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Systematic Review of the Effect of Pneumococcal Conjugate Vaccine Dosing Schedules on Vaccine-type Nasopharyngeal Carriage

Katherine E. Fleming-Dutra, MD,† Laura Conklin, MD,† Jennifer D. Loo, MPH,† Maria Deloria Knoll, PhD,‡ Daniel E. Park, MSPH,‡ Jennifer Kirk, MSc,§ David Goldblatt, MBChB, PhD,¶ Cynthia G. Whitney, MD, MPH,† and Katherine L. O'Brien, MD, MPH‡*

Background: Pneumococcal conjugate vaccines (PCV) reduce nasopharyngeal carriage of vaccine type (VT) pneumococci, an important driver of vaccine programs' overall benefits. The dosing schedule that best reduces carriage is unclear.

Methods: We performed a systematic review of English language publications from 1994 to 2010 (supplemented post hoc with studies from 2011) reporting PCV effects on VT carriage to assess variability in effect by dosing schedule.

Results: We identified 32 relevant studies (36 citations) from 12,980 citations reviewed. Twenty-one (66%) evaluated PCV7; none used PCV10 or PCV13. Five studies evaluated 2 primary doses and 13 three primary doses. After the first year of life, 14 evaluated 3-dose primary series with PCV booster (3+1), seven 3 doses plus 23-valent polysaccharide booster "3+1PPV23," five "3+0," four "2+1," three "2+1PPV23" and two "2+0." Four studies directly compared schedules. From these, 3 primary doses reduced VT carriage more than 2 doses at 1–7 months following the series (1 study significant; 2 borderline). In a study, the 2+1 schedule reduced VT carriage more than 2+0 at 18, but not at 24 months of age. One study of a 23-valent pneumococcal polysaccharide vaccine booster showed no effect. All 16 clinical trials with unvaccinated controls and 11 observational studies with before-after designs showed reduction in VT carriage.

Conclusions: The available literature demonstrates VT-carriage reduction for 2+0, 2+1, 3+0 and 3+1 PCV schedules, but not for 23-valent pneumococcal polysaccharide vaccine booster. Comparisons between schedules show that 3 primary doses and a 2+1 schedule may reduce carriage more than 2 primary doses and a 2+0 schedule, respectively.

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From the *Epidemic Intelligence Service, Centers for Disease Control and Prevention, Atlanta, GA; †Respiratory Diseases Branch, Division of Bacterial Diseases, National Center for Immunizations and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, GA; ‡International Vaccine Access Center, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD; §Westat Inc., Rockville, MD; and ¶Institute of Child Health, University College London, London, United Kingdom.

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Address for correspondence: Katherine E. Fleming-Dutra, MD, 1600 Clifton Road, NE, Mailstop C-25, Atlanta, GA 30333. E-mail: Keflemi@emory.edu.

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Streptococcus pneumoniae (pneumococcus) colonizes the human nasopharynx, particularly in young children, and is part of the normal nasopharyngeal (NP) bacterial flora.[1] Although pneumococcal colonization is usually asymptomatic, in some cases, it progresses to a disease state, with spread from the nasopharynx resulting in sinusitis, otitis media, pneumonia and invasive diseases, such as bacteremia and meningitis.[2] Vaccines targeting pneumococcus have been shown to differ in their protective efficacy against NP carriage. The 23-valent pneumococcal polysaccharide vaccine (PPV23), licensed in 1983, protects against invasive pneumococcal disease (IPD, infection of a normally sterile body site) in adults,[3] but not against NP carriage.[4] Pneumococcal conjugate vaccine (PCV), first licensed for infant use in 2000, protects against invasive and non-IPD[5] and against acquisition and density of vaccine serotype (VT) NP carriage.[6,7] PCV use among children leads to simultaneous decreases in VT IPD and carriage in non-vaccinated age groups (eg, adults), demonstrating that infant and toddler NP carriage is an important driver of pneumococcal transmission in the household and community.[8] Based on the precondition of NP carriage for development of disease and its role in transmission, the effect of PCV on VT carriage is important and may be used along with other data to infer PCV impact on disease.

PCV7 and PCV10 were initially licensed for 3 primary doses plus a booster (3+1 schedule), and PCV7, PCV10 and PCV13 were later granted licenses in Europe and elsewhere for schedules using 2 primary doses plus a booster (2+1).[9–11] However, we lack a clear understanding of the full impact of reduced-dose schedules relative to 3+1. One previous report reviewed clinical trials, cohort and case-control studies that made direct comparisons of various PCV schedules within each study; however, only 2 studies from the large body of evidence on PCV and NP-carriage effects met the report's inclusion criteria for NP-carriage evaluations.[12]

We examined the larger set of literature regarding PCV dosing schedules to address the following key policy questions regarding direct effects of vaccine on VT carriage: (1) What is the evidence that a 3-dose primary series is superior or inferior to a 2-dose primary series? (2) If only 3 doses are used, is there any evidence to prefer a 2+1 or a 3+0 schedule? (3) What is the evidence that a schedule including a booster dose is superior to one without a booster dose? and (4) Is there evidence to support the choice of PCV or PPV23 as a booster dose?

METHODS

Literature Search

This analysis is part of a larger project describing the impact of PCV dosing schedules on IPD, immunogenicity, NP carriage,

pneumonia and indirect effects.[13–16] Details on the literature search terms and methods used in this systematic review are described elsewhere (see Methods Appendix[17]). 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, NP colonization, IPD, pneumonia and on indirect effects among unvaccinated populations. Articles published in 14 databases, from ad hoc unpublished sources and abstracts from meetings of the International Symposium on Pneumococci and Pneumococcal Disease (1998–2010) and the Interscience Conference on Antimicrobial Agents and Chemotherapeutics (1994–2010), were searched. We included all randomized controlled clinical trials, 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 PPV23 was used as a booster dose, but not if used 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 on relevant data for this project. Details on the search methods are provided elsewhere (Methods Appendix[17]).

Data Abstraction

Citations recovered through the literature search went through several stages of independent review to determine their eligibility, as described elsewhere (Methods Appendix[17]). 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; co-administered vaccines; country; age at each dose and date of study and publication. Additional data abstracted for the direct effect of PCV on VT NP carriage included age at each NP specimen collection.

Inclusion and Exclusion Criteria

We included data published from randomized controlled trials, nonrandomized trials, surveillance databases and observational studies of PCV schedules on VT carriage. We included all PCV products (denoted as PCV with a number indicating the valency, eg, PCV7). We excluded studies with all vaccination series beginning after 12 months of life, studies that only reported data before or after PCV introduction but not for both periods and studies that did not report direct PCV effects on VT carriage.

Pneumococcal Vaccine Dosing Schedules

We included PCV schedules with 2 primary doses only (2+0), 2 primary doses plus a PCV booster (2+1) or a PPV23 booster (2+1PPV23), 3 primary doses only (3+0) and 3 primary doses plus a PCV booster (3+1) or a PPV23 booster (3+1PPV23).

Data Analysis

Because the included studies used various designs and methods, we were unable to perform a meta-analysis. Thus, we summarized the data across studies in descriptive analyses to provide an overview of the amount and variability of data by schedule. 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. VT was defined as each study defined it, based on the product used. No studies included PCV products with serotype 19A; none classified 19A as VT. Two PCV7 studies included serotype 6A as a VT.[18,19] We defined percent VT carriage as the percentage of children sampled who carried a VT strain, except in 7 citations that only reported percent of pneumococcal isolates that were VT, in which case this percent was used.[7,20–25]

For clinical trials, we abstracted the difference in VT-carriage prevalence with confidence intervals (CI) between vaccinated children and controls. If not reported, we calculated the difference in carriage between vaccinated children and controls. We separated clinical trials into those that directly compared NP effects of various schedules and trials that evaluated effects only between a given schedule and unvaccinated controls. We separated these latter trials into those that examined carriage early (during the first year of life or prior to any booster dose given in the study) and late (after the first year of life or after any booster dose given in the study).

For pre- and postvaccine introduction observational studies among age groups targeted for vaccination, we calculated percent change in VT carriage by defining the baseline prevalence as the mean of all data points reported prior to introduction. In cases where only the postintroduction VT-carriage prevalence over a period was provided, we calculated percent change from the baseline prevalence to the reported prevalence and assigned it to the median year of the date range provided. When possible, the year of vaccine introduction was excluded from these calculations. 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) for analyses. Statistical significance was defined as $P < 0.05$.

RESULTS

Description of Included Studies

Of 12,980 citations reviewed, 145 had carriage data; of these, 36 met inclusion criteria for VT carriage among children targeted to receive the vaccine (Fig. 1).[4,7,18–51] These 36 citations represented 32 study families with 4 supplemental citations. Among the 32 studies, 25 (78%) were published in 2003 or later; 17 (53%) were from Europe or North America (Table 1).[52] Seven (22%) evaluated children at high risk for pneumococcal disease, such as children with HIV or sickle cell disease, indigenous children or children with acute pneumonia or otitis media. Twenty-one (66%) studies evaluated PCV7; no studies evaluated PCV10 or PCV13.

Direct Comparisons of Dosing Schedules Within Studies: Clinical Trials

Among the 32 studies, 4 directly compared VT-carriage reduction among dosing regimens. The first study, conducted in Fiji, compared 0, 1, 2 and 3 PCV7 doses (given at 14 weeks, 6 and 14 weeks or 6, 10 and 14 weeks, respectively) with and without a PPV23 booster at 12 months.[4] The investigators found a significant difference in VT-carriage prevalence between the 2- and 3-dose groups at 9 months; the 3-dose group had significantly less VT carriage [odds ratio 0.30 (CI: 0.09–0.9)]. At 6, 12 and 17 months of age, VT carriage among the 2- and 3-dose groups was not significantly different. The receipt of a PPV23 booster showed no effect on VT carriage, as no difference in VT carriage at 17 months was

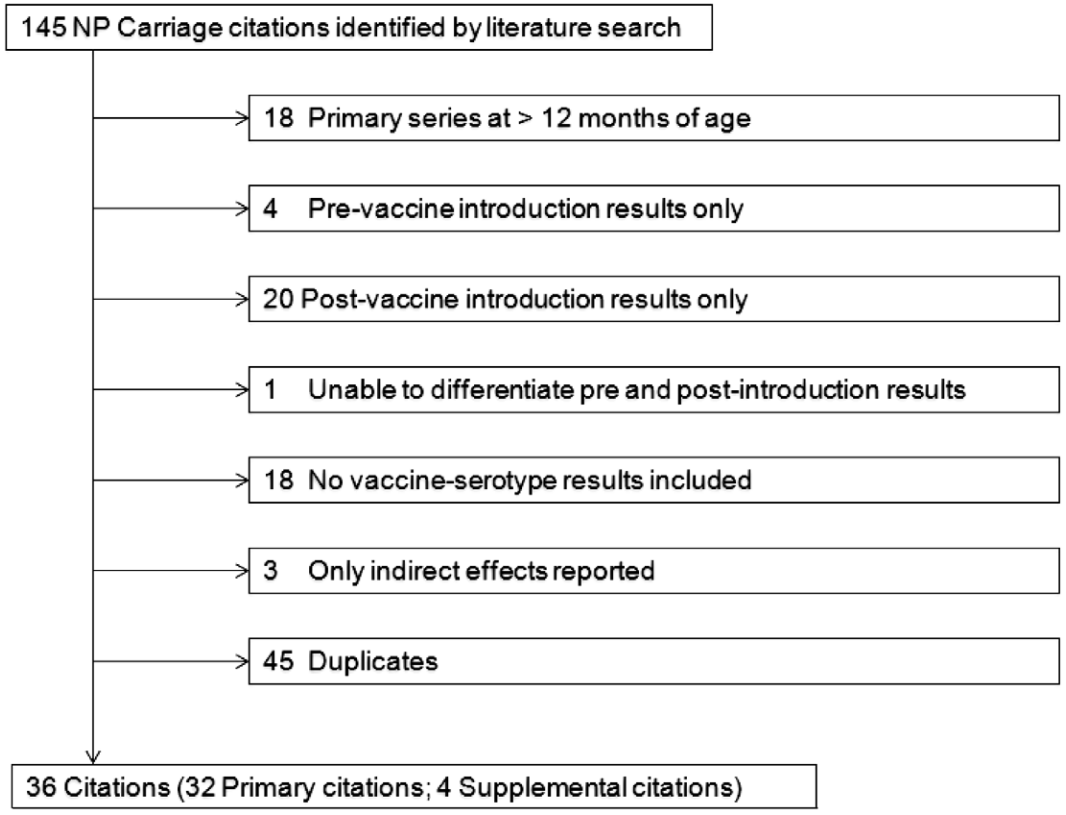

FIGURE 1. Literature search results for carriage citations identified from search strategy, as strategy as detailed in the Methods Appendix.[17] Study families include 1 or more citation generated from a single protocol or data collection system, and the primary citation identifies the citation within each study family that contains the most detailed information regarding vaccine-type carriage. Supplemental citations contain additional data not contained in the citation for the primary study.

seen between those who did and did not receive the PPV23 booster in each PCV dosing group.[4] The second study, conducted in The Gambia, compared 1, 2 and 3 PCV7 doses (given at 2 months, 2 and 3 months and 2, 3 and 4 months); all children received a PPV23 booster at 10 months.[44] At 11 months, 3 PCV doses showed a borderline significant reduction in VT carriage compared with 2 PCV doses (10.0% vs. 16.7%, $P = 0.056$). However, at 5 and 15 months, the VT carriage prevalence was not significantly different among children who received 2 and 3 doses.[44] The third study, conducted in Israel with PCV7, compared a 3+1 schedule (2, 4, 6 and 12 months) with 2+1 (4, 6 and 12 months) and 0+2 (12 and 18 months) schedules.[19] Between 7 and 12 months of age (prebooster), the mean VT prevalence was nonsignificantly lower in the 3+1 group when compared with the 2+1 group (22.6% vs. 28.4%, $P = 0.089$). The 0+2 group between 7 and 12 months, that is, before children were vaccinated, had a mean VT prevalence of 35.2%, which was significantly higher than the 3+1 group ($P < 0.001$). Between 13 and 18 months (ie, after the booster dose) and between 19 and 30 months, the 3+1 and 2+1 groups had equivalent VT prevalence, but both groups had significantly lower VT prevalence than the 0+2 group.[19] A fourth study, conducted in the Netherlands, compared children who received PCV7 at 2 and 4 months (2+0); 2, 4 and 11 months (2+1) and unvaccinated controls.[48] At 12, 18 and 24 months of age, children in the 2+0 and 2+1 groups had significantly less VT carriage than unvaccinated controls. Although children in the 2+1 group had a significantly lower prevalence of VT carriage at 18 months (16%) than the 2+0 group (24%, $P = 0.01$), no difference was found at 24 months.[48]

Early Assessment of VT Carriage During First Year of Life: Clinical Trials

Ten clinical trials evaluated 2- and 3-dose primary regimens during the first year of life compared with control subjects who received either placebo or no vaccine. Two trials examined both regimens[4,19]; 1 trial examined only a 2-dose regimen[48] and 7 studies examined only a 3-dose regimen (Fig. 2).[7,27,29,38,43,46,50] These 10 trials included 23 study arms. All 5 arms evaluating a 2-dose primary series found reductions in VT-carriage prevalence among PCV recipients compared with controls, although only 1 arm reached statistical significance. Of 18 arms, 17 with 3-dose primary regimens observed reductions in VT carriage; 11 arms were statistically significant. One 3-dose primary series arm (Merck, PCV7) observed a nonsignificant increase of VT-carriage prevalence at 7 months of age.[50]

Two trials examined the VT-carriage effect of 3 primary doses but provided results that could not be compared with other studies. One, a clinical trial in Iceland, examined 81 children who received PCV8 conjugated to diphtheria or tetanus toxoid given in 3 primary doses (3, 4 and 6 months) and 40 unvaccinated controls.[34] Swabs were collected at 3, 4, 6, 7, 10, 14 and 18 months. For swabs at ages ≤6 months, VT carriage was not significantly different between controls (21%) and vaccinees (18%, $P = 0.5$). Vaccinees were then given either a PCV8 booster or a PPV23 booster at 13 months, but results from swabs at ages >6 months were not reported separately for those who received PCV8 and PPV23 boosters and thus are not presented here.[34] The other study, a trial conducted in Kenya, compared 3 primary doses of PCV7 starting at either birth

TABLE 1. Characteristics of Included Study Families (n = 32)

	n (%)
Publication date	
1994–1998	3 (9)
1999–2002	4 (13)
2003–2006	5 (16)
2007–present	20 (63)
Study type	
Clinical trial	19 (59)
Pre-post trend survey	11 (34)
Other observational*	2 (6)
United Nations Region[52]	
Africa	7 (22)
Asia	5 (16)
Europe	11 (34)
Latin America	1 (3)
North America	6 (19)
Oceania	2 (6)
High risk	
None	25 (78)
HIV-infected	1 (3)
Sickle cell disease	1 (3)
Indigenous	3 (9)
Acute illness†	2 (6)
Dosing schedule‡	
Carriage assessed during first year of life§	
2 primary dose series	5 (16)
3 primary dose series	13 (41)
Carriage assessed after first year of life¶	
2+0	2 (6)
2+1	4 (13)
2+1PPV23	3 (9)
3+0	5 (16)
3+1	14 (44)
3+1PPV23	7 (22)
Product‖	
PCV7-Wyeth/Pfizer	21 (66)
PCV9-Wyeth	4 (13)
PCV11-Sanofi	2 (6)
Other PCV**	5 (16)
Type of vaccine introduction	
Available through study	20 (63)
National immunization program	5 (16)
High-risk introduction	3 (9)
Private introduction	3 (9)
Private and high-risk introduction	1 (3)

*One cohort study[33] and 1 open-label, prospective, observational trial.[32]

† Acute otitis media or pneumonia at time of NP swab collection.

‡‡Percentages add up to >100%, as studies may have multiple dosing schedules and may have assessed carriage both during and after the first year of life.

§Total study arms with carriage specimens during the first year of life (n = 18).

¶Total study arms with carriage specimens after the first year of life (n = 35).

‖Products are listed as PCV, valency and manufacturer name.

**Includes PCV4-Sanofi, PCV5-Wyeth, PCV7-Merck, PCV8-Sanofi and PCV11-GlaxoSmithKline.

or 6 weeks of age with subsequent doses at 10 and 14 weeks and found no significant differences in VT carriage at 18 and 36 weeks among the regimens.[51]

Late Assessment of VT Carriage After the First Year of Life: Clinical Trials

Thirteen clinical trials (14 citations) assessed VT carriage with samples taken after the first year of life (Fig. 3). Two trials examined 2+0 schedules[4,48]; one 2+1[48]; two 2+1PPV23[4,42]; four 3+0[4,27,37,41]; five 3+1[7,30,39,45,46,50] and four 3+1PPV23.[4,29,35,42] Among the 29 arms reported in these 13 studies, 28 showed reduction in VT compared with control subjects; 15 arms were statistically significant (Fig. 3). One arm conducted among South African children with HIV who received a 3+0 PCV9 schedule had a nonsignificant increase in VT carriage when compared with controls.[37]

Impact of Vaccine Introduction on VT Carriage: Observational Studies

Results by schedule from 11 observational, pre/post-vaccine introduction studies (13 citations) are shown in Figure 4.[18,20–26,28,31,36,47,49] All observational studies used PCV7. None examined a 3+0 schedule. Two observational studies examined 2+1 schedules. One conducted in England with national introduction with a catch-up campaign showed a statistically significant reduction.[18] A study in Switzerland with private-market introduction among children <2 years of age with acute otitis media or pneumonia also showed reduction; statistical significance was not reported.[21] Five studies in the United States,[22,24,25,31,47,49] 2 in France[20,28] and 1 in Portugal[23] evaluated 3+1 schedules: all showed reductions in VT carriage. Five studies were statistically significant[20,22,23,28,31] and 3 studies (4 citations) did not report statistical significance.[24,25,47,49] Finally, 1 study among Australian Aboriginal children showed a significant reduction in VT carriage following a 3+1PPV23 schedule,[36] while a British study among children with sickle cell disease found a nonsignificant reduction in VT carriage following a 3+1PPV23 schedule.[26]

Additional observational studies met inclusion criteria but were not comparable to other studies because of their unique designs. A cohort study from Korea evaluated the effect of a 3+1 schedule (given at 2, 4, 6 and 16.5 months), following PCV7 private-market introduction.[33] This study compared vaccinated children in daycare from a highly vaccinated region to unvaccinated children in daycare from a region with low vaccination rates.[33] At mean ages of 35.2 months for vaccinated and 42.3 months for unvaccinated children, VT carriage was found in 4 (2%) of 200 vaccinated and 33 (16.5%) of 200 unvaccinated children.[33] An open-label, prospective study in Mexico evaluated VT-carriage acquisition in children receiving either 3 PCV7 doses (given between 6 weeks and 6 months) or 2 doses (given between 7 and 11 months); no unvaccinated controls were included in the study.[32] VT acquisition decreased over time in both the 2- and 3-dose primary regimens, but the groups were not directly compared. An observational follow-up study to a clinical trial in the Philippines compared children with pneumonia between 6 weeks and 23 months old, who had received PCV11 or placebo at a median age of 7, 12 and 16 weeks.[40] VT was reduced in the PCV11 group versus placebo; quantitative results were not provided.[40]

Finally, a pre/postintroduction study from France also included a sub-analysis examining the effect of the booster dose.[28] PCV7 was licensed in France in 2001 and reimbursed for children with high-risk medical or living conditions in 2003 using a schedule of 2, 3 and 4 months with a booster in the second year of life.[53] In this study, children 6–24 months with acute otitis media in French day care centers were enrolled in annual cross-sectional surveys from 2001 to 2006.[28] Among children >1 year of age during all years of the study, VT carriage was 44.4% in unvaccinated children, 23.9% in children vaccinated without a booster dose and 11.8% in children vaccinated with the booster dose.[28]

DISCUSSION

We found that all schedules reviewed—2+0, 2+1, 2+1PPV23, 3+0, 3+1 and 3+1PPV23—reduced carriage of VTs of pneumococcus compared with no PCV. However, the strength of evidence supporting each schedule varies and effects differ among the schedules. First, in studies with direct comparisons of 2 versus 3 primary doses, 3 doses result in a greater reduction in VT carriage compared with 2 doses at 1–7 months following the primary series.[4,19,44] However, measurable differences in

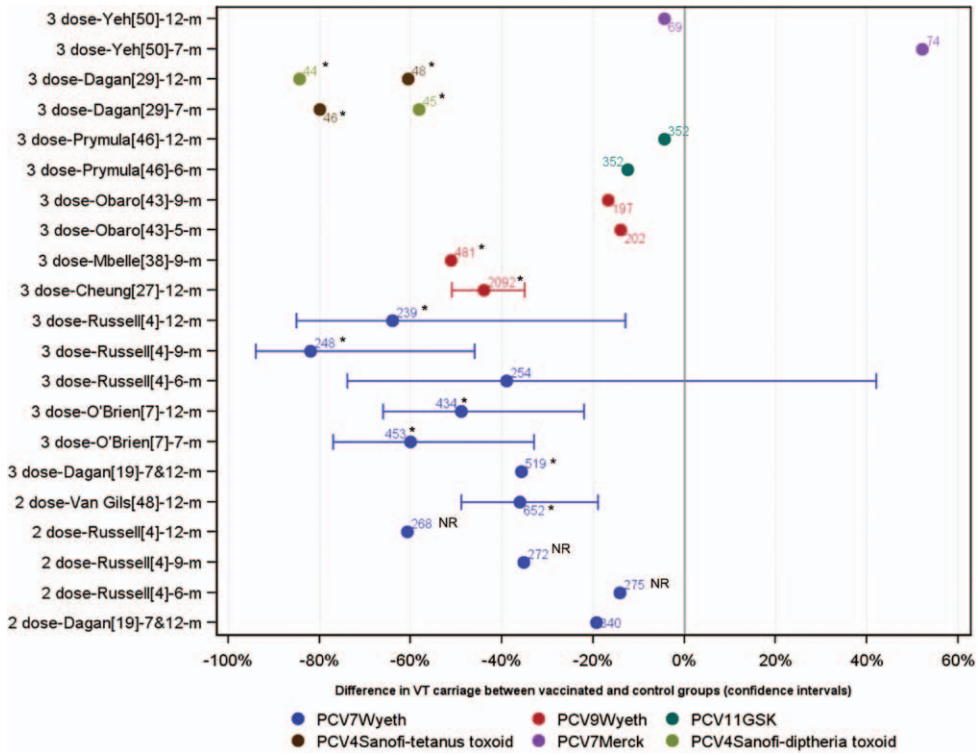

FIGURE 2. Difference in VT carriage prevalence between vaccinated and unvaccinated or placebo groups for clinical trials by primary dosing series (2 or 3 doses) for carriage assessed in the first year of life.[4,7,19,27,29,38,43,46,48,50] Two and 3 primary doses were given between 6 weeks and 6 months for all regimens. Studies denoted on *y*-axis with primary dosing series (2 or 3 doses), first author's last name (with reference number in brackets) and mean or median age in months (m) of children at time of NP specimen collection. Products are listed as PCV-valency and manufacturer name. Confidence intervals are displayed by error bars. Data points are labeled with sample size, an asterisk (*) if statistically significant when compared with controls and/or NR if statistical significance was not reported. All others were not statistically significant. GSK, GlaxoSmithKline.

VT-carriage reduction between 2 and 3 primary doses are not seen on further follow up following primary vaccination in schedules with PCV boosters,[19] PPV23 boosters[4,44] or no boost.[4] Differences between the schedules are difficult to discern when comparing the impact of 2- and 3-dose primary series between studies rather than within studies.

Very little evidence is available on VT-carriage prevalence after the first year of life in children who received a 2-dose schedule without a booster dose. Both clinical trials that evaluated 2+0 schedules after the first year of life demonstrated reductions in VT carriage.[4,48] However, in 1 of these studies, the 2+1 schedule reduced VT carriage more than the 2+0 schedule at 1 of 3 time points, suggesting that the 2+1 schedule may be better than the 2+0.[48] Furthermore, there is no evidence regarding effect of 2+0 schedules on VT carriage from observational studies or for long-term effects of this schedule since no country is using this schedule. Concerns regarding the immunogenicity of 2+0 schedules and the lack of evidence regarding the impact of 2+0 schedules on IPD, pneumonia and indirect effects have precluded its use in national immunization programs to date.

More evidence is needed regarding the optimal timing of the doses in a 3-dose schedule, but available evidence supports the use of both 2+1 and 3+0 schedules. While no published studies directly compare the impact of 2+1 and 3+0 schedules on VT carriage, both schedules reduce VT carriage compared with no PCV use. A study of 2+1, 3+0 and 3+1 schedules using PCV7 from Israel was done and has been published in part.[19,54] Results suggest that the 2+1 schedule results in similar VT-carriage prevalence to 3+1 when VT-carriage prevalence is sampled after the booster doses; however, 2+1 appears to be inferior to 3+1 prior to the booster dose. Additionally, this study directly compared 3+0 and 3+1 schedules and showed no difference in VT-carriage prevalence. These data suggest that 2+1 and 3+0 schedules may have similar effects on VT carriage after the first year of life, but these schedules were not directly compared in this study. It is important to note that data supporting 2+1 schedules come from a clinical trial and 2 observational studies in Europe (the Netherlands,[48] England[18] and Switzerland),[21] whereas data supporting a 3+0 schedule come from clinical trials in middle income and developing countries (Philippines,[40,41] Fiji,[4] The Gambia[27] and South Africa).[37] While both 3+0 and 2+1 schedules appear to be effective, differences between 2+1 and 3+0 schedules may exist that are relevant to settings with particular pneumococcal transmission patterns, burden of disease or colonization. For example, vaccine programs serving populations with disease early in life, heavy transmission and young age of transmitters may prefer 3+0 schedules; however, the data in our review do not provide a conclusive determination of which schedule is optimal for each of these settings.

Some evidence suggests that schedules with PCV boosters may provide additional reductions in VT carriage.[28,48] The available evidence does not support the use of schedules with PPV23 boosters for improving NP-carriage reductions. While no studies directly compared PCV and PPV23 boosters, a Fijian study compared schedules with and without PPV23 boosters and showed no benefit of 2+1PPV23 and 3+1PPV23 schedules compared with 2+0 and 3+0 schedules, respectively, despite boosts in antibodies seen with PPV23 boosters.[4]

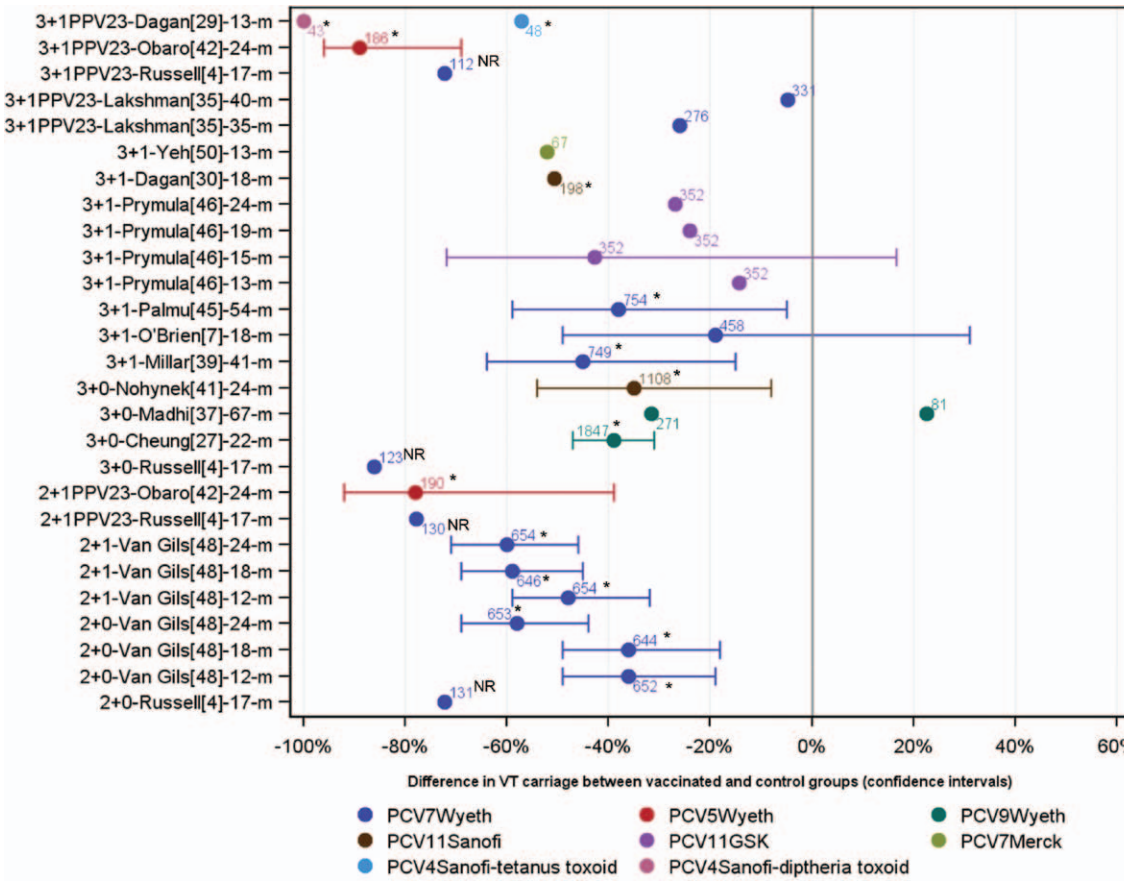

FIGURE 3. Difference in VT-carriage prevalence between vaccinated and unvaccinated or placebo groups for clinical trials by dosing series for carriage assessed after the first year of life.[4,7,27,29,30,35,37,39,41,42,45,46,48,50] All primary doses were given between 6 weeks and 6 months of age (6 weeks to 4 months for 2 doses, 6 weeks to 6 months for 3 doses), and booster doses given at 11–18 months of age. Studies denoted on *y*-axis with schedule, first author's last name (with reference number in brackets) and mean or median age in months (m) of children at time of NP specimen collection. Products are listed as PCV-valency and manufacturer name. Confidence intervals are displayed by error bars. Data points are labeled with sample size, an asterisk (*) if statistically significant when compared with controls, and NR if statistical significance compared with controls was not reported. All others were not statistically significant. GSK, GlaxoSmithKline.

Determining the relative benefit for NP-carriage reductions of 1 schedule over another is difficult. Limited data are available from studies with direct comparisons between schedules. Few are conducted in regions where child mortality is high, and some studies were in the setting of catch-up campaigns, which would blur the measured effect of the primary schedule. These limitations should be considered when assessing the potential benefits of particular schedules. For example, while 2+1 schedules reduced VT carriage in 2 observational studies, it is important to note that 1 study was conducted among vaccinated children in the setting of a private-market introduction,[21] where vaccinated children may have lower inherent risk of colonization, and 1 study was conducted among all children <5 years old in the setting of a national immunization program with a catch-up campaign.[18] Furthermore, only 7 NP studies evaluated PCV schedule impact in children at high risk for colonization and disease; the only study to specifically evaluate children with HIV failed to show efficacy of a 3+0 schedule on VT carriage.[37] None of the studies included evaluated PCV10 or PCV13, which are currently being used in national immunization programs. However, a study in France, conducted in the year following the switch from PCV7 to PCV13, showed a significant reduction in the additional 6 serotypes included in PCV13 among children partially and fully vaccinated with PCV13 when compared with those vaccinated with PCV7.[55] This study was not included in this analysis due to a lack of pre-PCV introduction data for PCV13 serotypes.[55]

This analysis focused on VT carriage and did not address the effect of dosing schedules on all pneumococcal carriage or non-VT carriage, as the impact on VT carriage is the most important factor for policy makers when deciding which dosing schedules to recommend. Most studies show that PCV does not affect the overall prevalence of all-serotype pneumococcal carriage,[4,7,18–23,27,31,36,39,41,43] although some show a reduction at some or all time points.[19,25,28,48] Additionally, most studies show that non-VTs increase in prevalence following PCV,[4,7,18,19,23,27,28,31,36,38,39,42,48] although a few studies show no change at some or all time points.[4,7,19] Many, but not all, non-VTs have lower invasive potential than most VT strains, meaning that they are less likely to cause IPD if carried,[18] and invasive potential does not appear to change with time[47,56] or vaccine introduction.[47] Thus, the potential for many replacing serotypes to cause IPD is not as high as for serotypes included by currently available PCV products.

This analysis has several strengths and limitations. The strengths of this analysis are its comprehensive nature with the diversity of countries and study designs included. Very few NP studies directly compare schedules, and this analysis allows for all

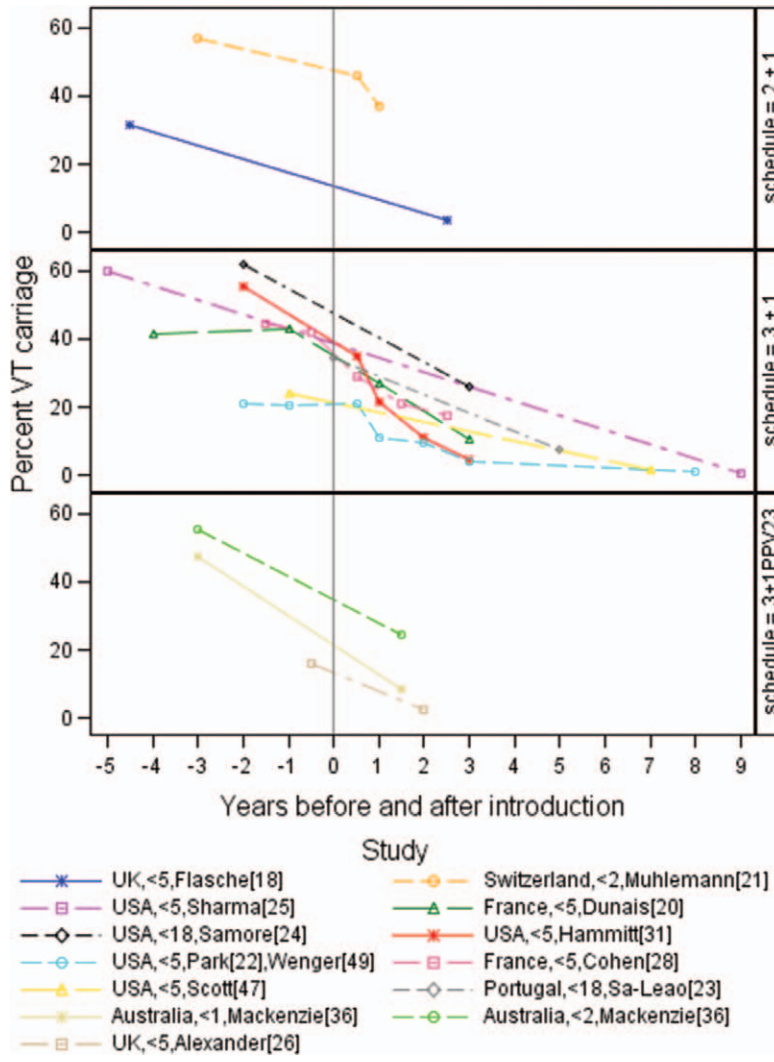

FIGURE 4. Percent of vaccine-type carriage among children in pre-post trend studies over time by schedule. Year of PCV introduction is denoted as year 0. Studies, which include the primary citation and any supplemental citations, are identified by country, age group in years of children at time of NP specimen collection, and by first author's last name (with reference number in brackets).[18,20–26,28,31,36,47,49]

of the supporting evidence for each of these regimens to be considered. However, the analysis is limited because fully differentiating the relative magnitude of the impact on VT carriage of each schedule is not possible. Geographic region, socioeconomic level and other factors affect carriage of pneumococci and thus confound our ability to compare magnitudes of impact across studies. Additionally, we were unable to account for vaccine coverage in the target populations or the presence of catch-up campaigns due to limited information in the study reports.

In conclusion, 2+0, 2+1, 3+0 and 3+1 schedules all reduce pneumococcal VT carriage. Importantly, the evidence indicates that 3 primary doses may reduce VT carriage more than 2 primary doses; that both 2+1 and 3+0 schedules are effective; PCV booster doses may be helpful, especially in the setting of 2 primary doses and the use of PPV23 boosters after a PCV schedule does not further reduce VT carriage. Our analysis supports recent recommendations by the Pan American Health Organization and the World Health Organization for the use of 3 doses of PCV and the acceptability to be administered either as 3+0 or 2+1 schedule.[57,58] However, NP carriage is only part of the picture, and the effect of each schedule on IPD, pneumonia, immunogenicity and indirect effects in the context of local epidemiology and programmatic considerations should be considered by public health when recommending and countries when choosing a schedule.

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