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Systematic Review of the Effect of Pneumococcal Conjugate Vaccine Dosing Schedules on Immunogenicity

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Background: Despite the breadth of studies demonstrating benefits of pneumococcal conjugate vaccine (PCV), uncertainty remains regarding the optimal PCV dosing schedule in infants.

Methods: We conducted a systematic literature review of PCV immunogenicity published from 1994 to 2010 (supplemented post hoc with studies from 2011). Studies included for analysis evaluated ≥2 doses of 7-valent or higher product (excluding Aventis-Pasteur PCV11) administered to nonhigh-risk infants ≤6 months of age. Impact of PCV schedule on geometric mean antibody concentration (GMC) and proportion of subjects over 0.35 mcg/mL were assessed at various time points; the GMC 1 month postdose 3 (for various dosing regimens) for serotypes 1, 5, 6B, 14, 19F and 23F was assessed in detail using random effects linear regression, adjusted for product, acellular diphtheria-tetanus-pertussis/whole-cell diphtheria-tetanus-pertussis coadministration, laboratory method, age at first dose and geographic region.

Results: From 61 studies, we evaluated 13 two-dose (2+0) and 65 three-dose primary schedules (3+0) without a booster dose, 11 "2+1" (2 primary plus booster) and 42 "3+1" schedules. The GMC after the primary series was higher following 3-dose schedules compared with 2-dose schedules for all serotypes except for serotype 1. Pre- and postbooster GMCs were generally similar regardless of whether 2 or 3 primary doses were given. GMCs were significantly higher for all serotypes when dose 3 was administered in the second year (2+1) compared with ≤6 months of age (3+0).

Conclusions: While giving the third dose in the second year of life produces a higher antibody response than when given as part of the primary series in the first 6 months, the lower GMC between the 2-dose primary series and booster may result in less disease protection for infants in that interval than those who completed the 3-dose primary series. Theoretical advantages of higher antibodies induced by giving the third dose in the second year of life, such as increased protection against serotype 1 disease, longer duration of protection or more rapid induction of herd effects, need to be evaluated in practice.

Key Words: pneumococcal conjugate vaccine, immunogenicity, immunization schedule

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Over 25% of the 7.6 million deaths occurring in children <5 years of age worldwide in 2010 were due to pneumonia, sepsis and meningitis.[1] *Streptococcus pneumoniae* is a leading cause of these diseases, estimated by the World Health Organization (WHO) to kill over 500,000 children in 2008[2]; over 90% of these deaths occur in developing countries. Three licensed pneumococcal conjugate vaccines (PCVs) include antigens from 7, 10 or 13 of the >91 known pneumococcal serotypes (PCV7, PCV10 and PCV13), which account for many severe pneumococcal disease (PD) episodes worldwide.[3]

PCVs are being introduced rapidly into an increasing number of countries, but the optimal dosing schedule(s) is unclear. The first widespread introduction was with PCV7 in the United States using a 4-dose schedule (3+1 administered at 2, 4, 6 and 12–15 months of age); with this schedule, there has been virtual elimination of vaccine-type invasive pneumococcal disease (VT-IPD) in children <5 years of age.[4] However, not all countries use this schedule or these ages for vaccine administration. Other PCV schedules used around the world include 2 primary doses plus a booster (2+1) and 3 primary doses without a booster (3+0); for example, the United Kingdom schedule is at 2, 4 and 13 months of age and Australia uses a 2-, 4- and 6-month schedule. Numerous studies have been conducted showing direct and indirect PCV7 efficacy and impact on disease given at various dosing regimens (reviewed in this supplement)[5–8]; similar studies are now being conducted on the more recently licensed PCV10 and PCV13 products. However, much is still unknown regarding an optimal schedule, which may vary by serotype, epidemiologic setting (ie, child mortality rate, community HIV prevalence or pneumococcal burden) and immunization program characteristics (ie, vaccine coverage, timeliness). Furthermore, the impact of catch-up campaigns as part of PCV introduction on disease control is not characterized or fully understood in its relationship to dosing schedule choices.

PCV regimens in use vary by number of doses, age at dosing, interval between doses, use of a booster dose, PCV product and booster product [PCV vs. 23-valent pneumococcal polysaccharide vaccine (PPV23)]. The optimum PCV schedule for a particular setting may depend not only on immunogenicity but also on the

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routine immunization program, expected coverage rates and ages at actual vaccination.

The scientific community does not have consensus on which PCV schedules are optimal for a given epidemiologic setting. Furthermore, there is no consensus on what gaps remain in the evidence base that would assist with policy development. Consequently, we conducted a comprehensive, systematic review of available data evaluating the effect of PCV dosing schedules on immunogenicity, nasopharyngeal carriage, IPD, pneumonia and indirect effects. The aim of this work was to provide the evidence base for a strategic analysis of key information gaps required to guide PCV policy development in relation to the WHO's Expanded Programme for Immunization schedule. Results for the clinical outcomes are presented elsewhere.[5–8]. In this report, we assessed the effects on immunogenicity of the number of PCV doses, interval between doses, age at dosing, timing of a third dose and impact of a booster dose.

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.[5–8] Details on the literature search terms and methods used in this systematic review are described in the Methods Appendix.[9] 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 PPV 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. Details on the search methods are provided in the Methods Appendix.[9]

Data Abstraction

Citations recovered through the literature search went through several stages of independent review to determine their eligibility, as described earlier. 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 one 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 abstracted for the immunogenicity outcome included antibody levels; age at each dose and blood draw and antibody assay methods. Geometric mean antibody concentration (GMC) with confidence interval was abstracted for immunoglobulin G (IgG) antibody determined by enzyme-linked immunoabsorbent assay (ELISA). We also abstracted the percentage of children with serotype-specific IgG concentration >0.35 μg/mL [or >0.2 μg/mL if the GlaxoSmithKline ELISA method was used (GSK, Middlesex, United Kingdom)], defined previously as the correlate of observed efficacy for VT-IPD across the randomized trials.[10–13] Results of other assays were abstracted if performed, such as opsonophagocytic assay (OPA) and avidity. If age at vaccination for PCV product or coadministered vaccines were not described, recommended ages for receiving doses from that country's national immunization plan for the year when the study was conducted were used.

Inclusion and Exclusion Criteria

Study arms meeting the following criteria were included in analyses: subjects immunized with at least 2 doses of PCV, with the first dose ≤4 months and last primary dose ≤6 months of age; licensed PCV with 7 or more antigens, or unlicensed PCV but sufficiently similar to a licensed PCV, and ELISA IgG GMC or percentage >0.35 μg/mL (or >0.2 μg/mL if GSK ELISA method used) provided for any of the 6 serotypes of interest (1, 5, 6B, 14, 19F and 23F). Data following immunization with PPV23 were excluded. Results from populations at high risk for PD were excluded (ie, HIV-infected, sickle cell disease, those with chronic illness and indigenous populations). Antibody responses to serotypes 1 and 5 were excluded from analyses for PCVs not containing these serotypes (eg, PCV7, PCV8). Antibody responses to the Aventis PCV11 were substantially higher than those of other PCV products and studies of this product were limited to a 3-dose primary series schedule; therefore, we excluded studies of Aventis PCV11 because they obscured our ability to assess the effect of dosing schedule on the antibody response.

Pneumococcal Vaccine Dosing Schedules

Any study arm with immunogenicity data after a second primary dose, including study arms eventually receiving a third primary dose, was defined as "2 primary doses"; "3 primary doses" was defined as any study arm with immunogenicity data after a third primary dose, whether a booster dose was given. Schedules "2+0" and "2+1" refer to 2 primary doses without and with 1 PCV booster dose, respectively; "3+0" and "3+1" schedules refer to 3 primary doses without and with 1 PCV booster dose, respectively. A booster dose was defined as immunization with PCV between 9 and 18 months of age in infants who had completed a 2-dose or 3-dose primary series. Mean age at immunization, if available, defined age at each dose; otherwise, scheduled age was used. To collapse into schedules, age was rounded to the nearest 2 weeks. Interval between doses was determined by number of months between first and second primary dose; all but 1 study retained the same interval between first and second as between second and third primary doses.

Data Analysis

Because most studies did not directly compare 1 PCV dosing schedule to another, we followed an ecological regression approach to compare dosing schedules across studies. We fitted random effects meta-regression models of log-transformed GMC levels by serotype, weighting by the inverse of their variances, to account for intrastudy variation for studies assessing more than one study arm. We calculated robust standard errors to account for multiple arms within studies.[14,15] We adjusted for study-specific covariates: age at

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first dose, geographic region, PCV product, type of coadministered diphtheria-tetanus-pertussis (DTP) vaccine [ie, whole-cell (DTwP) vs. acellular (DTaP) pertussis], and ELISA method. For comparisons of immunogenicity at different time points, such as postprimary versus postboost and preboost versus postboost, only studies with data for both time points were included in the analyses. For studies that did not report the variance of the GMC (between 10% and 18% among analyses), we assigned the median of the variances reported by studies with the same region, coadministered DTP vaccine and age at first dose. To investigate the effect of this simple imputation approach, we conducted analyses with and without the studies missing variance; there was no association between absence of variance estimates and GMC.

To calculate 95% confidence intervals for the proportion of children with antibody concentrations above the cut-off, we used the normal approximation interval with proportion (p)=(X+2)/(n+4), a near approximation to the Wilson interval method, which is valid for extreme values (ie, p = 100%).[16,17]

Statistical significance was defined as $P < 0.05$; there was no adjustment for multiple testing. SAS version 9.2 (SAS Institute Inc., Cary, NC) was used for all analyses.

RESULTS

Of 12,980 citations reviewed, we identified 113 with immunogenicity data, of which 61 had data relevant for analysis.[18–78] More studies evaluated 3-dose primary schedules than 2-dose primary schedules (Table 1); every geographic region evaluated a 3-dose primary schedule, whereas there were no 2-dose primary schedules evaluated in the Latin America/Caribbean region. Only Europe evaluated 1 booster dose following 2 primary doses (2+1), whereas all but Oceania evaluated 3+1 schedules. Most studies (74%) evaluated PCV7 and few (21%) evaluated PCVs with serotypes 1 and 5.

TABLE 1. Characteristics of Studies and Study Arms by Number of Primary Doses and Schedule

	Study Arms* by Dose Schedule				Arms with Postdose GMC Data†		Studies‡
	2+0§ (N = 13)	2+1 (N = 11)	3+0 (N = 65)	3+1 (N = 42)	2 doses (N = 25)	3 doses (N = 86)	(N = 61)
Region¶							
Africa	3	0	6	3	3	8	6
Asia	2	0	13	3	4	12	9
Oceania	2	0	2	0	1	1	1
Europe	3	11	24	26	12	40	30
North America	3	0	18	9	5	21	13
Latin America/ Caribbean.	0	0	4	1	0	4	3
Publication year‖							
1994–1998	2	0	5	2	2	5	5
1999–2002	2	0	14	9	5	19	12
2003–2006	1	3	7	16	6	22	16
2007–2010	6	8	39	13	11	37	26
2011	2	0	2	2	1	3	2
ELISA method**							
Wyeth/Other	12	10	55	28	23	66	49
GSK	1	1	12	14	2	20	13
PCV product							
Wyeth-7	6	7	37	20	11	42	38
Wyeth-9	3	2	9	3	5	11	7
Wyeth-13 (Pfizer)	0	1	4	0	1	2	3
GSK-10	1	1	6	7	2	10	9
GSK-11	0	0	1	3	0	4	3
Aventis-8	0	0	6	2	4	8	4
Merck-7	3	0	4	7	2	9	7
Coadministered DTP vaccine							
DTaP	5	11	22	23	12	32	32
DTwP	8	0	43	19	13	53	30
Interval between doses 1 and 2							
1 month	5	2	36	14	8	36	29
2 months	8	9	31	28	17	50	40
Age first dose							
Birth	0	0	0	1	0	1	1
6 weeks	3	0	6	2	3	7	6
2 months	8	4	52	36	14	69	47
3 months	1	7	7	3	5	7	9
4 months	1	0	2	0	3	2	2

*A study may present immunogenicity data for 1 or more groups of children, defined as study arms. Study arms may be distinguished by immunization schedule (eg, 2-dose vs. 3-dose schedule or age at first dose) or PCV product (eg, PCV10 vs. PCV7).

†"2 doses" summarizes study arms with immunogenicity GMC data after a second primary dose, regardless of whether a third primary dose or booster dose was given; "3 doses" summarizes study arms with immunogenicity GMC data after a third primary dose, regardless of whether a booster dose was given. A study arm with immunogenicity data after a second and third dose will appear in both columns. Numbers describe only study arms with GMC data.

§2+0, 2 primary doses without a booster dose; 2+1, 2 primary doses plus a booster dose; 3+0, 3 primary doses without a booster dose; 3+1, 3 primary doses plus a booster dose. Arms that received a different product for the third or fourth dose than was administered in the first 2 or 3 doses (eg, boosted with PPV23) are described as "2+0" and "3+0," respectively. Numbers describe study arms with either GMC or proportion above specific value.

‡Number of unique studies with at least 1 study arm for the indicated characteristic.

¶Regions were defined by UN region.[79]

‖Year study conducted was not specified for most studies, so publication year is presented instead.

**The "Wyeth/other" method included any laboratory method other than the GSK laboratory method.

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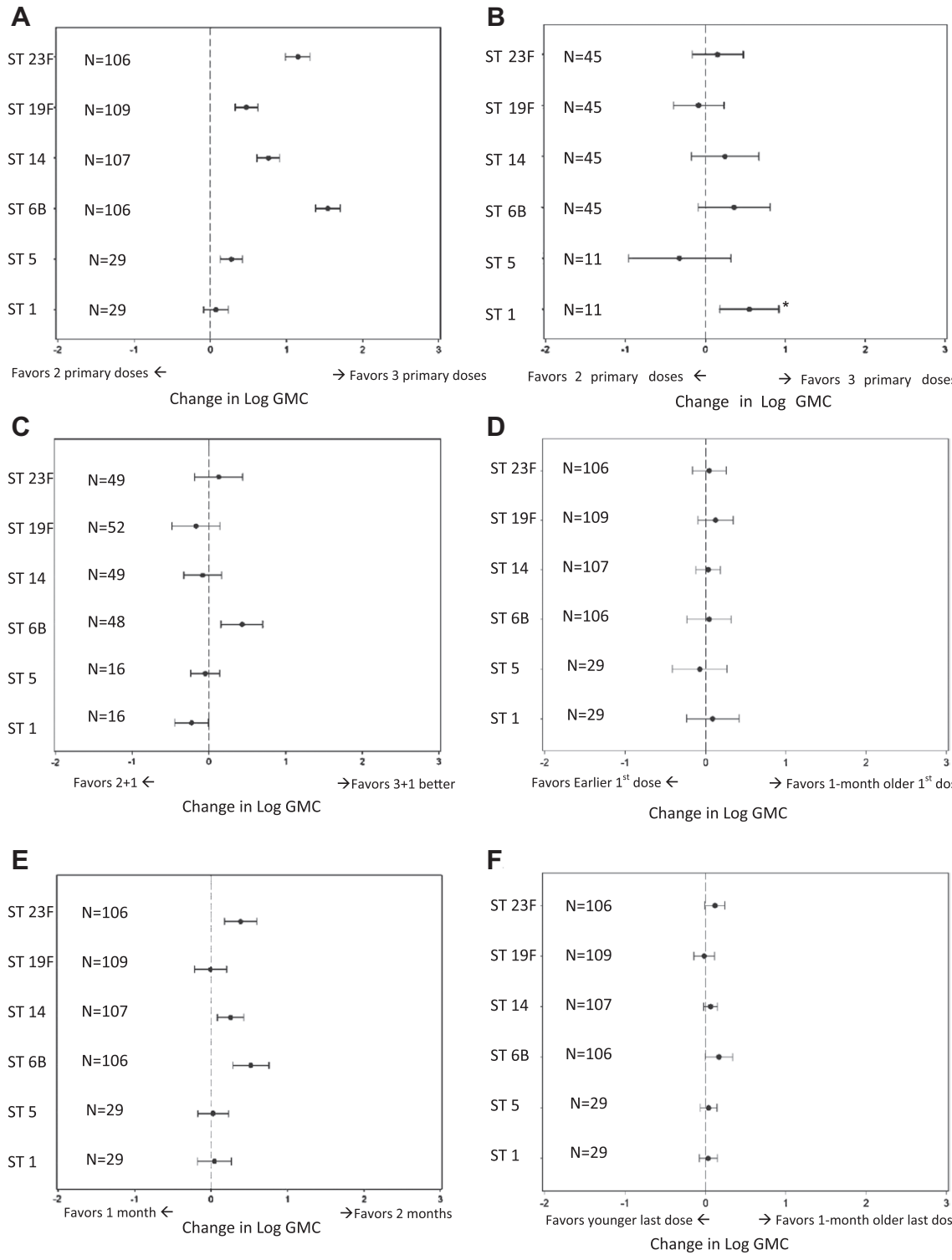

FIGURE 1. Effect of primary PCV dosing schedule on GMC by serotype. A) 2-dose versus 3-dose primary schedule on postprimary (~7 months) GMC; B) 2-dose versus 3-dose primary schedule on preboost (~12 months) GMC; C) effect of 2-dose versus 3-dose primary schedule on postboost (~13 months) GMC; D) effect of delaying age at first dose by 1 month on postprimary (~7 months) GMC; E) effect of increasing the interval between doses from 1 to 2 months on postprimary (~7 months) GMC and F) effect of delaying age at last dose by 1 month on postprimary (~7 months) GMC. Adjusted for age at first dose, geographic region, PCV product, coadministration of DTaP versus DTwP and laboratory method (GSK vs. Wyeth/other). N is the number of study arms. Asterick indicates that the significant ST1 finding in Figure 1B is due to 1 study where the two 2-dose arms had lower GMCs than the two 3-dose arms.[33] Otherwise, when looking at other studies, there is no difference.

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The GSK ELISA method was used to evaluate postprimary GMCs in all GSK PCV10 study arms, 4 of 7 GSK PCV11 study arms, 11 of 72 PCV7 study arms and no (0/54) study arms of other products. Very few studies reported avidity or functional OPA responses to evaluate the effect of number of doses on those outcomes. Immunogenicity varied by region, PCV product, coadministration with DTaP (ST14 only) and ELISA method.[80] Schedule effects were adjusted for these covariates in all analyses.

2-dose Versus 3-dose Priming Schedules

Of 61 studies included in the 2-dose versus 3-dose primary series analysis, 6 directly compared these different schedules and 9 additional studies provided after dose 2 results for 13 study arms eventually receiving a third primary dose. GMC results were available for 25 two-dose and 86 three-dose study arms (Table 1). The 3-dose primary schedule produced significantly higher postprimary GMC antibody response than the 2-dose schedule for all except serotype 1 (Fig. 1A,B). However, the number of primary doses did not meaningfully affect GMCs measured in the second year of life [ie, prebooster (Fig. 1B) or postbooster GMCs (Fig. 1C)], except the postboost response to serotype 6B, which was significantly higher in children who received 3 primary doses.

Timing of Primary Schedule

We evaluated the age at first dose, interval between doses and age at last dose, while adjusting for whether 2 or 3 primary doses were administered; albeit, each is a factor of the other 3 so they cannot be disentangled entirely. Administering the first dose at 1 month of age (eg, at 3 months vs. 2 months of age) did not meaningfully affect the postprimary GMCs (Fig. 1D). However, increasing the interval between doses from 1 to 2 months significantly increased the postprimary GMCs for serotypes 6B, 14 and 23F (Fig. 1E). Increasing the age at last dose had a similar effect to increasing months between doses although the effect size was smaller and did not reach statistical significance (Fig. 1F). Among the studies in the meta-analysis, only one directly compared interval of dosing while holding age at first dose constant, and it did so in a randomized trial setting.[33] That study's findings support the meta-analysis results; it showed that children randomly assigned to a 2-month interval between 2 primary doses had significantly higher postprimary GMCs for serotypes 6B, 14 and 23F and preboost GMCs at 1 year of age for serotypes 4, 6B and 23F compared with children who received their 2 primary doses with 1-month interval.

Booster Dose Effect

Of 53 study arms evaluating a PCV booster dose (generally in the second year of life), 11 (21%) had received a 2-dose primary schedule and 42 (79%) a 3-dose primary schedule. The booster dose increased GMCs from pre- to postbooster for all serotypes regardless of the priming schedule (Fig. 3A). Postbooster GMCs (mean age 13.5 months) were also significantly higher than postprimary GMC (mean age 7.2 months) for all serotypes regardless of the priming schedule (Fig. 3B).

3+0 Versus 2+1 Schedules

There were 58 studies with immunogenicity data on 2+1 or 3+0 schedules; GMC results were available for 86 "3+0" and

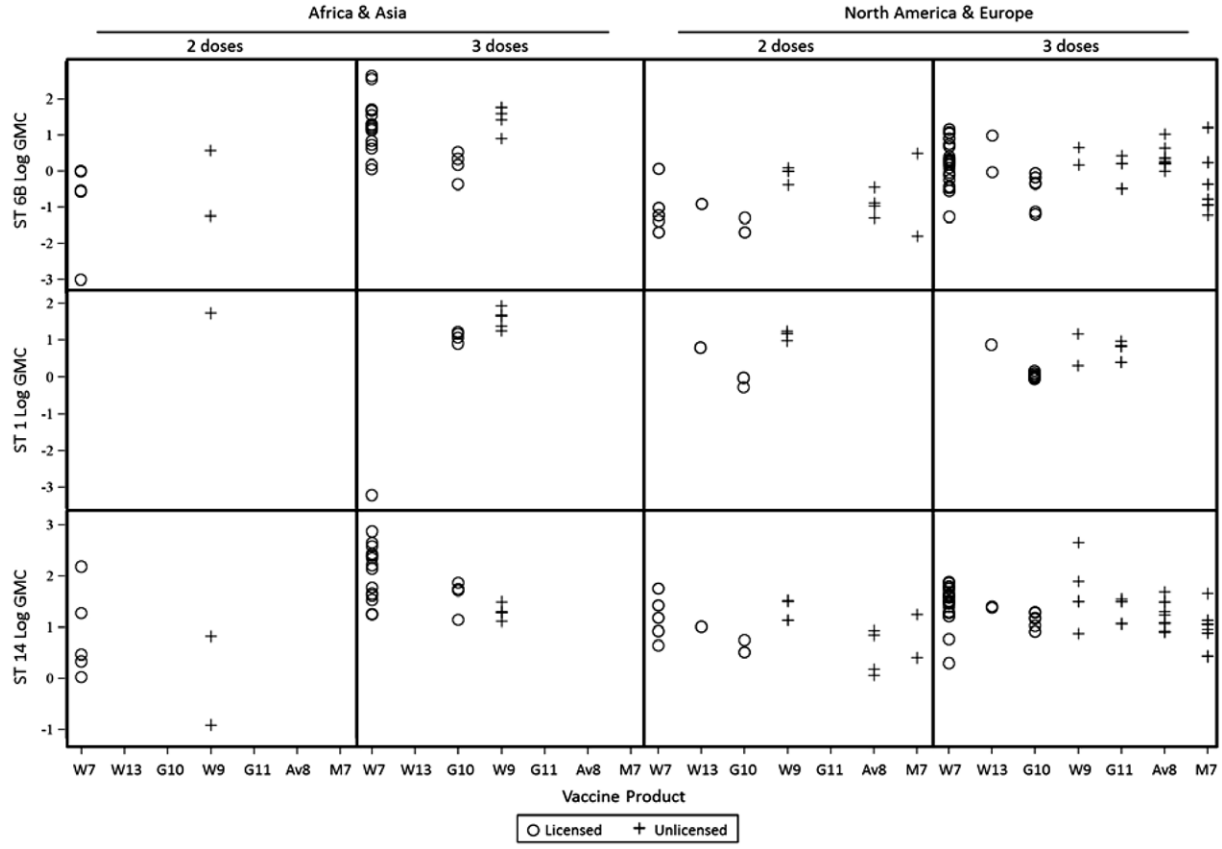

FIGURE 2. Log GMC by serotype, geographic region and number of primary series PCV doses. PCV product is indicated by manufacturer [W, Wyeth (Pfizer); G, GSK; A, Aventis; M, Merck] and valency (ie, number of serotypes it contains) on the *x*-axis, and by (o) for licensed or precursor or (+) for unlicensed product.

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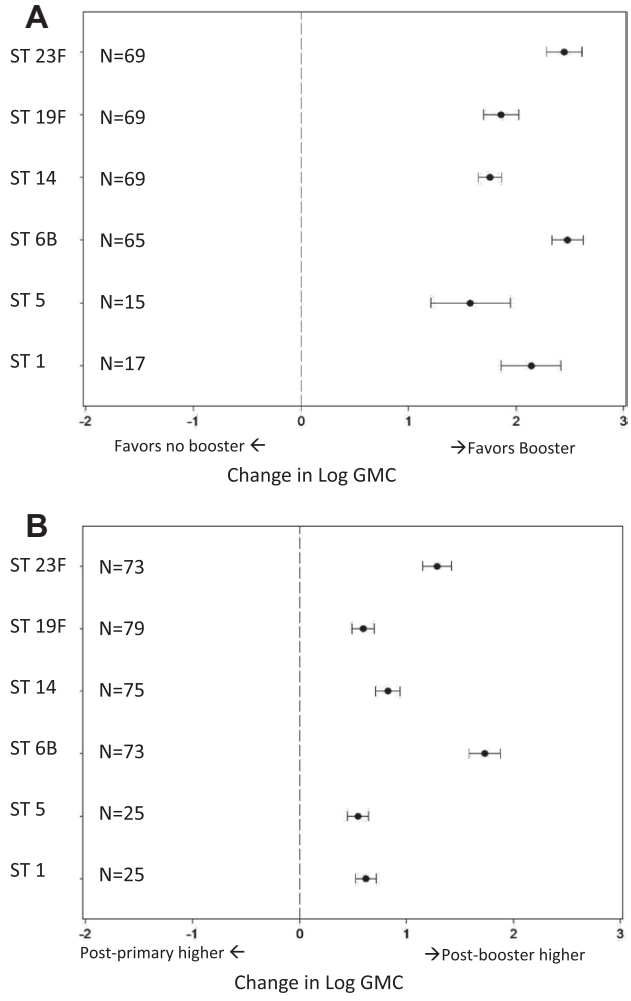

FIGURE 3. Effect of PCV booster dose in second year of life on GMC by serotype. A) Change in GMC pre- to postbooster; B) Change in GMC from postprimary (~7 months) to postbooster (~13 months).

11 "2+1" study arms. The unadjusted median postbooster GMC response (in µg/mL) of 2+1 schedules (median age at blood draw 12.5 months) compared with the postprimary response of 3+0 schedules (median age at blood draw 7.0 months) was 5.1 versus 2.5, 3.4 versus 3.0, 7.4 versus 1.4, 12.0 versus 4.7, 7.7 versus 3.6, 4.5 versus 1.7 for serotypes 1, 5, 6B, 14, 19F and 23F, respectively. After adjusting for geographic region, age at first dose, coadministration of DTaP versus DTwP, PCV product and ELISA laboratory method, the mean 2+1 postbooster antibody response (median age at blood draw 12.5 months) was significantly higher than the 3+0 postprimary response (median age at blood draw 7.0 months) for all serotypes (Figs. 4 and 5), although the covariates are tightly correlated and so confounding might not be entirely controlled for.

Proportion Achieving IPD Correlate of Protection Cut-off

The percentage of children with IgG antibody concentrations >0.35 µg/mL (or >0.20 µg/mL for GSK ELISA) was high and comparable for both 2-dose and 3-dose primary schedules for all serotypes except for 6B and 23F (Fig. 6). For these serotypes, the proportion of children above the threshold was higher for those

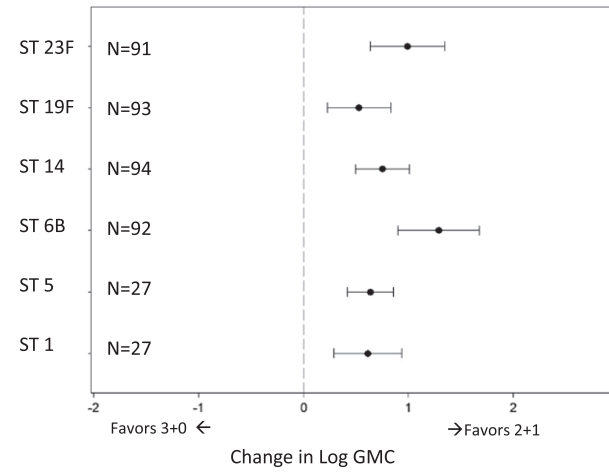

FIGURE 4. Difference in post-third dose GMC when changing from 3+0 (GMC at 6 months) to 2+1 (GMC at 15 months) PCV schedule.

receiving a 3-dose than a 2-dose primary schedule; 17/24 (70.8%) 3-dose study arms reported over 80% of subjects above the cut-off for serotype 6B compared with 3/13 (23.1%) 2-dose study arms. For serotype 23F, results were 21/24 (87.5%) compared with 4/11 (36.4%), respectively.

Only one 2+1 study presented percentage response data following the booster dose, which showed >96% response (IgG antibody concentrations ≥0.2 µg/mL) using the GSK ELISA for all serotypes except for 6B which had 88% response; response was also high (>87% for all serotypes) using the 0.35 µg/mL cut point.[72]

DISCUSSION

In general, a 3-dose primary schedule induced higher antibody than a 2-dose schedule for most serotypes assessed and a booster dose induced higher antibodies over those following the primary dose schedule for all serotypes. The degree to which higher antibody concentrations are important for protecting against serious disease is not established; there may be a threshold above which higher circulating antibody concentrations are not meaningfully more protective for an individual. While the aggregate, population-based correlate of protection used to license new PCV vaccines is 0.35 µg/mL, higher IgG levels may be important in protecting against NP colonization, conferring herd immunity, prolonging individual protection and, up to a point, may correlate at the individual level with disease protection. It is likely that the true threshold will vary by both serotype and disease syndrome, with higher concentrations probably required for mucosal infection like nonbacteremic pneumonia compared with systemic infection like invasive pneumococcal sepsis.

While both 2+1 and 3+0 schedules show evidence of robust immunogenicity for the serotypes evaluated (1, 5, 6B, 14, 19F and 23F), determining which schedule produced a superior response for serotypes 1 and 5 was not possible because data were limited, especially for 2+1 regimens (N = 4 study arms). In addition, the analyses for serotypes 1 and 5 included mostly studies of unlicensed formulations. Restricting analyses for serotypes 1 and 5 to only licensed products (ie, GSK PCV10 and Wyeth PCV13) provided very few studies for analysis: there was only one 2+1 study for each GSK PCV10 and Wyeth PCV13, and 6 and four 3+0 studies, respectively).

Considering options for a 3-dose schedule, which is recommended by the WHO and for which GAVI Alliance funding is

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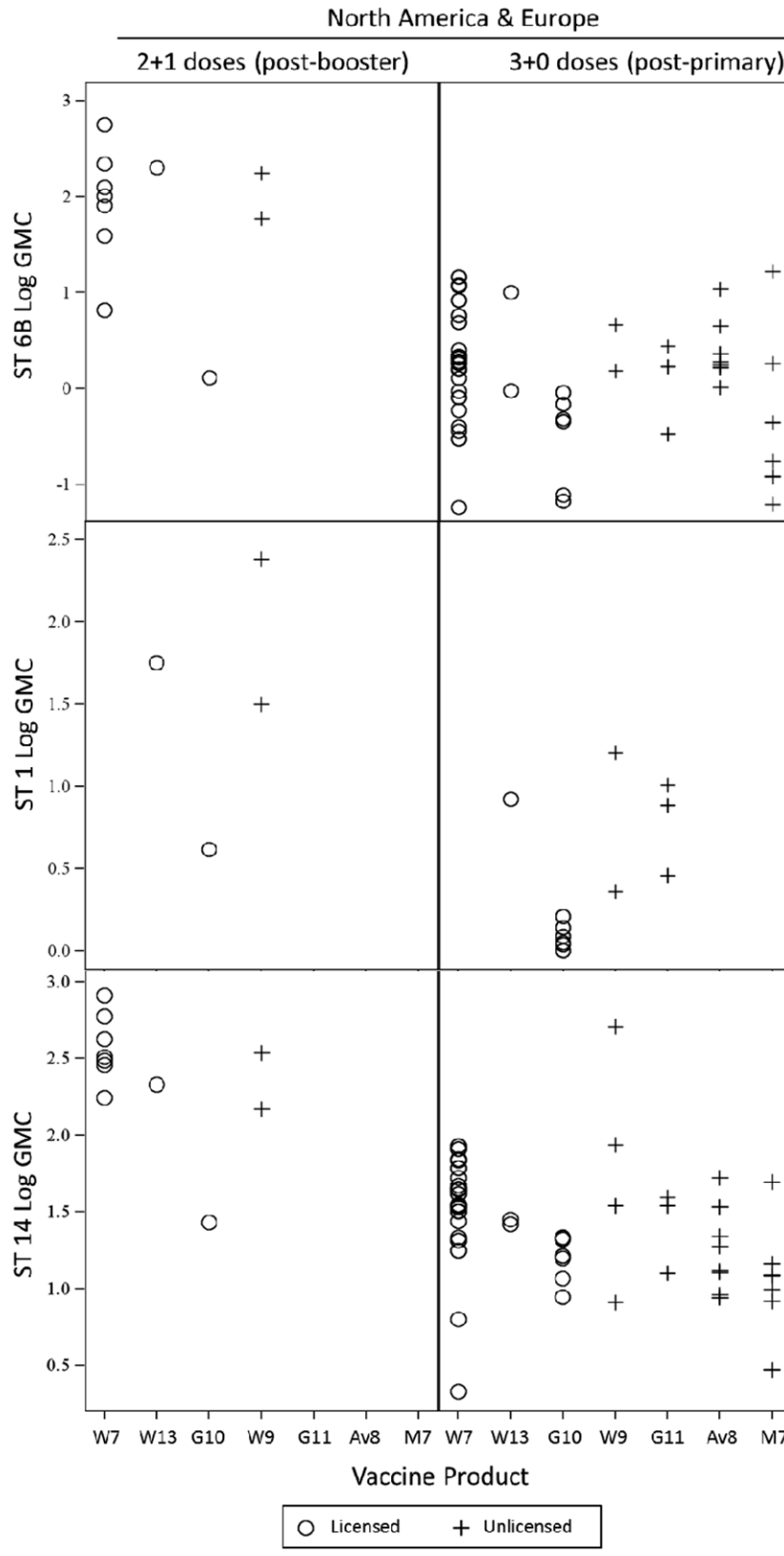

FIGURE 5. After postdose-3 log GMC, by serotype and PCV schedule: 2+1 (postbooster) versus 3+0 (postprimary). PCV product is indicated by manufacturer and valency (ie, number of serotypes it contains). W, Wyeth (Pfizer); G, GSK; A, Aventis; M, Merck.

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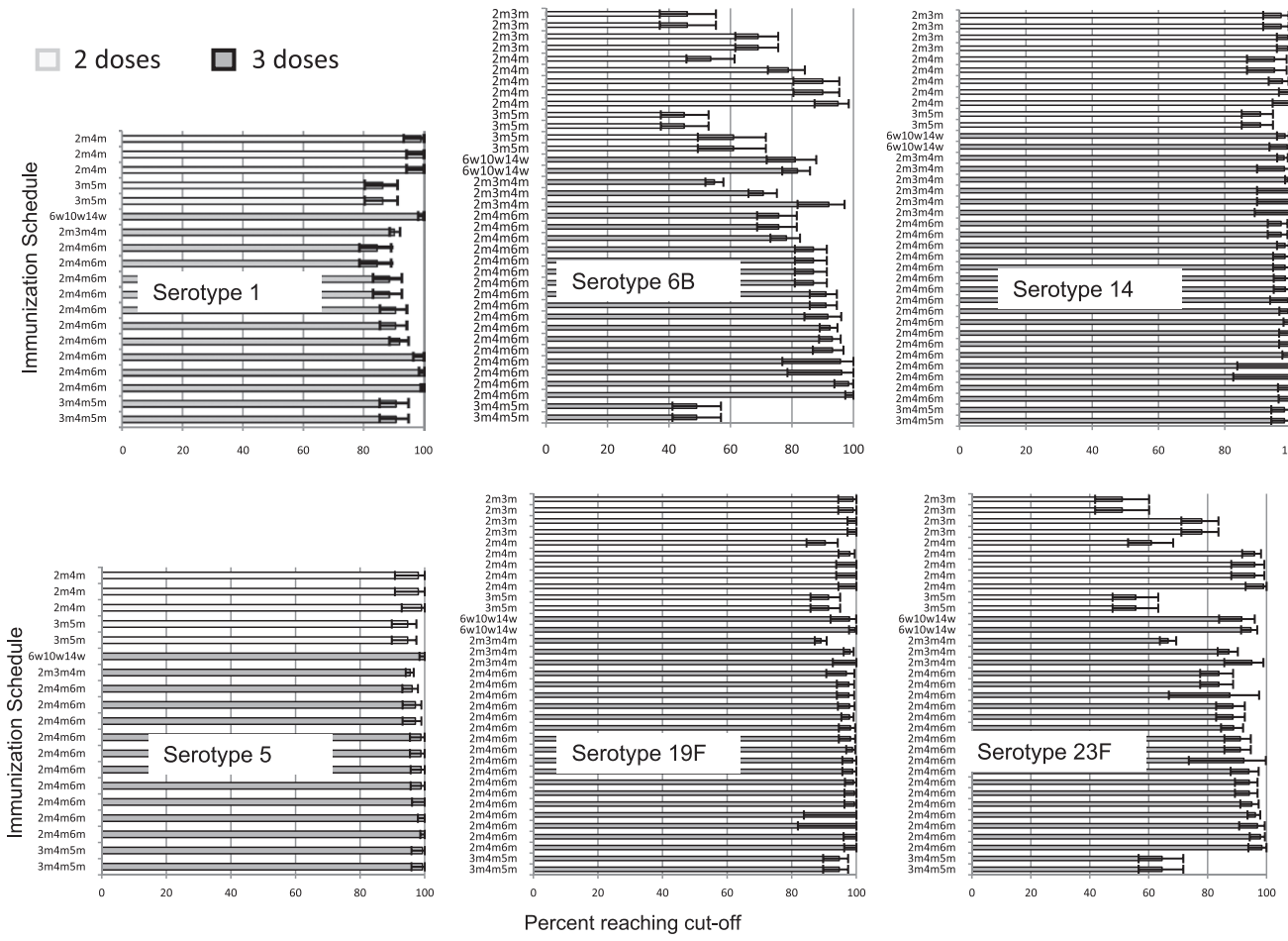

FIGURE 6. Proportion of children achieving >0.35 μg/mL (or >0.2 μg/mL if GSK ELISA used), by serotype, number of doses in primary series and immunization schedule. Each bar represents results from one study arm. Schedule is noted on the *y*-axis in months (m) or weeks (w). Error bars are 95% confidence intervals.

available for resource-limited countries, administering the third dose as a booster in the second year of life (2+1) induced higher antibodies than using the third dose to complete a primary series (3+0). However, for many epidemiologic settings, the first year of life is a time of high disease burden, so the advantage of delaying the third dose until the age of 1 year to achieve higher responses may be offset by the risk of leaving infants relatively at risk with lower antibodies after 2 primary doses.

While the use of meta-analysis allowed us to incorporate data from a large number of studies, controlling for study differences in covariates and confounding factors is a challenge in meta-analyses. Head-to-head studies that directly compare different schedules are more robust since they inherently control for potential confounders by keeping all covariates the same except the schedule, ideally through randomization. There were only 6 head-to-head randomized controlled trials that evaluated 2-dose versus 3-dose primary schedules. These were systematically reviewed in detail by investigators at the University of Berne who found that 3 primary doses provided higher antibody concentrations compared with 2 primary doses.[81] While there was representation across regions and a variety of schedules evaluated, their analysis was limited to just these 6 trials and all but 1 evaluated 3-dose schedules with a 1-month interval between doses compared with 2-dose schedules with a 2-month interval between doses (ie, age at dosing was 2 and 4 vs. 2, 3, and 4 months); dosing interval, therefore, confounds the relationship between antibody response and number of doses administered in that analysis. Our analyses included an additional 13 study arms where the antibody response after dose 2 was compared with that after dose 3 in the same individual. We also included a wealth of immunogenicity data available from studies evaluating only one schedule. Our more inclusive analyses reinforce the findings from the University of Berne analysis of head-to-head trials that not only 3 primary doses provide improved immunogenicity compared with 2 primary doses for most serotypes, but also enabled assessment of schedule effects in a broader variety of settings and combinations and enabled assessment of the timing of doses with respect to age at administration and months between doses.

Because most of the analysis was based on between-study comparisons rather than direct comparisons within a study, controlling for potential confounders of immunogenicity is essential when drawing inferences about dosing schedule effects. For some analyses, covariates such as coadministration of DTaP versus DTwP or the interval between doses (eg, 6, 10 and 14 weeks vs. 2, 4 and 6 months) could not be completely adjusted for because these factors are region specific and therefore linked. We could only compare 2+1 and 3+0 schedules within Europe because there were no eligible 2+1 schedule studies from other regions. Disentangling the effect of number of doses from the effect of age at each immunization or interval between primary doses is nearly impossible because as one factor changes necessarily at least one more also has to change.

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Serum IgG antibody concentration ≥0.35 μg/mL (or ≥0.20 μg/mL for studies using the GSK ELISA) after the primary series is considered a correlate for licensure of PCV products as they predict aggregate vaccine efficacy against vaccine serotype IPD among the immunized population.[13] We observed the same trend in the percentage meeting this cutoff for the 2-dose and 3-dose priming schedules as with GMCs but with less differentiation between these 2 schedules. It is our assessment that GMC is a more finely differentiating metric of the various dosing schedules than the proportion above the licensure threshold; however, it is not known which measure is more meaningful and predictive of clinical impact. We emphasize GMC values for several reasons. First, the population level protection effects are dependent on NP colonization. Preventing pneumococcal colonization is critical for population benefits of a pneumococcal vaccination program, since protection against colonization will necessarily mean protection against disease as well as reduced transmission in the community. Studies evaluating the correlation of antibody and protection against NP colonization have shown that antibody concentrations in the range of 4–5 μg/mL correlate with protection, although this is likely a marker of immune response and not the direct effector of protection.[82–84] Second, the prevention of pneumococcal pneumonia is the primary syndrome of concern for PCV programs, since most pneumococcal deaths that occur in young children globally are due to pneumonia, and the threshold for prevention of pneumococcal pneumonia is estimated to be significantly > 0.35 μg/mL (K.L.O.B. and G.D., unpublished data). Third, given the mucosal nature of pneumococcal pneumonia (when compared with IPD syndromes), it is not entirely clear whether circulating antibody or mucosal cells are the more important effector molecule for its prevention, although passive antibody studies (eg, studies evaluating administration of bacterial polysaccharide immunoglobulin) would argue for a role of circulating pneumococcal serum antibody.[85] Functional OPA may be a better predictor of protection than serum IgG; however, few studies assessed functional responses, so we were restricted to evaluating dosing schedule impact on serum IgG.

This, the largest such analysis of existing PCV immunogenicity data conducted to date, contributed to the WHO Strategic Advisory Group of Experts statement regarding optimizing PCV dosing schedules[86] and will help to guide PCV policy development in relation to the WHO's Expanded Programme for Immunization schedule. We have shown improved immunogenicity for 3 doses compared with 2 doses for most serotypes when serum IgG GMC is used as the metric for comparison. As expected, the 2+1 schedule leads to significantly higher antibody concentrations following the third dose, because it is administered remote from the primary series and acts as a booster dose when compared with the 3+0 schedule where the third dose is administered in the primary series. The tradeoff, therefore, is fundamentally between higher antibody concentrations in the second year of life following the booster with a 2+1 schedule and higher antibody concentrations in the first year of life from a 3-dose instead of a 2-dose primary schedule. While the relative merits of these 2 approaches will likely vary by serotype, disease syndrome and vaccine program, in practice, the herd effects induced by a successful vaccination program may minimize the impact on disease burden caused by schedule-related differences in immune response.

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