaccines, conjugate"[mesh]
"Pneumococcal Vaccines"[mesh]
"streptococcal vaccines"[mesh]
(("conjugate" OR "conjugated" OR "pneumococcal"[all fields] OR "streptococcal"[all fields])
AND
("vaccine"[tiab] OR "vaccines"[tiab] OR "vaccination"[tiab] OR "vaccinated"[tiab] OR "immunization"[tiab] OR "immunisation"[tiab] OR "immunized"[tiab] OR "immunised"[tiab]))
(("Pneumococcal"[all fields] OR "pneumococcus"[all fields] OR "capsular"[all fields])
AND
("polysaccharide"[all fields])
AND
("vaccine"[tiab] OR "vaccines"[tiab] OR "vaccination"[tiab] OR "vaccinated"[tiab] OR "immunization"[tiab] OR "immunisation"[tiab] OR "immunized"[tiab] OR "immunised"[tiab]))
"PncCRM197"[all fields]
"PCV"[all fields]
"Pneumovax"[all fields]
"Pnu-Imune" [all fields]
"Pnu Imune"[all fields]
"PnuImune"[all fields]
"pneu immune"[all fields]
"pnu immune"[all fields]
"pneumo 23"[all fields]
"pneumopur"[all fields]
"streptopur"[all fields]
"streptorix"[all fields]
"PncOMPC vaccine" [Substance Name]
"PncOMPC"[all fields]
("Pneumococcal"[all fields] AND "polysaccharide"[all fields] AND "meningococcal"[all fields] AND "outer"[all fields] AND "membrane"[all fields] AND "protein"[all fields] AND "complex"[all fields])
"five-valent pneumococcal conjugate vaccine"[substance name]
"five-valent"[all fields]
"5-valent"[all fields]
"PCV5"[all fields]
"PCV-5"[all fields]
"heptavalent pneumococcal conjugate vaccine"[substance name]
"heptavalent"[all fields]
"PNCRM7"[all fields]
"PNCRM-7"[all fields]
"PCV7"[all fields]
"PCV-7"[all fields]
"seven-valent"[all fields]
" 7-valent"[all fields]
"Prevenar"[all fields]
"Prevnar"[all fields]
"10-valent pneumococcal vaccine"[substance name]
"Ten-valent"[all fields]
"10-valent"[all fields]
"PCV10"[all fields]
"PCV-10"[all fields]
"13-valent pneumococcal vaccine"[substance name]
"Thirteen-valent"[all fields]
"13-valent"[all fields]
"PCV13"[all fields]
"PCV-13"[all fields]
"nine-valent"[all fields]
"9-valent"[all fields]
"PCV9"[all fields]
"PCV-9"[all fields]
"two-valent"[all fields]
"2-valent"[all fields]
"PCV2"[all fields]
"PCV-2"[all fields]
"three-valent"[all fields]
"3-valent"[all fields]
"PCV3"[all fields]
"PCV-3"[all fields]
"four-valent"[all fields]
"4-valent"[all fields]
"PCV4"[all fields]

(*Continued*)

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TABLE 1. Continued

Search Terms	
	"PCV-4"[all fields]
	"six-valent"[all fields]
	"6-valent"[all fields]
	"PCV6"[all fields]
	"PCV-6"[all fields]
	"7vPnC"[all fields]
	"7vCRM"[all fields]
	"PHiD-CV"[all fields]
	(("23-valent"[all fields]
	"23vPPV"[all fields]
	"PPV23"[all fields]
	"PPSV23"[all fields]
	"23-valent pneumococcal capsular polysaccharide vaccine"[substance name]
	"pneumococcal surface protein"[all fields]
	"pneumococcal surface proteins"[all fields]
	"pneumococcal protein"[all fields]
	"pneumococcal proteins"[all fields]
	"streptococcal surface protein"[all fields]
	"streptococcal surface proteins"[all fields]
	"streptococcal protein"[all fields]
	"streptococcal proteins"[all fields]
Additional search elements:	
Additional controlled vocabulary used in EMBASE (pathogen/outcome terms):	
"streptococcus pneumonia"[EMTREE term]	
"lower respiratory tract infection"[EMTREE term]	
"bacterial pneumonia"[EMTREE term]	
"lobar pneumonia"[EMTREE term]	
"community acquired pneumonia"[EMTREE term]	
Additional controlled vocabulary in EMBASE (vaccine terms):	
"Pneumococcus vaccine"[EMTREE term]	
"Streptococcus vaccine"[EMTREE term]	
"Pneumococcus polysaccharide"[EMTREE term]	
Adjacency searching (near 5) used in:	
EMBASE	
Global Health	
Biological Abstracts	
Biological Abstracts/RRM	
Pascal BioMed	
Cochrane Library	
Animal limits used in:	
PubMed	
EMBASE	
Biological Abstracts	
Biological Abstracts/RRM	
Other limits:	
English language	
Date: 1994–current	
Not needed – pneumococcal/streptococcal finds that did not yield additional material:	
Pneumococcal Pneumonia	
Pneumococcal Pneumonias	
Pneumococcal Meningitis	
Pneumococcal Infection	
Pneumococcal Infections	
Pneumococcal mortality	
Pneumococcal mortalities	
Streptococcal infection	
Streptococcal infections	

each database. The following 14 electronic databases were used in this analysis:

- EMBASE
- PubMed
- Biological Abstracts (BA)
- Pascal Biomed
- Global Health
- BioAbst/Reports, Reviews, Meetings
- Cochrane Library
- Regional databases
  - African Index Medicus (AIM)
  - Western Region Index Medicus (WPRIM)
  - Index Medicus for Eastern Med. Region (IMEMR)
  - Index Medicus for South-East Asia Region (IMSEAR)
  - Latin America and Caribbean Health Sciences Info. (LILACS)
  - Pan-American Health Org. (PAHO)
  - IndiaMed (IndMed)

In addition to the electronic literature search, all abstracts from meetings of the International Symposium on Pneumococci and Pneumococcal Disease (1998–2010) and the Interscience Conference on Antimicrobial Agents and Chemotherapy (1994–2010)

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were also searched. Additional articles in 2010–2011 included after the end date of the electronic literature search (September 2010), were identified on an ad hoc basis.

Inclusion and Exclusion Criteria

We included all data published from January 1994 to September 2010 including any PCV schedule on one or more outcomes of interest (IPD, pneumonia, NP carriage, immunogenicity [antibody concentrations and functional antibody measures]) in children less than 15 years of age targeted to receive vaccine. Fifteen years of age was selected to allow for inclusion of data on catch-up schedules. We also included studies reporting indirect effects (NP colonization, IPD and pneumonia) of PCV on groups not targeted to receive vaccine, including unvaccinated children, older children and adult populations.

Data on licensed or about-to-be licensed products (eg, from Wyeth [now Pfizer, New York, NY] and GlaxoSmithKline, Philadelphia, PA) as well as products that are no longer being pursued (eg, products from Merck and Aventis [now Sanofi Pasteur, Swiftwater, PA]) were included. We included the latter products, because many attributes of dosing and relative immunogenicity may be generalizable across PCV products.

We excluded any studies that focused on vaccine target groups older than 15 years of age or that evaluated pneumococcal polysaccharide vaccine (PPV) in a primary series or as a single dose, although we included studies using PPV as a booster dose. We also excluded studies published before 1994 as these studies are likely to evaluate product formulations that differ too much from licensed products to provide relevant information for our study objectives. Studies with non-analyzable data (eg, from cross-sectional studies that only report data before or after PCV introduction and would not allow for calculating impact), studies focusing on maternal doses of pneumococcal vaccine (PPV or PCV), dose ranging studies and review articles were also excluded.

Data Abstraction and Cleaning

Two independent reviewers with expertise in pneumococcal disease (J.D.L. and L.C.) screened the titles and abstracts of all references identified by the search strategy to create a master list of potentially relevant references for full-text review. To identify any missing relevant references, the list was then reviewed by senior staff members (C.G.W. and K.O.B.) and a second pass through the original title/abstract list was performed. Abstracts for all references flagged for inclusion were reviewed to determine if the full report was eligible to be included in the analysis. Full-text articles or abstracts (ie, from International Symposium on Pneumococci and Pneumococcal Disease and Interscience Conference on Antimicrobial Agents and Chemotherapeutics) from all eligible references were abstracted for a predetermined set of variables and data recorded directly into a 2003 Microsoft Access (Microsoft Corporation, Redmond, WA) database. This information was used to generate "groups" of reports based on outcome of interest: IPD, pneumonia, immunogenicity and NP carriage.

A full-text review was then performed on all citations (both articles and conference abstracts) within each "group," and detailed information from the citations was abstracted into a larger standardized database (2007 Microsoft Access). All citations were independently double abstracted for quality control. To guide abstractors in the review of citations, standard operating procedures and data collection forms with standardized variables were developed and reviewers were trained on abstraction methods. All abstractors participated in weekly calls with the project team to troubleshoot issues and discuss progress updates or receive other relevant information.

We defined "study families" as abstracts or articles generated from a single protocol, population, or surveillance system or other data collection system. For each study family, we identified a single "primary study" or main publication, which was identified through de-duplication of the data following the full double abstraction of each citation. For all outcomes, we identified "primary data" since data were sometimes found across >1 publication. Abstracts and articles containing supplemental data or substudies were considered secondary citations. All abstractions were then adjudicated and data cleaned to create an analyzable dataset.

Data Analysis

We summarized the data in descriptive analyses to provide an overview of the amount and variability of the data by schedules and outcomes. All analyses were conducted using SAS 9.2 and 9.3 (SAS Institute Inc., Cary, NC). Outcome-specific inclusion criteria and analyses are described in each outcome-specific publication.

RESULTS

We identified 12,980 references through the literature search or by other means (ie, data were identified through a presentation, meeting or personal communication) (Fig. 1). A double review of titles and abstracts for relevance yielded 1456 references for abstraction of basic information. Based on abstracted information (eg, citation information, study type, outcome, PCV product and schedule), we identified 769 publications or abstracts, containing 827 outcomes, to be fully reviewed and abstracted. Of those, 39 primary studies were identified for inclusion for analysis on IPD, 63 on immunogenicity, 32 on NP carriage, 45 on pneumonia and 36 on indirect effects.

The analyzed data represented all regions: 77 (37%) studies from Europe, 73 (35%) from North America, 20 (10%) from Africa, 16 (8%) from Asia, 16 (8%) from Oceania and 7 (3%) from Latin America and the Caribbean. The majority of studies (79%, n = 164) focused on PCV7 (Wyeth/Pfizer), 5% (n = 11) on PCV10 (GlaxoSmithKline) and 1% (n = 3) on PCV13 (Wyeth/Pfizer); other formulations presented included PCV4 (Sanofi), PCV5 (Wyeth), PCV7 (Merck), PCV8 (Sanofi), PCV9 (Wyeth) and PCV11 (GlaxoSmithKline). The numbers and percentages represent a totality of all data analyzed across outcomes and could therefore include duplicated counts of individual studies that presented data on multiple outcomes. For individual studies with multiple outcomes, data for each outcome were treated as an individual study.

Six studies (3%) evaluated a 2+0 schedule, 40 (19%) a 2+1 schedule, 74 (36%) a 3+0 schedule and 124 (66%) a 3+1 schedule.

CONCLUSION

The methodology used for this systematic literature review has allowed us to present the breadth and depth of literature concerning the impact of PCV dosing schedules on immunogenicity, NP colonization and disease outcomes. Our review found that the majority of literature concentrated on immunogenicity or IPD outcomes with a smaller proportion focusing on pneumonia or NP carriage, indicating a lack of evidence regarding the impact of PCV against these less-specific outcomes. Findings from our review also identified overall gaps in data from lower income settings, PCV10 and PCV13 and schedules using 2+1 or 3+0 regimens. Until recently, PCV7 was the only licensed vaccine product and mostly available only in higher-income countries that could afford to finance the vaccine on their own. Furthermore, most early evidence of impact evaluated the use of a 3+1 schedule, with alternative schedules only recently being evaluated. Because of the heterogeneity of the study methods and results presented between studies, we were unable to conduct a formal meta-analysis, which might have allowed us to make summary comparisons of various dosing schedules. We were, however, able to fully describe the available

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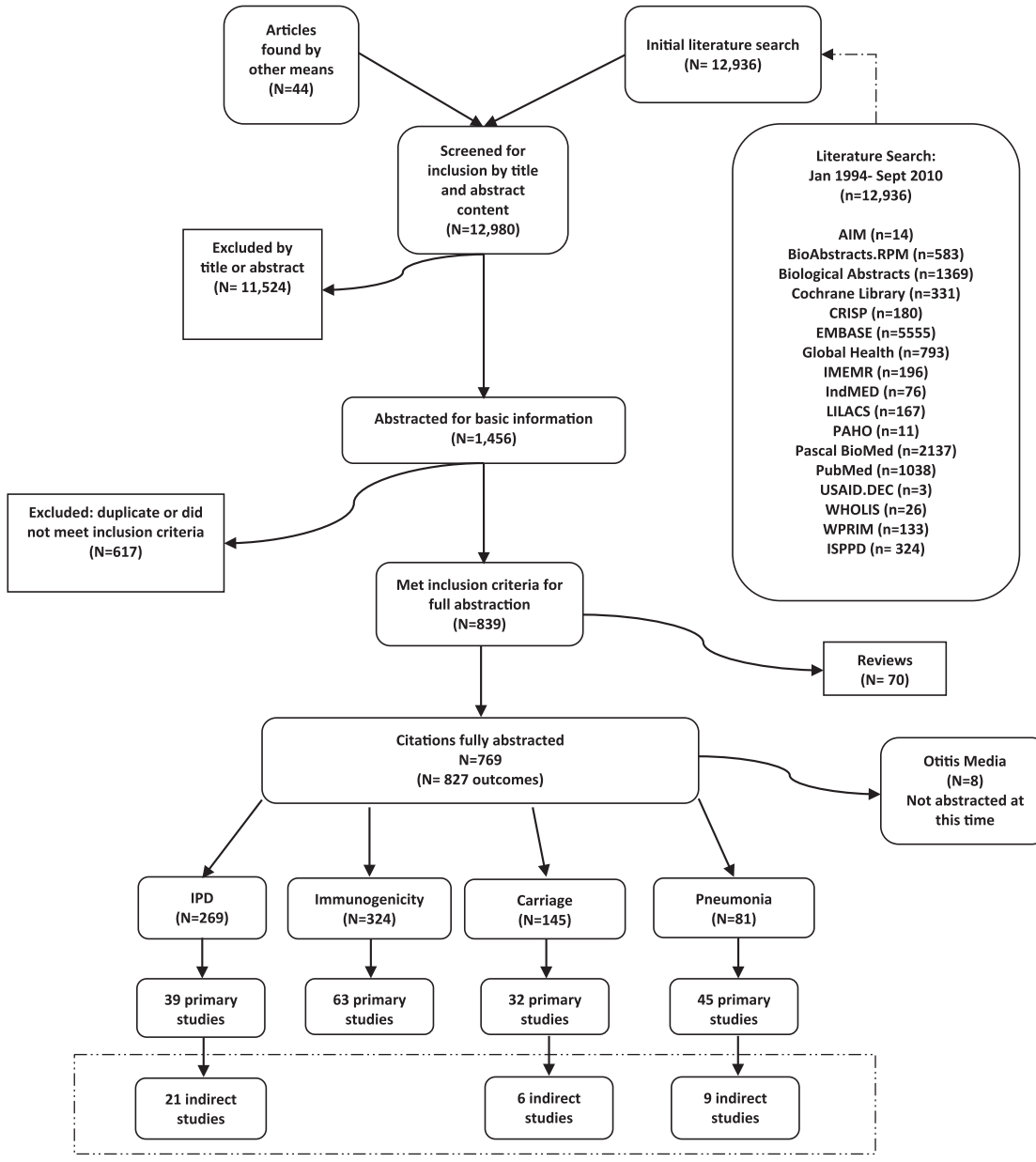

FIGURE 1. Flow chart of included citations.

data for each PCV dosing schedule and provide stakeholders with complete knowledge regarding the impact of PCV on immunogenicity, carriage and disease.

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