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Safety, reactogenicity and immunogenicity of a booster dose of the 10-valent pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV) in Malian children

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Keywords: PHiD-CV, pneumococcal conjugate vaccine, safety, reactogenicity, immunogenicity, Mali, booster, antibody persistence

Abbreviations: AE(s), adverse event (s); ATP, according-to-protocol; CI, confidence interval; DTPw-HBV-IPV/Hib, diphtheria-tetanus-whole-cell pertussis hepatitis B virus and *Haemophilus influenzae* type b vaccine; ELISA, enzyme-linked immunosorbent assay; GAVI, Global Alliance for Vaccines and Immunization; GMC, geometric mean concentration; GMT, geometric mean titre; GSK, GlaxoSmithKline; IPD, invasive pneumococcal disease; LAR, legally acceptable representative; OPA, opsonophagocytic activity; OPV, oral polio vaccine; PCV, pneumococcal conjugate vaccine; PHiD-CV, pneumococcal non-typeable *Haemophilus influenzae* (NTHi) protein D conjugate vaccine; SAE, serious adverse event; SAS, statistical analysis system; SD, standard deviation; 7vCRM, 7-valent pneumococcal CRM_{197} conjugate vaccine; TVC, total vaccinated cohort; WHO, World Health Organization

Background: Primary vaccination with the 10-valent pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV) was previously shown to be immunogenic and well tolerated in Malian children. Data on booster vaccination with a fourth consecutive dose of PHiD-CV are available for Europe, Asia and Latin America but are lacking for Africa. The present study evaluated further the safety, reactogenicity and immunogenicity of a fourth consecutive (booster) dose of PHiD-CV.

Results: Low incidences of AEs with grade 3 intensity (2.1% of subjects) were observed. There were no reports of large swelling reactions and serious adverse events. One month post-booster vaccination, for each vaccine pneumococcal serotype, at least 97.8% of subjects had antibody concentrations ≥ 0.2 μg/ml, and at least 97.1% of subjects had opsonophagocytic activity ≥ 8. From pre- to post-booster, a 12.3-fold increase in anti-protein D geometric mean concentration was observed.

Methods: This phase III, open-label study was conducted in Ouelessebougou, Mali, between November 2009 and June 2010. The study population consisted of Malian children previously primed (3 doses) with PHiD-CV in study NCT00678301 receiving a fourth consecutive (booster) dose of PHiD-CV in the second year of life. The incidences of adverse events (AEs) with grade 3 intensity (primary objective) or of any intensity (secondary objective), and the immunogenicity (secondary objective) of the PHiD-CV booster dose were assessed.

Conclusion: A booster dose of PHiD-CV was well tolerated when administered to Malian children in the second year of life and was highly immunogenic for all 10 vaccine pneumococcal serotypes and NTHi protein D. (ClinicalTrials.gov identifier: NCT00985465).

Introduction

Globally, approximately 1.6 million children under 5 years of age die from pneumonia annually, and nearly half of pneumonia-related deaths occur in sub-Saharan Africa.[1] To date, donors such as the Global Alliance for Vaccines and Immunization (GAVI) support the introduction of pneumococcal conjugate vaccines in low-income countries in Africa.[2]

Among circulating pneumococcal serotypes, serotype 1 is one of the most common causes of invasive pneumococcal disease

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Table 1. Incidence of solicited local and general symptoms reported during the 4 days post-vaccination period following PHiD-CV booster dose (total vaccinated cohort)

Symptom	Type	PHiD-CV (n = 141) % [95% CI]
Pain	Any	28.4 (21.1–36.6)
	Grade 3	0.0 (0.0–2.6)
Redness	Any	12.1 (7.2–18.6)
	Grade 3	1.4 (0.2–5.0)
Swelling	Any	47.5 (39.1–56.1)
	Grade 3	0.0 (0.0–2.6)
Drowsiness	Any	0.0 (0.0–2.6)
	Grade 3	0.0 (0.0–2.6)
Fever (Axillary)	Any	24.1 (17.3–32.0)
	Grade 3	0.0 (0.0–2.6)
Irritability	Any	5.7 (2.5–10.9)
	Grade 3	0.0 (0.0–2.6)
Loss of appetite	Any	0.7 (0.0–3.9)
	Grade 3	0.0 (0.0–2.6)

n = number of subjects with the documented dose. Pain of grade 3 intensity, the limb was spontaneously painful or the child cried when the limb was moved passively; grade 3 redness/swelling, diameter > 30mm, drowsiness of grade 3 intensity, prevented normal activity; grade 3 fever > 39.5°C; grade 3 irritability, crying that could not be comforted/ prevented normal activity; grade 3 loss of appetite, child did not eat at all; 95% CI = 95% confidence interval.

(IPD) and an important cause of pneumonia and empyema in many developing countries, potentially contributing to high mortality rates.[3,4]

For pneumococcal vaccines, the World Health Organization (WHO) recommends a 3-dose primary vaccination schedule at 6, 10, 14 weeks of age without booster vaccination.[5] However, a previous 3-dose primary vaccination study in Gambian infants receiving a 9-valent pneumococcal conjugate vaccine at 6, 10, 14 weeks of age showed that IPD caused by pneumococcal serotype 1 could not be prevented despite high antibody geometric mean concentrations (GMCs) and a high proportion of children with antibody concentrations above 0.35 μg/ml.[6] The timing of serotype 1 pneumococcal disease further suggests the need for evaluation of a booster dose.[7] Since pneumococcal conjugate vaccines (PCVs) have been rolled out in Africa and since the WHO is currently reviewing its vaccination schedule recommendations, an evaluation of booster responses to PCVs in African children in the second year of life could provide some valuable insight.

The 10-valent pneumococcal non-typeable *Haemophilus influenzae* (NTHi) protein D conjugate vaccine [PHiD-CV; *Synflorix*™, GlaxoSmithKline (GSK) Vaccines] contains pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F.

Given the antibiotic resistance of pneumococcal serotype 6A,[8] the observed reduction of IPD due to serotype 6A following vaccination with the 7-valent pneumococcal CRM_{197} conjugate vaccine (7vCRM; Prevenar/Prevnar™, Pfizer Inc.) and the cross-reactivity with serotype 6B in PHiD-CV,[9] immune cross-reactive responses against serotype 6A are considered clinical relevant. Similarly, cross-reactive responses against serotype 19A following PHiD-CV vaccination might also be clinically relevant.

A 3-dose primary vaccination course with the PHiD-CV vaccine was previously shown to be well tolerated and immunogenic in Malian and Nigerian infants.[10] Various booster vaccination studies with PHiD-CV conducted in Europe, Asia and Latin America have shown that a fourth consecutive (booster) dose was well tolerated and immunogenic in young children.[11-19] The objectives of this booster study in Malian children were to assess the safety in terms of adverse events (AEs) with grade 3 intensity (primary objective), AEs of any intensity and the immunogenicity (secondary objectives) of a fourth consecutive (booster) dose of PHiD-CV.

Results

Study population. A total of 158 subjects who completed the three-dose primary vaccination course with PHiD-CV in study NCT00678301 were invited to participate in the present booster study. Of these, 11 subjects who were planned to be enrolled in this booster study did not participate due to the following reasons: parent/guardian could not be contacted (n = 1), parents/guardians not willing to participate (n = 5), or moved out of the study area (n = 5). Out of the 147 remaining children, 141 received a booster dose of PHiD-CV and 140 completed the study. Six subjects did not receive the booster dose of study vaccine due to history of seizures or progressive neurological disorder (n = 5) or heart murmur diagnosed after the primary vaccination course (n = 1). One subject had consent withdrawal not due to an AE. All subjects were part of the total vaccinated cohort (TVC) and the according-to-protocol (ATP) immunogenicity.

The mean age (± Standard Deviation [SD]) at the time of booster vaccination was 17.0 ± 1.11 months and the mean weight (± SD) was 9.30 ± 1.09 kg. All children were African and 53.2% were female.

Reactogenicity and safety. During the 31-d post-booster vaccination period, at least one AE (solicited and/or unsolicited, local and/or general) was reported for 92.2% of subjects. Events considered causally related to vaccination and those followed by a medically attended visit were reported for 68.1% and 92.2% of subjects, respectively. Concerning the primary endpoint, at least one AE with grade 3 intensity (solicited and/or unsolicited, local and/or general) was reported for 2.1% of subjects.

Swelling was the most frequently reported solicited local symptom (47.5% of subjects). Redness was the only reported grade 3 symptom (1.4% of subjects) (**Table 1**). No large swelling reactions were reported.

Incidences of solicited general symptoms were low (≤ 5.7% of subjects), apart from fever which was reported for 24.1% of subjects. There were no reports of solicited general symptoms with grade 3 intensity (**Table 1**).

At least one unsolicited AE was reported for 67.4% of subjects. Allergic bronchitis (27% of subjects) and rhinitis (18.4% of subjects) were the most frequently reported AEs. One unsolicited AE (malaria) with grade 3 intensity was reported for one subject; this was not considered causally related to vaccination. All

reported unsolicited AEs were followed by a medically attended visit.

No subject was withdrawn due to an AE. No serious adverse events (SAEs) were reported during the study.

Use of antipyretic medication during the 4 days following booster vaccination was reported for 29.8% of subjects. There were 6 reports (4.3% of subjects) of prophylactic use of antipyretics.

Immunogenicity. *Persistence 11–18 months post-primary vaccination.* As expected, a decline in antibody GMCs was observed in the time period after primary vaccination[10] and before booster vaccination for all the vaccine pneumococcal serotypes with the exception of serotype 6B. A decline was also observed for the geometric mean titers (GMTs) of opsonophagocytic activity (OPA) with the exception of serotype 7F (**Fig. 2**).

Prior to booster vaccination, for each of the vaccine pneumococcal serotypes, at least 54.3% of subjects had persisting antibody concentrations ≥ 0.20 μg/ml and at least 32.4% had OPA titers ≥ 8 except for serotype 18C (14.7%) (**Table 2**).

Immune response to booster vaccination. Robust increases in antibody GMCs and OPA GMTs were observed one month post-booster vaccination. Depending on the serotype, antibody GMCs and OPA GMTs increased 6.7- to 32.6-fold and 2.8- to 402.2-fold, respectively, compared with pre-booster values. Post-booster antibody GMCs and OPA GMTs exceeded post-primary levels (**Figs. 1 and 2**).

For each of the vaccine pneumococcal serotypes, at least 97.8% of subjects had antibody concentrations ≥ 0.2 μg/ml and at least 97.1% of subjects had OPA titers ≥ 8, one month post-booster vaccination (**Table 2**).

Both IgG antibodies measured with an enzyme-linked immunosorbent assay (ELISA) and OPA against the cross-reactive serotypes 6A and 19A were induced (**Table 2** and **Figs. 1 and 2**).

After the PHiD-CV booster dose, all subjects had measurable antibodies against protein D. The anti-protein D antibody GMC was 3710.1 (95% CI: 3109.0–4427.4) EL.U/ml, with a 12.3-fold increase with respect to the pre-booster time point (**Table 2**).

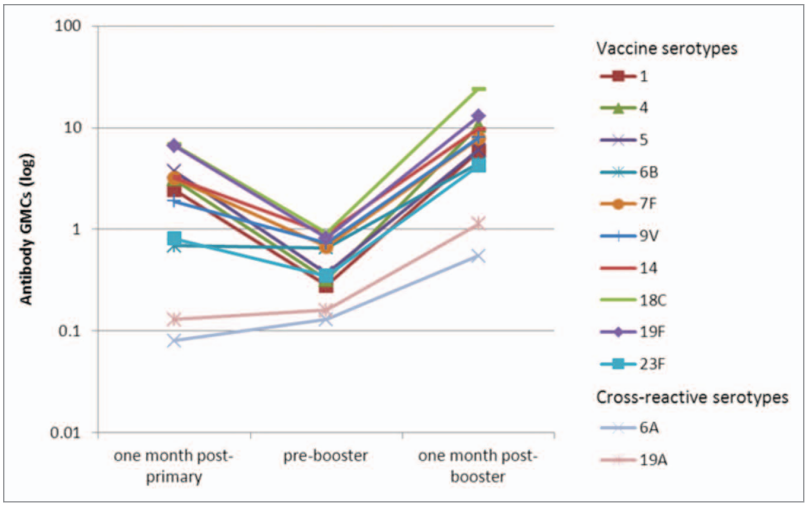

Figure 1. Kinetics of serotype-specific antibody geometric mean concentrations (GMCs, GSK's 22F-inhibition ELISA) for vaccine pneumococcal serotypes and cross-reactive serotypes 6A and 19A, post-primary, pre-booster and post-booster vaccination with PHiD-CV (ATP immunogenicity cohort). GMC, geometric mean concentration; ATP, according-to-protocol; GSK's 22F-ELISA, GlaxoSmithKline's 22F-inhibition enzymelinked immunosorbent assay. Note: Immunogenicity results related to one month post- primary were derived from the primary vaccination study NCT00678301 by re-calculation based on the ATP immunogenicity cohort of the booster study

Discussion

A fourth consecutive (booster) dose of PHiD-CV in the second year of life was shown to be well-tolerated and highly immunogenic in Malian children. The observed safety and reactogenicity profile of a fourth consecutive (booster) dose of PHiD-CV is in line with previous PHiD-CV booster vaccination studies conducted in Europe, Asia and Latin America.[11,15-19] The most commonly unsolicited AEs reported were in line with what could be expected in the pediatric age group studied. No SAEs were reported.

The decline in antibody GMCs and OPA GMTs prior to booster vaccination may indicate that subjects could benefit from a booster dose. The robust increases in antibody GMCs and OPA GMTs between pre- and post-booster time points are indicative of adequate priming of the immune system during primary PHiD-CV vaccination. One month after PHiD-CV booster vaccination in the second year of life, for each of the 10 vaccine pneumococcal serotypes, high percentages of children had antibody concentrations ≥ 0.2 μg/ml and an OPA titer ≥ 8. Although some biological effect of protein D against NTHi was previously observed with a candidate 11-valent pneumococcal conjugate vaccine,[20] anti-protein D immune responses are difficult to interpret since no serological correlate of protection exists.

The effect of PHiD-CV on cross-reactive serotypes 6A and 19A is not unexpected, given the structural similarity of the serotype specific capsular polysaccharides of cross-reactive serotypes 6A and 19A with polysaccharides from serotypes 6B and 19F contained in PHiD-CV.[21,22] Previous experience has shown significant reductions of serotype 6A disease following introduction of 7vCRM not containing serotype 6A, but only 6B. These cross-reactive immune responses might therefore be of clinical significance.

Overall, post-booster immune responses in the present study were higher than those reported in previous booster studies with PHiD-CV, with the exception of OPA booster responses in Asian children.[12,14-19] Although regional variations in immune responses to vaccines have been seen previously, the underlying mechanisms are still not fully understood.[12,14,16,23-26]

A potential limitation of the present booster study includes the fact that assessment of the reactogenicity and safety were not blinded and could be subject to observer bias. Another possible limitation of the study could be the lack of control for the prevalence of antibodies due to environmental transmission and/

Table 2. Percentage of children with antibody concentrations ≥ 0.2 μg/ml (22F-inhibition ELISA) and OPA titers ≥ 8 for vaccine pneumococcal serotypes and cross-reactive serotypes 6A and 19A, seropositivity rates and GMCs for anti-protein D antibodies pre- and 1 months post-booster dose (ATP immunogenicity cohort)

	ELISA, % ≥ 0.2 μg/ml (95% CI)				OPA, % ≥ 8 (95% CI)			
	N	pre-booster	*N*	post-booster	*N*	pre-booster	*N*	post-booster
Vaccine serotypes								
1	140	54.3 (45.7–62.7)	139	100 (97.4–100)	139	32.4 (24.7–40.8)	139	97.1 (92.8–99.2)
4	140	59.3 (50.7–67.5)	139	100 (97.4–100)	139	51.1 (42.5–59.6)	139	100 (97.4–100)
5	140	75.0 (67.0–81.9)	139	100 (97.4–100)	133	39.1 (30.8–47.9)	139	100 (97.4–100)
6B	140	86.4 (79.6–91.6)	139	97.8 (93.8–99.6)	116	67.2 (57.9–75.7)	134	98.5 (94.7–99.8)
7F	140	92.1 (86.4–96.0)	139	100 (97.4–100)	133	99.2 (95.9–100)	136	100 (97.3–100)
9V	140	90.0 (83.8–94.4)	139	100 (97.4–100)	100	86.0 (77.6–92.1)	111	100 (96.7–100)
14	140	89.3 (82.9–93.9)	139	99.3 (96.1–100)	112	66.1 (56.5–74.7)	109	99.1 (95.0–100)
18C	140	97.9 (93.9–99.6)	139	100 (97.4–100)	95	14.7 (8.3–23.5)	106	100 (96.6–100)
19F	140	87.1 (80.4–92.2)	139	100 (97.4–100)	124	34.7 (26.4–43.7)	127	98.4 (94.4–99.8)
23F	140	66.4 (58.0–74.2)	139	99.3 (96.1–100)	132	53.8 (44.9–62.5)	137	98.5 (94.8–99.8)
Cross-reactive serotypes								
6A	140	40.0 (31.8–48.6)	139	71.9 (63.7–79.2)	127	30.7 (22.8–39.5)	126	58.7 (49.6–67.4)
19A	140	39.3 (31.1–47.9)	139	82.7 (75.4–88.6)	138	16.7 (10.9–24.0)	134	71.6 (63.2–79.1)
Protein D								
	≥ 100 EL.U/ml				GMC			
	139	89.2 (82.8–93.8)	139	100 (97.4–100)	139	301.1 (257.7–351.8)	139	3710.1 (3109.0–4427.4)

N = number of subjects with available results, 95% CI = 95% confidence interval; ATP, according-to-protocol; 22F-ELISA, 22F-inhibition enzyme-linked immunosorbent assay; OPA, opsonophagocytic activity; GMC, geometric mean titer.

or exposure, and for the reactogenicity and safety of PHiD-CV since the group of unprimed PHiD-CV subjects of the primary vaccination study NCT00678301 was assigned to receive catch-up vaccination. Nevertheless, it appears unlikely that the lack of a control group would have impacted the conclusions.

In conclusion, a fourth consecutive (booster) dose of PHiD-CV administered to Malian children in the second year of life, was well tolerated and highly immunogenic for all 10 vaccine pneumococcal serotypes and NTHi protein D.

Materials and Methods

Study design and participants. This phase III, open-label, single-center study was conducted in Mali between November 2009 and June 2010. The study population consisted healthy children who were previously primed with PHiD-CV (3 doses) co-administered with DTPw-HBV/Hib and OPV in study NCT00678301 conducted between, June 2008 and December 2009 and who received a booster dose of PHiD-CV at 15–21 months of age.

The study was undertaken according to Good Clinical Practice guidelines and the Declaration of Helsinki. The study protocol was approved by the Ethical Committee of the Faculty of Medicine, Pharmacy and Dentistry of the University of Bamako. Authorization to conduct the study was obtained from the Ministry of Health. Before enrolment in the study, written informed consent was obtained from the parent(s)/legally acceptable representative(s) [LAR(s)], countersigned by an independent literate witness when the parent(s) /LAR(s) were illiterate.

Vaccines not included in the routine immunization schedule could be given at least one month before or after study vaccine administration. Vaccines recommended through national immunization campaigns were allowed at any time. Vaccines and date of administration were recorded by the study investigator. There was a follow-up visit 1 months post-booster vaccination at 16–22 months of age.

Study vaccine. PHiD-CV (*Synflorix*™) manufactured by GSK Biologicals S.A., contained 1 μg of each capsular polysaccharide for pneumococcal serotypes 1, 5, 6B, 7F, 9V, 14 and 23F, and 3 μg for serotype 4 conjugated individually to protein D, 3 μg of serotype 18C capsular polysaccharide conjugated to tetanus toxoid, and 3 μg of serotype 19F capsular polysaccharide conjugated to diphtheria toxoid. The vaccine was administered intramuscularly into the deltoid or anterolateral region of the thigh.

Safety and reactogenicity assessment. Local (pain, redness, swelling at the injection site) and general (fever, drowsiness, irritability, loss of appetite) symptoms were actively solicited for 4 days (day 0–3) following vaccination and were evaluated in all subjects using diary cards that were completed by study staff.

Unsolicited AEs were recorded within a 31-d (day 0–30) follow-up period after vaccination and SAEs, defined as any medical event resulting in death, any life-threatening event or any event causing disability, or requiring hospitalization or prolongation of hospitalization, were recorded during the entire study period up to 1 months following booster vaccination. This was done through active questioning by the investigator at each study visit.

For each solicited and unsolicited symptom, medically attended visits defined as hospitalisation, an emergency room visit or a visit to or from medical personnel (medical doctor) for any reason, were recorded.

The intensity of solicited symptoms was graded on a scale from 0 to 3. Pain at the injection site was considered to have a grade 3 intensity if the child cried when the limb was moved/was spontaneously painful, redness and swelling at the injection site if the diameter was > 30 mm and fever if axillary temperature was > 39.5°C. Grade 3 irritability/drowsiness was defined as crying that could not be comforted/prevented normal activity, and loss of appetite was considered grade 3 if the child did not eat at all. Grade 3 intensity for all other AEs was defined as preventing normal everyday activity and/or causing parents/guardians to seek medical advice.

All solicited local symptoms were defined in the protocol to be considered causally related to vaccination. For all other AEs, assessment of causal relationship to vaccination was based on the investigator's clinical judgment. Use of therapeutic and prophylactic antipyretic medication was recorded within 4 days following booster vaccination. A use of antipyretic was considered to be prophylactic when it was given in the absence of fever and any other symptom, to prevent them from occurring.

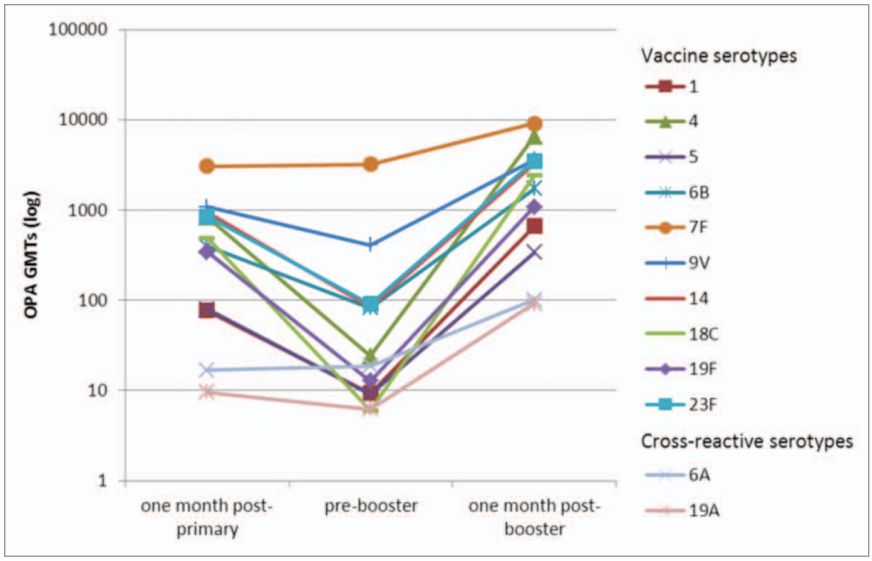

Figure 2. Kinetics of serotype-specific OPA geometric mean titres (GMTs) for vaccine pneumococcal serotypes and cross-reactive serotypes 6A and 19A, post-primary, pre-booster and post-booster vaccination with PHiD-CV (ATP immunogenicity cohort). ATP, according-to-protocol; OPA , opsonophagocytic activity; GMT, geometric mean titre.

Immunogenicity assessment. Blood samples were collected before and one month after vaccination. Serum samples were stored at -20°C until analyzed at GSK Biologicals' Laboratory (Rixensart, Belgium) and SGS Laboratory (Ghent, Belgium).

GSK Biologicals' 22F-inhibition ELISA was used to measure anti-pneumococcal serotype-specific total IgG concentrations using a threshold antibody concentration of 0.2 μg/ml, as described previously.[27-29]

OPA was measured by a pneumococcal killing assay with a cut-off opsonic titer of 8 as described previously.[30] Antibodies against NTHi protein D were measured with an ELISA assay developed by GSK Biologicals with an assay cut-off of 100 EL.U/ml. Serological results of blood samples collected one month post-primary vaccination in study NCT00678301 were re-calculated to show kinetics of immune responses over time. Data quality was assured by internal quality control procedures. Additionally, the same laboratory tests[27-30] for which quality procedures are in place to ensure stability of the test results were used in the primary and booster vaccination studies.

Statistical analysis. The analysis of safety and reactogenicity was performed on the TVC. The immunogenicity analysis was done on the ATP immunogenicity cohort comprising all children with assay results available and who complied with the procedures and interval for blood sampling as defined in the protocol.

Immunogenicity results one month post-primary were derived from the primary vaccination study NCT00678301 by re-calculation based on the ATP immunogenicity cohort of the booster study.

The sample size was contingent on the number of Malian subjects who received a full vaccination course (i.e., 3-dose primary vaccination) in study NCT00678301 with the PHiD-CV vaccine.

The primary safety endpoint was the occurrence of grade 3 AEs (solicited and/or unsolicited, local and/or general) within 31 days (day 0–30) after vaccination.

Secondary safety endpoints were occurrences of solicited symptoms (local and general) within 4 days (day 0–3) after vaccination, unsolicited AEs within 31 days (day 0–30) after vaccination, and SAEs during the entire study period.

Secondary immunogenicity endpoints included concentrations of antibodies and opsonophagocytic titers against vaccine pneumococcal serotypes, cross-reactive pneumococcal serotypes 6A and 19A, and anti-protein D antibody concentrations.

Antibody GMCs, OPA GMTs, and percentages of children reaching the predefined immunological thresholds, were determined with 95% confidence intervals (95% CIs) for each vaccine pneumococcal serotype and cross-reactive serotypes 6A and 19A. Anti-protein D antibody GMCs and seropositivity rates were calculated with 95% CIs.

Incidences of symptoms and AEs were calculated with exact 95% CI.

The statistical analyses were performed using the Statistical Analysis System (SAS) Drug and Development (SDD), web portal version 3.5 with SAS version 9.2.

Trademark Statement

Synflorix is a trademark of the GlaxoSmithKline group of companies. Prevenar/Prevnar is a trademark of Pfizer, Inc.

Previous Publications

Parts of the results of this study were presented at the 7th World Congress of the World Society for Paediatric Infectious Diseases (WSPID), Melbourne, Australia, November 16–19, 2011.

Authors' Contribution

AD helped plan the reported study, collected data and provided interpretation of the results. A.D., G.S., A.M., Y.S., A.B., Y.D., A. Diallo, A. Dolo, contributed to the data collection. A.D. and O.D. oversaw the conduct of the study. NF helped design the study, FS and NF did the statistical analyses and interpret the results; L.S., D.B. designed and planned the study, L.S., A.S. and D.B. helped interpret the results. All authors critically reviewed the different drafts of the manuscript and approved the final version.

Financial Disclosure

This study was sponsored by GlaxoSmithKline Biologicals SA. GSK Biologicals was involved in all stages of the study conduct and analysis and took in charge all costs related to the development of this manuscript.

Potential Conflicts of Interest

A.D., A.M., Y.S., A.B., A.Diallo, A.Dolo, G.S., Y.D. and O.D. declare that their institution has received grants from the GlaxoSmithKline group of companies; A.D. has also received travel fees from the GlaxoSmithKline group of companies; A.S. works as consultant for GlaxoSmithKline Biologicals; L.S., N.F., F.S. and D.B. are employed by the GlaxoSmithKline group of companies, and L.S. and D.B. own stocks.

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