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 (Pediatr Infect Dis J 2014;33:S140–S151)

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.5 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 Appendix15). 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 Chemotherapy (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 Appendix15). 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 post introduction 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 PCV1057 (Table 1).
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. 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, 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 and 5 observational studies. 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
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.31 Of the two 2+1 studies on empyema, one found a 22% decline in empyema,32 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 RCTs22,23,25,26 from various regions (Table 2) and 2 observational studies, both from Australia34,49 (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 trials20,31,38,57 and 20 observational studies that evaluated the impact of a 3+1 schedule on pneumonia endpoints (8 on clinical pneumonia,9,21,27,36,37,43,48,51 4 on radiologically confirmed pneumonia,40,43,52,55 7 on empyema24,32,33,39,44,48,51 and 12 on pneumococcal pneumonia17,19,21,33,37,42,44,46,48,51) (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 significance6,43 or found significant reductions only in children <2 years of age19,37,48 (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**                                                   |                           |
| 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%)              |
| Papua New Guinea | Richmond et al.18        | Randomized, nonblind                | PCV7 (Wyeth)    | 0, 1 and 2 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)         |                           |
| 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%)         |
| 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%)         |
| 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%)      |
| 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%)    |
| United States    | Hansen et al.28          | 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%)        |
| 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%)  |
| Germany          | Adam and Fehnle29        | 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.
| 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   | 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           | Patrzalek et al.55 | Clinical reading (not WHO) by 2 independent radiologists | Sentinel surveillance  | 3, 5, 13 months          | <2                         | 2                   | 2–4 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. pneumonia 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/Population | Reference | Age Groups Evaluated (years) | Dosing Schedule for PCV† | Definition | Study Design | Percent Change in Baseline Measure (per Postintroduction year) | Percent Change at Latest Year Post-PCV Introduction |
|-------------------|-----------|-----------------------------|--------------------------|------------|-------------|----------------------------------------------------------------|-------------------------------------------------|
| Australia         | Jardine et al.49 | <2, 2–4 | 2, 4 and 6 months | Clinical pneumonia | Population-based surveillance | −2 years: −38‡ | −2 years: −77‡ |
| Australia         | Jardine et al.49 | <2, 2–4 | 2, 4 and 6 months | Pneumococcal pneumonia | Population-based surveillance | −2 years: −77‡ | −2 years: −67‡ |
| Australia         | Roche et al.45 | <2 | 3 | Passive, population-based surveillance | Isolation of S. pneumoniae from blood or nucleic acid test + clinical or radiological confirmation | −45§ | −45§ |

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

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 | 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       | <2 years: 1296.9 cases/100,000 | 4                           | <2 years: −39                                      |
| 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       | <2 years: 1267 hospitalizations/100,000 | 7                           | <2 years: −33                                      |
| 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       | 402 hospitalizations/100,000 | 7                           | 2–4 years: no change                              |
| United States | Li and Tancredi51         | 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       | <2 years: 6.6 cases/1000        | 4                           | <1 year: −19‡                                       |
| United States | Simonsen et al.19         | ICD-9 or ICD-10 codes                        | Sentinel surveillance                 | 2, 4, 6 and 12–15 months | <2 years             | 2–5 years       | <2 years: 1026.5 cases/100,000 | 7                           | <2 years: −28                                      |
| United States | Zhou et al.21             | ICD-9 or ICD-10 codes                        | Cohort study                          | 2, 4, 6 and 12–15 months | <2 years             | 2–4 years       | <2 years: 1267 hospitalizations/100,000 | 7                           | 2–4 years: −1‡                                      |
| CXR pneumonia  |                            |                                              |                                       |                          |                      |               |                               |                             |                                                     |
| Canada        | Twele et al.25             | 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‡                                      |
| 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       | <1 year: 3.8 cases/1000        | 4                           | <1 year: −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       | <2 years: 17% (121/709) of admissions 2–5 years: 36% (69/180) of admissions <5 years: 21% (190/889) of admissions | 5                           | <2 years: −41‡                                      |
| 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)
| Country       | Reference                | Case Definition                                      | Study Design                          | Dosing Schedule for PCV* | Age Groups Evaluated | Years Baseline Data | Baseline Measure (Per Year) | Years Post-Introduction Data | Percent Change at Latest Year Post-PCV Introduction† |
|--------------|--------------------------|------------------------------------------------------|---------------------------------------|--------------------------|----------------------|----------------------|---------------------------|-----------------------------|-------------------------------------------------|
| 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; 3.4 episodes/100,000 2–4 years: 3.8 episodes/100,000 | 5                    | <2 years: +289 2–4 years: +344 | 4                          | −2.9‡                                           |
| United States| Grijalva et al.37        | ICD-9 or ICD-10 codes                                | Sentinel surveillance                 | 2, 4, 6 and 12–15 months  | <2 years            | 3                    | 26.2 cases/100,000      | 4                          | −65                                             |
| United States| Grijalva et al.46        | ICD-9 or ICD-10 codes                                | Sentinel surveillance                 | 2, 4, 6 and 12–15 months  | <2 years            | 4                    | 27 hospitalizations/100,000 2–4 years: 12 hospitalizations/100,000 | 7                          | −61                                             |
| United States| Kaplan et al.46          | Isolation of *S. pneumoniae* from sterile site + clinical diagnosis | Active, sentinel surveillance         | 2, 4, 6 and 12–15 months  | <5 years            | 6                    | 30.5 pneumococcal isolates/yr | 2                          | −39‡                                           |
| United States| Liand Tancredi31         | 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, pleural fluid or lung + radiological confirmation | 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                    | 25.9 cases/100,000      | 7                          | −51                                             |
| United States| Zhou et al.31            | 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                    | 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.29        | 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)
| Country                | Study Design               | Age Groups Evaluated | Dosing Schedule post PCV Dosing and Pneumonia | Case Definition | Measure (Per Year) | Data Baseline | Data Post-PCV Introduction | Percent Change at Latest Year | Years Post-PCV Introduction | Reference |
|-----------------------|----------------------------|----------------------|---------------------------------------------|-----------------|-------------------|----------------|--------------------------|-------------------------------|-----------------------------|-----------|
| United States         | Cohort study               | <18 years            | 2, 4, 6 and 12–15 months                   | ICDC 9 codes    | <18 years: 3.5 hospitalizations/100,000 | 2             | 2–4 years: +178          | +80                           | 5                           | Hendrickson et al.39        |
| United States         | Cohort study               | <2 years             | 2, 4, 6 and 12–15 months                   | ICDC 9 codes    | <2 years: 3.5 hospitalizations/100,000 | 2             | 2–4 years: +178          | +708                          | 7                           | Grijalva et al.48           |
| United States         | Cohort study               | <10 years            | 2, 4, 6 and 12–15 months                   | ICDC 9 codes    | <2 years: 3.5 hospitalizations/100,000 | 2             | 2–4 years: +178          | +708                          | 7                           | Li and Tancredi51          |
| United States         | Cohort study               | <18 years            | 2, 4, 6 and 12–15 months                   | ICDC 9 codes    | <18 years: 3.5 hospitalizations/100,000 | 2             | 2–4 years: +178          | +708                          | 7                           | Schultz et al.24           |
| United States         | Cohort study               | <10 years            | 2, 4, 6 and 12–15 months                   | ICDC 9 codes    | <18 years: 3.5 hospitalizations/100,000 | 2             | <2 years: +100           | <18 years: -86.2            | 7                           | Singleton et al.20         |
| United States         | Cohort study               | <18 years            | 2, 4, 6 and 12–15 months                   | ICDC 9 codes    | <18 years: 3.5 hospitalizations/100,000 | 2             | 2–4 years: +178          | +708                          | 7                           | Zolletti et al.60          |

*All percent changes are statistically significant (P < 0.05) unless otherwise noted.

**NS, not significant. NR, statistical significance not reported. ¶Endpoint also includes empyema-associated hospitalization rate.

║Negative percent change indicates a percent reduction; positive percent change indicates a percent increase.

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.6,82

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.6,82 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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