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The Differential Impact of Coadministered Vaccines, Geographic Region, Vaccine Product and Other Covariates on Pneumococcal Conjugate Vaccine Immunogenicity

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Background: Antipneumococcal capsular polysaccharide antibody concentrations are used as predictors of vaccine efficacy against vaccine serotype (ST) pneumococcal disease among infants. While pneumococcal conjugate vaccines (PCV) are recommended globally, factors associated with optimal PCV immune response are not well described. We aimed to systematically assess local setting factors, beyond dosing schedule, which may affect PCV antibody levels.

Methods: We conducted a literature review of PCV immunogenicity, abstracting data from published reports, unpublished sources, and conference abstracts from 1994 to 2010 (and ad hoc 2011 reports). Studies included in this analysis evaluated ≥ 2 primary doses of PCV before 6 months of age in non–high-risk populations, used 7-valent or higher PCV products (excluding Aventis-Pasteur and Merck products) and provided information on geometric mean concentration (GMC) for STs 1, 5, 6B, 14, 19F or 23F. Using random effects meta-regression, we assessed the impact of geographic region, coadministered vaccines and PCV product on postprimary GMC, adjusting for dosing schedule and ELISA laboratory method.

Results: Of 12,980 citations reviewed, we identified 103 vaccine study arms for this analysis. Children in studies from Asia, Africa and Latin America had significantly higher GMC responses compared with those in studies from Europe and North America. Coadministration with acellular pertussis DTP compared with whole-cell DTP had no effect on PCV immunogenicity except for ST14, where GMCs were higher when coadministered with acellular pertussis DTP. Vaccine product, number of PCV doses, dosing interval, age at first dose and ELISA laboratory method also affected the GMC.

Conclusions: PCV immunogenicity is associated with geographic region and vaccine product; however, the associations and magnitude varied by ST. Consideration of these factors is essential when comparing PCV immunogenicity results between groups and should be included in the evidence base when selecting optimal PCV vaccine schedules in specific settings.

Key Words: pneumococcal conjugate vaccine, immunogenicity, immunization

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Following the licensure of the first pneumococcal conjugate vaccine (PCV), subsequent pneumococcal formulations have relied on antipneumococcal capsular polysaccharide antibody concentration measurements for their evaluation and licensure. A geometric mean concentration (GMC) of 0.35 μg/mL of serotype (ST)-specific anticapsular IgG has been recommended by the World Health Organization (WHO) as the population correlate of protection against invasive pneumococcal disease (IPD) in infants to be used for licensure of new products.[1–3] Evaluations of nasopharyngeal (NP) carriage have suggested that higher antibody concentrations correlate with protection against mucosal infection; however, those measured systemic antibody concentrations are likely a marker for local mucosal immunologic processes and not the effector mechanism.[4–7] The suggestion that circulating IgG is not the effector mechanism for prevention of NP colonization is reinforced by studies showing that pneumococcal polysaccharide vaccine has no impact on colonization in situations where it has been shown to be immunogenic.[6,8] Factors that may affect the antibody response to PCV include the number of and interval between doses, geographic region (where maternal transmission of antibodies and age of first exposure to pneumococcus may vary), age at first dose, coadministered vaccines and the PCV product used.

PCV is recommended by the WHO for use in the routine infant immunization schedules of all countries, especially those with a high disease burden.[9] The WHO has recommended PCV since 2007 and the recommended schedule until 2012 has been a 3-dose primary series schedule without a subsequent booster. However, studies have shown that although 3-dose primary series schedules produce higher antibody concentrations compared with 2-dose primary series schedules, a 2-dose primary series with a booster dose also confers high antibody concentrations.[10,11] Accordingly, the WHO now recognizes a 2-dose primary series with a booster as an acceptable alternate schedule.[12] Many countries have already introduced PCV using a 3-dose primary series schedule with a booster or 1 of the WHO recommended schedules.[13–17] However, it is not known whether any of these schedules are suboptimal from a disease impact perspective in the context of other cofactors related to the geographic region, coadministered vaccines and PCV product.

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Given the conditions or setting in which a PCV is to be used, the combination of effects may be important for determining the optimal dosing schedule. The objectives of this article were to identify which factors affect the postvaccination pneumococcal antibody response other than dosing schedule and to illustrate estimated antibody concentrations for various common epidemiologic situations rather than presenting results solely as the relative change in antibody concentration from 1 setting to another.

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.[11,18–21] Details on the literature search terms and methods used in this systematic review are described elsewhere (see Methods Appendix[22]). 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 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 pneumococcal polysaccharide vaccine was used as a booster dose, but not as a primary dose. Titles and abstracts were reviewed twice and those with relevant content on 1 of the 5 outcomes (immunogenicity, carriage, invasive disease, pneumonia and indirect effects) underwent full review using a standardized data collection instrument. We did not search non-English language literature because of the low likelihood they would have relevant data for this project. Details on the search methods are provided in the Methods Appendix.[22]

Data Abstraction

Citations recovered through the literature search went through several stages of independent review to determine their eligibility, as described elsewhere.[22] Citations meeting inclusion criteria were categorized on an outcome specific basis into "study families," where each family included abstracts or publications generated from a single protocol, population, surveillance system or other data collection system relevant to that outcome. Investigators identified primary data from the individual studies making up each study family for inclusion in the analysis. The primary data were selected as the most current and complete data available for that study family. In some cases, these data were drawn from >1 publication within a family. We also defined "study arms" as a group of children distinguished by immunization schedule or PCV product.

We abstracted core information on the following: number of children in a "study arm"; PCV manufacturer, valency and conjugate protein; coadministered vaccines; country; age at each dose and date of study and publication. Additional data abstracted for the analysis on immunogenicity covariates included study population characteristics (HIV status, sickle cell disease, indigenous subgroups and other high-risk groups) and ELISA laboratory methods. Results that were abstracted included ELISA IgG GMC, the percentage of children with ST-specific antibody concentrations >0.35 μg/mL [or 0.2 μg/mL if GlaxoSmithKline (GSK) ELISA method used], and whether other assays were performed such as opsonophagocytic assay and avidity measures.

Inclusion and Exclusion Criteria

Study arms meeting the following criteria were included in the analysis: children immunized with at least 2 primary doses of PCV, with a first dose at ≤ 4 months of age and the last primary dose at ≤ 6 months of age; used licensed or similar to licensed PCV products 7-valent or higher and provided information on ELISA IgG GMC for any of the 6 STs of interest (1, 5, 6B, 14, 19F or 23F). Merck and Aventis products were excluded because they were not pursued for licensure and contained carriers that are not the same as those used in licensed products. Study arms evaluating only high-risk populations, including those with HIV infection, sickle cell disease, chronic illness and indigenous subgroups, were excluded.

Pneumococcal Vaccine Dosing Schedules

Study arms with immunogenicity data after a second or third primary dose were defined as "2 primary dose" or "3 primary dose" arms, respectively. Any 3 primary dose schedules that provided immunogenicity data following the second dose were also included with the 2 primary dose schedules. "2+0" and "2+1" schedules refer to 2 primary doses without and with a booster dose, respectively. A booster dose was defined as immunization between 9 and 18 months of age where infants had already received 2 or more doses of PCV. 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 the number of months between first and second primary dose.

Data Analysis

We aimed to assess the effect of PCV dosing schedules and study-specific covariates on mean ST-specific GMCs while considering that most studies did not have intrastudy comparisons of schedules. We therefore followed an ecological regression approach to compare dosing schedules across studies. We fitted random effects meta-regression models of log-transformed GMC levels by ST, weighting by the inverse of their variances and calculating robust standard errors to account for multiple arms within studies.[23,24] We evaluated the effect of geographic region, PCV product and coadministered diphtheria, tetanus and pertussis vaccine (DTP), adjusted for the effect of the other covariates and for number of doses, age at first dose, interval between doses and ELISA laboratory method. For studies that did not report the variances of the GMC, we assigned the average variance reported by studies within the same region. A detailed description of how missing values were accounted for can be found in the accompanying immunogenicity article.[11]

Using the coefficients for each covariate, the regression model output was used to estimate the GMC for combinations of region, coadministered DTP type and schedule, including potential schedules that have not been studied in the existing literature. The most common vaccine schedule in a given region was used as the reference group to compute GMC for other schedules. The PCV9 vaccine was used as the reference to generate GMC values for STs 1 and 5, and PCV7 (Prevnar) was used as the reference for STs 6B, 14, 19F and 23F.

Analyses were done in SAS 9.2 (SAS Institute Inc., Cary, NC) and STATA 11 (StataCorp, College Station, TX).

RESULTS

Of 12,980 citations reviewed, we identified 62 studies on immunogenicity, of which 52[15,25–75] used licensed or similar to licensed PCV products 7-valent or higher, yielding 103 vaccine arms eligible for analysis (Table 1). There were only 2 study arms

TABLE 1. Characteristics of Included Study Arms by Region

Characteristic		Total (N = 103)	Number of Study Arms by Region (% in Region)				
			Africa (N = 10)	Asia/Oceania (N = 18)	Europe (N = 55)	North America (N = 13)	Latin America (N = 7)
Schedule characteristics							
Number of primary doses*	3	80	8 (80.0)	13 (72.2)	40 (72.7)	12 (92.3)	7 (100)
	2	23	2 (20.0)	5 (27.8)	15 (27.3)	1 (7.7)	0
Interval between doses	1 month	42	9 (90.0)	6 (33.3)	27 (49.1)	0	0
	2 months	61	1 (10.0)	12 (66.7)	28 (50.9)	13 (100)	7 (100)
Age at first dose	0 months	1	1 (10.0)	0	0	0	0
	6 weeks	9	4 (40.0)	5 (27.8)	0	0	0
	2 months	72	5 (50.0)	6 (33.3)	41 (74.5)	13 (100)	7 (100)
	3 months	16	0	2 (11.1)	14 (25.5)	0	0
	4 months	5	0	5 (27.8)	0	0	0
Age at last dose	10 weeks	2	1 (10.0)	1 (5.6)	0	0	0
	14 weeks	7	4 (40.0)	3 (16.7)	0	0	0
	3 months	3	1 (10.0)	0	2 (3.6)	0	
	4 months	31	4 (40.0)	1 (5.6)	25 (45.5)	1 (7.7)	0
	5 months	18	0	4 (22.2)	13 (23.6)	1 (7.7)	0
	6 months	42	0	9 (50.0)	15 (27.3)	11 (84.6)	7 (100)
Covariate characteristics							
DTP	DTwP	56	10 (100)	12 (70.6)	13 (23.6)	7 (53.9)	4 (57.1)
	DTaP	46	0	5 (29.4)	42 (76.4)	6 (46.2)	3 (42.9)
PCV product	PCV7	62	4 (40.0)	16 (88.9)	29 (52.7)	12 (92.3)	1 (14.3)
	PCV9	19	5 (50.0)	0	11 (20.0)	0	3 (42.9)
	PCV13	3	0	0	2 (3.6)	1 (7.7)	0
	PCV10	15	1 (10.0)	2 (11.1)	9 (16.4)	0	3 (42.9)
	PCV11	4	0	0	4 (7.3)	0	0
Laboratory method	Wyeth	75	9 (90.0)	15 (83.3)	38 (69.1)	10 (76.9)	3 (42.9)
	GSK	28	1 (10.0)	3 (16.7)	17 (30.9)	3 (23.1)	4 (57.1)

*A study arm with immunogenicity data after a second and third dose will appear in both rows.

from the Oceania region (Fiji) and these were grouped with the Asia region. Studies were conducted in all regions of the world, but there were no studies evaluating a 2-dose primary series in the Latin America region. The Americas had the least diversity in the schedules evaluated and only evaluated schedules of 2-month intervals between doses starting at the age of 2 months. The most common schedules found among all study arms were 2-, 4- and 6 month schedules (37.9%) and 2-, 3- and 4-month schedules (23.3%), with most of them conducted in either North America or Europe. In Africa, most studies used either a 2-, 3- and 4-month schedule (40%) or 6-,10- and 14-week schedule (30%). In Latin America and Asia, a 2-, 4- and 6-month schedule was most common.

Common Covariate Groupings

In every region, except Africa, we found diversity in the type of DTP vaccine coadministered with PCV; in Africa, all studies used whole-cell DTP (DTwP) as the coadministered vaccine (Table 2). DTwP was used in many studies in every region except Europe. Except Africa, every region had 2-, 4- and 6-month schedules evaluated with both acellular pertussis DTP (DTaP) and DTwP enabling comparison of the effect of DTP within and between regions without confounding by other factors. 2+1 schedules were administered with DTaP only, all from European settings (data not shown). Only in Europe could we compare DTaP with DTwP for different PCV schedules (3, 4 and 5 months and 2 and 4 months). PCV7 was evaluated in all regions. Only 1 and 2 non-PCV7 products were evaluated in North America and Asia/Oceania, respectively, and Europe was the only region with analyzable data on all 5 PCV products.

Effect of Covariates on PCV Immunogenicity

Regression analysis controlling for covariates found that 3 primary PCV doses produced significantly higher GMCs than 2 primary doses (Table 3). We also noted higher GMCs for schedules that had 2-month intervals between doses in the primary series compared with 1-month intervals for STs 6B, 14 and 23F, although these results were not significant. Age at first dose, interval between doses, number of doses and age at last dose were interrelated (3 of these factors determine the fourth); therefore, we could not evaluate all of these factors independently. All but 1 study retained the same interval between first to second and second to third primary doses. In our analysis, we evaluated age at first dose and age at last dose separately and found higher GMCs with increasing age, although this was only significant for ST6B with a 1.29-fold increase for each month of increasing age.

Geographic region was associated with both pre- and post immunization GMC values (Fig. 1). Although preimmunization GMC data were sparse, GMCs appeared lowest in North America (N = 2 for STs 1 and 5, N = 9 for other STs) and Latin America (N = 1) and highest in Africa (N = 3 for STs 1 and 5, N = 5 for other STs). For some STs, preimmunization GMCs were inversely related to postimmunization GMCs; in that, if preimmunization GMCs were low relative to other regions, their postimmunization GMCs were high relative to other regions.

Type of DTP coadministered had no effect on immunogenicity for STs 6B, 19F and 23F, but DTaP was associated with 1.6-fold higher GMCs for ST14 than DTwP ($P < 0.01$) and 1.4- and 1.3-fold higher GMCs for STs 1 and 5, and the results were not significant (Fig. 2). When limiting evaluations to homogeneous settings in North America and Europe, DTaP coadministration remained associated with a higher GMC for ST14.

ST-specific postprimary GMCs varied by PCV product tested. Compared with PCV7, GSK PCV10 had lower GMCs for all STs evaluated in common, but significantly higher GMC for ST19F after adjusting for ELISA method (Table 3). PCV13 was also lower than PCV7 for the 4 STs evaluated in common, but there were few PCV13 studies and the difference was not statistically significant.

TABLE 2. Number of Study Arms Evaluating Vaccine STs by Region, Type of DTP Vaccine and Schedule

Region	DTP	Schedule	Study Arms by ST			
			6B, 14, 19F, 23F		1, 5	
			N	%	N	%
Africa	DTwP	2 and 3 months or 6 and 10 weeks	2	2.3%	1	3.0
		0,10 and 14 or 6, 10 and 14 weeks	4	4.6%	3	9.1
		2, 3 and 4 months	4	4.6%	3	9.1
Asia and Oceania	DTwP	6 and 10 weeks	1	1.1%	—	—
		4 and 6 months	3	3.4%	—	—
		6, 10 and 14 weeks	3	3.4%	1	3.0
		2, 4 and 6 months	3	3.4%	—	—
		4, 5 and 6 months	2	2.3%	—	—
	DTaP	2 and 4 months	1	1.1%	—	—
		1.5, 3 and 6 or 2, 4 and 6 months	3	3.4%	1	3.0
		3, 4, and 5 months	1	1.1%	—	—
Europe	DTwP	2, 3 and 4 months	5	5.7%	1	3.0
		2, 4 and 6 months	7*	8.0%	1	3.0
	DTaP	2 and 3 months	2	2.3%	—	—
		2 and 4 or 3 and 5 months	8	9.2%	6	18.2
		2, 3 and 4 or 3,4 and 5 months	12†	13.8%	4	12.1
		2, 4 and 6 months	6‡	6.9%	5	15.2
North America	DTwP	2 and 4 months	1	1.1%	—	—
		2, 4 and 6 months	6	6.9%	—	—
	DTaP	2, 4 and 6 months	6	6.9%	1	3.0
Latin America	DTwP	2, 4 and 6 months	4	4.6%	4	12.1
	DTaP	2, 4 and 6 months	3	3.4%	2	6.1
Total			87		33	

*N = 8 for ST19F.
†N = 14 for ST14.
‡N = 7 for ST19F.

Immunogenicity to all GSK products was evaluated using the GSK ELISA laboratory method, which is known to produce lower absolute values than other ELISA measurement methods.

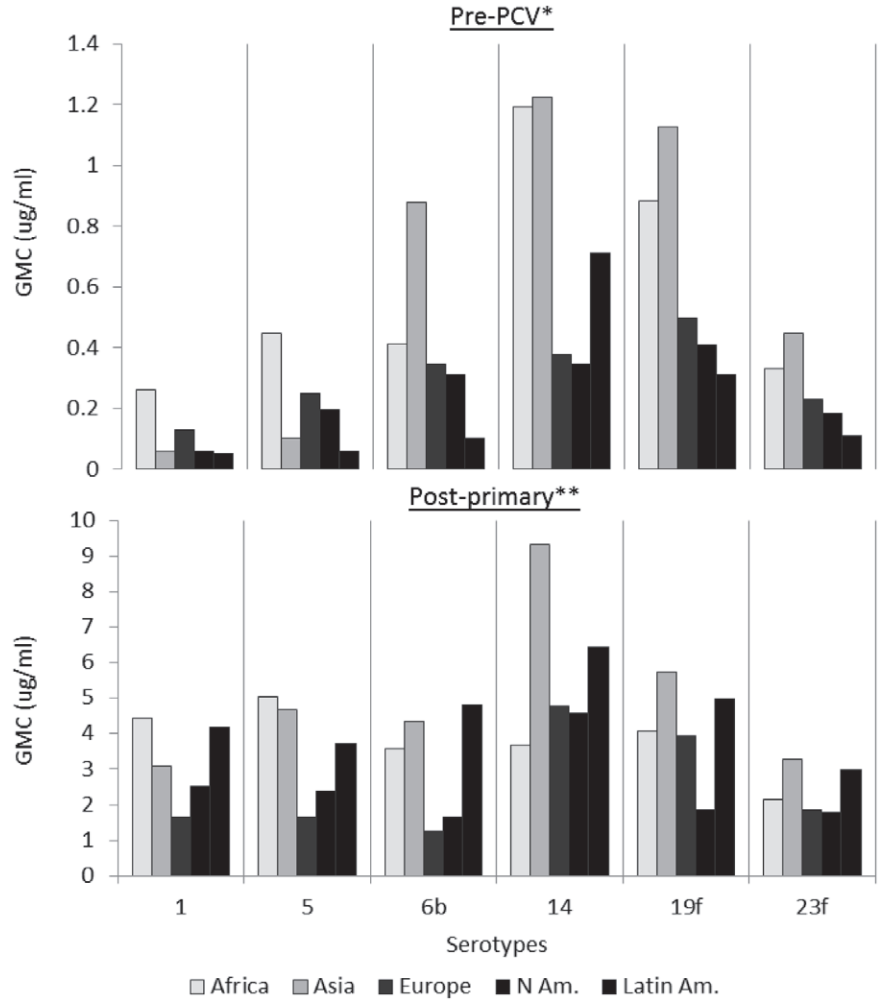
Predictive Analyses

Using the output from the regression model, we estimated GMCs for plausible schedules, including some which have not been reported in the existing literature, combined with DTP type for each region (Table 4). The projected change in GMC comparing the 3-dose 6-, 10- and 14-week schedule with a 2-dose 6- and 14-week schedule in Africa is relatively small for STs 1 and 5 (changing from GMC = 5.0 µg/mL for both STs to GMC = 4.77 and 3.88 µg/mL, respectively), but for the other STs the decrease in GMC is more substantial (ie, ST6B dropped from GMC 0.97 to 0.27 µg/mL, ST14 dropped from 2.51 to 1.33 µg/mL). Although this hypothetical schedule cannot be verified directly, a study by Ota et al[69] showed a

TABLE 3. Effect of Covariates on GMC, Adjusted for Dosing Schedule and Other Covariates

Characteristic		Fold change in GMC*					
		ST1 (N = 31)	ST5 (N = 32)	ST6B (N = 87)	ST14 (N = 89)	ST19F (N = 89)	ST23F (N = 87)
DTP	DTwP	Ref	Ref	Ref	Ref	Ref	Ref
	DTaP	1.36	1.33	1.18	1.60†	1.16	1.00
Region	Europe	Ref	Ref	Ref	Ref	Ref	Ref
	Africa	2.89†	4.22†	1.94‡	0.98	1.21	0.96
	Asia§	3.41†	3.17†	2.23†	1.73†	1.53†	1.76†
	North America	1.14	1.42	0.85	0.77	0.56†	0.69
	Latin America	2.59†	2.57†	1.79	1.35	1.44	1.36
PCV product	PCV7	—	—	Ref	Ref	Ref	Ref
	PCV9	Ref	Ref	1.99†	1.03	0.70	1.25
	PCV13	0.80	0.98	0.84	0.79	0.75	0.79
	PCV10	0.77	0.81	0.73‡	0.72†	1.66†	0.55†
	PCV11	0.93	0.95	0.62	0.58‡	1.29	0.53‡
Interval between doses	1 month	Ref	Ref	Ref	Ref	Ref	Ref
	2 months	1.05	1.03	1.88	1.34	0.96	1.56
Number of primary doses	3	Ref	Ref	Ref	Ref	Ref	Ref
	2	0.91	0.75‡	.15†	0.40†	0.68†	0.26†
Age first dose	1-month increase	1.15	1.02	1.29‡	1.11	1.11	1.18
Laboratory method	Wyeth	Ref	Ref	Ref	Ref	Ref	Ref
	GSK	0.52	1.19	0.50†	0.82	0.72	0.98

*Compared to reference group.
† $P < 0.01$; ‡$P < 0.05$ compared with reference group.
§Includes Fiji; there were no other studies in the Oceania region included in analysis.



*Pre-PCV GMC calculated using the average GMC in children <3m prior to PCV vaccination. N=3, 1, 2, 2, and 1 for STs 1 and 5 in Africa, Asia, Europe, North America, and Latin America, respectively. N= 5, 7, 8-10, 9, and 1 for all other serotypes in the same regions.

** Post-PCV GMC calculated using the average GMC following 3-dose schedules in each region. N=5, 2, 11, 1, and 6 for STs 1 and 5 in Africa, Asia, Europe, North America, and Latin America, respectively. N= 8, 13, 30-32, 10, and 7 for all other serotypes in the same regions.

FIGURE 1. Average pre- and post-PCV pneumococcal IgG GMC in children by ST and region.

GMC of 0.05 and 1.03 for STs 6B and 14, respectively, using a similar 2- and 3-month schedule; the GMC in the 3-dose group was 3.47 for ST 6B and 4.65 for ST 14. In Asia, the predicted fold change was similar, but because GMCs were higher in Asia than in Africa, the GMCs for the 2-dose 6- and 14-week schedule in Asia are similar to the GMCs for the 3-dose 6-, 10- and 14-week schedule in Africa (eg, for ST19F in Africa, the GMC = 4.26 µg/mL with 3 doses and in Asia, the GMC = 4.25 µg/mL for 2 doses).

Predicted GMC responses followed similar trends in North America and Europe. In North America, the predicted change in GMC comparing a 2-, 4- and 6-month schedule with a 2- and 4-month schedule coadministered with DTaP remains relatively small for STs 1 and 5 (changing from 3.00 and 2.34 µg/mL to 2.73 and 1.75 µg/mL, respectively). A larger change is predicted for the other STs, with GMCs changing from 1.09 to 0.16 and 4.50 µg/mL to 1.78 µg/mL for STs 6B and 14, respectively. Increasing the interval between primary doses from 1 to 2 months also tended to increase GMCs, although less substantially than increasing the number of doses. Lowest GMCs were predicted for 2-dose schedules with 1 month between doses. Nearly all schedules produced predicted GMCs above the 0.35 µg/mL value correlated with high vaccine efficacy in children except for certain 2-dose schedules in Europe, North America, Africa and Latin America for STs 6B and 23F.

DISCUSSION

The number of PCV doses, interval between doses, geographic region, PCV product and preimmunization antibody levels are all significantly associated with postprimary PCV IgG antibody concentration, but varied by ST. Within a region, the number of primary doses had the largest effect on postprimary GMC. Predicted GMCs were higher than the 0.35 µg/mL putative population-based

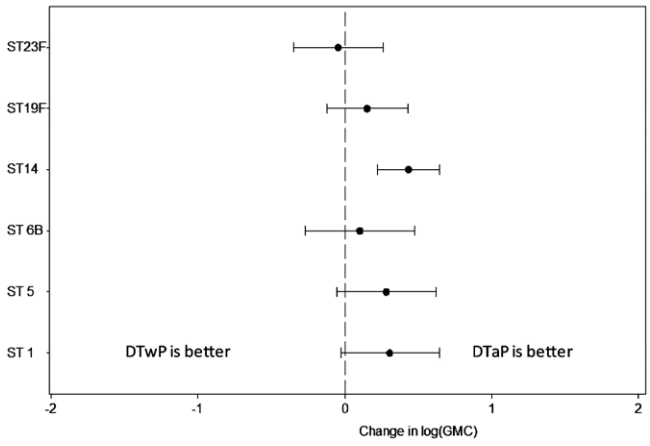


FIGURE 2. Effect of DTaP versus DTwP coadministration on postprimary PCV GMC for selected vaccine STs.

correlate of protection against IPD used for licensure for most estimated combinations of schedule and covariates, except for certain 2-dose schedules. Predicted postprimary GMCs for specific schedules varied by region; because of large differences in postimmunization antibody levels between regions, a 2-dose schedule in Asia could have higher GMCs than a 3-dose schedule in North America. Coadministration of PCV with DTaP compared with DTwP had no impact on the GMC response, except for ST14, where DTaP was associated with a higher GMC response.

Higher antibody responses may correlate with mucosal protection because they reflect a more robust local immune response, thus potentially reducing disease transmission and increasing herd or indirect protection.[4,5] In settings where GMC responses are lower, particularly in Europe and North America, 2-dose schedules can result in GMCs below the 0.35 µg/mL correlate of protection for some STs. A study in the United Kingdom that directly compared a 2- and 3-month primary schedule with a 2-, 3- and 4-month schedule with PCV7 found significantly reduced antibody responses to STs 6B, 23F and 18C, with GMCs of 0.19 and 0.22 µg/mL for STs 6B and 23F, respectively, in the 2-dose arm.[15] These GMC values are similar to the GMCs predicted for a 2- and 3-month schedule in our analysis (0.19 and 0.34 µg/mL for STs 6B and 23F, respectively).

The expanded valency PCV products, PCV13 (Pfizer) and PCV10 (GSK), both had lower GMCs than PCV7 (Pfizer) for 3 of the 4 STs compared in common, but PCV10 was found to have a higher GMC for ST19F, and both new products add STs 1 and 5 which showed antibody responses considerably greater than the 0.35 µg/mL threshold. The ST19F result is supported by all 4 available head-to-head evaluations of GSK PCV10 versus PCV7. The reduced effects for the other STs are supported in 2[25,39] of 3 head-to-head studies with available ST data.[25,39,71] The data were too sparse to directly compare immunogenicity of PCV13 versus PCV10, but given that both vaccines produced antibody levels above the desired 0.35 µg/mL threshold for all STs, the relevance of these findings for policy makers is unclear.

Age at first dose was significantly associated with immunogenicity in this analysis for ST6B only. However, because our analysis was dominated by studies with first dose at 6 weeks or older, reduced immunogenicity when the first dose is given at birth was obscured (only 1 study evaluating a birth dose was included). A study in Kenyan infants comparing a birth dose to a first dose at 6 weeks of age found lower GMCs in the birth dose group for STs 4, 9V, 18C and 19F at 18 weeks; however, there were no significant differences in the proportion of each group reaching the protective GMC of 0.35 µg/mL.[70]

The burden of pneumococcal disease by age for a particular region is an important consideration when determining the optimal age at first dose. If the peak incidence of IPD or pneumonia occurs within the first 6 months of life, an earlier age of first dose would be expected to prevent a greater proportion of disease, and according to our analyses, would not result in meaningfully lower GMCs than a later first dose.[76] The burden of disease is also important when considering increasing the interval between primary doses from 1 to 2 months, which significantly increases postprimary schedule immunogenicity for STs 6B, 14 and 23F. An increased interval could be particularly beneficial in situations where 2 primary doses are used; however, if much disease occurs early in life, shorter intervals may be beneficial in preventing disease despite the lower GMCs.

There were strong regional differences in the magnitude of the pneumococcal ST-specific immune response, with Asia, Africa and Latin America having the highest GMCs. Because of these differences, there is a limited extent to which findings in North America and Europe can be extrapolated fully to developing country settings. However, we still noted differences in GMCs for different numbers of doses and intervals in Asia, Africa and Latin America. Although developing country settings had high GMC responses, optimizing vaccine response in these settings remains important because factors associated with disease risk such as malnutrition, higher prevalence of colonization and early onset of colonization are more prevalent in low-income populations.

Coadministration of PCV with DTaP versus DTwP did not produce discernible differences in immunogenicity for STs 6B, 19F or 23F. Unexpectedly, coadministration with DTaP was significantly associated with higher immunogenicity for ST14 compared with DTwP. Studies of *Haemophilus Influenzae* type b (Hib) conjugate vaccines conjugated to diphtheria or tetanus revealed carrier-induced suppression when coadministered with DTP vaccines; the adjuvant property of whole-cell pertussis was absent in the newer DTaP products revealing carrier suppression and resultant lower Hib antibody concentrations.[77] Unfortunately, there are no randomized head-to-head comparisons of PCV coadministered with DTaP versus DTwP. A study by Dagan et al[78] evaluating PCV has shown a reduced ST-specific antibody response for STs conjugated to tetanus toxoids when coadministered with DTaP compared with DTwP; the same explanation as for Hib conjugate vaccine is believed to play a role. However, ST14 is not conjugated to tetanus toxoid, so there is no explanation for why this ST is affected by type of DTP coadministered. In the aforementioned study, ST14 demonstrated an attenuated response with DTaP coadministration, although this difference was only significant after the booster dose. Another study by Schuerman et al[79] comparing DTaP versus DTwP coadministration in similar study populations observed a trend towards an increased ST14 response with DTaP coadministration, although the difference was not statistically significant and disappeared after the booster dose. We found no other evidence in the published literature to support an increase in immunogenicity of ST14 with DTaP coadministration, suggesting that the increased ST14 immunogenicity from DTaP coadministration in this meta-analysis requires further evaluation.

Although we aimed to be comprehensive in identifying potentially relevant immunogenicity covariates, there may be factors that were not recognized or not captured completely. Very few studies directly compared covariates and between-study meta-analyses such as ours likely have residual confounding. We were unable to control for certain potential confounders because factors were sometimes region specific; studies in Africa used only DTwP and PCV13 was evaluated only in North America and Europe.

TABLE 4. Predicted Pneumococcal IgG GMCs* and Fold Change in GMC Relative to Traditional Schedule Generated by Linear Regression Modeling for Selected Combinations of Schedule and DTP by Region

Region	DTP	Schedule	ST1		ST5		ST6B		ST14		ST19F		ST23F	
			GMC†	Fold change‡	GMC	Fold change‡	GMC	Fold change‡	GMC	Fold change‡	GMC	Fold change‡	GMC	Fold change‡
Africa	DTwP	6, 10 and 14 weeks	5.01	Ref	5.02	Ref	0.97	Ref	2.51	Ref	4.26	Ref	0.90	Ref
		2, 4 and 6 months§	5.62	1.1	5.24	1.0	2.09	2.1	3.56	1.4	4.29	1.0	1.53	1.7
		3, 4 and 5 months	6.14	1.2	5.16	1.0	1.43	1.5	2.95	1.2	4.97	1.2	1.15	1.3
		6 and 14 weeks§	4.77	1.0	3.88	0.8	0.27	0.3	1.33	0.5	2.77	0.6	0.37	0.4
	DTaP	6, 10 and 14 weeks§	6.81	—	6.66	—	1.15	—	4.02	—	4.94	—	0.90	—
Asia¶	DTwP	2, 4 and 6 months	6.63	Ref	3.94	Ref	2.40	Ref	6.28	Ref	5.39	Ref	2.80	Ref
		6, 10 and 14 weeks§	5.91	0.9	3.77	1.0	1.12	0.5	4.43	0.7	5.36	1.0	1.65	0.6
		2 and 4 months§	8.18	1.2	3.91	1.0	0.41	0.2	3.98	0.6	4.25	0.8	0.72	0.3
	DTaP	2, 4 and 6 months	9.01	Ref	5.22	Ref	2.84	Ref	10.06	Ref	6.26	Ref	2.79	Ref
		6, 10 and 14 weeks§	8.03	0.9	5.00	1.0	1.33	0.5	7.09	0.7	6.22	1.0	1.64	0.6
		2 and 4 months§	8.18	0.9	3.91	0.7	0.41	0.1	3.98	0.4	4.25	0.7	0.72	0.3
Europe	DTwP	2, 4 and 6 months	1.95	Ref	1.24	Ref	1.08	Ref	3.63	Ref	3.53	Ref	1.59	Ref
		3, 4 and 5 months	2.13	1.1	1.22	1.0	0.74	0.7	3.01	0.8	4.09	1.2	1.20	0.8
		3 and 5 months§	2.02	1.0	0.95	0.8	0.20	0.2	1.60	0.4	2.66	0.8	0.48	0.3
	DTaP	2, 4 and 6 months	2.64	Ref	1.65	Ref	1.27	Ref	5.81	Ref	4.10	Ref	1.59	Ref
		3,4 and 5 months	2.89	1.1	1.62	1.0	0.87	0.7	4.81	0.8	4.75	1.2	1.19	0.8
		2 and 3 months	2.29	0.9	1.19	0.7	0.10	0.1	1.71	0.3	2.91	0.7	0.26	0.2
		3 and 5 months§	2.75	1.0	1.26	0.8	0.24	0.2	2.56	0.4	3.09	0.8	0.48	0.3
North America	DTaP	2, 4 and 6 months	3.00	Ref	2.34	Ref	1.09	Ref	4.50	Ref	2.30	Ref	1.10	Ref
		2 and 4 months§	2.73	0.9	1.75	0.7	0.16	0.1	1.78	0.4	1.56	0.7	0.28	0.3
		4 and 6 months§	3.58	1.2	1.82	0.8	0.26	0.2	2.21	0.5	1.92	0.8	0.39	0.4
Latin America	DTwP	2, 4 and 6 months	5.03	Ref	3.19	Ref	1.93	Ref	4.90	Ref	5.08	Ref	2.17	Ref
		2 and 4 months§	4.57	0.9	2.38	0.7	0.28	0.1	1.94	0.4	3.46	0.7	0.56	0.3
	DTaP	2, 4 and 6 months	6.84	Ref	4.23	Ref	2.28	Ref	7.85	Ref	5.90	Ref	2.16	Ref
		2 and 4 months§	6.21	0.9	3.16	0.7	0.33	0.1	3.11	0.4	4.01	0.7	0.56	0.3

*GMCs for PCV7 (or PCV9 if ST1 or ST5) using the WHO ELISA method.

†Adjusted for DTP, number of primary doses, interval between doses, age at first dose, region, product and laboratory method.

‡Compared to reference group.

¶ Includes Fiji; there were no other studies in the Oceania region included in analysis.

§ Hypothetical schedules for those without studies available in the current literature.

Determining the relative benefit of 1 schedule over another for the currently available PCV10 and PCV13 products was limited by the paucity of data for those vaccines, which also limited our ability to assess impact on STs 1 and 5. Because the individual components of the dosing schedule (number of doses, age of first dose, interval and age at last dose) are correlated (ie, fixing 3 variables determines the fourth), the exact attribution of each component is difficult to differentiate. Additionally, because the GSK ELISA method produces lower absolute GMCs compared with other ELISA methods, comparing studies using different assays confounds interpretations of differences in immunogenicity. Despite these limitations, we confirmed the results of the meta-analysis with studies reporting comparisons within a single population, or within a region if a study was not available, and found overall agreement in all cases.

This review identifies gaps in the existing literature and can direct future research in forming a robust knowledge base on which policy decisions can be made, particularly in developing countries where limited resources and uncertainty regarding which dosing schedule to implement can delay the introduction of life-saving vaccines. Developing an understanding of whether higher GMCs are associated with mucosal protection could have significant implications on how the cofactors explored in this analysis can impact disease transmission.

This review contributed to the WHO Strategic Advisory Group of Experts statement and revised Expanded Programme on Immunization guidelines regarding optimization of PCV dosing schedules.[12] We have attempted to quantify the effect of certain covariates on the immune response to PCV and have demonstrated the importance of adjusting for these factors when evaluating various dosing schedules. When considered together with programmatic factors, ST distribution, efficacy, cost effectiveness and burden of disease, our analysis contributes to an evidence base that can help policy makers optimize use of PCV in different settings.

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