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Systematic Review of the Effect of Pneumococcal Conjugate Vaccine Dosing Schedules on Prevention of Pneumonia

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Background: Pneumonia is the leading cause of morbidity and mortality among children <5 years of age globally. Pneumococcal conjugate vaccines (PCVs) are known to provide protection against vaccine serotype pneumococcal pneumonia; uncertainty exists regarding the optimum PCV dosing schedule.

Methods: We conducted a systematic review of studies published from 1994 to 2010 (supplemented post hoc with studies from 2011) documenting the effect of PCV dosing schedules on clinical and radiologically confirmed pneumonia, pneumococcal pneumonia and empyema among children of ages targeted to receive vaccine. Data on 2- and 3-dose schedules were included. Percent change of pneumonia incidence rates from baseline to most recent year post-PCV introduction was calculated.

Results: We identified 42 primary citations that evaluated PCV schedules and pneumonia. Thirty-seven (88%) were from North America, Europe or Australia; 37 (88%) evaluated PCV7 and 1 (2%) PCV10. Two studies (both observational) compared multiple schedules within the study. We found evidence of reduced clinical and radiologically confirmed pneumonia incidence for all schedules, including 2+1 (1 nonrandomized trial, 5 observational studies), 3+0 (5 randomized trials, 2 observational studies) and 3+1 (5 clinical trials, 24 observational studies) schedules. The magnitude of disease impact did not differ among schedules. Evidence for impact on pneumococcal pneumonia and empyema varied.

Conclusions: All schedules (2+1, 3+0 and 3+1) reduced clinical and radiologically confirmed pneumonia. Quantifying differences in pneumonia disease impact between schedules was difficult due to heterogeneity among studies in design, case definition and population. These findings support World Health Organization recommendations for 3-dose schedules administered as either 3+0 or 2+1 regimens. Pneumonia impact data are still needed on expanded serotype PCV products, developing country settings and the role for a booster dose.

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

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Globally, pneumonia caused by the bacterium, *Streptococcus pneumoniae*, is one of the leading causes of nonneonatal death in children <5 years of age and is estimated to cause over 500,000 deaths and nearly 14 million episodes of disease annually.[1,2] Fortunately, pneumococcal conjugate vaccines (PCVs) hold promise for preventing much of this burden and are one of the key interventions recommended by the Global Action Plan for Prevention and Control of Pneumonia as a means for rapidly reducing pneumonia deaths.[3–5]

Three PCV formulations, 7-valent (PCV7), 10-valent (PCV10) and 13-valent (PCV13), have been licensed and made commercially available. PCV7 was first licensed in 2000 using a 4-dose schedule (3 primary doses plus 1 booster, 3+1) and was shown to protect against the 7 vaccine serotypes that accounted for a significant fraction of pneumococcal disease globally.[6] Since 2010, PCV10 and PCV13 have also been licensed using a 4-dose schedule, although all formulations have been granted licensure in the European Union and elsewhere for schedules using 2 primary doses plus 1 booster (2+1) when used as part of a national immunization program.[7–9] In addition, the World Health Organization has recommended PCV for use on a schedule of 3 primary doses without a booster, a typical Expanded Program on Immunization schedule used in many developing countries.[4] The exact timing of recommended doses varies by country because more policy makers have added PCV to existing immunization schedules.

Recently, GAVI Alliance support has led to a rapid increase in the introduction of PCV into national immunization programs among developing countries.[10] These introductions, coupled with varying national schedules for administering PCV, have prompted questions about which infant dosing schedule maximizes the impact of PCV programs. To aid in policy development, we conducted a comprehensive, systematic review of PCV dosing schedules and their impact on pneumonia.

METHODS

Literature Search

This analysis is part of a larger project describing the impact of PCV dosing schedules on invasive pneumococcal disease (IPD), immunogenicity, nasopharyngeal carriage, pneumonia and indirect effects.[11–14] Details on the literature search terms and methods used in this systematic review are described elsewhere (see Methods Appendix[15]). In brief, a systematic

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literature review was performed to collect all available English language data published from January 1994 to September 2010 (supplemented post hoc with studies from 2011) on the effect of various PCV vaccination schedules among immunized children on immunogenicity, nasopharyngeal colonization, IPD, pneumonia and on indirect effects among unvaccinated populations. Articles published in 14 databases, from ad hoc unpublished sources and abstracts from meetings of the International Symposium on Pneumococci and Pneumococcal Disease (1998–2010) and the Interscience Conference on Antimicrobial Agents and Chemotherapeutics (1994–2010), were searched. We included all randomized controlled clinical trials (RCTs), nonrandomized trials, surveillance database analyses and observational studies of any PCV schedule on one or more outcomes of interest. Studies were included for abstraction if pneumococcal polysaccharide vaccine (PPV23) was used as a booster dose, but not as a primary dose. Titles and abstracts were reviewed twice and those with relevant content on 1 of the 5 outcomes (immunogenicity, carriage, invasive disease, pneumonia and indirect effects) underwent full review using a standardized data collection instrument. We did not search non-English language literature because of the low likelihood they would have relevant data for this project. Details on the search methods are provided in the Methods Appendix.[15]

Data Abstraction

Citations recovered through the literature search went through several stages of independent review to determine their eligibility, as described (see Methods Appendix[15]). Citations meeting inclusion criteria were categorized on an outcome-specific basis into "study families," where each family included abstracts or publications generated from a single protocol, population, surveillance system or other data collection system relevant to that outcome. Investigators identified primary data from the individual studies making up each study family for inclusion in the analysis. The primary data were selected as the most current and complete data available for that study family. In some cases, these data were drawn from >1 publication within a family. We also defined "study arms" as a group of children distinguished by immunization schedule or PCV product.

We abstracted core information on the following: number of children in a "study arm;" PCV manufacturer, valency and conjugate protein; co-administered vaccines; country; age at each dose and date of study and publication. Additional data abstracted for pneumonia included specific endpoints, case definitions, study design, study population and incidence rates or percent change.

This article presents the data on the direct effects of PCV on pneumonia in children of an age targeted for vaccination. As studies included a variety of case definitions for endpoints, findings were grouped by endpoint according to the following categories: clinical pneumonia (including lower respiratory tract infections and acute respiratory tract infections), radiologically confirmed pneumonia, pneumococcal pneumonia (including bacteremic pneumonia) and empyema.

Inclusion and Exclusion Criteria

We included data published during or after 1994 from clinical trials, surveillance database analyses and observational studies of PCV schedules on immunogenicity, IPD, nasopharyngeal carriage, pneumonia and indirect effects. We included all licensed and unlicensed PCV products (denoted as PCV with a number indicating the valency, eg, PCV7). We excluded studies with vaccination series beginning after 12 months of life, as well as observational studies that only reported data before or after PCV introduction but not for both periods. Unless ≥50% vaccination coverage was documented, observational studies were also excluded if vaccination was only available through the private sector or to high-risk groups. Studies that only provided incidence rates during the year of vaccine introduction, or did not specify a period, were excluded.

Pneumococcal Vaccine Dosing Schedules

We defined a primary series as either 2 or 3 doses received before 7 months of age. A booster dose was defined as a dose of PCV or PPV23 received after 9 months of age and after the completion of a primary series. A complete series was defined as the primary series plus any booster doses implemented in a population; examples of this include a 2-dose primary series with or without a booster (2+1, 2+0) or a 3-dose primary series with or without a booster (3+1, 3+0).

Data Analysis

Studies evaluating impact on pneumonia following PCV introduction used a variety of methods; the variety prevented us from performing a formal meta-analysis. Therefore, we conducted descriptive analyses of the amount and variability of the data and of the magnitude of the change in the pneumonia outcomes observed for each dosing schedule type. We also performed subanalyses to evaluate various endpoints related to pneumonia. Studies reporting only qualitative data with no ability to determine magnitude of impact were excluded from analysis.

For observational studies reporting pneumonia incidence over time, we calculated percent change as: (baseline incidence —post-PCV introduction incidence)/baseline incidence. Baseline incidence was defined as the mean of all data points reported before PCV introduction. When annual data on postintroduction incidence were available, we calculated percent change using the data point given for each year reported. When only the average postintroduction incidence rate over a period of years was provided, we calculated percent change from baseline to the reported rate and assigned it to the median year of the date range provided. When possible, incidence rates during the year of introduction were excluded from these calculations. We conducted all analyses using SAS 9.3 (SAS Institute Inc., Cary, NC).

RESULTS

Descriptive Characteristics of Included Studies

Of 12,980 citations reviewed, we identified 106 pneumonia outcome citations that met initial criteria for further evaluation (Fig. 1). After further review, 81 citations met inclusion criteria for full data abstraction; of these, 39 studies were excluded from analysis because they contained duplicate data of included studies or reported changes in pneumonia risk only qualitatively so magnitude of impact could not be assessed. Of the 42 included citations, 20 evaluated clinical pneumonia, 13 radiologically confirmed pneumonia, 16 pneumococcal pneumonia and 9 all-cause empyema; however, case definitions varied widely for each endpoint.[16–57]

Almost all (n = 39, 93%) citations of pneumonia were published during or after 2004. Most citations were from North America (n = 23, 55%), Europe (n = 9, 22%) or Oceania (n = 5, 12%), with the remaining 5 from Africa (n = 3, 7%), Asia (n = 1, 2%) and Latin America (n = 1, 2%). Although many studies focused on the general population of children, 6 citations focused on high-risk groups (ie, children with HIV or indigenous populations). Thirty-seven citations evaluated PCV7 and only one study evaluated PCV10[57] (Table 1).

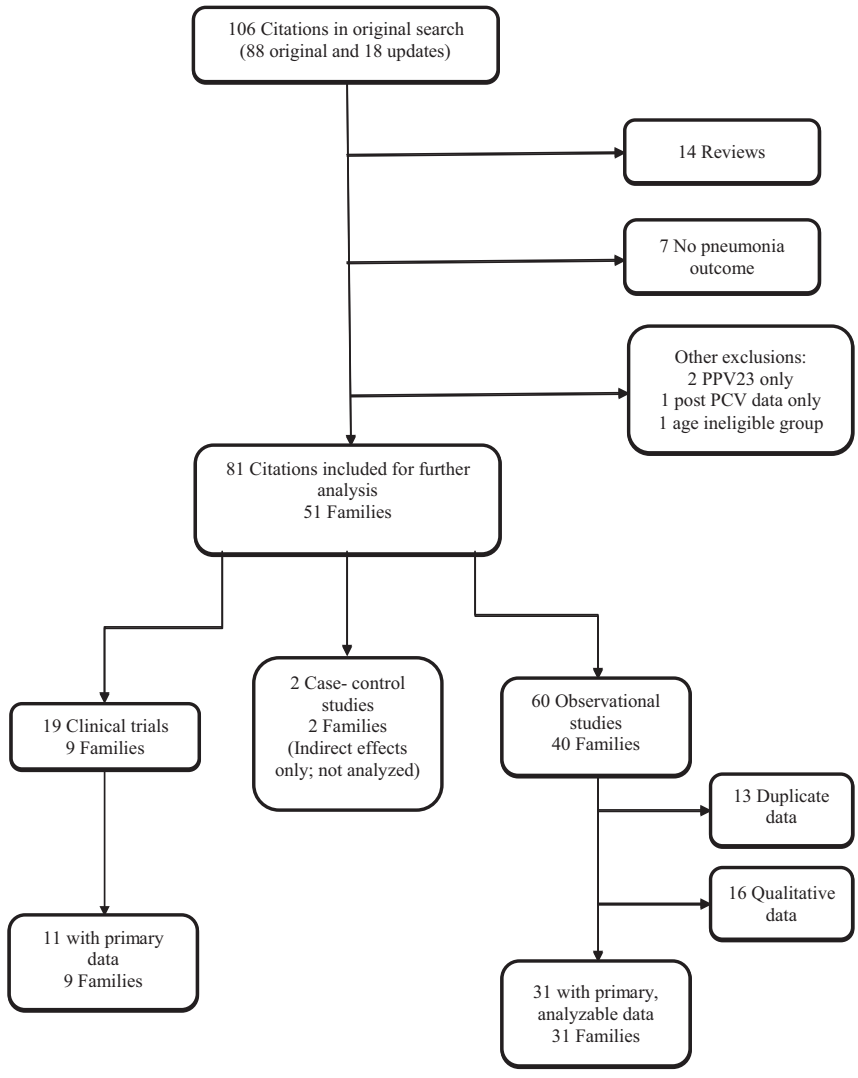

FIGURE 1. Flowchart of included citations.

Studies Directly Comparing Dosing Schedules (n = 2 Studies)

We identified only 2 studies, both observational, that compared the effectiveness of different PCV dosing schedules within the study itself. One study directly evaluated the impact of 2 versus 3 primary PCV doses against clinical pneumonia incidence in a general pediatric population.[28] This propensity-score-matched, case-cohort study conducted in the United States evaluated the rate of hospitalizations and ambulatory visits for lower respiratory tract infections and found that children who received 3 primary PCV doses had fewer ambulatory visits and hospitalizations up to the point of receipt of a booster dose (9.5 admissions per 1000 children) than those who only received 2 primary doses [17.3 admissions per 1000 children; rate difference = 7.8 cases per 1000 children (95% confidence interval (CI): 0.8–14.8)]. This difference disappeared after the booster dose was administered [23.2 admissions per 1000 children vs. 20.9 admissions per 1000 children for 3+1 vs. 2+1, respectively; rate difference = −2.3 cases per 1000 children (95% CI: −14.8 to 9.3)]. This difference between 2 and 3 primary doses was seen for children born in the 2002 birth cohort, but not for children born in 2003; the authors hypothesized that by 2003, 3 years after introduction of PCV7, herd effects had lessened the difference in risk between the 2 groups. The other study directly comparing dosing schedules, a retrospective cohort conducted among Australian Indigenous infants,[53] evaluated risk of clinical and radiologically confirmed pneumonia after each of 3 PCV7 primary doses plus 1 PPV23 booster (3+PPV23) but did not find evidence of reduced risk for either endpoint by number of doses.

Studies of Single Schedules

Two-dose Primary Schedules, With a Booster, in the General Population (n = 6 Studies)

Of studies assessing a single schedule, none evaluated the impact of 2 primary doses on pneumonia in the first year of life (ie, up to the point of receiving the booster dose) or in the second year of life without a booster dose (2+0). We identified 6 studies (6 citations) that evaluated the impact of a 2+1 schedule on pneumonia: one prospective cohort trial[35] and 5 observational studies.[16,30,34,50,54] The cohort study was a nonrandomized, single-blinded Italian study that found an impact of PCV7 on radiologically confirmed pneumonia (vaccine efficacy: 65%, 95% CI: 47–78%; Table 2). Parents participating in the study could choose whether to have their children vaccinated, and providers and

TABLE 1. Characteristics of Citations Included in Analysis

	Complete Dosing Schedule*			
	Total†	2+1	3+0	3+1‡
Characteristic	n = 42 (%)	n = 6 (%)	n = 7 (%)	n = 29 (%)
Year of publication				
1994–1998	1 (2)	0	0	1 (3)
1999–2002	2 (5)	0	0	2 (7)
2003–2006	12 (29)	0	3 (43)	9 (31)
2007–2011	27 (64)	6 (100)	4 (57)	17 (59)
Study type				
Clinical trial	11 (26)	1 (17)	5 (71)	5 (17)
Observational	31 (74)	5 (83)	2 (29)	24 (83)
Case-control	0	0	0	0
Region				
Africa	3 (7)	0	3 (43)	0
Asia	1 (2)	0	1 (14)	0
Australia/Oceania	5 (12)	0	3 (43)	2 (7)
Europe	9 (22)	5 (83)	0	4 (14)
Latin America	1 (2)	0	0	1 (3)
North America	23 (55)	1 (17)	0	22 (76)
PCV product				
PCV7	37 (88)	6 (100)	3 (43)	28 (97)
PCV9	3 (7)	0	3 (43)	0
PCV10	1 (2)	0	0	1 (3)
PCV11	1 (2)	0	1 (14)	0
PCV13	0	0	0	0
High-risk population				
HIV	2 (5)	0	2 (29)	0
Indigenous	3 (7)	0	0	3 (10)
Neonates	1 (2)	0	1 (14)	0
Endpoint				
Clinical pneumonia (including lower respiratory tract infections)	20 (47)	3 (50)	5 (71)	12 (39)
Radiologically confirmed pneumonia	13 (30)	3 (50)	3 (43)	7 (23)
Pneumococcal pneumonia	16 (37)	2 (33)	2 (29)	12 (39)
Empyema	9 (21)	2 (33)	0	7 (23)

*There were no citations that evaluated a 2+0 schedule.
†Numbers are not mutually exclusive as some citations presented findings on multiple characteristics.
‡3+1 schedules include 3+PPV23.

parents were not blinded to the intervention; these design limitations may explain why the point estimate is higher than that seen in blinded RCTs of pneumonia.

Of the 5 observational studies, 3 reported data on clinical pneumonia, 2 on radiologically confirmed pneumonia, 2 on pneumococcal pneumonia and 2 on empyema (Table 3). All studies evaluating the effectiveness of 2+1 PCV against clinical and radiologically confirmed pneumonia showed evidence of significant disease reduction after PCV introduction into the national immunization program. Results of the limited number of studies on pneumococcal pneumonia and empyema were mixed (Table 3). Of the 2 studies on pneumococcal pneumonia following 2+1 PCV dosing, 1 from Italy found a significant decline in hospitalizations for pneumococcal pneumonia after PCV introduction,[30] while the other from Belgium found no significant decrease in incidence of pneumococcal pneumonia in children <2 years of age and a significant increase in incidence in children 2–4 years of age.[16] Of the two 2+1 studies on empyema, one found a 22% decline in empyema,[50] while the other found no significant change in empyema rates following PCV introduction into the national immunization program.[34]

Three-dose Primary Schedules, With or Without Booster, in the General Population (n = 28 Studies)

Of studies assessing a single schedule, 5 (6 citations) evaluated a 3+0 schedule and 23 (24 citations) evaluated a 3+1 schedule on various pneumonia disease endpoints. Of the 3+0 schedule studies, we identified 3 RCTs[22,23,25,26] from various regions (Table 2) and 2 observational studies, both from Australia[45,49] (Table 4). Each of the RCTs showed efficacy against clinical or radiologically confirmed pneumonia; the clinical trial in the Philippines showed impact of PCV11 (Sanofi Pasteur, Lyon, France) on radiologically confirmed pneumonia but not clinical pneumonia.[25] Both observational studies showed significant reductions in disease burden following PCV introduction into the Australian national immunization program, with reductions ranging from 28% to 38% for clinical pneumonia and from 45% to 77% for pneumococcal pneumonia depending on the age group (Table 4).

We identified 3 clinical trials[29,31,38,57] and 20 observational studies that evaluated the impact of a 3+1 schedule on pneumonia endpoints (8 on clinical pneumonia,[19,21,27,36,37,43,48,51] 4 on radiologically confirmed pneumonia,[40,43,52,55] 7 on empyema[24,32,33,39,44,48,51] and 12 on pneumococcal pneumonia[17,19,21,33,37,41,42,44,46–48,51]) (Tables 2 and 5). All clinical trials and observational studies showed evidence of PCV benefit on clinical and radiologically confirmed pneumonia; however, 1 German study was a nonrandomized, single-blinded clinical trial, which limits interpretation of their findings,[29] and in some observational studies, the results did not reach statistical significance[36,43] or found significant reductions only in children <2 years of age[19,37,48] (Tables 2 and 5). Of the 7 observational studies that evaluated a 3+1 schedule on all-cause empyema, 5 found a significant increase in empyema rates after PCV introduction, with many attributing these increases to pneumococcal serotypes

TABLE 2. Summary Characteristics of Controlled Trials Evaluating a Pneumonia Endpoint, by Schedule

Country	Reference	Study Design	Vaccine Product	Dosing Schedule	Population	Endpoint and Case Definition	Vaccine Efficacy (95% CI)	
							Intent to Treat	Per Protocol
2+1 schedule								
Italy	Esposito et al.[35]	Nonrandomized, single-blind cohort	PCV7 (Wyeth)	3, 5 and 11 months	1555 Children (75–105 days) followed to 29 months of age	CXR pneumonia (non-WHO clinical reading)	65% (47–78%)	—
3+0 schedule								
Papua New Guinea	Richmond et al. [18]	Randomized, nonblind	PCV7 (Wyeth)	0, 1 and 2 months 1, 2 and 3 months	Neonates and infants followed to 18 months of age	Clinical pneumonia (syndromic diagnosis)	18% (4–31%)*	—
Philippines	Lucero et al.[25]	Randomized, double-blind	PCV11 (Sanofi)	6, 10 and 14 weeks	12,191 Children (<2 years of age) followed to 24 months of age	Clinical pneumonia (WHO IMCI), CXR pneumonia (WHO reading)	Clinical: –0.8% (–9.6% to 7.4%) CXR: 16% (–7.3% to 34.2%)	Clinical: 0.1% (–9.4% to 8.7%) CXR: 22.9% (–1.1% to 41.2%)
South Africa	Klugman et al.[22]	Randomized, double-blind	PCV9 (Wyeth)	6, 10 and 14 weeks	39,836 HIV– and HIV+ Children (<2 years of age)	CXR pneumonia (WHO reading)	HIV–: 20% (2–35%) HIV+: 13% (–7% to 29%)	HIV–: 25% (4–41%) HIV+: not reported
South Africa	Madhi et al.[26]	Randomized, double-blind	PCV9 (Wyeth)	6, 10 and 14 weeks	39,836 HIV– and HIV+ Children (<2 years of age)	Clinical pneumonia (WHO IMCI)	HIV–: 17% (7–26%) HIV+: 15% (5–24%)	HIV–: 23% (11–33%) HIV+: 14% (–4% to 28%)
The Gambia	Cutts et al.[23]	Randomized, double-blind	PCV9 (Wyeth)	11, 15 and 24 weeks	16,340 Children (6–51 weeks of age) followed for 2 years	Clinical pneumonia (WHO IMCI), CXR pneumonia (WHO reading)	Clinical: 6% (1–11%) CXR: 35% (26–43%)	Clinical: 7% (1–12%) CXR: 37% (27–45%)
3+1 schedule								
Latin America	Tregnaghi et al.[57]	Randomized, double-blind	PCV10 (GSK)	2, 4, 6 and 15–18 months	23,738 Children (6–16 weeks of age at enrollment)	CXR pneumonia (WHO reading)	—	23% (9–36%)
United States	Black et al.[31]	Randomized, double-blind	PCV7 (Wyeth)	2, 4, 6 and 12–15 months	37,868 Children (<3 years of age)	Clinical pneumonia (study defined)	6.0% (–1.5% to 11.0%)	4.3% (–3.5% to 11.5%)
United States	Hansen et al.[38]	Randomized, double-blind	PCV7 (Wyeth)	2, 4, 6 and 12–15 months	37,868 Children (<3 years of age)	CXR pneumonia (WHO reading)	25.5% (6.5–40.7%)	30.3% (10.7–45.7%)
United States	O'Brien et al.[56]	Randomized	PCV7 (Wyeth)	2, 4, 6 and 12–15 months	8292 Native American children	CXR pneumonia (WHO reading); inpatient cases only	–11.0% (–39.3% to 11.5%)	–8.0% (–37.0 to 14.9%)
Germany	Adam and Fehnle[29]	Nonrandomized, nonblind	PCV7 (Wyeth)	2, 3, 4 and 12–15 months	5984 Children (2–6 months of age) followed until 1 year after booster dose	Clinical pneumonia (syndromic diagnosis)	6.3% (–15.9% to 23.7%)	—

CXR, radiologically confirmed pneumonia; IMCI, Integrated Management of Childhood Illness.
*Vaccine efficacy was calculated VE = (1-incidence rate ratio) X 100.

TABLE 3. Summary Characteristics and Findings of Observational Studies Evaluating a Pneumonia Endpoint, 2+1 Schedules

Country	Reference	Case Definition	Study Design	Dosing Schedule for PCV*	Age Groups Evaluated (Years)	Years Baseline Data	Baseline Measure (Per Year)	Years Postintroduction Data	Percent Change at Latest Year Post-PCV Introduction†¶
Clinical pneumonia									
Canada	De Wals et al.[34]	ICD-9 or ICD-10 codes	Passive, sentinel surveillance	2, 4, 12 months	<5	7	3803 cases	2	−13.2‡
Italy	Ansaldi et al.[30]	ICD-9 or ICD-10 codes	Sentinel surveillance	3, 5, 11–12 months	<2	3	642.2 cases/100,000	3	−15.2
United Kingdom	Koshy et al.[50]	ICD-9 or ICD-10 codes	Population-based surveillance	2, 4, 13 months	<15	10	1335 admissions/ 1,000,000 (standardized by age and sex)	2	−19
CXR pneumonia									
Canada	De Wals et al.[34]	ICD-9 or ICD-10 codes	Passive, sentinel surveillance	2, 4, 12 months	<5	7	1660 cases	2	−72.3‡
Poland	Patrzałek et al.[54]	Clinical reading (not WHO) by 2 independent radiologists	Sentinel surveillance	3, 5, 13 months	<2 2–4	2	<2 years: 41.3 cases/1000 2–4 years: 6.1 cases/1000	2	<2 years: −10 2–4 years: −18
Pneumococcal pneumonia									
Belgium	Hanquet et al.[16]	Radiograph confirmation + isolation of *S. pneumoniae* from blood or pleural fluid	Active, population-based surveillance	8, 16 weeks; 12 months	<2, 2–4	1	<2 years: 25.5 cases/100,000 2–4 years: 20.1 cases/100,000	2	<2 years: −7.4§ 2–4 years: 45.3
Italy	Ansaldi et al.[30]	ICD-9 or ICD-10 codes	Sentinel surveillance	3, 5 and 11–12 months	<2	3	19.1 cases/100,000	3	−70.5
Empyema									
Canada	De Wals et al.[34]	ICD-9 or ICD-10 codes	Passive, sentinel surveillance	2, 4 and 12 months	<5	7	0.8/100,000 average annual rate	2	No change
United Kingdom	Koshy et al.[50]	ICD-9 or ICD-10 codes	Population-based surveillance	2, 4 and 13 months	<15	10	18 admissions/ 1,000,000 (standardized by age and sex)	2	−22

*All studies evaluated PCV7.
†All percent changes are statistically significant ($P < 0.05$) unless otherwise noted.
‡NR, statistical significance not reported.
§NS, not significant.
¶Negative percent change indicates a percent reduction; positive percent change indicates a percent increase.

TABLE 4. Summary Characteristics and Findings of Observational Studies Evaluating a Pneumonia Endpoint, 3+0 Schedules

Country	Reference	Case Definition	Study Design	Dosing Schedule for PCV*	Age Groups Evaluated (Years)	Years Baseline Data	Baseline Measure (per year)	Years Postintroduction Data	Percent Change at Latest Year Post-PCV Introduction†
Clinical pneumonia									
Australia	Jardine et al.[49]	ICD-9 or ICD-10 codes	Population-based surveillance	2, 4 and 6 months	<2, 2–4	7	No baseline measure reported	2	<2 years: –38‡ 2–4 years: –28‡
Pneumococcal pneumonia									
Australia	Jardine et al.[49]	ICD-9 or ICD-10 codes	Population-based surveillance	2, 4 and 6 months	<2, 2–4	7	No baseline measure reported	2	<2 years: – 77‡ 2–4 years: –67‡
Australia	Roche et al.[45]	Isolation of *S. pneumoniae* from blood or nucleic acid test + clinical or radiological confirmation	Passive, population-based surveillance	2, 4 and 6 months	<2	3	44 cases	2	–45§

*All studies evaluated PCV7.
†Negative percent change indicates a percent reduction; positive percent change indicates a percent increase.
‡$P < 0.05$.
§NR, statistical significance not reported.

not found in PCV7 or other pathogens such as multi-drug resistant *Staphylococcus aureus*.[32,33,39,48,51] Evidence for the impact of a 3+1 schedule on pneumococcal pneumonia varied (Table 5). Eight studies showed a decrease in pneumococcal pneumonia rates, 5 with significant findings.[17,19,21,37,48] Four studies found an increase, 2 with significant findings.[41,44] Of the 4 studies showing an increase in pneumococcal pneumonia rates, 2 were conducted in Spain while PCV7 coverage rates were <50%[44,47] and 1 was conducted in the United States[41] that noted a PCV7 shortage limiting vaccine availability. Two of the 4 studies with increases in pneumococcal pneumonia rates also documented an increase in invasive disease rates due to non-PCV7 serotypes.[41,44]

PCV Dosing Schedules in High-Risk Populations (n = 5 Studies)

Among 5 studies evaluating the impact of PCV on populations at high risk for pneumococcal disease, 2 (3 citations) used a 3+0 schedule and 3 used a 3+1 schedule. Two RCTs evaluated the impact of PCV7 among a high-risk population using a 3+0 schedule (Table 2).[18,22,26] One trial, conducted in South Africa, found a 13–15% efficacy against clinical and radiologically confirmed pneumonia in children with HIV. The other clinical trial, from Papua New Guinea, found PCV7 to be 18% (95% CI: 4–31%) efficacious against clinical pneumonia in neonates.[18] We identified 1 RCT[56] and 2 observational studies[20,52] from the United States and Australia that evaluated a 3+1 (3+PPV23 for Australian Indigenous) schedule in indigenous populations. The RCT, conducted among a population of American Indians in the United States, showed no efficacy against the first episode of radiologically confirmed pneumonia (authors' data, per protocol vaccine efficacy: –8.0%, 95% CI: –37.0% to 14.9%); however, only inpatient pneumonia cases were included in this analysis unlike other RCTs. One of the observational studies found a trend of declining incidence for clinical pneumonia in Australian Indigenous children; however, this finding was not significant ($P = 0.13$), and study investigators speculate the lack of sufficient follow-up time as a possible reason.[52] The other observational study, evaluating empyema in a US Alaskan Native pediatric population, found no change in empyema-associated hospitalizations following PCV introduction and rates remained higher than those for children in the general US population.[20] Study investigators did note an apparent increased rate in empyema due to *S. pneumoniae* and, in particular, episodes due to nonvaccine serotypes, which could explain the lack of change in overall empyema rates.

DISCUSSION

This analysis found strong evidence of PCV benefit against both clinical and radiologically confirmed pneumonia in the age group targeted for vaccination using 2+1, 3+0 and 3+1 schedules. Data from several RCTs, including trials in low-income settings, strongly support use of 3 primary dose schedules with or without a booster (ie, 3+0 or 3+1) for prevention of pneumonia. A large number of observational studies support use of either 3 primary doses, with or without a booster, or 2 primary doses plus 1 booster (2+1), which demonstrates the benefits of these schedules for pneumonia prevention in a routine immunization setting. Overall, half (21 of 42) of the studies in our review provided evidence for significant reductions in 1 or more disease endpoints. The evidence for 1 schedule over another and the impact of PCV in preventing pneumococcal pneumonia and empyema were less clear, given the small number of studies and their conflicting findings.

Immunization with PCV is critical to provide protection against pneumonia in the first year of life. However, quantifying the differences in benefit between 2-dose and 3-dose primary immunization schedules against pneumonia was difficult as only 2 studies

TABLE 5. Summary Characteristics and Findings of Observational Studies Evaluating a Pneumonia Endpoint, 3+1 Schedules

Country	Reference	Case Definition	Study Design	Dosing Schedule for PCV*	Age Groups Evaluated	Years Baseline Data	Baseline Measure (Per Year)	Years Postintroduction Data	Percent Change at Latest Year Post-PCV Introduction†
Clinical pneumonia									
United States	Balazs et al.[27]	Clinician diagnosis	Retrospective cohort	2, 4, 6 and 12–15 months	<3 years	3	0.60 episodes	2	−35 ($P = 0.06$)
United States	Grijalva et al.[36]	ICD-9 or ICD-10 codes	Passive, population-based surveillance	2, 4, 6 and 12–15 months	<2 years (outpatient only)	6	80 visits/1000	4	−31‡
United States	Grijalva et al.[37]	ICD-9 or ICD-10 codes	Sentinel surveillance	2, 4, 6 and 12–15 months	<2 years 2–4 years	3	<2 years: 1296.9 cases/100,000 2–4 years: 417.6 cases/100,000	4	<2 years: −39 2–4 years: −17‡
United States	Grijalva et al.[48]	ICD-9 or ICD-10 codes	Sentinel surveillance	2, 4, 6 and 12–15 months	<2 years 2–4 years	4	<2 years: 1267 hospitalizations/100,000 2–4 years: 402 hospitalizations/100,000	7	<2 years: −33 2–4 years: no change
United States	Li and Tancredi[51]	ICD-9 or ICD-10 codes	Population-based surveillance	2, 4, 6 and 12–15 months	<18 years	2	281.1 hospitalizations/100,000	2	−13§
United States	Nelson et al.[43]	ICD-9 or ICD-10 codes	Cohort study	2, 4, 6 and 12–15 months	<1 year 1–2 years 3–4 years	3	<1 year: 6.6 cases/1000 1–2 years: 4.7 cases/1000 3–4 years: 1.9 cases/1000	4	<1 year: −19‡ 1–2 years: −15 ‡ 3–4 years: +2‡
United States	Simonsen et al.[19]	ICD-9 or ICD-10 codes	Sentinel surveillance	2, 4, 6 and 12–15 months	<2 years 2–4 years	4	<2 years: 1026.5 cases/100,000 2–4 years: 307.5 cases/100,000	7	<2 years: −28 2–4 years: −1‡
United States	Zhou et al.[21]	ICD-9 or ICD-10 codes	Cohort study	2, 4, 6 and 12–15 months	<2 years	3	11.5 hospitalizations/1000 person-years	3	−52.4
CXR pneumonia									
Canada	Twele et al.[55]	WHO-standardized trained readers or WHO-adjudication of radiographs	Sentinel surveillance	2, 4, 6 and 12–15 months	<5 years	2	<1 year: 24.6% of admissions 1–2 years: 32.9% of admissions 2–5 years: 41.5% of admissions	2	<1 year: −4.6‡ 1–2 years: −12.2 2—5 years: −9.6
United States	Nelson et al.[43]	ICD-9 or ICD-10 codes + clinical radiograph reading (not WHO)	Cohort study	2, 4, 6 and 12–15 months	<1 year 1–2 years 3–4 years	3	<1 year: 3.8 cases/1000 1–2 years: 3.2 cases/1000 3–4 years: 1.2 cases/1000	4	<1 year: −10‡ 1–2 years: −9‡ 3–4 years: −10‡
United States	Rutman et al.[40]	Clinical reading (not WHO)	Cohort study	2, 4, 6 and 12–15 months	<2 years 2–4 years All <5 years	4	<2 years: 17% (121/709) of admissions 2–5 years: 38% (69/180) of admissions <5 years: 21% (190/889) of admissions	5	<2 years: −41‡ 2–4 years: +13‡ <5 years: −81‡
Australia	O'Grady et al.[52]	WHO-standardized trained readers or WHO-adjudication of radiographs	Cohort study	3+PPV23 2, 4, 6 and 18 months	<18 months, Indigenous	3	3.5 cases/1000 child-months	4	−12.3‡

(*Continued*)

TABLE 5. Continued

Country	Reference	Case Definition	Study Design	Dosing Schedule for PCV*	Age Groups Evaluated	Years Baseline Data	Baseline Measure (Per Year)	Years Postintroduction Data	Percent Change at Latest Year Post-PCV Introduction†
Pneumococcal pneumonia									
Spain	Aristegui et al.[47]	Isolation of *S. pneumoniae* from sterile site	Population-based surveillance	2, 4, 6 and 15–18 months	<2 years	3	14.4 cases/100,000	2	+8‡
Spain	Calbo et al.[33]	Isolation of *S. pneumoniae* from sterile site	Population-based surveillance	2, 4, 6 and 15–18 months	<5 years	3	32.32 cases/100,000	3	−2.9‡
Spain¶	Munoz et al.[44]	Isolation of *S. pneumoniae* from sterile site + clinical diagnosis (ICD-9 codes)	Active, sentinel surveillance	2, 4, 6 and 15–18 months	<2 years 2–4 years	5	<2 years: 3.4 episodes/100,000 2–4 years: 3.8 episodes/100,000	5	<2 years: +289 2–4 years: +344
United States	Grijalva et al.[37]	ICD-9 or ICD-10 codes	Sentinel surveillance	2, 4, 6 and 12–15 months	<2 years 2–4 years	3	<2 years: 26.2 cases/100,000 2–4 years: 27.1 cases/100,000	4	<2 years: −65 2–4 years: −73
United States	Grijalva et al.[48]	ICD-9 or ICD-10 codes	Sentinel surveillance	2, 4, 6 and 12–15 months	<2 years 2–4 years	4	<2 years: 27 hospitalizations/100,000 2–4 years: 12 hospitalizations/100,000	7	<2 years: −61 2–4 years: −26
United States	Kaplan et al.[46]	Isolation of *S. pneumoniae* from blood, pleural fluid or lung + radiological confirmation	Active, sentinel surveillance	2, 4, 6 and 12–15 months	<5 years	6	30.5 pneumococcal isolates/yr	2	−39‡
United States	Liand Tancredi[51]	ICD-9 or ICD-10 codes	Population-based surveillance	2, 4, 6 and 12–15 months	<18 years	2	8.9 hospitalizations/100,000	2	−45§
United States	Moore et al.[17]	Isolation of *S. pneumoniae* from sterile site + clinical or radiological confirmation	Active, population-based surveillance	2, 4, 6 and 12–15 months	<5 years	2	16.3 cases/100,000	6	−52
United States	Schutze et al.[41]	Isolation of *S. pneumoniae* from sterile site + clinical diagnosis	Cohort study	2, 4, 6 and 12–15 months	<20 years	7	13% (16 of 128) of invasive cases	2	+24
United States	Shafinoori et al.[42]	Isolation of *S. pneumoniae* from blood or cerebral spinal fluid + clinical diagnosis	Active, sentinel surveillance	2, 4, 6 and 12–15 months	"Children"	2	24% (19 of 80) of invasive cases	4	+5‡
United States	Simonsen et al.[19]	ICD-9 or ICD-10 codes	Sentinel surveillance	2, 4, 6 and 12–15 months	<2 years	4	<2 years: 25.9 cases/100,000 2–4 years: 11.8 cases/100,000	7	<2 years: −51 2–4 years: −17
United States	Zhou et al.[21]	ICD-9 or ICD-10 codes	Cohort study	2, 4, 6 and 12–15 months	<2 years	3	0.63 hospitalizations/1000 person-years	3	−57.6
Empyema									
Spain	Calbo et al.[33]	Isolation of *S. pneumoniae* from sterile site	Population-based surveillance	2, 4, 6 and 15–18 months	<5 years	3	1.7 cases/100,000	3	+400 ($P = 0.06$)
United States	Byington et al.[32]	ICD-9 or ICD-10 codes	Active, sentinel surveillance	2, 4, 6 and 12–15 months	<18 years	4	38 cases/yr	3	+88.1

(*Continued*)

TABLE 5. Continued

Country	Reference	Case Definition	Study Design	Dosing Schedule for PCV*	Age Groups Evaluated	Years Baseline Data	Baseline Measure (Per Year)	Years Postintroduction Data	Percent Change at Latest Year Post-PCV Introduction†
United States	Hendrickson et al.[39]	ICD-9 or ICD-10 codes	Cohort study	2, 4, 6 and 12–15 months	<18 years	5	13 total cases during baseline period	5	+80
United States	Grijalva et al.[48]	ICD-9 or ICD-10 codes	Sentinel surveillance	2, 4, 6 and 12–15 months	<2 years 2–4 years	4	<2 years: 3.5 hospitalizations/100,000 2–4 years: 3.7 hospitalizations/100,000	7	<2 years: +100‡ 2–4 years: +178
United States	Li and Tancredi[51]	ICD-9 or ICD-10 codes	Population-based surveillance	2, 4, 6 and 12–15 months	<18 years	2	2.2 hospitalizations/100,000	2	+70§
United States	Schultz et al.[24]	ICD-9 or ICD-10 codes	Active, sentinel surveillance	2, 4, 6 and 12–15 months	<18 years	2	29 *S. pneumoniae* isolates	2	–86.2
United States	Singleton et al.[20]	ICD-9 or ICD-10 codes	Active, population-based surveillance	2, 4, 6 and 12–15 months	<10 years, Alaskan native	5	46.3 average annual empyema-associated hospitalization rate	4	No change

*All studies evaluated PCV7.
†All percent changes are statistically significant ($P < 0.05$) unless otherwise noted.
‡NS, not significant.
§NR, statistical significance not reported.
¶Endpoint also includes empyema.
‖Negative percent change indicates a percent reduction; positive percent change indicates a percent increase.

directly compared different schedules within the same study. Pelton et al.[28] directly compared 2 versus 3 primary doses in an observational study of an immature immunization program and found that 3 primary doses were superior to 2 doses in preventing hospitalizations for clinical pneumonia before a booster dose, but only early in the vaccination program (presumably before the indirect effect matured). The other study, conducted among Australian Indigenous infants, also found that 3 primary doses were superior to 2 doses, but under the condition of almost no effect from receipt of 3 primary doses compared with receipt of 0 doses in preventing clinical pneumonia and an increased risk with receipt of 2 primary doses.[53] Study investigators speculated that replacement of vaccine serotypes with either nonvaccine serotypes or other respiratory pathogens carried in the nasopharynx may have increased clinical pneumonias among infants. The remaining studies evaluating a single schedule compared with no vaccination showed evidence of impact on pneumonia burden using 2+1, 3+0 or 3+1 schedules; there were no discernible differences in the magnitude of that impact according to a specific dosing schedule. Findings from individual studies were not comparable with each other as the measured impact was dependent on a variety of study methods, case definitions and populations, which, due to the heterogeneity of the data, we were unable to control for in analysis. Despite this limitation, our findings support the use of PCV in effectively reducing disease burden and complement a recent systematic review that evaluated the subset of PCV studies making direct schedule comparisons; because of limited or no data meeting inclusion criteria, that review was unable to assess clinical outcomes regarding pneumonia.[58]

In addition to the heterogeneity of study designs evaluating different PCV schedules, the nonspecificity of pneumonia endpoints and myriad case definitions complicated the ability to adequately summarize and interpret findings regarding impact of PCV schedules on pneumonia. Studies using more narrow and specific endpoints and case definitions, such as World Health Organization (WHO)–standardized definitions, likely provide a more accurate picture of PCV impact on disease specifically caused by pneumococcus. Studies that use a more generic endpoint, such as clinical pneumonia, are more prone to include cases caused by pathogens other than pneumococcus and mask any true impact. A few studies have assessed the impact of specificity of disease endpoints by retrospectively applying more specific case definitions and re-evaluating PCV impact. In each case, a higher efficacy was measured with increased specificity for the disease endpoint.[26,38,59,60] However, capturing cases with a more specific case definition is not always appropriate or feasible given limited resources (ie, access to laboratory or clinical diagnostics, population access to care, limited surveillance area) and confounding factors (ie, high burden of underlying conditions such as malaria or HIV) in many studies evaluating implementation in routine settings. We found evidence of this in our review of case definitions; the most rigorous and specific case definitions were more often used in the setting of controlled trials while observational studies were more likely to use nonspecific case definitions. Case definitions ranged in specificity and inclusion criteria with some studies using *International Classification of Diseases, 9th edition* (*ICD-9*) or *International Classification of Diseases, 10th edition* (*ICD-10*) administrative database codes or clinician diagnosis, while others used WHO-standardized definitions or laboratory confirmation. This lack of specificity and standardization within case definitions may explain some of the variability in findings and the inability to interpret reductions in certain disease endpoints. Nevertheless, our review found sufficient evidence of PCV impact against pneumonia outcomes: 12/20 (60%) studies found significant reductions in clinical pneumonia, 6/11 (55%) radiologically confirmed pneumonia and 7/16 (44%) pneumococcal pneumonia. It is

essential for future studies to consider more pneumococcal-specific and standardized case definitions to accurately and consistently measure the impact of PCV against pneumonia.

The studies included in this analysis represent a number of different settings and populations, which, while providing a breadth of data, also made it difficult to discern differences between schedules. Many data collected from settings of routine immunization focused on PCV7 and were from low disease burden, higher income countries, complicating the ability to extrapolate findings to other PCV products and to low- and middle-income countries, which often have higher rates of disease burden and more constrained resources. In addition, many populations in lower income countries have higher rates of underlying health conditions (eg, HIV or sickle cell disease) that can increase risk of developing pneumonia. We found only 6 studies that evaluated the impact of PCV in populations at higher risk for disease and magnitude of disease reduction varied greatly. Despite this limitation in geographical representation in settings of routine immunization, all RCTs evaluating 3+0 schedules were from low-income or lower-middle income countries and showed impact of PCV in these populations. As a greater number of countries have now introduced PCV into national immunization programs, ongoing studies in lower income settings and studies using various PCV products (PCV10 or PCV13) will contribute to additional evidence of impact.[61,62]

Our review of the literature on impact of PCV dosing schedules found evidence of impact on varying pneumonia endpoints using 2+1, 3+0 and 3+1 schedules, although the preponderance of evidence informed 3+1 schedules, with fewer data available regarding 2+1 and 3+0 schedules. Our findings support recommendations by the Pan American Health Organization and WHO for using a 3-dose regimen, which can be given as either 3+0 or 2+1, and given a lack of evidence supporting 2+0 schedules, choosing a schedule that ensures high coverage with a third dose is essential.[63,64] Furthermore, due to current data limitations and heterogeneity of the data, the optimal schedule in a given epidemiological setting for those 3 doses is dependent on a range of disease impact and programmatic considerations. As more countries make a decision to introduce PCV into national immunization programs, it will be essential for policy makers to consider programmatic and epidemiologic factors when making decisions regarding the ideal dosing schedule for their program. To ensure stakeholders are well-informed, more data are needed to evaluate PCV10 and PCV13 and the impact of these vaccines on pneumonia in developing countries. For all such studies, use of specific, standardized case definitions and evaluations that include direct schedule comparisons will greatly enhance the strength of evidence on which to formulate optimal dosing policies and achieve the greatest disease reductions for the doses administered.

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REFERENCES

1. O'Brien KL, Wolfson LJ, Watt JP, et al.; Hib and Pneumococcal Global Burden of Disease Study Team. Burden of disease caused by *Streptococcus pneumoniae* in children younger than 5 years: global estimates. *Lancet*. 2009;374:893–902.
2. World Health Organization. *Estimated Hib and pneumococcal deaths for children under 5 years of age. 2008*. Available at: http://www.who.int/immunization_monitoring/burden/Pneumo_hib_estimates/en/index.html. Accessed March 18, 2013.
3. Lucero MG, Dulalia VE, Parreno RN, et al. Pneumococcal conjugate vaccines for preventing vaccine-type invasive pneumococcal disease and pneumonia with consolidation on x-ray in children under two years of age. *Cochrane Database Syst Rev*. 2004:CD004977.
4. World Health Organization. Pneumococcal conjugate vaccine for childhood immunization—WHO position paper. *Wkly Epidemiol Rec*. 2007;12:93–104.
5. World Health Organization and UNICEF. *Global Action Plan for Prevention and Control of Pneumonia (GAPP)*. 2009. Available at: http://whqlibdoc.who.int/hq/2009/WHO_FCH_CAH_NCH_09.04_eng.pdf. Accessed March 18, 2013.
6. Johnson HL, Deloria-Knoll M, Levine OS, et al. Systematic evaluation of serotypes causing invasive pneumococcal disease among children under five: the pneumococcal global serotype project. *PLoS Med*. 2010;7:e1000348.
7. European Medicines Agency. *Prevenar*. 2011. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000323/human_med_000987.jsp&jsenabled=true. Accessed March 12, 2012.
8. European Medicines Agency. *Prevenar 13*. 2013. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/001104/human_med_001220.jsp&mid=WC0b01ac058001d124. Accessed October 16, 2013.
9. European Medicines Agency. *Synflorix*. 2011. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000973/human_med_001071.jsp&mid=WC0b01ac058001d124. Accessed March 12, 2012.
10. IVAC, Johns Hopkins Bloomberg School of Public Health. *Vaccine Information Management System (VIMS) Global Vaccine Introduction Report. March, 2013*. Available at: www.jhsph.edu/ivac/vims.html. Accessed April 15, 2013.
11. Conklin L, Loo JD, Kirk J, et al. Systematic review of the effect of pneumococcal conjugate vaccine dosing schedules on vaccine-type invasive pneumococcal disease among young children. *Pediatr Infect Dis J*. 2014;33 (Suppl 2):S109–S118.
12. Fleming-Dutra KE, Conklin L, Loo JD, et al. Systematic review of the effect of pneumococcal conjugate vaccine dosing schedules on vaccine-type nasopharyngeal carriage. *Pediatr Infect Dis J*. 2014;33 (Suppl 2):S152–S160.
13. Deloria Knoll M, Park D, Johnson TS, et al. Systematic review of the effect of pneumococcal conjugate vaccine dosing schedules on immunogenicity. *Pediatr Infect Dis J*. 2014;33 (Suppl 2):S119–S129.
14. Loo JD, Conklin L, Fleming-Dutra KE, et al. Systematic review of the indirect effect of pneumococcal conjugate vaccine dosing schedules on pneumococcal disease and colonization. *Pediatr Infect Dis J*. 2014;33 (Suppl 2):S161–S171.
15. Loo JD, Conklin L, Deloria Knoll M, et al. Methods for a systematic review of pneumococcal conjugate vaccine dosing schedules. *Pediatr Infect Dis J*. 2014;33 (Suppl 2):S182–S187.
16. Hanquet G, Lernout T, Vergison A, et al.; Belgian IPD Scientific Committee. Impact of conjugate 7-valent vaccination in Belgium: addressing methodological challenges. *Vaccine*. 2011;29:2856–2864.
17. Moore M, Pilishvili T, Farley M, et al. Trends in invasive pneumococcal pneumonia, selected US sites, 1998–2006. 6th International Symposium on Pneumococci and Pneumococcal Disease; June 8–12, 2008. Reykjavik, Iceland. Abstract 371.
18. Richmond P, Phuanukoonnon S, Jacoby P, et al. Effect of neonatal and early immunisation with heptavalent pneumococcal conjugate vaccine on morbidity and pneumonia in Papua New Guinea. 6th International Symposium on Pneumococci and Pneumococcal Disease; June 8–12, 2008. Reykjavik, Iceland. Abstract 345.
19. Simonsen L, Taylor RJ, Young-Xu Y, et al. Impact of pneumococcal conjugate vaccination of infants on pneumonia and influenza hospitalization and mortality in all age groups in the United States. *MBio*. 2011;2:e00309–e00310.
20. Singleton R, Holman R, Yorita K, et al. Pneumococcal empyema and pleural effusion among Alaska Native children less than 10 yrs of age. 6th International Symposium on Pneumococci and Pneumococcal Disease; June 8–12, 2008. Reykjavik, Iceland. Abstract 87.
21. Zhou F, Kyaw MH, Shefer A, et al. Health care utilization for pneumonia in young children after routine pneumococcal conjugate vaccine use in the United States. *Arch Pediatr Adolesc Med*. 2007;161:1162–1168.

22. Klugman KP, Madhi SA, Huebner RE, et al.; Vaccine Trialists Group. A trial of a 9-valent pneumococcal conjugate vaccine in children with and those without HIV infection. *N Engl J Med*. 2003;349:1341–1348.
23. Cutts FT, Zaman SM, Enwere G, et al.; Gambian Pneumococcal Vaccine Trial Group. Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in The Gambia: randomised, double-blind, placebo-controlled trial. *Lancet*. 2005;365:1139–1146.
24. Schultz KD, Fan LL, Pinsky J, et al. The changing face of pleural empyemas in children: epidemiology and management. *Pediatrics*. 2004;113:1735–1740.
25. Lucero MG, Nohynek H, Williams G, et al. Efficacy of an 11-valent pneumococcal conjugate vaccine against radiologically confirmed pneumonia among children less than 2 years of age in the Philippines: a randomized, double-blind, placebo-controlled trial. *Pediatr Infect Dis J*. 2009;28:455–462.
26. Madhi SA, Kuwanda L, Cutland C, et al. The impact of a 9-valent pneumococcal conjugate vaccine on the public health burden of pneumonia in HIV-infected and -uninfected children. *Clin Infect Dis*. 2005;40:1511–1518.
27. Balazs GC, Garcia FJ, Yamamoto LG. Conjugate heptavalent pneumococcal vaccine outcome improvements. *Hawaii Med J*. 2006;65:288–289.
28. Pelton SI, Weycker D, Klein JO, et al. 7-Valent pneumococcal conjugate vaccine and lower respiratory tract infections: effectiveness of a 2-dose versus 3-dose primary series. *Vaccine*. 2010;28:1575–1582.
29. Adam D, Fehnle K. Safety and effectiveness against respiratory tract infections for pneumococcal conjugate vaccine co-administered with routine vaccine combinations. *Vaccine*. 2008;26:5944–5951.
30. Ansaldi F, Sticchi L, Durando P, et al. Decline in pneumonia and acute otitis media after the introduction of childhood pneumococcal vaccination in Liguria, Italy. *J Int Med Res*. 2008;36:1255–1260.
31. Black SB, Shinefield HR, Ling S, et al. Effectiveness of heptavalent pneumococcal conjugate vaccine in children younger than five years of age for prevention of pneumonia. *Pediatr Infect Dis J*. 2002;21:810–815.
32. Byington CL, Korgenski K, Daly J, et al. Impact of the pneumococcal conjugate vaccine on pneumococcal parapneumonic empyema. *Pediatr Infect Dis J*. 2006;25:250–254.
33. Calbo E, Díaz A, Cañadell E, et al.; Spanish Pneumococcal Infection Study Network. Invasive pneumococcal disease among children in a health district of Barcelona: early impact of pneumococcal conjugate vaccine. *Clin Microbiol Infect*. 2006;12:867–872.
34. De Wals P, Robin E, Fortin E, et al. Pneumonia after implementation of the pneumococcal conjugate vaccine program in the province of Quebec, Canada. *Pediatr Infect Dis J*. 2008;27:963–968.
35. Esposito S, Lizioli A, Lastrico A, et al. Impact on respiratory tract infections of heptavalent pneumococcal conjugate vaccine administered at 3, 5 and 11 months of age. *Respir Res*. 2007;8:12.
36. Grijalva CG, Poehling KA, Nuorti JP, et al. National impact of universal childhood immunization with pneumococcal conjugate vaccine on outpatient medical care visits in the United States. *Pediatrics*. 2006;118:865–873.
37. Grijalva CG, Nuorti JP, Arbogast PG, et al. Decline in pneumonia admissions after routine childhood immunisation with pneumococcal conjugate vaccine in the USA: a time-series analysis. *Lancet*. 2007;369:1179–1186.
38. Hansen J, Black S, Shinefield H, et al. Effectiveness of heptavalent pneumococcal conjugate vaccine in children younger than 5 years of age for prevention of pneumonia: updated analysis using World Health Organization standardized interpretation of chest radiographs. *Pediatr Infect Dis J*. 2006;25:779–781.
39. Hendrickson DJ, Blumberg DA, Joad JP, et al. Five-fold increase in pediatric parapneumonic empyema since introduction of pneumococcal conjugate vaccine. *Pediatr Infect Dis J*. 2008;27:1030–1032.
40. Rutman MS, Bachur R, Harper MB. Radiographic pneumonia in young, highly febrile children with leukocytosis before and after universal conjugate pneumococcal vaccination. *Pediatr Emerg Care*. 2009;25:1–7.
41. Schutze GE, Tucker NC, Mason EO Jr. Impact of the conjugate pneumococcal vaccine in Arkansas. *Pediatr Infect Dis J*. 2004;23:1125–1129.
42. Shafinoori S, Ginocchio CC, Greenberg AJ, et al. Impact of pneumococcal conjugate vaccine and the severity of winter influenza-like illnesses on invasive pneumococcal infections in children and adults. *Pediatr Infect Dis J*. 2005;24:10–16.
43. Nelson JC, Jackson M, Yu O, et al. Impact of the introduction of pneumococcal conjugate vaccine on rates of community acquired pneumonia in children and adults. *Vaccine*. 2008;26:4947–4954.
44. Muñoz-Almagro C, Jordan I, Gene A, et al. Emergence of invasive pneumococcal disease caused by nonvaccine serotypes in the era of 7-valent conjugate vaccine. *Clin Infect Dis*. 2008;46:174–182.
45. Roche PW, Krause V, Cook H, et al.; Enhanced Invasive Pneumococcal Disease Surveillance Working Group; Pneumococcal Working Party of the Communicable Diseases Network Australia. Invasive pneumococcal disease in Australia, 2006. *Commun Dis Intell Q Rep*. 2008;32:18–30.
46. Kaplan SL, Mason EO Jr, Wald ER, et al. Decrease of invasive pneumococcal infections in children among 8 children's hospitals in the United States after the introduction of the 7-valent pneumococcal conjugate vaccine. *Pediatrics*. 2004;113(3 pt 1):443–449.
47. Aristegui J, Bernaola E, Pocheville I, et al. Reduction in pediatric invasive pneumococcal disease in the Basque Country and Navarre, Spain, after introduction of the heptavalent pneumococcal conjugate vaccine. *Eur J Clin Microbiol Infect Dis*. 2007;26:303–310.
48. Grijalva CG, Nuorti JP, Zhu Y, et al. Increasing incidence of empyema complicating childhood community-acquired pneumonia in the United States. *Clin Infect Dis*. 2010;50:805–813.
49. Jardine A, Menzies RI, McIntyre PB. Reduction in hospitalizations for pneumonia associated with the introduction of a pneumococcal conjugate vaccination schedule without a booster dose in Australia. *Pediatr Infect Dis J*. 2010;29:607–612.
50. Koshy E, Murray J, Bottle A, et al. Impact of the seven-valent pneumococcal conjugate vaccination (PCV7) programme on childhood hospital admissions for bacterial pneumonia and empyema in England: national time-trends study, 1997-2008. *Thorax*. 2010;65:770–774.
51. Li ST, Tancredi DJ. Empyema hospitalizations increased in US children despite pneumococcal conjugate vaccine. *Pediatrics*. 2010;125:26–33.
52. O'Grady KF, Carlin JB, Chang AB, et al. Effectiveness of 7-valent pneumococcal conjugate vaccine against radiologically diagnosed pneumonia in indigenous infants in Australia. *Bull World Health Organ*. 2010;88:139–146.
53. O'Grady KA, Lee KJ, Carlin JB, et al. Increased risk of hospitalization for acute lower respiratory tract infection among Australian indigenous infants 5–23 months of age following pneumococcal vaccination: a cohort study. *Clin Infect Dis*. 2010;50:970–978.
54. Patrzałek M, Albrecht P, Sobczynski M. Significant decline in pneumonia admission rate after the introduction of routine 2+1 dose schedule heptavalent pneumococcal conjugate vaccine (PCV7) in children under 5 years of age in Kielce, Poland. *Eur J Clin Microbiol Infect Dis*. 2010;29:787–792.
55. Twele L, Haider S, Nettel-Aguirre A, et al. Has the 7-valent pneumococcal conjugate vaccine (PCV7) reduced hospital visits and admissions for pneumonia in young children in Calgary? *Int J Antimicrob Agents*. 2009;34:S5-S6.
56. O'Brien KL. The effect of conjugate pneumococcal vaccine on pneumonia and otitis media among Navajo and White Mountain Apache children. 3rd International Symposium on Pneumococci and Pneumcooccal Disease; May 5-8, 2002, Anchorage, AK.
57. Tregnaghi MW, Sáez-Llorens X,López P, et al. Evaluating the efficacy of 10-valent pneumococcal non-typeable Haemophilus influenzae protein-d conjugate vaccine (PHID-CV) against community-acquired pneumonia in Latin America. European Society of Pediatric Infectious Disease; June 7–11, 2011. The Hague, Netherlands.
58. Scott P, Rutjes AW, Bermetz L, et al. Comparing pneumococcal conjugate vaccine schedules based on 3 and 2 primary doses: systematic review and meta-analysis. *Vaccine*. 2011;29:9711–9721.
59. Cheung YB, Zaman SM, Ruopuro ML, et al. C-reactive protein and procalcitonin in the evaluation of the efficacy of a pneumococcal conjugate vaccine in Gambian children. *Trop Med Int Health*. 2008;13:603–611.
60. Madhi SA, Kohler M, Kuwanda L, et al. Usefulness of C-reactive protein to define pneumococcal conjugate vaccine efficacy in the prevention of pneumonia. *Pediatr Infect Dis J*. 2006;25:30–36.
61. Cohen C, von Mollendorf C, Naidoo N, et al. South African IPD Case-Control Study Group. Effectiveness of seven-valent pneumococcal conjugate vaccine (PCV7) against invasive pneumococcal disease in South Africa: a matched case-control study. 8th International Symposium on Pneumococci and Pneumococcal Disease; March 11–15, 2012, Igacu Falls, Brazil.
62. Madhi SA, Groome M, Zar H, et al. Effectiveness of pneumococcal conjugate vaccine (PCV) against presumed bacterial pneumonia (PBP) in South African HIV-uninfected children: a case-control study. 8th International Symposium on Pneumococci and Pneumococcal Disease; March 11–15, 2012, Igacu Falls, Brazil. Abstract 8.
63. Pan American Health Organization. Technical Advisory Group on Vaccine-Preventable Diseases. Final Report; July 6–8, 2011, Buenos Aires, Argentina.
64. World Health Organization. Meeting of the Strategic Advisory Group of Experts on Immunization, November 2011—conclusions and recommendations. *Wkly Epidemiol Rec*. 2012:1–16.