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Systematic Review of the Effect of Pneumococcal Conjugate Vaccine Dosing Schedules on Vaccine-type Invasive Pneumococcal Disease Among Young Children

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Background: Pneumococcal conjugate vaccines (PCV) are being implemented globally using a variety of different schedules. The optimal schedule to maximize protection of vaccinated children against vaccine-type invasive pneumococcal disease (VT-IPD) is not known.

Methods: To assess the relative benefit of various PCV dosing schedules, we conducted a systematic review of studies published in English from 1994 to 2010 (supplemented post hoc with studies from 2011) on PCV effectiveness against VT-IPD among children targeted to receive vaccine. Data on 2-dose and 3-dose primary series, both with and without a booster ("2+0," "2+1," "3+0" and "3+1"), were included. For observational studies using surveillance data or case counts, we calculated percentage reduction in VT-IPD before and after PCV introduction.

Results: Of 4 randomized controlled trials and 31 observational studies reporting VT-IPD among young children, none evaluated a 2+0 complete series, 7 (19%) evaluated 2+1, 4 (11%) 3+0 and 27 (75%) 3+1. Most (86%) studies were from North America or Europe. Only 1 study (observational) directly compared 2 schedules (3+0 vs. 3+1); results supported the use of a booster dose. In clinical trials, vaccine efficacy ranged from 65% to 71% with 3+0 and 83% to 94% with 3+1. Surveillance data and case counts demonstrate reductions in VT-IPD of up to 100% with 2+1 (6 studies) or 3+1 (17 studies) schedules and up to 90% with 3+0 (2 studies). Reductions were observed as early as 1 year after PCV introduction.

Conclusions: These data support the use of 2+1, 3+0 and 3+1 schedules, although most data of PCV impact on VT-IPD among young children are from high-income countries using 3+1. Differences between schedules for impact on VT-IPD are difficult to discern based on available data.

Key Words: pneumococcal conjugate vaccine, immunization schedule, invasive disease, systematic review

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Streptococcus pneumoniae can cause a variety of clinical syndromes among both children and adults. When infection spreads to a normally sterile site, such as the brain or blood, the resulting syndrome, called invasive pneumococcal disease (IPD), is associated with significant morbidity and mortality. The burden of IPD falls disproportionately on young children, especially those in low-income countries, and persons at high risk of infection because of underlying medical conditions such as HIV or sickle cell disease.[1,2] A limited number of pneumococcal serotypes cause the majority of IPD in both high- and low-risk groups; 7 of these serotypes are included in the 7-valent pneumococcal conjugate vaccine (PCV7), first licensed in February 2000.[3] Within 6 years of PCV7 introduction in the United States, use of a 3-dose primary series with a booster in the second year of life (a "3+1" schedule) and a national catch-up campaign among those under 5 years of age nearly eliminated vaccine-type IPD (VT-IPD) among children targeted to receive the vaccine.[4] More recently, licensed PCV formulations that include 10 and 13 serotypes (PCV10 and PCV13, respectively) hold promise to further reduce the burden of pneumococcal disease.

Between 2000 and 2008, PCV7 was introduced into the national immunization programs of 26 countries, including 1 middle-income country.[5] As of December 2011, 77 countries offered PCV universally or had >50% coverage with the vaccine; 30 used a 3+1 schedule and 47 used a reduced dose schedule of either 3 primary doses without a booster (3+0) or 2 primary doses with a booster (2+1) (Sources: Database maintained by WHO, supplemented with data from VIMS [Vaccine Information Management System of IVAC] and individual country reports or press releases). Although immunogenicity data support the use of reduced dose schedules for most vaccine serotypes, whether reduced dose schedules can provide equivalent protection against VT-IPD to a 3+1 schedule when introduced into a national immunization program is unclear.[6] The World Health Organization currently recommends that countries introduce PCV as part of the Expanded Programme on Immunisation schedule, yet specific guidance on the relative effectiveness of different PCV dosing schedules in various settings is lacking.[7] Public health leaders newly considering PCV introduction, as well as those with established programs, face challenging decisions regarding the most appropriate dosing schedule for their populations, including the benefits of a 3-dose primary series compared with a 2-dose primary series, the benefits of a booster dose and whether a 3-dose series should be administered on a 2+1 or a 3+0 schedule. In this report, we attempt to provide insight

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into the relative benefits of different dosing schedules by presenting findings from a systematic review of the available literature on PCV dosing effects on VT-IPD among young children.

MATERIALS AND METHODS

Literature Search

This analysis is part of a larger project describing the impact of PCV dosing schedules on IPD, immunogenicity, nasopharyngeal carriage, pneumonia and indirect effects. Details on the literature search terms and methods used in this systematic review are described elsewhere (see Methods Appendix[8]). In brief, a systematic 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 trials (RCTs), nonrandomized trials, surveillance database analyses and observational studies of any PCV schedule on 1 or more outcomes of interest. Studies were included for abstraction if 23-valent 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 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.[8]

Data Abstraction

Citations recovered through the literature search went through several stages of independent review to determine their eligibility, as described elsewhere.[8] 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 more than 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; coadministered vaccines; country; age at each dose and date of study and publication. Additional data for the IPD outcome included rates of vaccine serotype IPD (per 100,000 population), absolute case counts of VT-IPD and reported percentage reduction in VT-IPD after PCV introduction. Data on both VT-IPD and VT pneumococcal bacteremia were considered duplicative, in which case only VT-IPD was included. We included both VT-meningitis and VT-IPD within a single study family to allow characterization of the meningitis outcome independently of VT-IPD.

Inclusion and Exclusion Criteria

We included all data published from RCTs, nonrandomized trials, case-control studies, indirect cohort studies, surveillance database analyses (population-based data) and case series (sentinel site data) using any PCV schedule if the citation or abstract reported data on VT pneumococcal meningitis, VT pneumococcal bacteremia or all VT-IPD. To describe the *direct* impact of the vaccine among young children, we only included studies that reported data on children targeted to receive vaccine; for surveillance analyses and case series, this meant limiting studies to those that reported impact of vaccine among children ≤2 years of age. For controlled trials, case-control studies and indirect cohort studies, data on children ≤5 years of age were also included as long as they were eligible to receive vaccine. We excluded studies that reported pneumococcal bacteremia only in the setting of clinical pneumonia as well as those that reported IPD

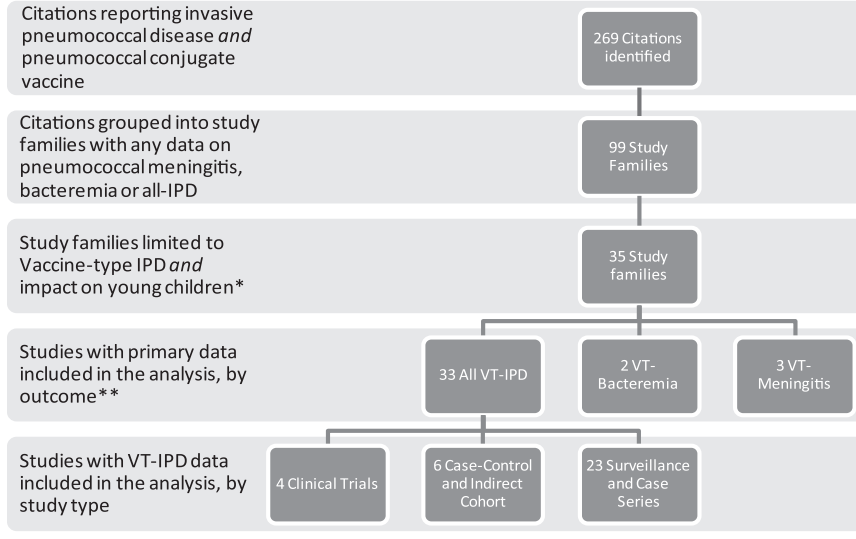

FIGURE 1. Literature search results for studies included in an analysis of the effect of vaccine dosing schedules on VT-IPD among young children. *These 35 study families represent 36 individual reports; 1 surveillance study family combined data from across 2 reports. **Bacteremia and meningitis reports were all surveillance and case series studies. Two studies reported both VT-meningitis and VT-bacteremia.

TABLE 1. Descriptive Characteristics of Studies Reporting the Impact of PCV Dosing Schedules on IPD Among Young Children by Type of Study Design

	Surveillance/Trend and Case Series Studies*	Case-Control and Indirect Cohort Studies	Clinical Trials	All Studies
	(n = 25)	(n = 6)	(n = 4)	(n = 35)
Date of publication				
1994–2002	0 (0%)	0 (0%)	1 (25%)	1 (2.9%)
2003–2006	3 (12.0%)	2 (33.3%)	3 (75%)	8 (22.9%)
2007–2010	22 (88.0%)	4 (66.7%)	0 (0%)	26 (74.2%)
Complete dosing series†				
2+0	0 (0%)	0 (0%)	0 (0%)	0 (0%)
2+1	6 (23.1%)	1 (16.7%)	0 (0%)	7 (19.4%)
3+0	2 (7.7%)	0 (0%)	2 (50%)	4 (11.1%)
3+1 or 3+PPV23	17 (76.9%)	5 (83.3%)	2 (50%)	27 (75.0%)
UN region‡				
Africa	0 (0%)	0 (0%)	2 (50%)	2 (5.7%)
Asia	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Oceania	3 (12.0%)	0 (0%)	0 (0%)	3 (8.6%)
Europe	12 (48.0%)	2 (33.3%)	0 (0%)	14 (35.0%)
Latin America and Caribbean	0 (0%)	0 (0%)	0 (0%)	0 (0%)
North American	10 (40.0%)	4 (66.7%)	2 (50%)	16 (47.7%)
Other region	0 (0%)	0 (0%)	0 (0%)	0 (0%)
PCV product†				
PCV7 (Wyeth)	25 (100%)	6 (100%)	2 (50%)	33 (94.3%)
PCV9	0 (0%)	0 (0%)	2 (50%)	2 (5.6%)
PCV11	0 (0%)	0 (0%)	0 (0%)	0 (0%)
PPV23	3 (12.0%)	0 (0%)	0 (0%)	3 (8.3%)
Outcome†				
VT-IPD	23 (92.0%)	6 (100%)	4 (100%)	33 (94.3%)
VT-meningitis	3 (12.0%)	0 (0%)	0 (0%)	3 (8.6%)
VT-bacteremia	2 (8.0%)	0 (0%)	0 (0%)	2 (5.7%)

*One VT-IPD study is comprised of 2 independent reports published in 2001 and 2006 (conducted in the US population using the same surveillance system). The later publication date is used.

†One study from Australia reported data using both a 3+0 and 3+PPV23 schedule.

‡United Nations "*Composition of macro geographical (continental) regions, geographical sub-regions, and selected economic and other groupings*" from http://unstats.un.org/unsd/methods/m49/m49regin.htm.

2+0, 2 doses without booster; 2+1, 2 doses plus booster; 3+0, 3 doses without booster; 3+1, 3 doses plus booster.

only among older age groups; these data are included in the articles on pneumonia and indirect effects, respectively, found in this supplement.[9,10] We also excluded review articles, those that only provided data for single serotypes and those that only reported data from either before or after PCV introduction but not from both periods.

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 alone for settings where no booster was planned, or the primary series plus the booster dose for settings where this was part of the planned schedule; specifically, these include a 2-dose primary series with or without a booster of PCV or PPV23 (2+1, 2+0) or a 3-dose primary series with or without a booster of PCV or PPV23 (3+1, 3+0).

Data Analysis

The studies identified in this systematic review represent heterogeneous designs. Even when clinical methods were similar

TABLE 2. Randomized Clinical Trials Evaluating Efficacy of PCV Dosing Schedules Against VT-IPD Among Young Children

Country (Citation)	Schedule	Schedule and Product	Total Sample Size	Population	VE (95% CI)
The Gambia (Cutts et al.)[13]	3+0	11, 15 and 24 weeks (PCV9, Wyeth)	17,437	General	71% (46–86)
South Africa (Klugman et al.)[12]	3+0	6, 10 and 14 weeks (PCV9, Wyeth)	39,836	HIV infected	65% (24–86)
				HIV uninfected	83% (39–97)
United States (Black et al.)[11]	3+1	2, 4, 6 and 12–15 months (PCV7, Wyeth)	37,868	General	94% (80–99)
United States (O'Brien et al.)[14]	3+1	2, 4, 6 and 12–15 months (PCV7, Wyeth)	8,292	Native American	82.6% (21.4–96.1)
Finland (Palmu et al.)[15]	3+1	≥6 weeks and 2 doses at ≥4 weeks intervals,	47,369	General	100% (83–100)
	2+1	booster at ≥11 months			92% (58–100)
		≥6 weeks and 2 doses at ≥8 weeks interval, booster at ≥11 months (PCV10, GSK)			

All studies were double-blind; VE estimates are intent-to-treat.

3+0, 3 doses without booster; 3+1, 3 doses plus booster

between studies, the analyses presented were often very different. We attempted to identify studies that would allow comparison between schedules either by (1) directly comparing PCV schedules within the same study, (2) including schedule-specific data compared with no vaccine within the same study or (3) including schedule-specific data that could be compared between studies using similar methodology (eg, among indirect cohort studies). Data were first summarized in descriptive analyses to provide an overview of the amount and variability of the data by schedule and study method.

For RCT, vaccine efficacy was used as the measure of impact. For surveillance database analyses and case series reporting VT-IPD over a given period, we calculated percentage reduction by defining baseline incidence as the mean of all data points reported before PCV introduction. When annual data on postintroduction incidence were available, we calculated percentage reduction from baseline using the data point given for each year reported. If annual data were not available, we used the percentage reduction reported in the study for the specified period. In cases where only the average postintroduction incidence rate over a period was provided, we calculated percentage reduction 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. To compare the impact of vaccine in early with late phases postintroduction, we grouped data into ≤3 years after PCV introduction and >3 years after introduction. When information on PCV dosing schedules within national immunization programs was not reported, we obtained it through data reported by World Health Organization (http://apps.who.int/immunization_monitoring/en/globalsummary/countryprofileselect.cfm) or the Vaccine Information Management System (http://www.jhsph.edu/ivac/vims).

Statistical significance was defined as $P < 0.05$; SAS version 9.2 (SAS Institute Inc., Cary, NC) was used for all analyses.

RESULTS

Of 12,980 citations reviewed, we identified 99 study families that included data on PCV and pneumococcal meningitis, bacteremia or all-IPD (Fig. 1). Of these, 35 study families (from 36 reports) included data on young children receiving PCV, 33 (94%) reported data on only VT-IPD, 2 (6%) reported on VT-meningitis and VT-IPD, 1 (3%) reported on VT-bacteremia and VT-meningitis and 1 (3%) reported only on VT-bacteremia (Appendix). The types of studies reporting these data included 4 clinical RCTs and 31 observational studies.

Most studies (n = 26; 74%) were published after 2007 and most were conducted in North America and Europe (n = 30; 86%), although studies from Africa (n = 2) and Oceania (n = 3) were also represented (Table 1). A 3+1 or 3+PPV23 schedule (n = 27; 75%) was more commonly evaluated than either 2+1 (n = 7; 19.4%) or 3+0 (n = 4; 11.1%). No studies evaluated routine use of a 2+0 schedule, although 5 (13.9%) observational studies looked at the effectiveness of a 2-dose primary series (ie, an incomplete series) in the setting of countries routinely using 2+1 or 3+1. Three studies, all of which were conducted in Australia, used PPV23 as a booster dose. All but 2 studies evaluated PCV7; these 2 evaluated a 9-valent vaccine (PCV9). None of the studies evaluated PCV10 or PCV13.

Randomized Controlled Trials

We identified 4 double-blind RCTs in 3 different countries; the studies evaluated vaccine efficacy against VT-IPD among young children for either a 3+0 or 3+1 schedule compared with no PCV (Table 2). No RCTs with VT-IPD outcomes directly compared dosing schedules or evaluated a 2+0 or 2+1 schedule. Two of

TABLE 3. Observational Studies That Estimated Vaccine Effectiveness Against VT-IPD of PCV Relative to No PCV Among Young Children for More Than 1 PCV Dosing Schedule (n = 6)

Study				VE Compared With No PCV (95% CI)			
Country	Study Design	Population age	Country PCV Schedule	2+0	2+1	3+0	3+1
Canada (Deceuninck et al.)[20]	Case-control	2–59 months	2+1	99% (90–100)	100% (15–100)	90% (24–100)	—
United States (Whitney et al.)[17]	Case-control	3–36 months	3+1	96%* (88–99)	98%* (75–100)	95%* (88–98)	100%* (94–100%)
Spain (Barricarte et al.)[18]	Case-control	<5 years	3+1	—	—	—	81%† (−46 to 97)
United States (de Serres)[19]	Indirect cohort	3–59 months	3+1	96%* (93–98)	—	98%* (95–99)	98%* (95 to 99)
United States (Mahon et al.)[16]	Indirect cohort	<5 years	3+1	70.5%* (28.0–87.9)	—	76.6%* (50.4—88.9)	90.5%* (17.7–98.9)
Germany (Ruckinger et al.)[21]	Indirect cohort	3–59 months	3+1	89.8%* (20.6–100.0)	—	94.6%* (69.7–99.5)	94.1%* (39.8–100.0)

*Adjusted.
†Schedule described as "complete vaccination."
2+0, 2 doses without booster; 2+1, 2 doses plus booster; 3+0, 3 doses without booster; 3+1, 3 doses plus booster.

TABLE 4. Included Observational Studies Documenting Impact of PCV Introduction on VT-IPD, Meningitis or Bacteremia Among Young Children Before and After Vaccine Introduction, by PCV Dosing Schedule Setting

Reference	Outcome, Group	Country	PCV Introduced With Catch-up Campaign	Surveillance Years Before Vaccine Introduction	Baseline Measure	Total Years Reported Postintroduction	Percentage Change at Maximum Years Postintroduction
2 + 1 schedule							
Foster et al.[23]	VT-IPD, general	United Kingdom	Yes	10	29.25/100,000	1	−74
Vestrheim et al. [24]	VT-IPD, general	Norway	Yes*	2	47.1/100,000	1	−71
De Wals et al. [25]	VT-IPD, general	Canada	Yes	3	87.3/100,000	3	−95
Harboe et al. [26]	VT-IPD, general	Denmark	Yes	8	36/100,000	1	−78
Miller et al. [27]	VT-IPD, general	England/Wales	Yes	7	40.8/100,000	4	−98
Hanquet et al. [28]	VT-meningitis, general	Belgium	Yes	2	13.39/100,000	1	−100
3 + 0 Schedule							
Roche et al. [29]	VT-IPD, general	Australia	Yes	3	67/100,000	1	−90
Lehmann et al. [30]	VT-IPD, general	Australia	Yes	8	58.35/100,000	2	−89
3+PPV23 schedule							
Krause et al. [31]	VT-IPD, indigenous	Australia	No	7	383/100,000	3	−91
Lehmann et al. [30]	VT-IPD, indigenous	Australia	No	5	118.5/100,000	6	−91
3 + 1 schedule							
Black et al.[32]	VT-IPD, general	United States	Yes	5	84.88/ 100,000	3	−100
Black et al. [33]							
Kellner et al. [34]	VT-IPD, general	Canada	Yes	4	55.5/100,000	5	−95
Reingold et al.[35]	VT-IPD, general	United States	Yes	2	160.5/100,000	5	−99
Ruckinger et al. [21]	VT-IPD, general	Germany	Yes	7	12.9/100,000	2	−73
Singleton et al. [36]	VT-IPD, general	United States	Yes	6	101.3/100,000	5	−98
Tyrrell et al. [37]	VT-IPD, general	Canada	Yes	2	83.5/100,000	4	−94
Munoz et al. [38]	VT-IPD, general	Spain	No	4	19.6/100,000	5	−11
Kaplan et al. [39]	VT-IPD, general	United States	Yes	6	240 cases	2	−99
Aristegui et al. [40]	VT-IPD, general	Spain	No	4	74.1/100,000	2	−33
Rendi-Wagner et al. [22]	VT-IPD, general	Austria	No	4	5.45/100,000	2	50
Rodenburg et al. [41]	VT-IPD, general	Netherlands	No	3	24.3/100,000	2	−67
Winters et al. [42]	VT-IPD, general	Canada	Yes	1	39 cases	2	−97
Singleton et al. [36]	VT-IPD, indigenous	United States	Yes	6	275.3/100,000	5	−96
Weatherholtz et al. [43]	VT-IPD, indigenous	United States	Yes	6	211.5/100,000	6	−100
Benito-Fernandez et al. [44]	VT-bacteremia, general	Spain	No	NR	NR	4	−79†
Lepoutre et al. [45]	VT-bacteremia, general	France	No	2	15/100,000	3	−60
Lepoutre et al. [45]	VT-meningitis, general	France	No	2	5/100,000	5	−81
Rendi-Wagner et al. [22]	VT-meningitis, general	Austria	No	4	2.6/100,000	2	−4

*Limited catch-up campaign.

†Change reported by study, individual data points not available for calculation.

NR, not reported; general, general population; indigenous, indigenous population

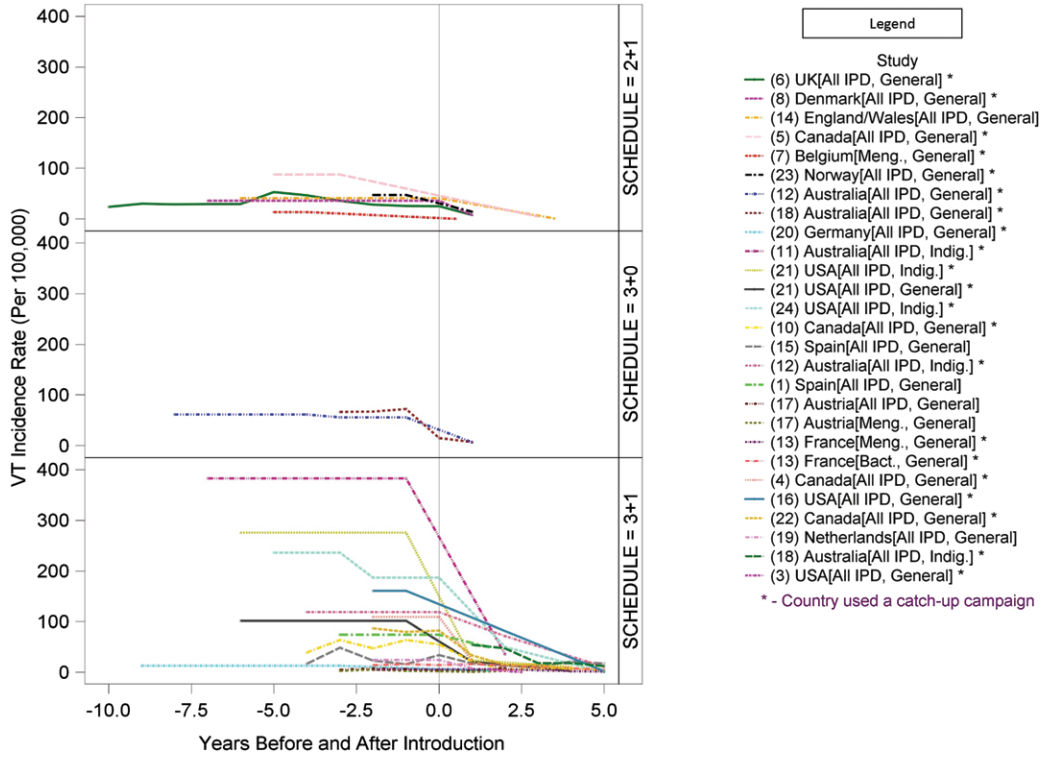

FIGURE 2. Incidence of VT-IPD among young children before and after vaccine introduction among countries implementing 2+1, 3+0 and 3+1 schedules. Reference number corresponds to Appendix A. VT, vaccine type; IPD, invasive pneumococcal disease; general, general population; indigenous, indigenous population; Bact, bacteremia; Mening, meningitis. 2+1, 2 doses plus booster; 3+0, 3 doses without booster; 3+1, 3 doses plus booster of PCV or PPV23. *Vaccine introduction occurred with catch-up campaign.

the RCTs—1 in The Gambia and the other in South Africa—used PCV9 in a 3+0 schedule setting and 2 used PCV7 in a 3+1 schedule setting in the United States.[11–14] In The Gambia, investigators compared 8189 vaccinated children to 8151 placebo controls and estimated efficacy against VT-IPD to be 71% in their intent-to-treat (ITT) analysis.[13] A similar ITT vaccine efficacy (83%) was demonstrated in the South Africa trial involving over 39,000 children[12]; the vaccine was slightly less efficacious (65%) among children infected with HIV. The 2 studies conducted in the United States both reported high ITT vaccine efficacy, 1 (VE 94%) was conducted in the general US population[11] and the other (VE 83%) was conducted among American Indian children, a population known to be at high risk for IPD.[14]

Case-Control and Indirect Cohort Studies

We identified 3 case-control studies and 3 indirect cohort studies that allowed for comparisons of different PCV schedules (Table 3). These studies were conducted in 4 different countries routinely using either 2+1 or 3+1 schedules and estimated vaccine effectiveness of various PCV schedules compared with no PCV in either a 2+1 or a 3+1 vaccine setting.[16–19] Despite varying study methods and settings, all studies used PCV7 and all showed significant effectiveness against VT-IPD among children targeted to receive vaccine. Across studies, point estimates of vaccine effectiveness among partially vaccinated children who had received 2 primary doses without a booster (2+0) ranged from 70% to 99%, 2+1 ranged from 98% to 100%, 3+0 ranged from 77% to 98% and 3+1 ranged from 81% to 100%. One case-control study, conducted in the United States, also directly analyzed the risk of VT-IPD between schedules.[17] In this analysis, a 3+1 schedule provided more protection against VT-IPD than a 3+0 schedule (odds ratio = 0, 95% CI: 0–0.87); other direct comparisons were not significant but the number of children vaccinated on either 2+1 or 2+0 schedule was relatively small.

Observational Surveillance Studies or Case Series Studies

We identified 25 surveillance or case series study families (26 citations) conducted in 12 countries that described the impact of national PCV introduction on any VT-IPD among young children (Table 4). Of these, 23 (92%) reported data on VT-IPD of any syndrome, 2 (8%) on VT-bacteremia without focus and 3 (12%) on VT-meningitis. Although surveillance methods varied and each study only reported the impact of 1 particular PCV dosing schedule, some general comparisons between schedules can be made across this group of reports. One similarity observed among nearly all studies was a significant impact of PCV introduction on VT-IPD over time in populations routinely using 2+1, 3+0 and 3+1 schedules; no data were available for a 2+0 schedule since no country routinely uses this schedule (Fig. 2). Reductions were also observed in the 4 studies conducted in indigenous populations: 2 conducted in Australia using 3+PPV23 and 2 conducted in the United States using a 3+1 schedule. Percentage reduction in VT-IPD ranged from 11% to 100% across studies, populations and time from vaccine introduction. A single study, conducted in Austria, reported an increase in VT-IPD (50% increase) and a 4% decrease in VT-meningitis 2 years after PCV7 introduction although the number of cases was small and coverage was only 25%.[22] In general, more

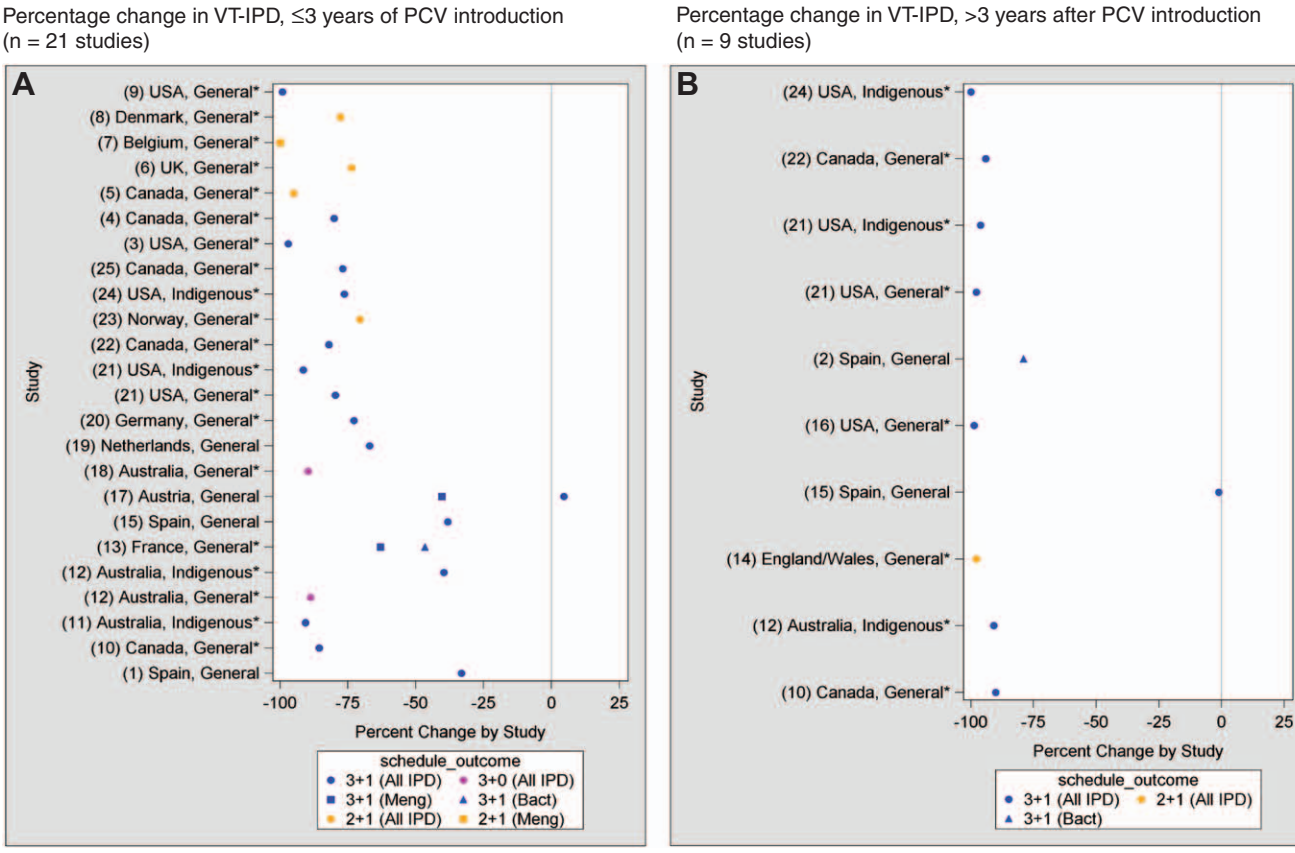

FIGURE 3. A, B) Percentage change in VT-IPD, meningitis and bacteremia among young children using 2+1, 3+0 and 3+1 schedules in the early and late postintroduction phase by country and group. (n = 25**). Reference number corresponds to Appendix. VT, vaccine type; IPD, invasive pneumococcal disease; general, general population; indigenous, indigenous population; Bact, bacteremia; Mening, meningitis. 2+1, 2 doses plus booster; 3+0, 3 doses without booster; 3+1, 3 doses plus booster of PCV or PPV23. *Vaccine introduction occurred with catch-up campaign. **Some studies did not report both early and late introduction changes in disease.

pronounced reductions were seen >3 years compared with ≤3 years post PCV introduction (Fig. 3A, B). Studies reporting percentage change in both pneumococcal bacteremia and meningitis all took place in countries using a 3+1 schedule and all demonstrated reductions in VT disease.

DISCUSSION

Our systematic review of the effect of different PCV dosing schedules on VT-IPD among young children demonstrates the effectiveness of PCV against VT-IPD (of all syndromes), VT-bacteremia and VT-meningitis, across diverse study methods, populations and dosing schedules. The study designs captured by this approach are highly varied and complement recent summary measures (ie, meta-analyses) which are limited to small numbers of studies of comparable designs.[6] In this way, our findings allow for a broader assessment of disease impact across different groups and time.

PCV7 was initially licensed with a 4-dose (3+1) schedule[46] and, not surprisingly, the vast majority of data on the impact of PCV on VT-IPD among young children identified in this review originate from established programs using 3+1 schedules. These studies showed that a 3+1 schedule reduced VT-IPD in a variety of settings and populations. Using schedules with fewer than 4 doses is of increasing interest to policy makers introducing PCV who aim to optimally reduce disease in both vaccinated children and unvaccinated contacts, but who also are working with limited budgets and crowded immunization schedules. No RCTs or observational studies included in this review evaluated the effects of a 2+0 schedule setting on VT-IPD; however, both 2+1 and 3+0 schedule settings have demonstrated impact in a variety of epidemiological contexts. A 3+0 PCV schedule has proven efficacy in 2 RCTs conducted in low-income settings[12,13] and demonstrated impact against VT-IPD among the general population of young children in Australia in 2 surveillance studies.[29,30] Effectiveness of a 2+1 dosing schedule has been shown effective against VT-IPD among partially vaccinated children in the United States where a 3+1 schedule is routinely used, and disease reductions were seen in several European countries and Quebec, Canada, where the national immunization program implemented a 2+1 schedule with a catch-up campaign. Since completion of our literature search, a cluster-randomized, double-blind clinical trial was published that directly compared a 2+1 schedule to a 3+1 schedule using a 10-valent protein D PCV (PCV10) in Finland.[15] In this study, vaccine effectiveness was 92% (95% CI: 58–100) with 2+1 doses and 100% (95% CI: 83–100%) with 3+1 doses, which is similar to estimates observed in clinical trials using 3+1 or 3+0 schedules in the United States, South Africa and The Gambia.[11–14] Additional population-based data emerging from South Africa, a country with high HIV prevalence, has demonstrated a significant reduction in VT-IPD among children <5 years old only 2 years following PCV introduction using a 2+1 schedule of PCV7 without catch-up.[47]

While differences in effectiveness may exist between 2+1 and 3+0 schedules, we found no studies that directly compared IPD outcomes from these schedules to each other. The 2 case-control studies that evaluated the effectiveness of both 2+1 and 3+0 doses of PCV, compared with no vaccine, were conducted in countries using 2+1 and 3+1 schedules with catch-up vaccination.[17,20] Both studies showed significant and similar reductions in VT-IPD among young children with either dosing schedule. Differences in impact between reduced dose schedules may be more significant in settings where PCV coverage is low and herd effects are not strong enough to allow for protection of unvaccinated individuals and high-risk groups. In addition, the sustainability of protection using reduced dose schedules has not yet been fully documented. Here, we observe reductions in VT-IPD using 3+1 and 3+PPV23 schedules up to 6 years after PCV introduction in the United States and Australia; however, further evaluation of 2+1 and 3+0 schedules is needed to determine whether they provide similar long-term protection.

One factor that may play a major role in differentiating between various reduced dose schedules is whether a booster dose confers added protection compared with a schedule without a booster dose. While this theory is supported by immunological and carriage data,[48,49] our search identified only 1 study that directly compared schedules to evaluate the benefit of a booster dose on VT-IPD outcomes.[17] This study found that a booster confers slightly higher protection against VT-IPD; however, other case-control and indirect cohort studies that compared various PCV dosing schedules against no vaccine all found similar point estimates of effectiveness for schedules with or without a booster.[16,18–21] All of these studies were conducted among the general population of young children. The 1 study that specifically evaluated the efficacy of PCV among HIV-infected children (an RCT in South Africa) suggested that a 3+0 schedule does not incur the same level of protection as in HIV-uninfected children.[12] In the absence of data to determine whether a PCV booster dose may benefit such high-risk populations, lessons may be learned from other protein-conjugate vaccines used in low-income settings with high HIV prevalence. In recent years, data from South Africa have demonstrated a small increase in invasive *Haemophilus influenzae* type b (Hib) incidence using a 3+0 schedule for Hib vaccine administered at 6, 10 and 14 weeks of age.[50] A similar but more marked phenomenon was observed in the United Kingdom using a 3+0 schedule for Hib at 2, 3 and 4 months of age.[51] In both countries, resurgence of Hib disease was controlled by the implementation of a booster dose. Although this phenomenon does not appear to be a common experience among other countries using Hib without a booster dose, there are few countries with sufficiently robust surveillance systems to identify such a resurgence should it occur. Whether lack of a PCV booster could result in a resurgence of VT-IPD disease in areas with high HIV prevalence or other risk factors for disease has yet to be seen.

Another important consideration for policy makers contemplating reduced dose schedules is whether a difference may exist between a 2-dose and 3-dose primary series. Minimal data exist on the benefits of a 2-dose primary series, and no studies directly compare 2 doses to 3 doses. The studies that have reported on IPD impact of a 2-dose primary series were all for partially vaccinated children in the setting of a national schedule using either 3 or 4 total doses.[16,17,19,20,52] Still, the ability for either 2 or 3 primary doses to provide some protection against VT-IPD is supported in the literature through several key studies. Three case-control and 3 indirect cohort studies in 4 different countries demonstrated a reduction in VT-IPD among young children who received either 2 or 3 primary doses compared with no vaccine.[16–20,52] Differences between the primary series were not discernible in these studies. Although not included in this systematic review, a difference between primary series was suggested in a descriptive report using IPD surveillance data over a period of 27 months from the Unites States. In this study, a greater number of invasive 6B breakthrough cases were seen among children who had received a 2-dose primary series compared with 3 doses.[53] This study was conducted in a country using a 3+1 schedule early after vaccine introduction and during a period of vaccine shortage, so therefore may not represent a true difference between a 2-dose primary series when compared with 3-dose primary series, especially for an established program; nevertheless its findings are consistent with immunological and carriage data that suggest a 3-dose primary series may provide better protection than 2 primary doses for some vaccine serotypes, in particular serotype 6B.[54–57] Ultimately, however, the number and schedule of doses to include in a primary series may depend on the setting. Using 3 doses in the primary series may be preferable to 2 doses to optimize protection of infants in the first year of life or where attaining high coverage for routine vaccinations given late in the first year of life or in the second year (ie, given with measles vaccine) is challenging or uncertain. In mature PCV programs (where VT carriage rates are low), the risk of disease experienced by children in the period before a booster dose may be sufficiently reduced such that the third priming dose is not a key element of a disease prevention strategy.

The studies captured by this review contribute to other systematic meta-analyses guiding policy decisions regarding PCV vaccine introduction.[6,58,59] While these reviews also suggest that 3-dose schedules may provide significant protection against VT-IPD in young children in high-income countries with established national immunization programs, the benefits of using different schedules may ultimately depend on the setting in which they are implemented. A 3-dose primary schedule may provide better protection in the first year of life when children are at highest risk of disease; however, a schedule with a booster dose (eg, 2+1) may provide enhanced long-term protection, in particular for serotype 1.[60] Our findings support decisions made by the Pan American Health Organization and World Health Organization to recommend 3-dose schedules (either 3+0 or 2+1) in countries with established programs, and the use of a 3-dose primary series in settings where vaccination coverage in the second year of life is low.[61,62] More studies are needed to fully evaluate expanded serotype PCV products (PCV10 and PCV13) and to assess whether 2+1, 3+0 and 3+1 schedules provide equal protection against pneumococcal serotypes that particularly affect children in the second year of life, especially in low-income countries and countries with a high burden of HIV.

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APPENDIX. Citations Included in a Systematic Review of the Effects of Pneumococcal Vaccine Dosing Schedules on VT-IPD Among Young Children, by Study Type, Outcome, Dosing Schedule and Country

Code	Citation(s)	Outcome	Age Group	PCV Schedule	Study Type	Country
Surveillance studies and case series reports						
1	Aristegui et al.[40]	IPD	<2 years	3+1	Surveillance	Spain
2	Benito-Fernandez et al. [44]	Bacteremia	3–36 months	3+1	Case series	Spain
3	Black et al. [32] Black et al. [33]	IPD	<2 years	3+1	Surveillance	United States
4	Bjornson et al. [63]	IPD	6–23 months	3+1	Surveillance	Canada
5	De Wals et al.[25]	IPD	<2 years	2+1	Surveillance	Canada
6	Foster et al. [23]	IPD	<2 years	2+1	Surveillance	United Kingdom
7	Hanquet et al. [28]	IPD, meningitis	<2 years	2+1	Surveillance	Belgium
8	Harboe et al. [26]	IPD	<2 years	2+1	Surveillance	Denmark
9	Kaplan et al. [39]	IPD	<2 years	3+1	Case series	United States
10	Kellner et al. [34]	IPD	<2 years	3+1	Surveillance	Canada
11	Krause et al. [31]	IPD	<2 years	3+PPV23	Surveillance	Australia
12	Lehmann et al. [30]	IPD	<2 years	3+0, 3+PPV23	Surveillance	Australia
13	Lepoutre et al. [45]	Meningitis, bacteremia	<2 years	3+1	Surveillance	France
14	Miller et al. [27]	IPD	<2 years	2+1	Surveillance	England/Wales
15	Munoz et al. [38]	IPD	<2 years	3+1	Surveillance	Spain
16	Reingold et al. 2008[35]	IPD	<2 years	3+1	Surveillance	United States
17	Rendi-Wagner et al. [22]	IPD, meningitis	<2 years	3+1	Surveillance	Austria
18	Roche et al. [29]	IPD	<2 years	3+0, 3+PPV23	Surveillance	Australia
19	Rodenburg et al. [41]	IPD	<2 years	3+1	Surveillance	Netherlands
20	Ruckinger et al. [21]	IPD	<2 years	3+1	Surveillance	Germany
21	Singleton et al. [36]	IPD	<2 years	3+1	Surveillance	United States
22	Tyrrell et al. [37]	IPD	<2 years	3+1	Surveillance	Canada
23	Vestrheim et al. [24]	IPD	<2 years	2+1	Surveillance	Norway
24	Weatherholtz et al. [43]	IPD	<2 years	3+1	Surveillance	United States
25	Winters et al.[42]	IPD	<2 years	3+1	Surveillance	Canada
Case-control and indirect cohort studies						
26	Barricarte et al. [18]	IPD	<5 years	3+1	Case-control	Spain
27	Deceuninck et al. [20]	IPD	2–59 months	2+1	Case-control	Canada
28	de Serres [19]	IPD	3–59 months	3+1	Indirect cohort	United States
29	Mahon et al. [16]	IPD	<5 years	3+1	Indirect cohort	United States
30	Ruckinger et al. [52]	IPD	3–59 months	3+1	Indirect cohort	Germany
31	Whitney et al. [17]	IPD	3–36 months	3+1	Case-control	United States
Clinical trials						
32	Black et al. [11]	IPD	2–15 months	3+1	Clinical trial	United States
33	Cutts et al.[13]	IPD	6–51 weeks	3+0	Clinical trial	The Gambia
34	Klugman et al. [12]	IPD	6–14 weeks	3+0	Clinical trial	South Africa
35	O'Brien et al. [14]	IPD	<2 years	3+1	Clinical trial	United States