

# Systematic Review of the Indirect Effect of Pneumococcal Conjugate Vaccine Dosing Schedules on Pneumococcal Disease and Colonization

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**Background:** To aid decision making for pneumococcal conjugate vaccine (PCV) use in infant national immunization programs, we summarized the indirect effects of PCV on clinical outcomes among nontargeted age groups.

**Methods:** We systematically reviewed the English literature on infant PCV dosing schedules published from 1994 to 2010 (with ad hoc addition of 2011 articles) for outcomes on children >5 years of age and adults including vaccine-type nasopharyngeal carriage (VT-NP), vaccine-type invasive pneumococcal disease (VT-IPD) and syndromic pneumonia.

**Results:** Of 12,980 citations reviewed, we identified 21 VT-IPD, 6 VT-NP and 9 pneumonia studies. Of these 36, 21 (58%) included 3 primary doses plus PCV or pneumococcal polysaccharide vaccine (PPV23) booster schedule (3+1 or 3+PPV23), 5 (14%) 3+0, 9 (25%) 2+1 and 1 (3%) 2+0. Most (95%) were PCV7 studies. Among observational VT-IPD studies, all schedules (2+1, 3+0 and 3+1) demonstrated reductions in incidence among young adult groups. Among syndromic pneumonia observational studies (2+1, 3+0 and 3+1), only 3+1 schedules showed significant indirect impact. Of 2 VT-NP controlled trials (3+0 and 3+1) and 3 VT-NP observational studies (2+1, 3+1 and 3+PPV23), 3+1 and 3+PPV23 schedules showed significant indirect effect. The 1 study to directly compare between schedules was a VT-NP study (2+0 vs. 2+1), which found no indirect effect on older siblings and parents of vaccinated children with either schedule.

**Conclusions:** Indirect benefit of a 3+1 infant PCV dosing schedule has been demonstrated for VT-IPD, VT-NP and syndromic pneumonia; 2+1 and 3+0 schedules have demonstrated indirect effect only for VT-IPD. The choice of optimal infant PCV schedule is limited by data paucity on indirect effects, especially a lack of head-to-head studies and studies of PCV10 and PCV13.

**Key Words:** pneumococcal conjugate vaccine, nasopharyngeal carriage, pneumonia, pneumococcal disease, indirect effects

(*Pediatr Infect Dis J* 2014;33:S161–S171)

Pneumococcal conjugate vaccines (PCV) have been available for use in infants for over a decade and have played an integral role in the prevention of disease caused by *Streptococcus pneumoniae* in children in higher income settings.<sup>1</sup> However, until recently, availability of PCV for children living in lower income countries has been limited. This situation is now changing. In 2011, 18 GAVI-eligible countries were approved to introduce PCV; an additional 19 have been approved.<sup>2</sup> As the feasibility of introducing PCV into childhood immunization programs has grown, the need to understand the number and the timing of doses, which will maximize both direct and indirect effects, has become a key question.

Much of the evidence regarding PCV impact has focused on young children targeted to receive vaccine using 2 primary doses plus a booster (2+1) or 3 primary doses with or without a booster (3+0 or 3+1).<sup>3–6</sup> Clinical trials and observational studies have demonstrated a significant direct impact of PCV on both vaccine-type invasive pneumococcal disease (VT-IPD) and pneumococcal and syndromic pneumonia among children <5 years of age.<sup>3,6</sup> Reductions in nasopharyngeal (NP) carriage of vaccine-type pneumococci (VT-NP), a necessary precursor to clinical disease, have also been demonstrated among young children receiving the vaccine.<sup>4</sup> Because pneumococci are transmitted through respiratory secretions, reductions in NP carriage of pneumococci are a key factor toward indirect effects of vaccine introduction and the establishment of “herd” protection. Through herd protection, infant immunization indirectly protects groups not targeted to receive the vaccine by reducing the circulation of vaccine-type bacteria. Prevention of disease among adults through herd protection has been shown to be an important benefit and a powerful driver of the cost effectiveness of a PCV program in high-income settings.<sup>7</sup> Whether different PCV dosing schedules may translate into noticeable differences in herd effects is unknown. Here, we present a systematic review of the literature summarizing the evidence on the indirect effects of PCV dosing schedules on VT-IPD, VT-NP-carriage and syndromic pneumonia among groups not targeted to receive the vaccine.

## 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.<sup>3–6</sup> Details on the literature search terms and methods used in this systematic review are described elsewhere (see Methods Appendix<sup>8</sup>). In brief, a systematic literature

Accepted for publication August 13, 2013.

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Support for this project was provided by Program for Appropriate Technology in Health (PATH) through funding from the Global Alliance for Vaccines and Immunisation (GAVI). The views expressed by the authors do not necessarily reflect the views of GAVI and/or PATH. M.D.K. has received support from Novartis for participation on a Data and Safety Monitoring Board, meeting travel reimbursement from Pfizer and grant support from Merck. D.G.'s laboratory performs contract and/or collaborative research for/with Pfizer, GlaxoSmithKline, Merck, Novartis and Sanofi Pasteur. D.G. has received travel or honorarium support for participation in external expert committees for Merck, Sanofi Pasteur, Pfizer and GlaxoSmithKline. K.O.B. received grant support from Pfizer, GlaxoSmithKline and has received travel or honorarium support for participation in external expert committees for Merck, Aventis-pasteur and GlaxoSmithKline. The authors have no other funding or conflicts of interest to declare.

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ISSN: 0891-3668/14/3301-S161

DOI: 10.1097/INF.0000000000000084

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, NP colonization, invasive pneumococcal disease, 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 1 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 the relevant data for this project. Details on the search methods are provided in the Methods Appendix.<sup>8</sup>

### Data Abstraction

Citations recovered through the literature search went through several stages of independent review to determine their eligibility, as described elsewhere.<sup>8</sup> 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 the 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. To assess indirect effects, we abstracted additional data from studies of the effects of PCV in unimmunized populations on VT-IPD, VT-NP carriage and syndromic pneumonia and included information on study design, case definitions and trends in the outcome of interest.

### Inclusion and Exclusion Criteria

We included the data published during or after 1994 from clinical trials, surveillance database analyses and observational studies of PCV schedules on VT-IPD, VT-NP carriage and syndromic pneumonia. 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 the observational studies that only reported data before or after PCV introduction but not for both periods. Unless  $\geq 50\%$  vaccination coverage was documented, the observational studies were also excluded if vaccination was only available through a private sector or only recommended for high-risk groups. Studies that only provided incidence rates during the year of vaccine introduction, or did not specify a time period, were excluded.

For IPD, we focused the analysis on the indirect effects among adults by including studies that reported data on specific age groups between 18 and 64 years (eg, 18–35 and 36–64 years), and those that were inclusive of age groups  $\geq 65$  or <18 years

(eg, the “general population”). Studies that only reported data on age groups <18 or  $\geq 65$  years were excluded.

### Pneumococcal Vaccine Dosing Schedules

We included PCV schedules with 2 or 3 primary doses without a booster dose (2+0 and 3+0) and with a booster dose (2+1 and 3+1). Schedules with either PCV or PPV23 boosters were included (2+PPV23 and 3+PPV23).

### Data Analysis

Because the included studies used a variety of designs and methods, we were unable to perform a formal meta-analysis. Thus, we summarized the data across studies in descriptive analyses to provide an overview of the amount and variability of data by outcome and schedule. For VT-NP carriage, each study was divided into arms, defined as a unique combination of vaccine schedule, age at NP specimen collection and vaccine product used. Studies could have multiple arms. Vaccine-type pneumococci were defined as each study defined them, based on the product used. For carriage, no studies included serotype 19A in VT and 1 included serotype 6A in VT.<sup>9</sup> For IPD, no studies included serotypes 19A or 6A in VT. We defined VT-NP carriage prevalence as the percentage of those sampled who carried VT pneumococci, except in 2 studies that only reported the percentage of pneumococcal isolates found that were VT.<sup>9,10</sup> The syndromic pneumonia endpoint included clinical pneumonia, radiologically confirmed pneumonia and pneumococcal (eg, bacteremic) pneumonia.

For observational studies reporting VT-IPD incidence over time, we calculated percent reduction by defining baseline incidence as the mean of all data points reported prior to introduction. When annual data on post introduction incidence were available, we calculated percent reduction from baseline using the data point given for each year reported. In cases where only the average post introduction incidence rate over a period was provided, we calculated percent 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. Percent reduction reported by the study was only used if no incidence rates were provided. Therefore, the percent reduction over time presented in this review may not always be identical to that reported by the study.

We used Microsoft Access 2003 and 2007 (Microsoft Corporation, Redmond, WA) for data abstraction and SAS 9.2 and 9.3 (SAS Institute Inc., Cary, NC) to perform all analyses.

## RESULTS

Of 12,980 citations reviewed, 36 studies (38 citations) met inclusion criteria for PCV indirect effects; of these, 21 were VT-IPD studies,<sup>11–31</sup> 9 were pneumonia syndrome studies<sup>11,32–39</sup> and 6 were VT-NP carriage studies<sup>9,10,40–45</sup> (Fig. 1). Among the 36 studies, all were published in 2003 or later, and 28 (78%) were from Europe or North America (Table 1). Almost all (95%) studies evaluated PCV7; none evaluated PCV10 or PCV13.

### Nasopharyngeal Carriage

This review identified 6 studies that evaluated the indirect impact of PCV on VT-NP carriage. All but 1 study were from North America, Europe or Australia. Five studies (83%) evaluated PCV7, including one with a PPV23 booster dose; 1 study (17%) evaluated PCV9. Three studies (50%) evaluated the impact of PCV on VT-NP carriage in indigenous populations.

Two studies (3 citations) among nonhigh-risk populations evaluated the indirect effects of either a 2+0 or 2+1 schedule (Table 2) on VT-NP carriage.<sup>41,44,45</sup> One individual RCT in the Netherlands found no VT-NP carriage indirect effect of PCV7 given in 2+0 and 2+1 dosing schedules among parents and siblings

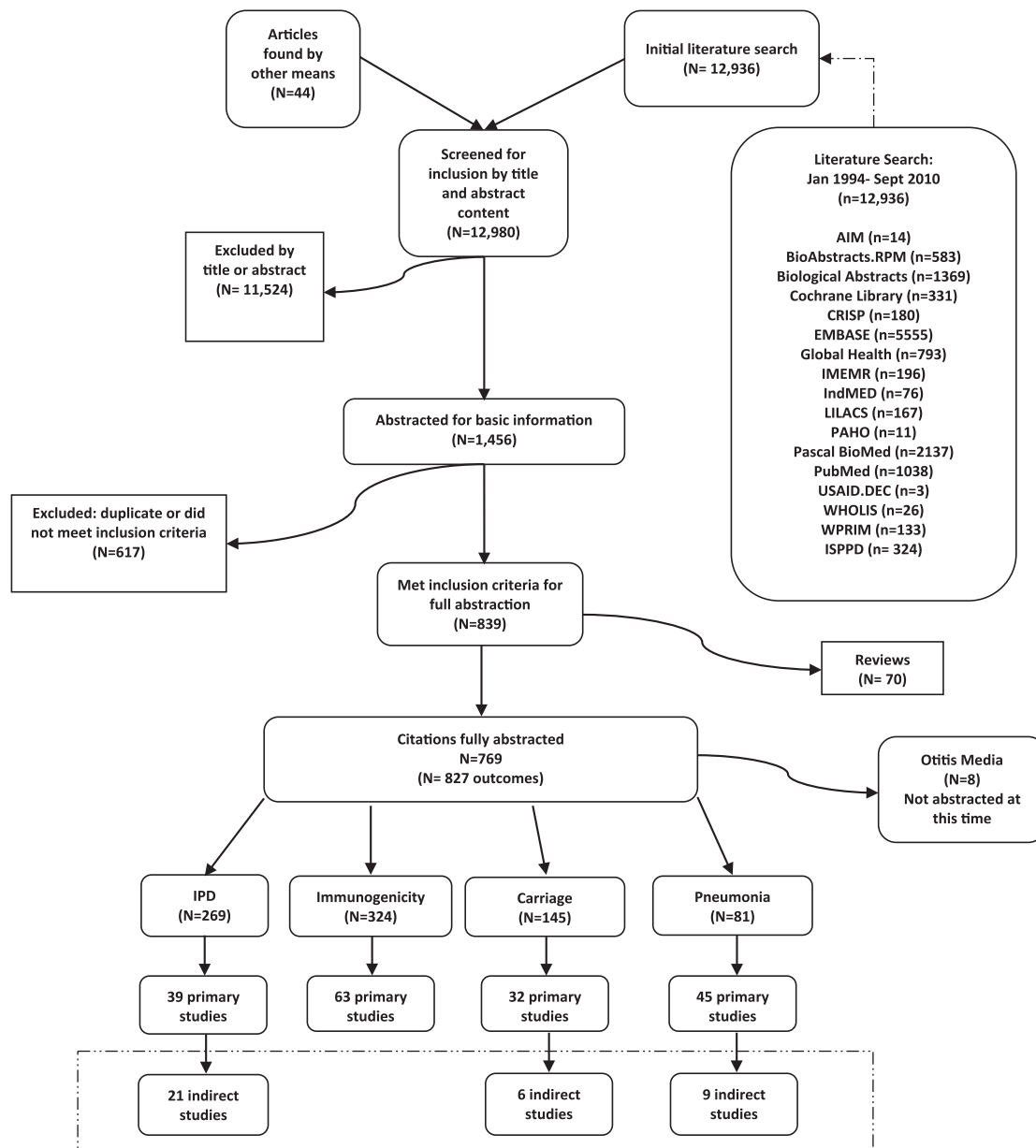


FIGURE 1. Flow chart of included citations.

of vaccinated and unvaccinated children.<sup>44,45</sup> One pre/postvaccine introduction observational study in the United Kingdom using a 2+1 schedule with catch-up through 2 years of age found a nonsignificant reduction in VT-NP carriage 2–3 years after PCV7 introduction among children and adults  $\geq 5$  years of age (Table 2).<sup>41</sup> There were no studies that evaluated 2+0 or 2+1 schedules in high-risk populations, such as indigenous and immunocompromised populations.

One study evaluated a 3+0 (Table 2) schedule on VT-NP carriage. This individual RCT found no effect on VT-NP carriage among unvaccinated younger siblings of children vaccinated with PCV9 or placebo in The Gambia.<sup>40</sup> There was 1 RCT and 2 observational studies that evaluated a 3+1 or 3+PPV23 schedule in high-risk populations; no studies evaluated a 3+0 schedule in high-risk populations (Table 2). The observational carriage study in Australia among Aboriginals with 3+PPV23 found a significant indirect reduction of VT-carriage among older children, but no difference

among adults.<sup>10</sup> A cluster-randomized, placebo-controlled trial evaluated VT-carriage indirect effects among the Navajo Nation and White Mountain Apache people.<sup>9,43</sup> During the trial, VT-carriage was reduced among household contacts (older and younger siblings) of PCV7 vaccinees, but reached statistical significance only for day-care-attending contacts.<sup>9</sup> However, at 3–15 months after completion of the trial, significant reductions were seen in VT-carriage among unvaccinated children  $< 5$  years of age and adults living in communities randomized to PCV7 compared with placebo.<sup>43</sup> Another observational study demonstrated a highly significant trend in reduction of VT-carriage prevalence among Alaskan Native adults in the 4 years following the introduction of PCV7 with a 3+1 schedule.<sup>42</sup>

### Invasive Pneumococcal Disease

We identified 21 studies documenting the impact of PCV introduction on incidence of VT-IPD among adult age groups,

**TABLE 1.** Summary of Characteristics from Included Studies

Variable	Number of Primary Studies		
	Carriage (n = 6)	IPD (n = 21)	Pneumonia (n = 9)
Study publication date			
1994–1998	0	0	0
1999–2002	0	0	0
2003–2006	2 (33%)	0	1 (11%)
2007–present	4 (67%)	21 (100%)	8 (89%)
Dosing schedule*			
2+0	1 (17%)	0	0
2+1	2 (33%)	6 (29%)	1 (11%)
3+0	1 (17%)	2 (10%)	2 (22%)
3+1†	3 (50%)	14 (67%)	6 (67%)
United Nations Region			
Africa	1 (17%)	0	1 (11%)
Asia	0	0	1 (11%)
Oceania	1 (17%)	3 (14%)	1 (11%)
Europe	2 (33%)	9 (43%)	2 (22%)
Latin America/Caribbean	0	0	0
North America	2 (33%)	9 (43%)	4 (44%)
Population			
General	3 (50%)	17 (81%)	9 (100%)
Indigenous	3 (50%)	4 (19%)	0
HIV-infected	0	2 (10%)	0

\*When not stated in the manuscript, dosing schedule was assigned according to national immunization program recommendations.

†3 + 1 schedule includes 3 primary doses plus a PCV or PPV23 booster dose.

**TABLE 2.** Summary of Vaccine-Type Nasopharyngeal Carriage Studies Evaluating Indirect Effects

Country	Reference	Study Design	Product	Dosing Schedule for PCV	Indirect Groups Evaluated	Detailed Findings
<b>2+0 schedules</b>						
Netherlands	Van Gils et al. <sup>44</sup>	Individual RCT compared to no vaccine	PCV7 (Wyeth)	2 and 4 months	Parents of vaccinated and control children	At vaccinated or control child's age 12 months: VT carriage: 8% in vaccine vs. 10% in control groups RR (95% CI) 0.86 (0.52–1.42) At vaccinated or control child's age 24 months: VT carriage: 5% in vaccine vs. 8% in control groups RR (95% CI) 0.61 (0.33–1.12)
	Van Gils et al. <sup>45</sup>	Individual RCT compared to no vaccine	PCV7 (Wyeth)	2 and 4 months	Siblings of vaccinated and control children	At vaccinated or control child's age 12 months: VT carriage: 24% in vaccine vs. 29% in control groups, not significant
<b>2+1 schedules</b>						
Netherlands	Van Gils et al. <sup>44</sup>	Individual RCT compared to no vaccine	PCV7 (Wyeth)	2, 4 and 11 months	Parents of vaccinated and control children	VT-carriage prevalence At vaccinated or control child's age 12 months: 9% in vaccine vs. 10% in control groups Relative Risk (95% CI) 0.93 (0.57–1.52) At vaccinated or control child's age 24 months: 6% in vaccine vs. 8% in control groups Relative Risk (95% CI) 0.66 (0.37–1.19)
	Van Gils et al. <sup>45</sup>	Individual RCT compared to no vaccine	PCV7 (Wyeth)	2, 4 and 11 months	Siblings of vaccinated and control children	VT-carriage prevalence At vaccinated or control child's age 12 months: 25% in vaccine vs. 29% in control groups, not significant
United Kingdom	Flasche et al. <sup>41</sup>	Pre/postvaccine introduction observational study	PCV7 (Wyeth)	2, 4 and 13 months with catch-up to 2 years of age	Family members of children <5 years at primary care clinics: 5–20 year olds >20 year olds	Vaccine introduction: September 2006 VT carriage prevalence Among 5–20 year olds: 2001/2: 9.9% (7.3–13.3%) 2008/9: 0% (0–6.4%) Among >20 year olds: 2001/2: 4.1% (3.0–5.5%) 2008/9: 2.3% (0–5.3%) VT carriage reduction not significant in ≥5 year olds, not broken down between 5–20 and >20 year olds

(Continued)

**TABLE 2.** Continued

Country	Reference	Study Design	Product	Dosing Schedule for PCV	Indirect Groups Evaluated	Detailed Findings
<b>3+0 schedules</b>						
The Gambia	Cheung et al. <sup>40</sup>	Individually randomized, placebo-controlled clinical trial	PCV9 (Wyeth)	3 doses starting at 6–51 weeks (median age at doses: 75, 122 and 169 days)	Cross-section of younger siblings of children who received PCV9 or placebo	VT carriage prevalence: At younger siblings average age of 3 months: 35.3% PCV9 vs. 37.1% placebo Risk Ratio (95% CI): 0.95 (0.78–1.16)
<b>3+1 schedules</b>						
United States	O'Brien et al. <sup>9</sup>	Cluster-randomized, placebo-controlled trial	PCV7 (Wyeth)	2, 4, 6 and 12–15 months	Navajo Nation and White Mountain Apache children and infants who were household contacts of vaccine or placebo-recipients	Percent of pneumococcal isolates that were VT+6A Among household children At vaccinee's age of 7 months: 40.5% PCV7 vs. 45.3% placebo Odds ratio (95% CI): 0.94 (0.66–1.34) Odds ratio (95% CI) for those in daycare: 0.30 (0.12–0.71) Odds ratio (95% CI) for those not in daycare: 1.78 (1.43–2.22)  At vaccinee's age of 12 months: 41.4% PCV7 vs. 40% placebo Odds ratio (95% CI): 1.63 (0.85–3.14) Odds ratio (95% CI) for those in daycare: 0.46 (0.13–1.62) Odds ratio (95% CI) for those not in daycare: 1.79 (0.99–3.24)  At vaccinee's age of 15 months: 39.0% PCV7 vs. 50.0% placebo Odds ratio (95% CI): 1.06 (0.84–1.34) Odds ratio (95% CI) for those in daycare: 0.25 (0.15–0.43) Odds ratio (95% CI) for those not in daycare: 1.31 (1.04–1.65)  Among household infants: 33.6% PCV7 vs. 47.8% placebo Odds ratio (95% CI): 0.48 (0.32–1.05) Odds ratio (95% CI) for those in household with PCV7-vaccinated member: 0.47 (0.21–1.05) Odds ratio (95% CI) for those in household without a PCV7-vaccinated member: 0.58 (0.32–1.01)
	Millar et al. <sup>43</sup>	Cluster-randomized, placebo-controlled trial	PCV7 (Wyeth)	2, 4, 6 and 12–15 months	Navajo Nation and White Mountain Apache, unvaccinated children and adults who were household contacts of vaccine or placebo-recipients; 3–15 months after completion of the trial	VT carriage prevalence Among unvaccinated children <5 years: 12.0% PCV7 vs. 19% placebo Odds ratio (95% CI) 0.57 (0.26–0.98) Among unvaccinated children 5–17 years: 7.5% PCV7 vs. 8.0% placebo Odds ratio (95% CI) 0.84 (0.56–1.29) Among unvaccinated adults ≥18 years: 2.4% PCV7 vs. 4.1% placebo Odds ratio (95% CI) 0.57 (0.33–0.99)
United States	Hammit et al. <sup>42</sup>	Pre/postvaccine introduction observational study	PCV7 (Wyeth)	2, 4, 6 and 12–15 months	Alaskan Native adults (≥18 years)	Vaccine introduction: January 2001 VT carriage prevalence 1998–2000: 28.4% 2001: 17.7% 2002: 13.5% 2003: 5.8% 2004: 4.5% P < 0.0001
<b>3+PPV23 schedules</b>						
Australia	Mackenzie et al. <sup>10</sup>	Pre/postvaccine introduction observational study	PCV7 (Wyeth)	2, 4, 6 and 18 months	Aboriginal adults and older children in the Northern Territory	Vaccine introduction: late 2001 Percent of pneumococcal isolates that were VT Among adults: 1996–1997 and 1999–2001: 25% 2002/4: 23.4% Odds ratio (95%) 0.92 (0.45–1.90) Among older children: 2000/1: 35.7% 2002/4: 21.1% Odds ratio (95%) 0.48 (0.28–0.82)

including 4 studies that specifically reported data on VT-meningitis (Table 3). All these studies were observational studies using either population-based surveillance or sentinel site data. No clinical trials of indirect effects among adults were identified in the published literature; we are aware of 1 such unpublished trial result that showed no effect in any age group (author data).<sup>46</sup> Six studies provided data on a high-risk population, either indigenous (n = 4; 19.0%) or HIV-infected (n = 2, 9.5%) persons. The definition of adult age group varied across studies; however, 4 (19.0%) reported data from the total population, including children <18 and adults ≥65 years of age.

Many studies reporting indirect effects of PCV on VT-IPD occurred in the setting of a 3+1 national immunization program (n = 12; 61.9%). Six studies (12.9%), conducted in the United Kingdom, Scotland, Italy, Denmark and Norway, occurred in a 2+1 setting. Three studies, all conducted in Australia, used a 3+PPV23 (among indigenous groups) and/or 3+0 (among nonindigenous groups) dosing schedule.<sup>23,26</sup> No studies used a 2+0 schedule and no direct comparisons among dosing schedules were identified.

Nearly all studies (n = 20; 95.2%) demonstrated a reduction in VT-IPD among at least 1 adult age group, regardless of dosing

schedule (2+1, 3+0, 3+PPV23 and 3+1). The degree of impact varied by a specific age group, the outcome measured and the number of years post introduction (Fig. 2). Reductions in VT-IPD were observed as early as 1 year after introduction. In general, reductions for all schedules were larger ≥3 years after introduction compared with reductions seen within 3 years of introduction (Fig. 3A, B).

Of the 12 studies, 9 (75.0%) using a 3+1 or 3+PPV23 schedule took place in countries where catch-up campaigns were implemented during national introduction. Reductions in VT-IPD among healthy adult groups in countries using 3+1 schedules ranged from 13% in Spain, 6 years after PCV introduction, to 92% in the United States, 7 years after introduction.<sup>11,25</sup> Vaccine-type meningitis was reduced by 73% among the general population in Canada and by 67% among adults ages 18–39 years in the United States, both within 5 years after PCV introduction.<sup>12,19</sup> One study conducted in the United States demonstrated a 67% reduction in VT-IPD among Alaskan Natives ages 18–44 years, also within 5 years after introduction.

Two studies identified in this review did not show a reduction in VT-IPD among a reported adult group using a 3+1 schedule.

**TABLE 3.** Summary of IPD Studies Evaluating Indirect Effects of 2+0, 2+1, 3+0, 3+1 and 3+PPV23 Schedules

Country	Author	Endpoints Evaluated	Indirect Groups Evaluated	Age Group (Years)	Number of Baseline Years Reported	Baseline Value (per 100,000 Unless Otherwise Noted)	Maximum Number of Years Reported After Introduction	Percent Change in VT-IPD
<b>2+1 schedule</b>								
United Kingdom	Miller et al. <sup>24</sup>	VT-IPD	General	15–44	7	3.30	4	-88
				45–64	7	7.70	4	-86
United Kingdom	Foster <sup>16</sup>	VT-meningitis	General	5–64	7	0.10	4	-70
				≥2	10	4.25	1	-22
Norway	Vestheim et al. <sup>30</sup>	VT-IPD	General	20–39	2	3.93	2	-22
				40–64	2	12.19	2	-60
Scotland	Flasche et al. <sup>15</sup>	VT-IPD	General	5–64	NS	NS	3	-53R
Denmark	Lambertsen et al. <sup>22</sup>	VT-IPD	General	5–65	NS	621 (CS)	2	-74
Italy*†	Del Grosso et al. <sup>14</sup>	VT-IPD	General	Gen Pop	3	227 (CS)	4	-15
<b>3+0 schedule</b>								
Australia	Lehmann et al. <sup>23</sup>	VT-IPD	General	15–29	8	1.85	2	-62
				30–49	8	2.30	2	-43
				50–64	8	4.35	2	-36
Australia	Roche et al. <sup>26</sup>	VT-IPD	General	15–49	3	2.30	1	-35
				50–64	3	5.10	1	-35
<b>3+PPV23</b>								
Australia	Lehmann et al. <sup>23</sup>	VT-IPD	Indigenous	15–29	5	4.7	6	6
				30–49	5	15.80	6	-54
				50–64	5	18.9	6	-43
Australia	Hanna et al. <sup>18</sup>	VT-IPD	Indigenous	≥15	3	16.00	6	-75
<b>3+1 schedule</b>								
Canada	Tyrrell et al. <sup>29</sup>	VT-IPD	General	Gen Pop	2	7.55	4	-67
Canada	Kellner et al. <sup>21</sup>	VT-IPD	General	16–64	4	3.60	5	-39
Canada	Bettinger et al. <sup>12</sup>	VT-Meningitis	General	Gen Pop	2	75(CS)	5	-73
United States	Cohen et al. <sup>13</sup>	VT-IPD	HIV+	18–64	2	681(α)	7	-91
United States	Weatherholtz et al. <sup>31</sup>	VT-IPD	Indigenous	18 to <40	6	5.50	6	-64
				40 to <65	6	16.5	6	-58
United States	Singleton et al. <sup>28</sup>	VT-IPD	General	18–44	6	4.10	5	-80
				Indigenous	18–44	6	6.00	5
United States	Moore et al. <sup>25</sup>	VT-IPD	General	18–49	2	7.60	8	-92
United States	Jacobs et al. <sup>20</sup>	VT-IPD	General	Gen Pop	1	131 (CS)	7	-92
United States	Hsu et al. <sup>19</sup>	VT-meningitis	General	18–39	2	0.30	5	-67
				40–64	2	0.62	5	-61
Spain*†	Ardanuy et al. <sup>11</sup>	VT-IPD	General	18–64	5	3.10	6	-13
				VT-meningitis	General	Adults	5	0.37
Spain*†	Grau et al. <sup>17</sup>	VT-IPD	HIV+	Adults	16	55 (CS)	6	-67
Netherlands*	Rodenburg et al. <sup>27</sup>	VT-IPD	General	5–49	3	1.40	2	0

\* Country did not have catch-up campaign.

† PCV was not part of national program; however, >50% coverage was reported.

CS, case series study; R, data were not available to calculate percent reduction; numbers here reflect those reported by the study; α, number given is the ratio of cases of IPD among HIV-infected persons per 100,000 persons 18–64 years of age living with AIDS; Genpop, general population; NS, not stated.

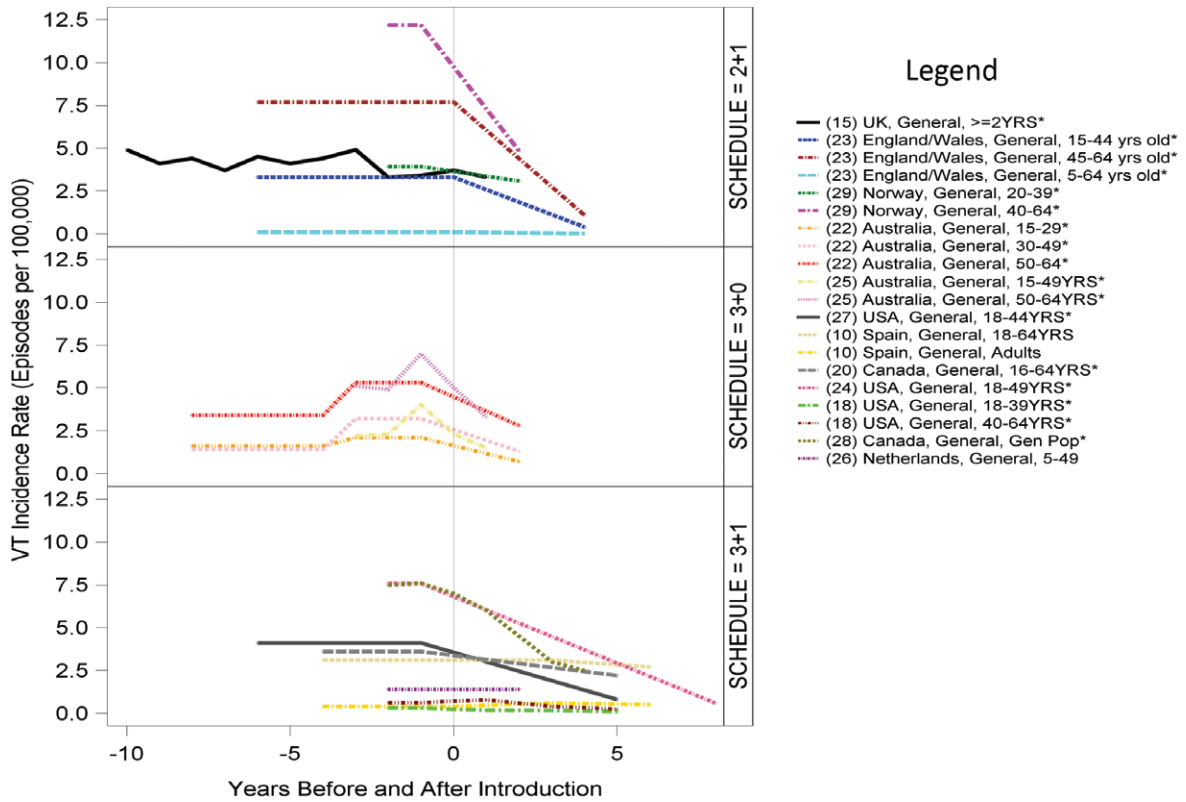


FIGURE 2. Incidence of vaccine-type IPD among adults before and after PCV introduction, by dosing schedule.

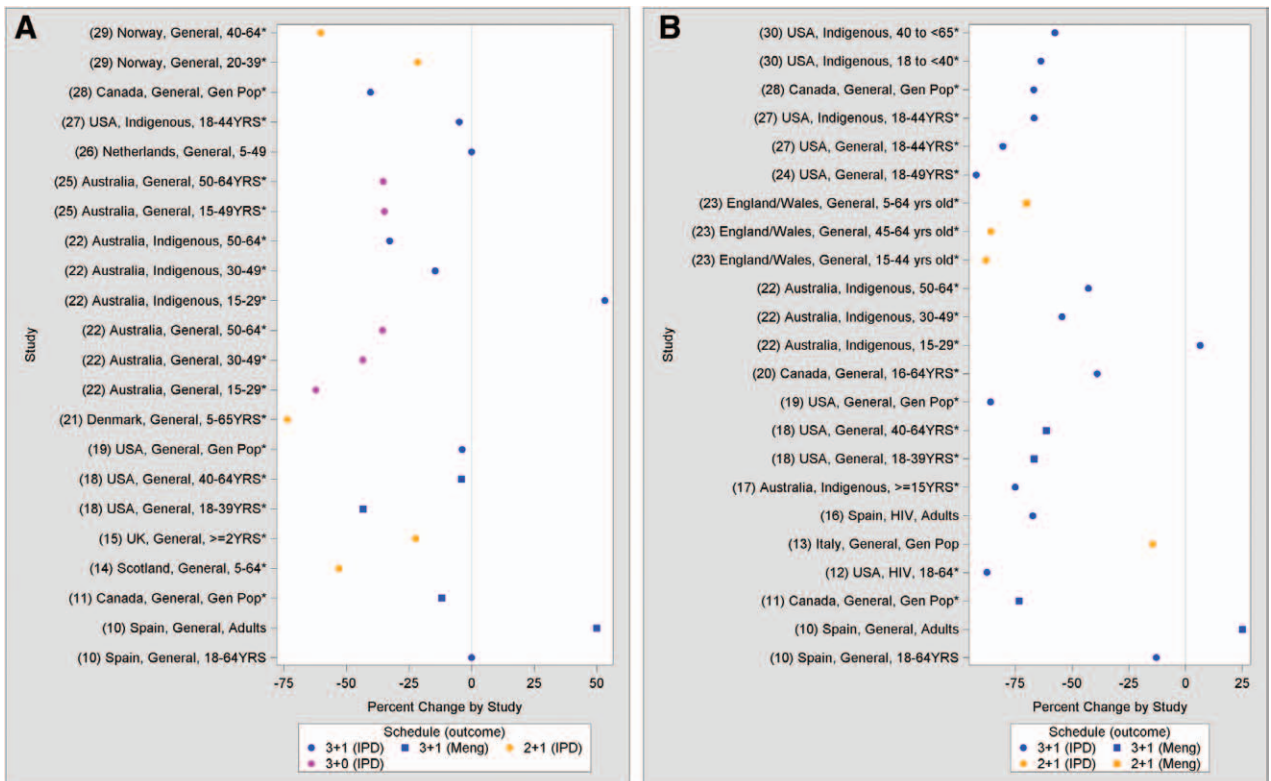


FIGURE 3. A, Percent change in vaccine-type IPD ≤3 years of PCV introduction (n=13 studies). B, Percent change in vaccine-type IPD >3 years of PCV introduction (n=15 studies).

In Spain, a 25% increase in VT-meningitis was observed among all adults, which was accompanied by a 13% reduction in VT-IPD among adults ages 18–64 years.<sup>11</sup> Factors cited as possibly contributing to this finding included a low PCV coverage (50% within 6 years after introduction for high-risk groups) and an increase in in-migration to the area that could have impacted the indirect effects of vaccine introduction. In the Netherlands, no change (0%) in VT-IPD was observed among 5–49 year olds 2 years following introduction.<sup>27</sup> Authors attributed the apparent absence of herd immunity despite high vaccine uptake among children (94%) to the lack of a catch-up campaign and short evaluation period.

We identified 2 studies reporting indirect effects of PCV on VT-IPD among adults with HIV. Both studies took place in settings using a 3+1 schedule. In the United States, Cohen et al. reported a 91% reduction in the incidence of VT-IPD among HIV-infected persons, from 681 per 100,000 persons 18–64 years of age living with AIDS in 1998/1999 to 64 per 100,000 persons in 2007. In Spain, Grau et al. reported a 67% reduction in VT-IPD among 4011

HIV-infected adults receiving care at a teaching hospital in Barcelona 6 years after vaccine introduction.

Of the 5 countries reporting data on the indirect effects of PCV on adult groups using a 2+1 schedule, all except Italy implemented some type of catch-up campaign among young children. Reported indirect effects on VT-IPD with a 2+1 schedule ranged from 15% among the general population in Italy to 88% among 15–44 year olds in England and Wales.<sup>14,24</sup> A 70% reduction in VT-meningitis was also observed among adults 5–64 years of age in England and Wales within 4 years after vaccine introduction.<sup>24</sup>

The 3 studies using either a 3+0 or a 3+PPV23 schedule all took place in Australia, where catch-up campaigns were conducted for both indigenous and nonindigenous children.<sup>23,26</sup> These studies demonstrated similar reductions in VT-IPD among indigenous (range 43–75%) and nonindigenous adults (range 35–62%) over 15 years of age, although 1 study demonstrated a 6% increase in VT-IPD among indigenous adults 15–29 years of age. In this study,

**TABLE 4.** Summary of Syndromic Pneumonia Studies Evaluating Indirect Effects of 2 + 1, 3 + 0 and 3 + 1 Schedules

Country	Reference	Study Design	Dosing Schedule for PCV7 (Wyeth)*	Endpoints Evaluated	Indirect Groups Evaluated (Years)	Detailed Findings	Findings
<b>2 + 1 schedules</b>							
Poland	Patzalek et al. <sup>38</sup>	Sentinel	3, 5 and 12 months	CXR pneumonia, all-cause hospitalizations	30–49 50–64 ≥65	No evidence to prove that PCV7 introduction decreased incidence in age groups over 4 years; risk of pneumonia in unvaccinated remained unchanged	↔
<b>3 + 0 schedules</b>							
Australia	Jardine et al. <sup>34</sup>	Population-based	2, 4 and 6 months	Clinical pneumonia, pneumococcal pneumonia	5–17 18–39 40–64	3–11% reduction (borderline significant) observed in age groups >4 years	✓
<b>3 + 1 schedules</b>							
Spain	Ardunuy et al. <sup>11</sup>	Sentinel	2, 4, 6 and 12–15 months	Pneumococcal pneumonia	Adults	39% increase (significant), although 27% reduction in PCV7 types. 81% increase in non-PCV7 types	↑
Taiwan	Lin et al. <sup>35</sup>	Passive, sentinel	3 + 1	Clinical pneumonia, all-cause mortality	5–64 ≥65	No significant reduction in 5–64; significant reduction in 65+ (64.1%); however, greater use of PPV23	✓
United States	Grijalva et al. <sup>33</sup>	Sentinel	2, 4, 6 and 12–15 months	Clinical pneumonia, pneumococcal pneumonia, empyema	18–39	26% reduction in clinical pneumonia in 18–39 years of age; rates declined in older groups but not significant 30% reduction in pneumococcal pneumonia	↓
United States	Nelson et al. <sup>37</sup>	Cohort study	2, 4, 6 and 12–15 months	Clinical pneumonia, CXR pneumonia	18–49 living with children	No reductions seen; >18 year age group had increased rates after PCV intro	↔
United States	Simonsen et al. <sup>39</sup>	Population-based	2, 4, 6 and 12–15 months	Pneumococcal pneumonia	5–17 18–39 40–64 ≥65	Significant reductions in all-cause pneumonia hospitalizations (5–17 and 18–39 years); 90–95% modeled reductions in pneumococcal pneumonia due to >18 year age group	↓

\*No studies with other PCV product met inclusion criteria.



**TABLE 5.** Summary of Syndromic Pneumonia Case–Control Studies Evaluating Indirect Effects of 3+0 and 3+1 Schedules

Case-control studies								
Country	Reference	Study Design	Vaccine Product (Manufacturer)	Dosing Schedule for PCV	n of Population	Population	Endpoint	Odds Ratio (95% CI)
South Africa	Albrich et al. <sup>32</sup>	Substudy of PCV9 clinical trial	PCV9 (Wyeth)	6, 10 and 14 weeks	255	Adults	All cause pneumonia	1.07 (0.79–1.45) (Crude)
							Pneumococcal pneumonia	1.00 (0.39–2.59) (Crude)
United States	Metlay et al. <sup>36</sup>	Risk factor analysis	PCV7 (Wyeth)	2, 4, 6, 12–15 months	842	Adults	Bacteremic pneumococcal pneumonia	0.2 (0.1–0.8) (Adjusted)

other indigenous adults 30–49 and 50–64 years of age experienced reductions of 54% and 43%, respectively.<sup>23</sup>

### Pneumonia

Nine observational studies in this review evaluated the impact of PCV dosing schedules on clinical or radiologically confirmed pneumonia in older children or adults (Table 4). Most studies (n = 7, 78%) were conducted in Europe, North America or Australia; the remaining 2 studies were from South Africa<sup>32</sup> and Taiwan.<sup>35</sup> There were no studies that evaluated indirect pneumonia effects on high-risk populations. Additionally, no studies directly compared various dosing schedules on indirect populations and no RCTs have evaluated the impact of PCV on pneumonia in unvaccinated populations.

Of the observational studies, 2 studies using 2+1<sup>38</sup> and 3+0<sup>34</sup> schedules showed almost no impact on clinical or radiologically confirmed pneumonia (Table 4). Of 5 studies using a 3+1 schedule,<sup>11,33,35,37,39</sup> 3 showed any impact on pneumonia (Table 4). The study conducted in Taiwan<sup>35</sup> found significant reductions in pneumonia only in adults ≥65 years of age, although the authors noted an increase in use of PPV23 among this population during the study period.

This analysis also found 2 case-control studies evaluating PCV impact on pneumonia in unvaccinated populations (Table 5). One study, conducted in South Africa, evaluated the impact of a 3+0 schedule on adults residing with children enrolled in an RCT for PCV9.<sup>32</sup> This study found no impact against pneumonia in adults during the clinical trial. The authors noted possible reasons for a lack of impact, including a large burden of HIV among adults in South Africa, timing of doses given in the infant schedule, the lack of a booster dose and <20% coverage in <5 year olds in the community during the trial. Another case-control study conducted in the United States after implementation of PCV7 into the national immunization program showed an 80% reduction in the odds of getting bacteremic pneumococcal pneumonia in adults that resided with a vaccinated child.<sup>36</sup>

### DISCUSSION

Our review identified a substantial body of research evaluating whether PCV use in young children leads to indirect effects in other age groups, although there are more data supporting some schedules than others. Most of the data were from studies evaluating 2 or 3 primary dose schedules with a booster dose (2+1, 3+1 or 3+PPV23), and among these, studies evaluating a 3+1 dosing schedule were most common. While studies have evaluated pneumonia, VT-NP carriage and VT-IPD, the demonstration of indirect effects was most consistent across studies and for all schedules for VT-IPD.

Because the first countries to introduce PCV used a 3+1 schedule, most of the available literature on indirect effects is for that schedule. The weight of evidence suggests that the use of a 3+1

schedule as part of a routine vaccination program for all infants will result in reduction of carriage and disease in age groups not targeted to receive PCV. Of 12 studies that we identified evaluating the 3+1 schedule for VT-IPD, only 2 showed no evidence of reductions in VT-IPD in unimmunized age groups; both took place in countries without catch-up campaigns and vaccine coverage in the population may have been insufficient to demonstrate indirect effects.<sup>11,27</sup> VT-NP carriage studies have also shown indirect effects with 3+1 schedules. The impact on VT-NP carriage was observed in high-risk populations; no NP carriage studies with indirect effects were conducted in general populations. Studies of syndromic pneumonia only showed an impact with 3+1 schedules. Among 6 studies evaluating the 3+1 schedule, only 2, from Spain<sup>11</sup> and the United States,<sup>37</sup> observed increases in overall trends of pneumonia (pneumococcal, clinical and radiologically confirmed), with authors of both studies speculating that the overall increases were due to increases in nonvaccine serotype disease, although other secular trends could have contributed.

A smaller but growing number of studies have examined 3-dose (2+1 and 3+0) schedules. Most policy makers recently adopting PCV have used 1 of these schedules and the World Health Organization recently updated their recommendation for PCV to be used on either of these 3-dose schedules.<sup>47</sup> Our review did not find sufficient data to directly compare these 2 schedules or to make conclusions regarding the impact of these schedules on VT-NP carriage or syndromic pneumonia; statistically significant indirect effects for pneumonia and VT-NP carriage using 2+1 and 3+0 schedules were not observed in any of the 6 studies of these outcomes identified by our review, although many of these studies were conducted early in the immunization programs or evaluated nonspecific endpoints. Despite these limitations, both 3-dose schedules appear to have indirect effects on VT-IPD when introduced nationally. Substantial reductions in VT-IPD were observed among young adult groups in 5 European countries using a 2+1 national immunization schedule.<sup>14–16,22,24,30</sup> In countries with catch-up campaigns, this reduction was observed as early as 1 year after vaccine introduction. Two studies evaluated 3+0 schedules for indirect effects on VT-IPD and both found significant reductions. One 3+0 study in Australia did find 3–11% reductions in pneumonia; however, these findings were only borderline significant.<sup>34</sup> Additionally, a 3+PPV23 schedule in Australia showed a decrease in VT-NP carriage among older children but not among adults.<sup>10</sup> However, other studies suggest that PPV23 boosters do not affect VT-carriage,<sup>48</sup> and thus a 3+PPV23 schedule likely approximates a 3+0 schedule in terms of benefits against VT-carriage.

This review also found studies of indirect effects of PCV on high-risk populations, including 9 studies evaluating PCV on either VT-NP carriage<sup>9,10,42,43</sup> or VT-IPD<sup>13,17,18,23,28,31</sup>; no studies evaluated pneumonia and all used 3+1 or 3+PPV23 schedules. Seven studies focused on the impact of PCV on indigenous populations, including Australian Indigenous, Alaskan Native and American Indian

populations, and 2 focused on HIV-infected populations. Despite these varying populations, the findings were consistent. All studies noted reductions in disease in older children and adults, suggesting indirect impact of PCV on high-risk populations. These observations may be of relevance to countries with a high burden of HIV or vulnerable populations at higher risk of pneumococcal disease.

While the strength of this analysis is the diversity of settings and study designs included, both for high-risk and nonhigh-risk populations, there are some limitations to our analysis. The heterogeneity of the data did not allow for direct comparisons among schedules and since many factors contribute to the indirect impact of a vaccine schedule, this analysis was unable to fully address the wide variability in study settings and factors that may contribute to the relative impact of PCV schedules (eg, vaccine coverage, presence of a catch up campaign, proportion of the population under 5 years of age, HIV prevalence). Additionally, few data points exist for most of the outcomes we evaluated. Only 1 study directly compared impact among dosing schedules; this VT-NP study from the Netherlands showed no impact of either a 2+0 or a 2+1 schedule on NP carriage in older siblings and parents of vaccinated and unvaccinated children participating in an individual RCT. This study was the only study to evaluate a 2+0 schedule.<sup>44,45</sup> Furthermore, some of the studies presented here were small and/or were substudies of clinical trials and therefore may not accurately represent the herd protection of vaccine introduction in a broad population. Many of the studies took place over relatively short periods; since full realization of herd effects in a population may take years,<sup>1</sup> study periods of just a few years likely underestimate the measured herd effects in some studies. As PCV introductions in lower- and middle-income countries have only recently occurred,<sup>49</sup> almost all data on impact from routine use came from high-income, early introducing countries with more mature immunization programs, which may be more likely to show indirect effects; however, a number of studies are ongoing and data will likely be available soon on the impact of routine use of PCV on unvaccinated older children and adults in lower- and middle-income settings.

The findings of our review suggest to policy makers that, should they adopt either a 3- or 4-dose PCV schedule, indirect effects are likely to add to the overall benefits seen from their program. The evidence to date is strong for the 3+1 schedule and is growing for the 3-dose schedules (2+1 and 3+0). More data to support evidence of herd effects from countries using either the 2+1 or 3+0 schedule would be useful, in particular for the outcomes of VT-NP carriage and pneumonia, from developing country settings where transmission may be more intense and across a wider age range than in high-income populations and for the new generation of conjugate vaccines (PCV10 and PCV13). Because studies of PCV effect on NP carriage in vaccinated children show that 3- and 4-dose schedules reduce colonization,<sup>4</sup> we anticipate that with time and more study, vaccination of infants using all of these schedules will be found to prevent a variety of disease syndromes and colonization in unvaccinated age groups. For policy makers trying to determine the best schedule to adopt for their national PCV program, the evidence summarized here on indirect effects should provide an adjunct to data on the direct benefits of various PCV schedules for infants and to programmatic and epidemiologic factors specific to their situation that would drive their decisions on PCV use.

## ACKNOWLEDGMENTS

The authors gratefully acknowledge the tremendous support for abstracting data from the following: Becky Roberts, Karrie-Ann Toews and Carolyn Wright from the Centers for Disease Control and Prevention, Respiratory Diseases Branch; Catherine Bozio, Rose Chang, Jamie Felzer, Amy Fothergill, Sara Gelb, Kristen

Hake, Sydney Hubbard, Grace Hunte and Shuling Liu from Emory University Rollins School of Public Health; Bethany Baer, Subash Chandir, Stephanie Davis, Sylvia Kauffman, Min Joo Kwak, Paulami Naik and Meena Ramakrishnan from The Johns Hopkins Bloomberg School of Public Health and T. Scott Johnson from Biostatistics Consulting.

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