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# Immunization of Preterm Infants With 10-Valent Pneumococcal Conjugate Vaccine

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# Immunization of Preterm Infants With 10-Valent Pneumococcal Conjugate Vaccine

**WHAT'S KNOWN ON THIS SUBJECT:** Preterm infants are at increased risk for pneumococcal infections, and there are few published studies on pneumococcal vaccine. Reports of decreased immunogenicity with some vaccines in this infant group warranted research on use of 10-valent pneumococcal vaccine (PHiD-CV) in preterm infants.

**WHAT THIS STUDY ADDS:** PHiD-CV was well tolerated and generally as immunogenic in preterm infants as in term infants when given as a 3-dose primary vaccination followed by a booster dose. These results reveal that preterm infants would benefit from PHiD-CV vaccination.

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**KEY WORDS**

premature infants, pneumococcal conjugate vaccine, *Streptococcus pneumoniae*, safety, immune response

**ABBREVIATIONS**

7vCRM—7-valent pneumococcal conjugate vaccine
PHiD-CV—pneumococcal nontypeable *Haemophilus influenzae* protein D conjugate vaccine
GSK—GlaxoSmithKline
DTPa-HBV-IPV/Hib—combined diphtheria-tetanus-acellular pertussis-hepatitis B virus inactivated poliovirus, and *H influenzae* type b vaccine
NTHi—nontypeable *H influenza*
AE—adverse event
SAE—serious AE
ELISA—enzyme-linked immunosorbent assay
OPA—opsonophagocytic activity
ELU—ELISA unit
CI—confidence interval
GMC—geometric mean concentration
GMT—geometric mean titer
DTPa-IPV/Hib—combined diphtheria-tetanus-acellular pertussis-inactivated poliovirus, and *H influenzae* type b vaccine

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## abstract

**OBJECTIVE:** The safety and immunogenicity of the 10-valent pneumococcal nontypeable *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV) in preterm infants were assessed in this study.

**METHODS:** Three parallel groups of infants received 3-dose primary immunization with PHiD-CV at 2, 4, and 6 months of age and a booster dose at 16 to 18 months: preterm I (gestation period $\geq$ 27 and $<$31 weeks, $N = 50$); preterm II ($\geq$31 and $<$37 weeks, $N = 87$); and term ($\geq$37 weeks, $N = 149$). Solicited symptoms and adverse events were recorded. Immune responses to PHiD-CV and coadministered vaccine antigens were measured.

**RESULTS:** The incidence of solicited general symptoms was similar across groups, and the frequency of grade 3 general symptoms was low. Incidences of redness and swelling were generally lower in preterm infants. PHiD-CV was immunogenic for each of the 10 vaccine pneumococcal serotypes (postprimary, $\geq$92.7% of infants reached enzyme-linked immunosorbent assay antibody concentrations $\geq$ 0.2 $\mu$g/mL and postbooster, $\geq$97.6%) and for protein D, with a trend for lower postprimary geometric mean antibody concentrations and opsonophagocytic activity (OPA) titers in preterm infants for some pneumococcal serotypes. Postbooster, $\geq$91.9% of subjects in each group had an OPA titer $\geq$ 8 for each of the vaccine serotypes. Pneumococcal antibody concentrations and OPA titers after priming and booster vaccination were comparable between the 2 preterm groups.

**CONCLUSIONS:** PHiD-CV was well tolerated and immunogenic in preterm infants when given as a 3-dose primary vaccination, with robust enzyme-linked immunosorbent assay antibody and OPA booster responses in the second year of life. *Pediatrics* 2011;128:e290–e298

Preterm infants are at increased risk for pneumococcal infections.[1,2] One study revealed a ninefold higher risk for invasive pneumococcal disease in infants born at a gestational age of <32 weeks compared with term infants.[2]

Clinical data on the 7-valent pneumococcal conjugate vaccine (7vCRM with diphtheria CRM197 as a protein carrier, containing capsular polysaccharides derived from serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F; Prevenar/Prevnar; Pfizer, formerly Wyeth Pharmaceuticals Inc, Philadelphia, PA) support its use in preterm infants.[2–5] The 10-valent pneumococcal nontypeable *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV; Synflorix, GlaxoSmithKline [GSK] Biologicals, Rixensart, Belgium) was shown to be immunogenic, presents a good safety profile in term infants, and can be coadministered with other pediatric vaccines.[6–12] Reports of decreased immunogenicity with some childhood vaccines in preterm infants[13] warranted research on the use of PHiD-CV in this infant group. This study was designed to assess the safety and immunogenicity of PHiD-CV primary and booster immunization in preterm infants born after 27 weeks of gestation.

## METHODS

### Study Design, Vaccines, and Participants

This study, carried out between October 2006 and March 2009 in Spain and Greece, was approved by the appropriate independent ethics committees and institutional review boards and conducted in accordance with the Declaration of Helsinki (Somerset West 1996 version) and good clinical practice guidelines. Infants received 3-dose primary immunization with PHiD-CV coadministered with diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliovirus and *H influenzae* type b vaccine (DTPa-HBV-IPV/Hib; Infanrix hexa, GSK Biologicals) at ~2, 4, and 6 months of age, followed by a booster dose of PHiD-CV coadministered with a booster dose of DTPa-IPV/Hib (Infanrix IPV/Hib, GSK Biologicals) at 16 to 18 months of age. PHiD-CV contained 1 $\mu$g of each capsular polysaccharide for pneumococcal serotypes 1, 5, 6B, 7F, 9V, 14, and 23F conjugated individually to nontypeable *H influenzae* (NTHi) protein D and 3 $\mu$g for serotypes 4 (conjugated to protein D), 18C (conjugated to tetanus toxoid), and 19F (conjugated to diphtheria toxoid). Infants aged 8 to 16 weeks were enrolled in parallel groups (1:2:3 stratification ratio): preterm group I (gestation period $\geq$ 27 and < 31 weeks); preterm group II (gestation period $\geq$ 31 and <37 weeks), and term group (gestation period $\geq$ 37 weeks). Term infants were free of obvious health problems, and preterm infants were medically stable and did not require significant medical support. Written informed consent was obtained from parents or legal guardians. The licensed meningococcal group C tetanus toxoid conjugate vaccine, NeisVac-C (Baxter Healthcare Corp, Beltsville, MD), was administered at ~3 and 5 months of age (preterm infants were offered a third dose at 7 months) according to national recommendations, but this was not considered a study vaccine.

### Reactogenicity and Safety Assessment

Local (pain, redness, swelling at the injection site) and general (fever, drowsiness, irritability, loss of appetite) symptoms were reported by parents/guardians on diary cards for 4 days (days 0–3) after each vaccine dose. Large swelling reactions (any local swelling with diameter > 50 mm and/or any noticeable diffuse injection site swelling or increased circumference of the injected limb) were recorded after booster vaccination. Other unsolicited adverse events (AEs) were recorded for 31 days (days 0–30) after each vaccine dose; and serious AEs (SAEs), defined as any medical event that resulted in death, any life-threatening event, or any event causing disability or required hospitalization or prolongation of hospitalization, were recorded until 6 months after booster vaccination.

Symptoms were scored on a 3-grade intensity scale. Grade 3 pain at the injection site was considered if the infant cried when the limb was moved/was spontaneously painful, and redness and swelling at the injection site if the diameter was >30 mm. Fever was considered grade 3 if rectal temperature was >40°C. Grade 3 irritability was considered if the infant cried and could not be comforted/prevented normal activity, and for loss of appetite if the infant did not eat at all. Grade 3 intensity for all other symptoms and AEs was defined as preventing normal everyday activity and/or causing parents/guardians to seek medical advice. Injection-site reactions were by default considered causally related to vaccination, and the causal relationship of all other AEs was assessed by investigators, using their clinical judgment. Use of therapeutic and prophylactic antipyretic medication was recorded.

### Immunogenicity Assessment

Immunogenicity assessments were performed on blood samples obtained before and 1 month after primary vaccination, and before and 1 month after booster vaccination. Serum samples were stored at −20°C until analyzed at GSK Biologicals' laboratory in Rixensart, Belgium (for pneumococcal, protein D, DTPa, and Hib responses) or a designated validated laboratory (for HBV and polio responses). The GSK Biologicals laboratory and designated laboratories have established quality

control procedures and an established quality system.

GSK's 22F-inhibition enzyme-linked immunosorbent assay (22F-ELISA) was used to measure anti-pneumococcal serotype-specific immunoglobulin G concentrations.[14,15] An antibody concentration of 0.2 $\mu$g/mL measured by GSK's 22F-ELISA was shown to be equivalent to 0.35 $\mu$g/mL as determined by the World Health Organization reference laboratory ELISA without 22F-inhibition.[16] Opsonophagocytic activity (OPA) was measured to assess functional antibody activity after primary and booster vaccination by a killing assay using a HL60 cell line.[17] The results were presented as the reciprocal of dilution of serum (opsonic titer) able to sustain 50% killing of live pneumococci under the assay conditions, with a cutoff opsonic titer of 8.[18] Immune responses were also determined for the pneumococcal cross-reactive serotypes 6A and 19A. Antibodies against NTHi protein D were measured by an in-house ELISA with an assay cutoff of 100 ELISA units (ELUs)/mL.

Immune responses to the coadministered vaccine antigens were analyzed according to standard techniques described previously[8] (ELISA, except for polio, where a microneutralization assay was used), in a randomly selected subset of 50% of subjects (keeping the 1:2:3 group ratio).

### Statistical Analysis

Safety analysis was performed on the total vaccinated cohort according to 2 groups: pooled preterm I and preterm II group; and term group. Pooling the preterm groups allowed for a balanced reactogenicity/safety analysis in terms of number of subjects in the pooled group versus number in the term group. Incidences of symptoms were calculated with 95% confidence intervals (CIs) after each vaccine dose. Immunogenicity analysis was performed on the according-to-protocol immunogenicity cohort, defined as vaccinated subjects who met all eligibility criteria, complied with protocol-defined procedures, and with antibody assay results available. Geometric mean antibody concentrations (GMCs) and/or geometric mean OPA titers (GMTs) were determined in each group with 95% CIs for each vaccine pneumococcal serotype, cross-reactive serotypes 6A and 19A, and protein D. GMCs, GMTs, and seropositivity/seroprotection rates were calculated with 95% CIs for antibodies against the coadministered vaccine antigens. Randomization for serologic testing was generated at GSK Biologicals by using a standard SAS program (SAS Institute, Inc, Cary, NC).

## RESULTS

A total of 286 subjects (175 in Spain and 111 in Greece) were enrolled for primary vaccination, and 245 (167 in Spain and 78 in Greece) returned for the booster dose. Figure 1 shows the numbers of subjects in the different cohorts and reasons for exclusion. In the 5-month extended safety follow-up periods after vaccination, 269 infants were contacted postprimary vaccination (48 in preterm I, 82 in preterm II, and 139 in term group), and 229 were contacted postbooster dose (42, 67, and 120, respectively). Demographic characteristics for the 3 groups are shown in Table 1.

### Reactogenicity and Safety

The incidence of fever $>$ 39°C (rectal temperature) occuring within 4 days after each of the vaccine doses was low in both groups, although higher after the booster dose (Table 2). Three cases of grade 3 fever (rectal temperature $>$ 40°C) were reported (Table 2), all in the term group; 2 were considered to be causally related to vaccination. The use of antipyretic medication within 4 days postvaccination was similar in both groups (after 17.4% [95% CI: 13.8%–21.5%] of primary vaccine doses in the pooled preterm group, 16.7% [95% CI: 13.3%–20.5%] of primary doses in the term group, and 23.3% of booster doses in both groups). On few occasions, antipyretic medication was taken prophylactically (after 0.7% [95% CI: 0.2%–2.2%] and 0.9% [95% CI: 0.3%–2.4%] of primary doses in the pooled preterm group and term group, respectively, and after 4.3% [95% CI: 1.4%–9.8%] and 1.6% [95% CI: 0.2%–5.5%] of booster doses in the pooled preterm group and term group, respectively).

The most frequently reported solicited general AE after primary and booster vaccination was irritability. Incidences of grade 3 solicited general AEs were low (Table 2). Most solicited general AEs were considered to be causally related to vaccination. In both groups, the incidences of solicited local AEs after each of the vaccine doses were within the same range at the PHiD-CV and DTPa-based combination vaccine injection sites (Table 3), with incidences of redness and swelling generally higher in the term group than in the preterm group. Grade 3 solicited local AEs were reported after $\leq$5.3% of primary vaccine doses in both groups and booster doses in preterm infants, but tended to be higher after booster vaccination in the term group (Table 3).

Large swelling reactions after booster vaccination were reported for 6 subjects (all in the term group); 1 at the PHiD-CV injection site and 5 at the DTPa-IPV/Hib injection site. All were local or diffuse swelling reactions not involving adjacent joints that developed within 2 days after booster vaccination and resolved without sequelae within 4 days.

SAEs were reported in 31 subjects from the first primary vaccination dose until 1 month after dose 3 (18 from the preterm group, 13 from the term group), 1 of which was fatal. The

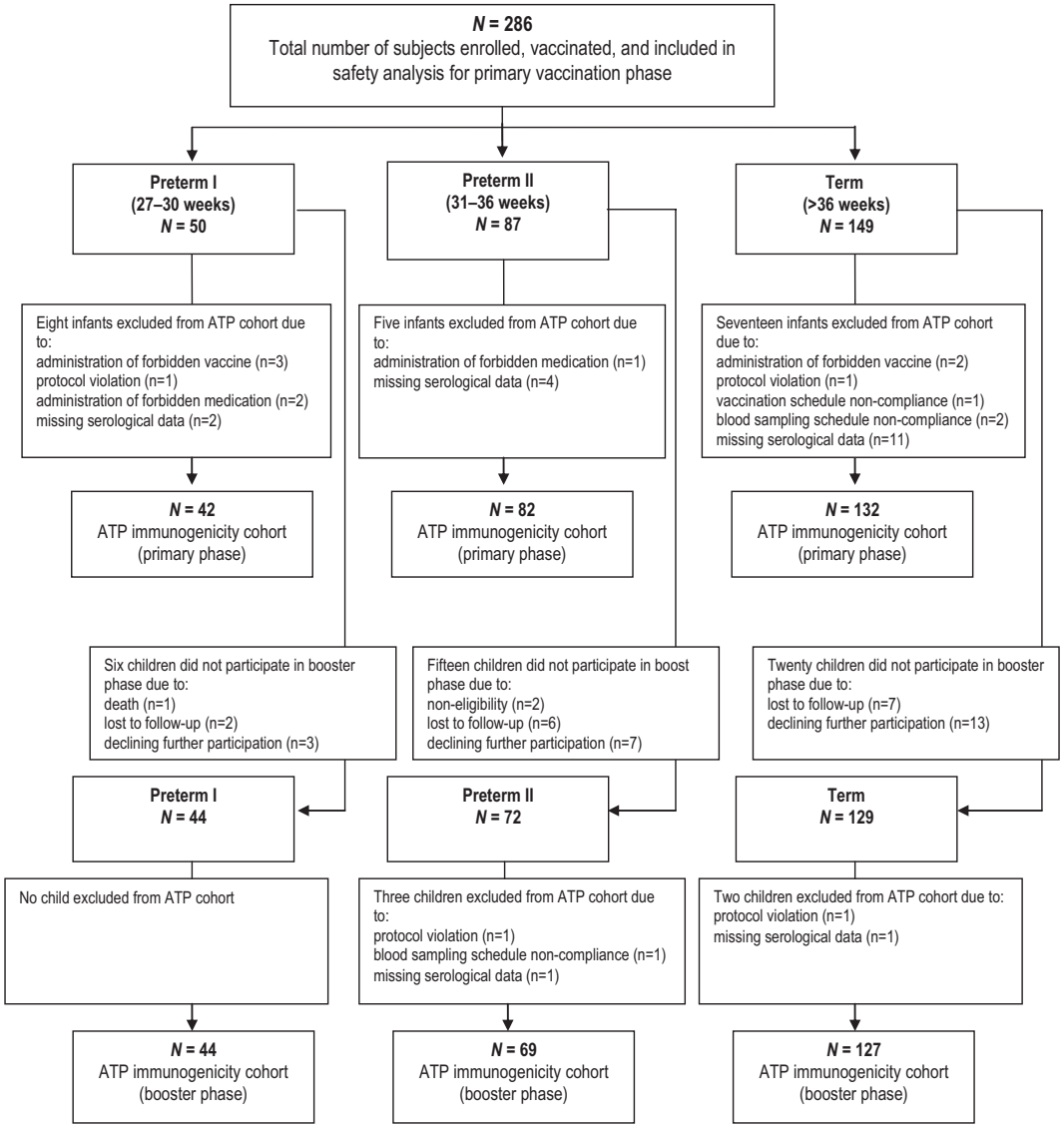


**FIGURE 1**
Trial profile. Number of subjects who did not complete the study: 16 did not complete the primary vaccination phase because of consent withdrawal (9 infants), move from the study area (3), loss to follow-up (3), and a fatal SAE (1) not considered to be causally related to vaccination; 11 did not complete the booster phase because of loss to follow-up (6 children) and consent withdrawal (5). ATP indicates according-to-protocol.

**TABLE 1** Demographic Characteristics (Total Vaccinated Cohort)

| | Preterm I | Preterm II | Term |
|---|---|---|---|
| Primary vaccination, *N* | 50 | 87 | 149 |
| Mean age at dose 1 ± SD, wk | 11.0 ± 3.20 | 9.5 ± 1.45 | 9.3 ± 1.45 |
| Mean weight at dose 1 ± SD, kg | 3.2 ± 0.78 | 4.2 ± 0.76 | 5.2 ± 0.71 |
| Mean weight at birth ± SD, kg | 1.2 ± 0.29 | 2.0 ± 0.47 | 3.2 ± 0.44 |
| Mean gestational period ± SD, wk | 28.6 ± 1.10 | 33.5 ± 1.69 | >36 |
| Gender, female/male, % | 38.0/62.0 | 46.0/54.0 | 41.6/58.4 |
| Race, % | | | |
| White/Caucasian/European heritage | 72.0 | 88.5 | 94.0 |
| American Indian[a] | 8.0 | 6.9 | 1.3 |
| African heritage/black | 4.0 | 1.1 | 2.7 |
| White/Arabic/North African heritage | 2.0 | 0 | 1.3 |
| Asian/Southeast Asian heritage | 0 | 1.1 | 0 |
| Other | 14.0 | 2.3 | 0.7 |
| Booster vaccination, *N* | 44 | 72 | 129 |
| Mean age ± SD, mo | 16.8 ± 0.63 | 17.2 ± 0.68 | 16.6 ± 0.73 |

[a] Includes North, South, and Central American Indians.

fatal SAE (choking because of aspiration) occurred 25 days after the third vaccine dose in an infant from preterm group I and was assessed by the investigator as not causally related to vaccination. One SAE was considered to be causally related to vaccination (pyrexia, preterm group). During the 5-month extended safety follow-up period after primary vaccination, SAEs were reported for 19 of 269 infants (11 in the preterm group, 8 in the term group); none were considered as caus-

**TABLE 2** Incidence of Solicited General Symptoms Within 4 Days (Days 0–3) After Each Vaccine Dose (Total Vaccinated Cohort)

| Symptom | Intensity | Pooled Preterm Group, % (95% CI) | | | | Term Group, % (95% CI) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Dose 1 ($N$ = 135) | Dose 2 ($N$ = 133) | Dose 3 ($N$ = 131) | Booster Dose ($N$ = 112) | Dose 1 ($N$ = 146) | Dose 2 ($N$ = 141) | Dose 3 ($N$ = 138) | Booster Dose ($N$ = 122) |
| Irritability | Any | 39.3 (31.0–48.0) | 38.3 (30.1–47.2) | 30.5 (22.8–39.2) | 32.1 (23.6–41.6) | 50.0 (41.6–58.4) | 37.6 (29.6–46.1) | 31.9 (24.2–40.4) | 40.2 (31.4–49.4) |
| | Grade 3[a] | 4.4 (1.6–9.4) | 3.0 (0.8–7.5) | 2.3 (0.5–6.5) | 1.8 (0.2–6.3) | 6.2 (2.9–11.4) | 1.4 (0.2–5.0) | 0.7 (0.0–4.0) | 1.6 (0.2–5.8) |
| Drowsiness | Any | 32.6 (24.8–41.2) | 24.1 (17.1–32.2) | 13.7 (8.4–20.8) | 18.8 (12.0–27.2) | 36.3 (28.5–44.7) | 24.1 (17.3–32.0) | 15.9 (10.3–23.1) | 27.0 (19.4–35.8) |
| | Grade 3[a] | 0.7 (0.0–4.1) | 0.8 (0.0–4.1) | 3.1 (0.8–7.6) | 0.9 (0.0–4.9) | 1.4 (0.2–4.9) | 0.0 (0.0–2.6) | 0.7 (0.0–4.0) | 0.8 (0.0–4.5) |
| Fever (rectal) | ≥38.0°C | 30.4 (22.8–38.9) | 30.1 (22.4–38.6) | 12.2 (7.1–19.1) | 30.4 (22.0–39.8) | 26.0 (19.1–33.9) | 24.1 (17.3–32.0) | 18.1 (12.1–25.6) | 32.0 (23.8–41.0) |
| | >39.0°C | 1.5 (0.2–5.2) | 0.8 (0.0–4.1) | 0.8 (0.0–4.2) | 7.1 (3.1–13.6) | 3.4 (1.1–7.8) | 0.7 (0.0–3.9) | 2.2 (0.5–6.2) | 4.9 (1.8–10.4) |
| | >40.0°C | 0.0 (0.0–2.7) | 0.0 (0.0–2.7) | 0.0 (0.0–2.8) | 0.0 (0.0–3.2) | 0.7 (0.0–3.8) | 0.0 (0.0–2.6) | 0.7 (0.0–4.0) | 0.8 (0.0–4.5) |
| Loss of appetite | Any | 24.4 (17.5–32.6) | 26.3 (19.1–34.7) | 19.8 (13.4–27.7) | 23.2 (15.8–32.1) | 24.7 (17.9–32.5) | 16.3 (10.6–23.5) | 15.9 (10.3–23.1) | 28.7 (20.9–37.6) |
| | Grade 3[a] | 0.0 (0.0–2.7) | 1.5 (0.2–5.3) | 0.8 (0.0–4.2) | 0.0 (0.0–3.2) | 0.0 (0.0–2.5) | 0.0 (0.0–2.6) | 0.0 (0.0–2.6) | 0.8 (0.0–4.5) |

$N$ is the number of subjects with documented dose.

[a] Adverse event of grade 3 intensity: irritability such as crying that could not be comforted/prevented normal activity; drowsiness that prevented normal activity; loss of appetite or if infant did not eat at all.

**TABLE 3** Incidence of Solicited Local Symptoms at Each Injection Site Within 4 Days (Days 0–3) After Each Vaccine Dose (Total Vaccinated Cohort)

| Symptom | Injection Site | Intensity | Pooled Preterm Group, % (95% CI) | | | | Term Group, % (95% CI) | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Dose 1 ($N$ = 135) | Dose 2 ($N$ = 133) | Dose 3 ($N$ = 131) | Booster Dose ($N$ = 112) | Dose 1 ($N$ = 146) | Dose 2 ($N$ = 141)[c] | Dose 3 ($N$ = 138) | Booster Dose ($N$ = 122) |
| Pain | PHiD-CV | Any | 26.7 (19.4–35.0) | 24.8 (17.7–33.0) | 20.6 (14.0–28.6) | 37.5 (28.5–47.1) | 35.6 (27.9–44.0) | 23.4 (16.7–31.3) | 26.8 (19.6–35.0) | 48.4 (39.2–57.6) |
| | | Grade 3[b] | 4.4 (1.6–9.4) | 4.5 (1.7–9.6) | 1.5 (0.2–5.4) | 4.5 (1.5–10.1) | 3.4 (1.1–7.8) | 0.7 (0.0–3.9) | 1.4 (0.2–5.1) | 1.6 (0.2–5.8) |
| | DTPa[a] | Any | 24.4 (17.5–32.6) | 23.3 (16.4–31.4) | 17.6 (11.5–25.2) | 33.9 (25.3–43.5) | 32.9 (25.3–41.1) | 26.4 (19.3–34.5) | 26.8 (19.6–35.0) | 46.7 (37.6–56.0) |
| | | Grade 3[b] | 2.2 (0.5–6.4) | 5.3 (2.1–10.5) | 1.5 (0.2–5.4) | 2.7 (0.6–7.6) | 3.4 (1.1–7.8) | 0.7 (0.0–3.9) | 3.6 (1.2–8.3) | 2.5 (0.5–7.0) |
| Redness | PHiD-CV | Any | 24.4 (17.5–32.6) | 25.6 (18.4–33.8) | 22.1 (15.4–30.2) | 27.7 (19.6–36.9) | 41.1 (33.0–49.5) | 44.7 (36.3–53.3) | 39.9 (31.6–48.5) | 50.8 (41.6–60.0) |
| | | >30 mm | 0.7 (0.0–4.1) | 0.0 (0.0–2.7) | 1.5 (0.2–5.4) | 2.7 (0.6–7.6) | 0.0 (0.0–2.5) | 4.3 (1.6–9.0) | 3.6 (1.2–8.3) | 10.7 (5.8–17.5) |
| | DTPa[a] | Any | 22.2 (15.5–30.2) | 20.3 (13.8–28.1) | 20.6 (14.0–28.6) | 23.2 (15.8–32.1) | 32.9 (25.3–41.1) | 45.7 (37.3–54.3) | 41.3 (33.0–50.0) | 45.1 (36.1–54.3) |
| | | >30 mm | 0.0 (0.0–2.7) | 0.0 (0.0–2.7) | 0.8 (0.0–4.2) | 1.8 (0.2–6.3) | 0.0 (0.0–2.5) | 1.4 (0.2–5.1) | 5.1 (2.1–10.2) | 12.3 (7.0–19.5) |
| Swelling | PHiD-CV | Any | 18.5 (12.4–26.1) | 15.0 (9.4–22.3) | 14.5 (9.0–21.7) | 21.4 (14.2–30.2) | 41.1 (33.0–49.5) | 36.2 (28.3–44.7) | 31.9 (24.2–40.4) | 40.2 (31.4–49.4) |
| | | >30 mm | 0.7 (0.0–4.1) | 0.0 (0.0–2.7) | 0.8 (0.0–4.2) | 0.9 (0.0–4.9) | 0.7 (0.0–3.8) | 1.4 (0.2–5.0) | 1.4 (0.2–5.1) | 6.6 (2.9–12.5) |
| | DTPa[a] | Any | 14.8 (9.3–21.9) | 15.8 (10.0–23.1) | 13.7 (8.4–20.8) | 17.0 (10.5–25.2) | 33.6 (26.0–41.8) | 39.3 (31.1–47.9) | 36.2 (28.2–44.8) | 36.9 (28.3–46.1) |
| | | >30 mm | 0.0 (0.0–2.7) | 0.0 (0.0–2.7) | 0.8 (0.0–4.2) | 0.9 (0.0–4.9) | 1.4 (0.2–4.9) | 1.4 (0.2–5.1) | 3.6 (1.2–8.3) | 9.8 (5.2–16.6) |

[a] Doses 1–3, DTPa-HBV-IPV/Hib vaccine; booster dose, DTPa-IPV/Hib vaccine.

[c] $N$ = 140 for DTPa; $N$ is the number of subjects with documented dose.

[b] Grade 3 pain: crying when limb was moved/spontaneously painful.

ally related to vaccination. No SAEs were reported within 1 month after booster vaccination. During the 5-month extended safety follow-up after booster vaccination, 4 of 229 children reported at least 1 SAE, 3 in the preterm group and 1 in the term group; none were considered causally related to vaccination. Unsolicited AEs were reported after 12.4% (95% CI: 9.4%–16.1%) of primary doses in the preterm group and 19.0% (95% CI: 15.4%–23.0%) in the term group, and after 14.7% (95% CI: 8.8%–22.4%) of booster doses in the preterm group and 18.6% (95% CI: 12.3%–26.4%) in the term group. Upper respiratory tract infections were among the most frequently reported unsolicited AEs in all groups, together with injection site nodules after primary and booster vaccination in the term group. One episode of apnea was reported in a preterm infant after the first primary dose but was not considered to be related to study vaccination and resolved without sequelae. Few unsolicited symptoms were considered to have grade 3 intensity (after ≤1.2% of primary and booster vaccine doses in all groups).

## IMMUNOGENICITY

### Immune Responses to PHiD-CV Primary Vaccination

Before the first vaccination dose, percentages of subjects with antibody concentrations ≥ 0.2 μg/mL tended to be higher in the term group than in the 2 preterm groups for most of the vaccine serotypes (Table 4). One month after the third primary dose, for each of

**TABLE 4** Percentages of Subjects With ELISA Antibody Concentrations ≥ 0.2 μg/mL and OPA Titers ≥ 8 Against Individual Pneumococcal Vaccine Serotypes and Cross-reactive Serotypes 6A and 19A (According-to-Protocol Immunogenicity Cohorts)

| | Group | ELISA, % ≥ 0.2 μg/mL (95% CI) | | | | | OPA, % ≥ 8 (95% CI) | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | *N* | Preprimary | Postprimary | *N* | Postbooster | *N* | Postprimary | *N* | Postbooster |
| Serotypes | | | | | | | | | | |
| 1 | Preterm I | 42 | 4.8 (0.6–16.2) | 97.6 (87.4–99.9) | 43 | 100 (91.8–100) | 34 | 58.8 (40.7–75.4) | 37 | 91.9 (78.1–98.3) |
| | Preterm II | 81 | 2.5 (0.3–8.6) | 100 (95.6–100) | 66 | 100 (94.6–100) | 72 | 68.1 (56.0–78.6) | 52 | 94.2 (84.1–98.8) |
| | Term | 131 | 12.2 (7.1–19.1) | 99.2 (95.8–100) | 119 | 99.2 (95.4–100) | 110 | 72.7 (63.4–80.8) | 99 | 93.9 (87.3–97.7) |
| 4 | Preterm I | 41 | 0.0 (0.0–8.6) | 97.6 (87.1–99.9) | 43 | 100 (91.8–100) | 36 | 100 (90.3–100) | 36 | 97.2 (85.5–99.9) |
| | Preterm II | 80 | 2.5 (0.3–8.7) | 98.8 (93.4–100) | 66 | 100 (94.6–100) | 73 | 98.6 (92.6–100) | 55 | 100 (93.5–100) |
| | Term | 130 | 8.5 (4.3–14.6) | 100 (97.2–100) | 119 | 100 (96.9–100) | 111 | 99.1 (95.1–100) | 100 | 100 (96.4–100) |
| 5 | Preterm I | 40 | 2.5 (0.1–13.2) | 100 (91.6–100) | 43 | 100 (91.8–100) | 34 | 85.3 (68.9–95.0) | 34 | 94.1 (80.3–99.3) |
| | Preterm II | 81 | 3.7 (0.8–10.4) | 100 (95.6–100) | 66 | 100 (94.6–100) | 74 | 93.2 (84.9–97.8) | 50 | 96.0 (86.3–99.5) |
| | Term | 131 | 14.5 (9.0–21.7) | 100 (97.2–100) | 119 | 100 (96.9–100) | 109 | 95.4 (89.6–98.5) | 93 | 98.9 (94.2–100) |
| 6B | Preterm I | 41 | 2.4 (0.1–12.9) | 92.7 (80.1–98.5) | 42 | 100 (91.6–100) | 35 | 85.7 (69.7–95.2) | 35 | 94.3 (80.8–99.3) |
| | Preterm II | 79 | 7.6 (2.8–15.8) | 95.1 (88.0–98.7) | 66 | 98.5 (91.8–100) | 69 | 85.5 (75.0–92.8) | 51 | 96.1 (86.5–99.5) |
| | Term | 129 | 20.2 (13.6–28.1) | 93.9 (88.3–97.3) | 119 | 100 (96.9–100) | 104 | 81.7 (72.9–88.6) | 98 | 93.9 (87.1–97.7) |
| 7F | Preterm I | 42 | 2.4 (0.1–12.6) | 100 (91.4–100) | 43 | 100 (91.8–100) | 36 | 100 (90.3–100) | 37 | 100 (90.5–100) |
| | Preterm II | 79 | 13.9 (7.2–23.5) | 100 (95.6–100) | 66 | 100 (94.6–100) | 74 | 100 (95.1–100) | 49 | 100 (92.7–100) |
| | Term | 129 | 20.2 (13.6–28.1) | 100 (97.2–100) | 118 | 100 (96.9–100) | 113 | 100 (96.8–100) | 99 | 100 (96.3–100) |
| 9V | Preterm I | 42 | 2.4 (0.1–12.6) | 97.6 (87.1–99.9) | 43 | 100 (91.8–100) | 36 | 100 (90.3–100) | 38 | 100 (90.7–100) |
| | Preterm II | 80 | 12.5 (6.2–21.8) | 100 (95.6–100) | 66 | 100 (94.6–100) | 72 | 100 (95.0–100) | 47 | 100 (92.5–100) |
| | Term | 130 | 28.5 (20.9–37.0) | 100 (97.2–100) | 119 | 100 (96.9–100) | 103 | 100 (96.5–100) | 100 | 100 (96.4–100) |
| 14 | Preterm I | 41 | 51.2 (35.1–67.1) | 100 (91.4–100) | 43 | 100 (91.8–100) | 36 | 100 (90.3–100) | 36 | 100 (90.3–100) |
| | Preterm II | 79 | 55.7 (44.1–66.9) | 100 (95.6–100) | 66 | 100 (94.6–100) | 73 | 100 (95.1–100) | 52 | 100 (93.2–100) |
| | Term | 129 | 70.5 (61.9–78.2) | 100 (97.2–100) | 119 | 100 (96.9–100) | 112 | 98.2 (93.7–99.8) | 99 | 100 (96.3–100) |
| 18C | Preterm I | 42 | 21.4 (10.3–36.8) | 100 (91.4–100) | 43 | 100 (91.8–100) | 34 | 100 (89.7–100) | 37 | 100 (90.5–100) |
| | Preterm II | 80 | 17.5 (9.9–27.6) | 100 (95.5–100) | 66 | 100 (94.6–100) | 68 | 95.6 (87.6–99.1) | 50 | 100 (92.9–100) |
| | Term | 131 | 32.1 (24.2–40.8) | 98.5 (94.6–99.8) | 119 | 99.2 (95.4–100) | 102 | 97.1 (91.6–99.4) | 100 | 100 (96.4–100) |
| 19F | Preterm I | 41 | 34.1 (20.1–50.6) | 100 (91.6–100) | 43 | 100 (91.8–100) | 35 | 88.6 (73.3–96.8) | 36 | 100 (90.3–100) |
| | Preterm II | 80 | 32.5 (22.4–43.9) | 100 (95.6–100) | 66 | 100 (94.6–100) | 74 | 95.9 (88.6–99.2) | 52 | 98.1 (89.7–100) |
| | Term | 130 | 57.7 (48.7–66.3) | 100 (97.2–100) | 119 | 100 (96.9–100) | 110 | 95.5 (89.7–98.5) | 96 | 100 (96.2–100) |
| 23F | Preterm I | 41 | 9.8 (2.7–23.1) | 95.1 (83.5–99.4) | 42 | 97.6 (87.4–99.9) | 36 | 97.2 (85.5–99.9) | 37 | 100 (90.5–100) |
| | Preterm II | 80 | 8.8 (3.6–17.2) | 96.3 (89.7–99.2) | 66 | 100 (94.6–100) | 72 | 97.2 (90.3–99.7) | 54 | 100 (93.4–100) |
| | Term | 130 | 27.7 (20.2–36.2) | 95.4 (90.3–98.3) | 119 | 99.2 (95.4–100) | 109 | 100 (96.7–100) | 99 | 100 (96.3–100) |
| Cross-reactive serotypes | | | | | | | | | | |
| 6A | Preterm I | 40 | 12.5 (4.2–26.8) | 38.1 (23.6–54.4) | 42 | 85.7 (71.5–94.6) | 33 | 75.8 (57.7–88.9) | 34 | 91.2 (76.3–98.1) |
| | Preterm II | 79 | 17.7 (10.0–27.9) | 49.4 (38.1–60.7) | 66 | 86.4 (75.7–93.6) | 66 | 81.8 (70.4–90.2) | 50 | 90.0 (78.2–96.7) |
| | Term | 128 | 28.1 (20.5–36.8) | 52.7 (43.7–61.6) | 118 | 83.1 (75.0–89.3) | 96 | 60.4 (49.9–70.3) | 95 | 83.2 (74.1–90.1) |
| 19A | Preterm I | 41 | 24.4 (12.4–40.3) | 23.8 (12.1–39.5) | 42 | 76.2 (60.5–87.9) | 31 | 6.5 (0.8–21.4) | 38 | 60.5 (43.4–76.0) |
| | Preterm II | 81 | 27.2 (17.9–38.2) | 49.4 (38.1–60.7) | 66 | 83.3 (72.1–91.4) | 69 | 14.5 (7.2–25.0) | 52 | 57.7 (43.2–71.3) |
| | Term | 128 | 43.0 (34.3–52.0) | 58.0 (49.1–66.6) | 118 | 83.9 (76.0–90.0) | 105 | 16.2 (9.7–24.7) | 95 | 58.9 (48.4–68.9) |

*N* is the number of subjects with available results. The number of subjects tested by ELISA postprimary varied slightly from preprimary for the different serotypes depending on the number of sera available.

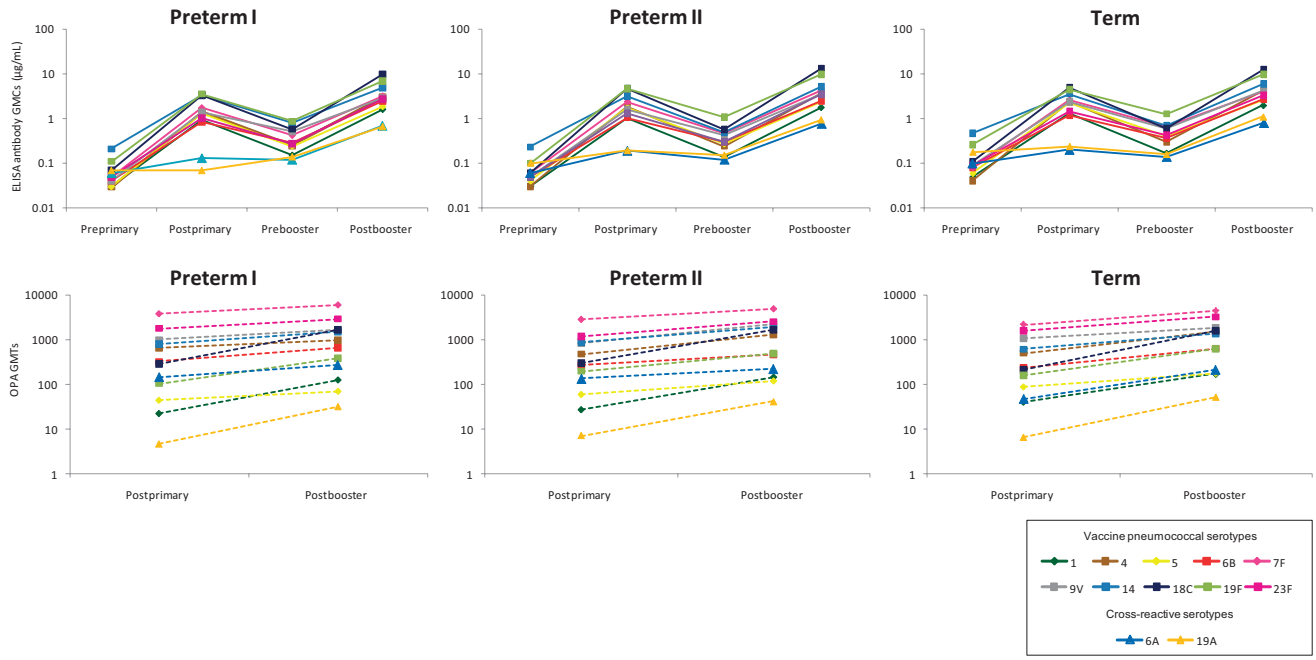


**FIGURE 2**
Kinetics of pneumococcal antibody concentration (ELISA antibody GMCs, $\mu$g/mL) and OPA GMTs during the study.

the vaccine serotypes, at least 92.7% of infants in each group had antibody concentrations $\geq$ 0.2 $\mu$g/mL (Table 4). Antibody GMCs were lower in preterm group I for serotypes 4, 5, and 9V and in preterm group II for serotype 9V compared with those in the term group (no overlap of 95% CIs) (Fig 2).

For most vaccine pneumococcal serotypes, at least 93.2% of subjects had OPA titers $\geq$ 8, except for serotypes 5 and 19F in the preterm I group and, in all groups, serotypes 1 and 6B (Table 4). The OPA GMT was lower for serotype 5 in preterm group I compared with that in the term group (nonoverlapping 95% CIs) (Fig 2). Anti-protein D antibody GMCs were within the same range in preterm I (1688.6 [95% CI: 1320.1–2159.8] ELU/mL), preterm II (1415.4 [95% CI: 1167.1–1716.5] ELU/mL), and term (1496.8 [95% CI: 1283.4–1745.8] ELU/mL) infants.

## Immune Responses to PHiD-CV Booster Vaccination

Robust increases (5.7- to 24.3-fold) in antibody concentrations were measured from pre- to postbooster in all 3 groups for each vaccine pneumococcal serotype (Fig 2), and at least 97.6% of subjects in each group developed antibody concentrations $\geq$ 0.2 $\mu$g/mL for each of the vaccine serotypes 1 month after booster vaccination (Table 4). Antibody GMCs were within the same ranges in the 3 groups (Fig 2). For each of the vaccine serotypes, at least 91.9% of subjects in preterm I, at least 94.2% in preterm II, and at least 93.9% in the term group had OPA titers $\geq$ 8 (Table 4). Although the OPA GMT was lower for serotype 5 in preterm group I compared with that in the term group (no overlap of 95% CIs), OPA GMTs for other vaccine serotypes were in the same ranges for all groups (Fig 2).

The percentages of subjects with antibody concentrations $\geq$ 0.2 $\mu$g/mL were high in the 3 groups for the cross-reactive serotypes 6A and 19A, as were the percentages of subjects with OPA titers $\geq$ 8 for serotype 6A (Table 4). Increases in anti-protein D antibody GMCs were observed after booster vaccination, with antibody GMCs within the same range in preterm I (1892.9 [95% CI: 1415.1–2532.2] ELU/mL), preterm II (1576.5 [95% CI: 1232.7–2016.1] ELU/mL), and term (1533.6 [95% CI: 1278.2–1840.1] ELU/mL) groups.

## Immune Responses to Coadministered DTPa-Based Combination Vaccines

One month after both primary and booster vaccination, all subjects were seroprotected/seropositive for antibodies against the antigens of the coadministered vaccines, except 1 subject in preterm group I after primary vaccination who was not seroprotected against polio type 3 (Supplemental Table 5). Because of limited serum availability, sample sizes for evaluation of these immune responses were sometimes very small in the preterm groups, and results might be difficult to interpret. In general, antibody GMCs/GMTs were nevertheless within the same ranges across groups and in line with previous experience with these DTPa-based combination vaccines when administered separately.[19]

## DISCUSSION

The results of this study showed that PHiD-CV was immunogenic for all vaccine pneumococcal serotypes and protein D and was well tolerated in both preterm and term infants when given as a 3-dose primary vaccination series followed by a booster dose. The preterm population recruited in the study had a gestational age of at least 27 weeks; preterm infants with a gestational age $<$ 27 weeks were not included because the critical medical condition of extremely premature infants makes it difficult to enroll them in a clinical trial and to draw blood for immunogenicity analyses.

Incidences of fever and other solicited general symptoms in this study were generally similar across all groups and in line with previous primary and booster vaccination studies of term infants in which PHiD-CV was coadministered with DTPa-based combination vaccines.[7]

After each dose, incidences of redness and swelling in preterm infants were lower than in the term group. This seems to be in line with results from a study of the 7vCRM vaccine in which an analysis of nearly 7000 doses administered to preterm infants and $>$10 500 doses given to term infants reveled that local reactions were less frequent in preterm-born children.[5] However, in another 7vCRM vaccine study, there were no significant differences in local AEs between preterm and term infants, apart from swelling $>$ 2.4 cm, which was significantly more frequent in the preterm group.[2] Previous DTPa-HBV-IPV/Hib vaccine studies in preterm infants also revealed no significant differences in local AEs between preterm and term infants.[20,21]

One of the reasons why preterm infants are at higher risk for infections is because maternal antibodies are transferred to the fetus mainly during the last months of pregnancy. Therefore, premature birth results in concentrations of transplacentally acquired maternal antibodies that are lower in preterm infants than in gestationally mature infants.[22] This was also observed in the present study; prevaccination antibody concentrations tended to be higher for most of the serotypes in the term group compared with the preterm groups.

For each of the vaccine serotypes, the percentages of subjects who reached the ELISA antibody threshold of 0.2 $\mu$g/mL were high after primary and booster vaccination in all 3 groups, with antibody responses in line with those measured in other European PHiD-CV vaccination studies.[6,11,12] No adjustment was made for multiple comparisons among the 3 groups because the study had descriptive immunogenicity objectives only. The immunogenicity results of the present study also seem to be in line with those from 7vCRM vaccination trials in preterm infants,[2–4] although comparisons are hampered by differences in study methodologies and laboratory assays.

As reported in previous pneumococcal conjugate vaccine studies,[4,11,12] a decrease in serotype-specific antibody concentrations and OPA titers was observed between the postprimary and prebooster time points. However, effective priming of the immune system in all groups was indicated by strong antibody responses after the booster dose. Similarly, OPA titers, which tended to be lower after priming for some pneumococcal serotypes in preterm infants than in the term group, showed a good booster response, with $>$90% of subjects in each group reaching OPA titers $\geq$ 8 for the different vaccine serotypes after booster vaccination. There were no significant differences in pneumococcal antibody concentrations or OPA titers between the 2 preterm groups after priming or booster vaccination.

PHiD-CV contains 3 different carrier proteins, and therefore induces T-cell help triggered by different T-cell epitopes to allow anti-polysaccharide responses in infants. Our results indicate that this indeed happened because anti-polysaccharide responses were observed against all serotypes included in the vaccine at an age when no or very low responses would be expected with nonconjugated plain polysaccharide vaccines. In addition, each of the 3 carrier proteins used induced or enhanced carrier protein-specific antibody responses (anti-protein D, anti-tetanus toxoid, and anti-diphtheria toxoid). These anti-polysaccharide and anti-protein responses can only be explained by T-cell involvement.

## CONCLUSIONS

PHiD-CV was proven to be well tolerated and generally as immunogenic in preterm infants as in term infants when given as a 3-dose primary vaccination followed by a booster dose. These results suggest that preterm infants, who are at high risk for bacterial infections, would benefit from PHiD-CV vaccination.

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# Immunization of Preterm Infants With 10-Valent Pneumococcal Conjugate Vaccine

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