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Immunogenicity and safety of 11- and 12-valent pneumococcal non-typeable *Haemophilus influenzae* protein D-conjugate vaccines (11vPHiD-CV, 12vPHiD-CV) in infants: Results from a phase II, randomised, multicentre study

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ABSTRACT

Background: We assessed 2 investigational 11- and 12-valent vaccines, containing capsular polysaccharides of 10 serotypes as in the pneumococcal non-typeable *Haemophilus influenzae* protein D-conjugate vaccine (PHiD-CV) and CRM_{197}-conjugated capsular polysaccharides of serotypes 19A (11-valent) or 19A and 6A (12-valent).

Methods: In this phase II, partially-blind, multicentre study (NCT01204658), healthy infants were randomised (1:1:1:1) to receive 11vPHiD-CV, 12vPHiD-CV, PHiD-CV, or 13-valent CRM_{197}-conjugate pneumococcal vaccine (PCV13), at 2, 3, and 4 (primary series), and 12–15 months of age (booster dose), co-administered with DTPa-HBV-IPV/Hib. Confirmatory objectives assessed non-inferiority of investigational vaccines to comparators (PHiD-CV for common serotypes; PCV13 for 19A and 6A), in terms of percentage of infants with pneumococcal antibody concentrations $\geq$0.2 μg/mL and antibody geometric mean concentrations, post-primary vaccination. Reactogenicity and safety were assessed.

Results: 951 children received $\geq$1 primary dose, 919 a booster dose. Pre-defined immunological non-inferiority criteria were met simultaneously for 9/11 11vPHiD-CV serotypes (all except 23F and 19A) and 10/12 12vPHiD-CV serotypes (all except 19A and 6A); thus, non-inferiority objectives were reached.

Abbreviations: AE, adverse event; ATP, according-to-protocol; CI, confidence interval; CRM197, non-toxic cross-reacting mutant of diphtheria toxin isolated from cultures of *Corynebacterium diphtheriae* strain C7 (β197); DTPa-HBV-IPV/Hib, diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliovirus and *Haemophilus influenzae* type b vaccine; ELISA, enzyme-linked immunosorbent assay; EL.U, ELISA units; GMC, geometric mean concentration; GMT, geometric mean titre; IgG, immunoglobulin G; IPD, invasive pneumococcal disease; OPA, opsonophagocytic activity; PCV, pneumococcal conjugate vaccine; PHiD-CV, pneumococcal non-typeable *Haemophilus influenzae* protein D-conjugate vaccine; SAE, serious adverse event; TT, tetanus toxoid; TVC, total vaccinated cohort; UL, upper limit; WHO, World Health Organization.

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For each PHiD-CV serotype, percentages of children with antibody concentrations ≥0.2 μg/mL were ≥96.7% post-primary (except 6B [≥75.2%] and 23F [≥81.1%]), and ≥98.1% post-booster vaccination. For each PHiD-CV serotype except serotype 1, ≥81.0% and ≥93.9% of children had opsonophagocytic activity titres ≥8, post-primary and booster vaccination. AEs incidence was similar across all groups. SAEs were reported for 117 children (29 in the 11vPHiD-CV group, 26 in the 12vPHiD-CV group, 38 in the PHiD-CV group and 24 in the PCV13 group); 4 SAEs were considered vaccination-related. No fatal events were recorded.

Conclusion: Addition of 19A and 6A CRM_{197}-conjugates did not alter immunogenicity of the PHiD-CV conjugates; for both investigational vaccines post-booster immune responses to 10 common serotypes appeared similar to those elicited by PHiD-CV. Safety and reactogenicity profiles of the investigational vaccines were comparable to PHiD-CV.

Clinical trial registry: NCT01204658.

1. Introduction

Streptococcus pneumoniae is an important cause of childhood diseases, including acute otitis media, pneumonia, non-invasive and invasive pneumococcal disease (IPD), which together account for a large proportion of deaths in children <5 years of age worldwide [1].

Two pneumococcal conjugate vaccines (PCVs) are currently widely used and have shown effectiveness against various pneumococcal diseases: the pneumococcal non-typeable *Haemophilus influenzae* protein D-conjugate vaccine (PHiD-CV, *Synflorix*, GSK) [2] and the 13-valent CRM_{197}-conjugate PCV (PCV13, *Prevenar 13/Prevnar 13*, Pfizer) [3]. These PCVs contain 10 and 13 pneumococcal antigens, respectively and additionally offer the potential to protect against vaccine-related serotypes belonging to the same serogroups as those contained in the vaccines. For example, PHiD-CV was shown to offer protection against disease due to serotype 19A through cross-reactive antibodies elicited by the 19F polysaccharide conjugate [4].

There is growing evidence showing that PHiD-CV and PCV13 have a comparable, significant impact on IPD [5,6]. However, despite their success, the burden of disease caused by serotypes not included in these vaccines remains important [7]. This could potentially be addressed by adding more polysaccharide conjugates to currently licensed formulations. However, adding additional antigens could lead to increased reactogenicity or immunological interference, as previously observed for other vaccines [8,9], and this possibility needs to be assessed.

We evaluated the immunogenicity and safety of 2 investigational 11- and 12-valent PHiD-CV vaccines that include capsular polysaccharides of serotypes 19A (11vPHiD-CV) and 6A and 19A (12vPHiD-CV) conjugated to CRM_{197}.

This study aimed to demonstrate immunological non-inferiority of 11vPHiD-CV and 12vPHiD-CV when compared to the 2 licensed vaccines, 1 month after a 3-dose primary vaccination.

2. Methods

2.1. Study design and participants

This was a phase II, randomised, partially-blind, multicentre study conducted in Czech Republic, Germany, Poland and Spain, between July 2012 and January 2014.

Healthy infants 6–12 weeks of age who had not been previously vaccinated against *S. pneumoniae* and did not meet any of the exclusion criteria (Supplementary Material, Text S1) were enrolled in the study, after written informed consent was obtained from parents or legally acceptable representatives.

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.vaccine.2018.07.023.

Infants were randomised (1:1:1:1) into 4 groups to receive 1 of the 2 investigational vaccines (11vPHiD-CV or 12vPHiD-CV), PHiD-CV, or PCV13, administered at approximately 2, 3, and 4 months (primary series) and 12–15 months of age (booster dose) (3 + 1 schedule).

Investigational study vaccines are described in Text S2. A diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliovirus and *H. influenzae* type b vaccine (DTPa-HBV-IPV/Hib, *Infanrix hexa*, GSK) was co-administered as part of the routine immunisation programme. To comply with the national immunisation schedule, all Spanish children also received a licensed meningococcal serogroup C-tetanus toxoid conjugate vaccine, administered concomitantly with the study vaccine at approximately 2, 4 and 12–15 months of age.

Treatment allocation was performed by a central internet-based randomisation system through a minimisation algorithm accounting for study centre. The study was conducted in a partially-blinded manner: double-blind for the 3 PHiD-CV groups, but single-blind (investigators were aware of the administered vaccine) for the PCV13 group, due to differences in the vaccines' presentation.

The study was conducted in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice. The protocol, amendments, and informed consent forms were reviewed and approved by national Independent Ethics Committees. The study is registered at ClinicalTrials.gov (NCT01204658) and available at https://www.gsk-clinicalstudyregister.com/study/116485.

2.2. Study objectives

The first co-primary objectives were to demonstrate that 11vPHiD-CV co-administered with DTPa-HBV-IPV/Hib as a 3-dose primary vaccination course is non-inferior for at least 9 out of 11 vaccine pneumococcal serotypes to PHiD-CV (for 10 serotypes) or to PCV13 (for 19A) in terms of percentage of children with antibody concentrations ≥0.2 μg/mL and antibody geometric mean concentrations (GMCs). The second co-primary objectives assessed non-inferiority of 12vPHiD-CV in the same terms, for at least 10 out of 12 pneumococcal serotypes to PHiD-CV (for 10 serotypes) and to PCV13 (for 6A and 19A).

Secondary objectives included assessing the immune response to pneumococcal serotype-specific polysaccharides and to protein D post-primary and post-booster vaccination, antibody persistence 8–11 months after the last primary dose, and safety and reactogenicity of the 2 investigational vaccines.

2.3. Immunogenicity

Blood samples of approximately 3.5 mL (pre-vaccination) or 5 mL (1 month post-primary vaccination, pre- and 1 month post-booster vaccination) were collected and sera were stored at maximum −20 °C. Pneumococcal serotype-specific immunoglobulin G (IgG) antibodies were measured by 22F-inhibition enzyme-linked immunosorbent assay (ELISA) [10]. For each group, immune responses to each serotype were expressed as antibody GMCs and the percentage of children with IgG concentrations ≥0.2 μg/mL, which is equivalent to concentrations of ≥0.35 μg/mL as measured by the non-22F ELISA of the World Health Organization (WHO) reference laboratory [11]. Antibody opsonophagocytic activity (OPA) was measured by a killing-assay [12] and assessed as the percentage of children with titres ≥8 and geometric mean titres (GMTs). Anti-protein D antibodies were quantified by an in-house ELISA with a cut-off of 100 ELISA Units (EL.U)/mL.

2.4. Safety and reactogenicity

All events were reported by parents or legally acceptable representatives using diary cards. Solicited local and general symptoms within 4 days post-vaccination (days 0–3), and unsolicited adverse events (AEs) within 31 days post-vaccination (days 0–30), graded by intensity, were recorded. Large swelling reactions were recorded post-booster dose. Serious adverse events (SAEs) were defined as any untoward medical occurrences that resulted in death, were life-threatening, required or prolonged hospitalisation, or resulted in disability or incapacity, and were collected throughout the study.

2.5. Statistical analyses

A total of 940 infants (235 per group) were to be enrolled. Assuming 85% of enrolled participants would be evaluable, power of the study to demonstrate non-inferiority was 97% for the first confirmatory objective and 90% for the second one (Text S3).

Immunogenicity analyses were performed on the according-to-protocol (ATP) cohorts for immunogenicity for primary or booster vaccination, which included all evaluable study participants (according to the eligibility criteria and compliance with the study procedures) with available assay results for at least 1 study vaccine component. OPA and protein D analyses were carried out on subsets of approximately 50% of randomly selected children from each group.

Non-inferiority of 11vPHiD-CV was demonstrated if the upper limit (UL) of the 2-sided 95.9% CI (1-sided $\alpha = 2.05\%$) of the difference in percentages of infants with pneumococcal antibody concentrations ≥0.2 μg/mL between comparator and investigational groups was lower than 10%, and if the UL of GMC ratios (comparator/investigational group) was below a limit of 2 for at least 9 out of 11 vaccine pneumococcal serotypes. Non-inferiority of 12vPHiD-CV was assessed as a second sequential co-primary objective using the UL of the 2-sided 95.8% CI (1-sided $\alpha = 2.08\%$), with the same non-inferiority criteria for at least 10 out of 12 serotypes. The study power was sufficient to demonstrate non-inferiority for 9/11 (for 11vPHiD-CV) or 10/12 (for 12vPHiD-CV) serotypes, in line with the WHO guidance that meeting non-inferiority criteria for each serotype contained in the candidate vaccine is not an absolute requirement [13]. All other comparisons were descriptive, and they should be interpreted with caution, since no adjustment for multiplicity was performed.

Safety and reactogenicity assessments were carried out on total vaccinated cohorts (TVCs) for primary or booster vaccination, which included all children who received at least 1 primary dose, or the booster dose, respectively. The percentages of doses followed by solicited and unsolicited AEs, grade 3 symptoms and AEs with causal relationship to vaccination were tabulated with exact 95% CI for each group.

Analyses were performed using SAS in SAS Drug and Development web portal.

3. Results

3.1. Demographics

The TVC included 951 children for primary vaccination, and 919 for booster vaccination. Distribution among groups and reasons for exclusion from the ATP cohorts for immunogenicity are detailed in Fig. 1. The groups were balanced in terms of age and sex distribution; most participants were of White Caucasian heritage (Table S1).

3.2. Immunogenicity

3.2.1. Non-inferiority assessment

One month post-primary vaccination, for the difference between the comparator and 11vPHiD-CV group in the percentage of infants with pneumococcal antibody concentrations ≥0.2 μg/mL the ULs of the 95.9% CIs were below the non-inferiority margin for each of the 10 PHiD-CV serotypes except 23F (Fig. 2A, Table S2). Non-inferiority criteria in terms of antibody GMC ratios between the comparator and 11vPHiD-CV groups were also met for all serotypes, except 19A (Fig. 2B, Table S3). Non-inferiority of the investigational 11vPHiD-CV was therefore demonstrated.

For 10 of the 12vPHiD-CV serotypes (all except 23F and 6A), the UL of the 2-sided 95.8% CI of the difference in the percentage of children with antibody concentrations ≥0.2 μg/mL between comparator and 12vPHiD-CV vaccines was below 10%. The ULs of the 95.8% CIs of the antibody GMC ratios were below the non-inferiority margin for each of the 10 PHiD-CV serotypes, and above it for serotypes 19A and 6A (Fig. 2B, Table S3). Therefore, 12vPHiD-CV was shown to be non-inferior to comparator vaccines.

3.3. Immune response to pneumococcal serotypes and protein D

One month post-primary vaccination, for each of the 10 PHiD-CV serotypes except 6B and 23F, at least 96.7% of infants in the groups receiving the investigational vaccines had antibody concentrations ≥0.2 μg/mL. In the comparator groups, these percentages were at least 94.5%, except for serotypes 6B and 23F in the PHiD-CV group. For serotype 19A, antibody concentrations ≥0.2 μg/mL were observed in at least 95.8% of infants in both investigational groups, and for serotype 6A in 88.3% of infants in the 12vPHiD-CV group. In the comparator (PCV13) group, this percentage was 99.5% for both serotypes (Table 1).

Pre-booster dose, for each of the 10 PHiD-CV serotypes except serotype 1, at least 83.1% of infants in the investigational groups had antibody concentrations ≥0.2 μg/mL, compared to 86.4% in the PHiD-CV group (Table 1). For serotype 19A, the percentages of infants with antibody concentrations ≥0.2 μg/mL were 76.9% and 73.9% in 11vPHiD-CV and 12vPHiD-CV groups respectively, compared to 76.4% in the PCV13 group. For serotype 6A, 94.4% and 90.7% of infants in the 12vPHiD-CV and PCV13 groups, respectively, had antibody concentrations ≥0.2 μg/mL (Table 1).

One month post-booster vaccination, for each PHiD-CV serotype and serotype 19A, the percentages of toddlers with antibody concentrations ≥0.2 μg/mL in both investigational groups increased to at least 98.1% (Table 1).

For each of the PHiD-CV serotypes, antibody GMCs increased from pre-vaccination levels post-primary vaccination, decreased

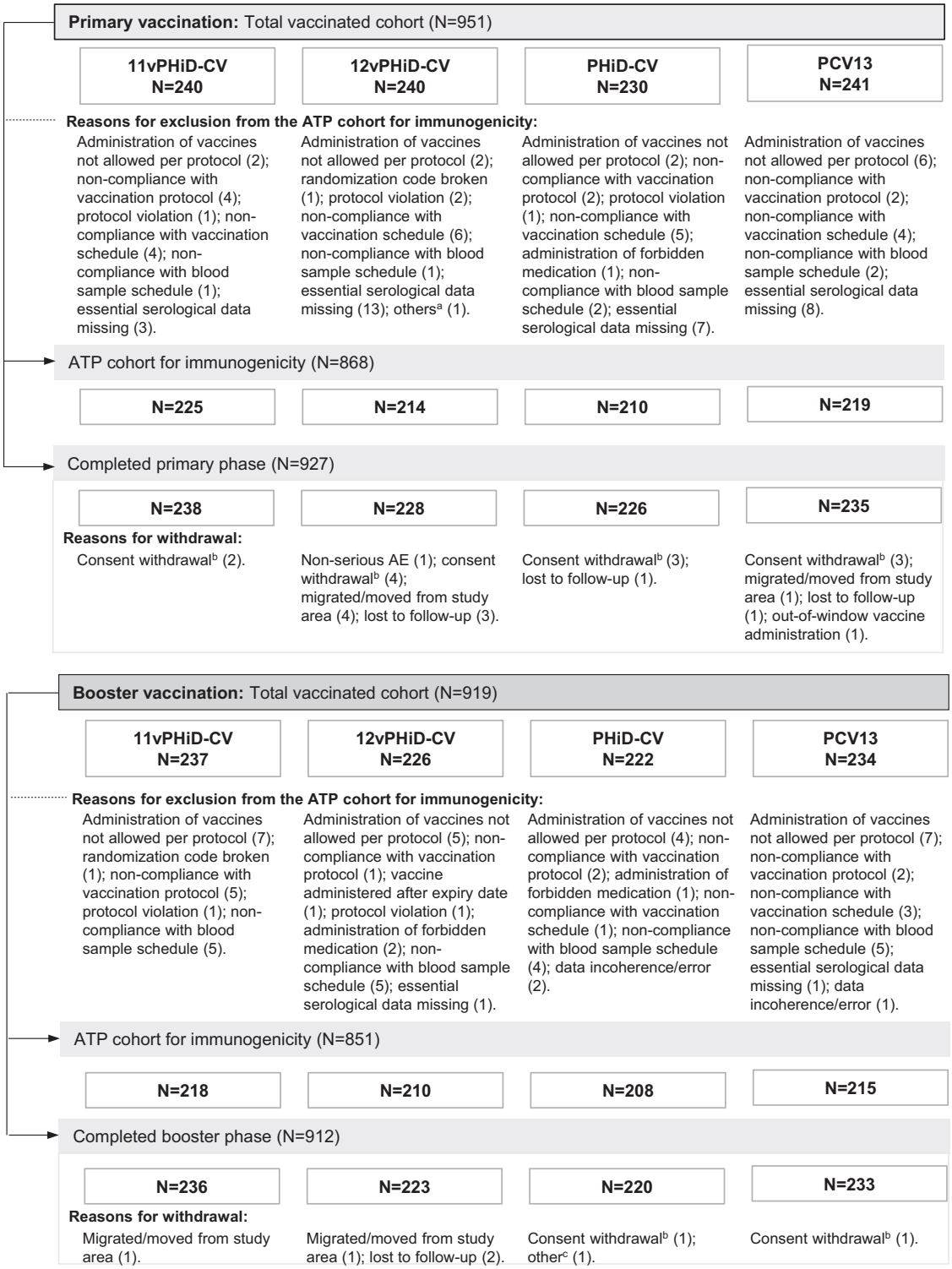

Fig. 1. Participant flow chart. N, number of infants/toddlers in each group; ATP, according-to-protocol; AE, adverse event. Note: [a] Pre-vaccination temperature too high; [b] not due to an adverse event; [c] mother not mobile.

pre-booster dose (but remained higher than at baseline), and increased again post-booster vaccination. The ranges were similar across the 3 PHiD-CV groups, except for serotype 6B post-booster dose, for which antibody GMCs were significantly higher in the 12vPHiD-CV group compared with the other 2. Antibody GMCs were considerably higher in the PCV13 than in PHiD-CV groups for serotype 19A post-primary and post-booster vaccination, and for serotype 6A post-primary vaccination, while higher pre-booster values were observed for serotype 6A in the 12vPHiD-CV than in the PCV13 group (non-overlapping 95% CIs; Table 1).

One month post-primary vaccination, for each of the 10 PHiD-CV serotypes except serotype 1, at least 81.0% of infants receiving the investigational vaccines or PHiD-CV had OPA titres ≥8. These percentages increased post-booster vaccination to at least 93.9%. For serotype 6A, all infants in the 12vPHiD-CV group had OPA titres ≥8 post-booster vaccination (Table 2). OPA results are not cur-

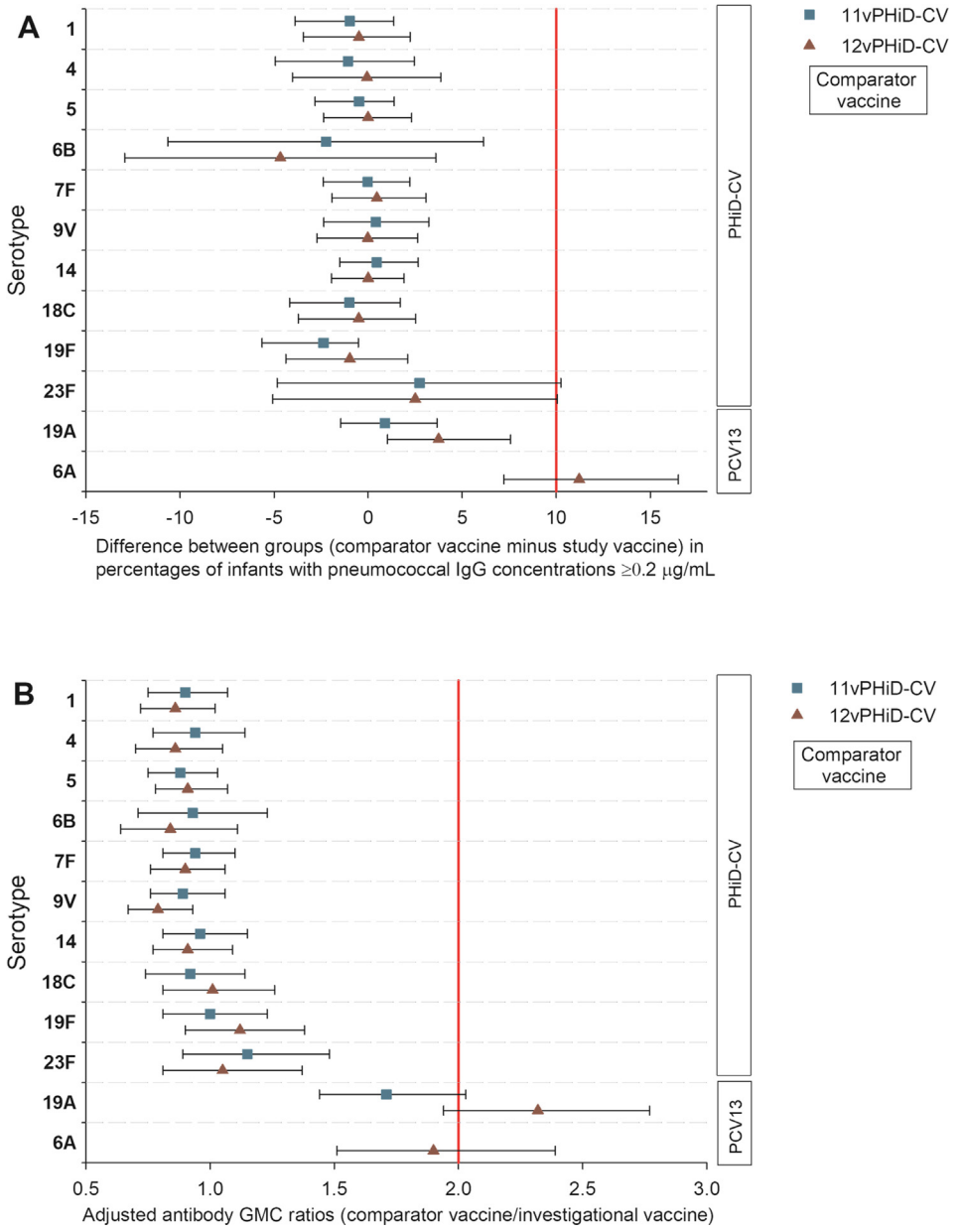

Fig. 2. Non-inferiority of 11vPHiD-CV and 12vPHiD-CV compared to PHiD-CV or PCV13 in terms of percentage of infants with antibody concentrations ≥0.2 µg/mL (A), and antibody GMC (B), one month after primary vaccination (according-to-protocol cohort for immunogenicity). Adjusted GMC, geometric mean concentration adjusted for baseline concentration. Note: Error bars indicate 95.9% (comparator/11vPHiD-CV) or 95.8% (comparator/12vPHiD-CV) confidence intervals. The vertical red lines indicate the non-inferiority margins for the upper limits of the confidence intervals. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

rently available for serotype 19A, but will be disclosed at a later time.

Immune responses to protein D appeared similar across the PHiD-CV groups at all timepoints (Table 3).

3.4. Safety and reactogenicity

Following primary vaccination, pain at the injection site was the most frequent local symptom, reported after 37.5–40.2% of doses in the investigational groups, and after 35.4–37.9% of comparator vaccine doses. Irritability/fussiness was the most frequently reported general symptom, after 53.5% (for PCV13) to 61.7% (for 12vPHiD-CV) of doses (Table 4). The same symptoms were the most frequently reported post-booster dose in all groups (Table 4). Slightly higher incidences of injection site pain post-booster dose (after 47.6–54.9% of doses in all groups) compared to post-primary vaccination were observed. Grade 3 solicited symptom incidence was below 6.2% post-primary vaccination, and below 8.2% post-booster vaccination in each group (Table 4).

Six toddlers (3 each in the 12vPHiD-CV and PHiD-CV groups) had large swelling reactions at the injection site of the PCV post-booster dose.

Post-primary vaccination, at least 1 unsolicited AE was reported after 23.4–27.2% of doses in each group (Table 4). The most frequent unsolicited symptom was upper respiratory tract infection, reported following 6.9–7.4% of doses in the investigational groups, and 4.9–8.5% of doses in the comparator groups. Post-booster vaccination, unsolicited AEs were reported after 29.1–33.3% of doses in the 3 PHiD-CV groups (Table 4), with upper respiratory tract infection as the most frequent symptom, following 4.6–7.1% of

Table 1
Percentages of infants with pneumococcal serotype-specific antibody concentrations ≥0.2 μg/mL and antibody GMCs, by timepoint (according-to-protocol cohort for immunogenicity).

		11vPHiD-CV			12vPHiD-CV			PHiD-CV			PCV13		
		N	% (95% CI)	GMC (95% CI)	N	% (95% CI)	GMC (95% CI)	N	% (95% CI)	GMC (95% CI)	N	% (95% CI)	GMC (95% CI)
1	Pre	219	12.8 (8.7–17.9)	0.06 (0.05–0.07)	207	17.4 (12.5–23.3)	0.06 (0.06–0.07)	203	11.8 (7.7–17.1)	0.05 (0.05–0.06)	207	10.6 (6.8–15.6)	0.05 (0.04–0.06)
	Post-pri	222	99.5 (97.5–100)	1.54 (1.37–1.74)	214	99.1 (96.7–99.9)	1.59 (1.41–1.79)	210	98.6 (95.9–99.7)	1.37 (1.21–1.54)	218	99.5 (97.5–100)	2.18 (1.97–2.42)
	Pre-bst	216	61.6 (54.7–68.1)	0.26 (0.24–0.30)	206	62.1 (55.1–68.8)	0.26 (0.24–0.30)	202	64.9 (57.8–71.4)	0.26 (0.23–0.29)	210	89.5 (84.6–93.3)	0.44 (0.40–0.48)
	Post-bst	214	100 (98.3–100)	2.49 (2.21–2.82)	203	99.5 (97.3–100)	2.18 (1.94–2.46)	201	100 (98.2–100)	2.25 (2.01–2.53)	209	100 (98.3–100)	3.84 (3.50–4.22)
4	Pre	219	11.9 (7.9–16.9)	0.05 (0.04–0.06)	208	8.7 (5.2–13.3)	0.05 (0.04–0.05)	203	8.4 (5.0–13.1)	0.04 (0.04–0.05)	209	9.1 (5.6–13.8)	0.05 (0.04–0.05)
	Post-pri	222	97.7 (94.8–99.3)	1.78 (1.56–2.02)	214	96.7 (93.4–98.7)	1.99 (1.73–2.28)	210	96.7 (93.3–98.6)	1.68 (1.47–1.93)	218	100 (98.3–100)	2.83 (2.60–3.09)
	Pre-bst	213	89.2 (84.2–93.0)	0.49 (0.44–0.54)	203	86.7 (81.2–91.0)	0.48 (0.43–0.54)	203	87.7 (82.4–91.9)	0.50 (0.45–0.56)	210	81.9 (76.0–86.9)	0.41 (0.37–0.46)
	Post-bst	214	100 (98.3–100)	3.89 (3.49–4.34)	203	100 (98.2–100)	4.18 (3.77–4.63)	202	100 (98.2–100)	4.06 (3.7–4.45)	209	100 (98.3–100)	3.86 (3.43–4.35)
5	Pre	219	14.6 (10.2–20.0)	0.07 (0.06–0.08)	208	17.3 (12.4–23.1)	0.07 (0.06–0.08)	202	16.3 (11.5–22.2)	0.07 (0.06–0.08)	210	18.6 (13.6–24.5)	0.07 (0.06–0.08)
	Post-pri	222	100 (98.4–100)	2.48 (2.24–2.74)	214	99.5 (97.4–100)	2.37 (2.13–2.64)	209	99.5 (97.4–100)	2.19 (1.97–2.44)	218	99.1 (96.7–99.9)	2.81 (2.52–3.13)
	Pre-bst	213	87.8 (82.6–91.9)	0.51 (0.46–0.57)	202	89.1 (84.0–93.0)	0.51 (0.45–0.57)	199	88.4 (83.2–92.5)	0.48 (0.43–0.53)	208	95.7 (91.9–98.0)	0.77 (0.69–0.85)
	Post-bst	215	100 (98.3–100)	3.23 (2.88–3.64)	203	100 (98.2–100)	3.31 (2.98–3.68)	202	100 (98.2–100)	3.05 (2.75–3.38)	209	100 (98.3–100)	6.84 (6.12–7.66)
6B	Pre	219	20.5 (15.4–26.5)	0.07 (0.06–0.08)	208	23.6 (18.0–29.9)	0.08 (0.06–0.09)	200	18.0 (12.9–24.0)	0.07 (0.06–0.08)	209	29.7 (23.6–36.4)	0.10 (0.08–0.12)
	Post-pri	222	77.5 (71.4–82.8)	0.51 (0.42–0.61)	214	79.9 (73.9–85.1)	0.58 (0.48–0.69)	210	75.2 (68.8–80.9)	0.48 (0.40–0.58)	218	78.4 (72.4–83.7)	0.49 (0.42–0.58)
	Pre-bst	213	83.1 (77.4–87.9)	0.57 (0.49–0.65)	202	90.6 (85.7–94.2)	0.64 (0.56–0.74)	199	86.4 (80.9–90.9)	0.59 (0.51–0.69)	209	56.5 (49.4–63.3)	0.22 (0.19–0.25)
	Post-bst	214	98.1 (95.3–99.5)	2.66 (2.34–3.03)	205	98.5 (95.8–99.7)	4.09 (3.60–4.66)	203	99.0 (96.5–99.9)	2.53 (2.24–2.86)	209	99.0 (96.6–99.9)	3.80 (3.34–4.33)
7F	Pre	220	32.7 (26.6–39.4)	0.12 (0.10–0.14)	211	38.4 (31.8–45.3)	0.13 (0.11–0.16)	202	32.7 (26.3–39.6)	0.13 (0.11–0.15)	211	32.7 (26.4–39.5)	0.11 (0.10–0.14)
	Post-pri	223	99.6 (97.5–100)	2.30 (2.10–2.52)	214	99.1 (96.7–99.9)	2.44 (2.18–2.72)	210	99.5 (97.4–100)	2.20 (1.97–2.47)	219	100 (98.3–100)	3.16 (2.91–3.43)
	Pre-bst	213	98.1 (95.3–99.5)	1.04 (0.94–1.16)	203	98.5 (95.7–99.7)	0.99 (0.89–1.10)	200	97.5 (94.3–99.2)	0.94 (0.84–1.05)	207	99.0 (96.6–99.9)	1.21 (1.11–1.32)
	Post-bst	214	100 (98.3–100)	4.88 (4.40–5.40)	203	100 (98.2–100)	4.57 (4.14–5.04)	201	100 (98.2–100)	4.31 (3.91–4.75)	209	100 (98.3–100)	6.34 (5.80–6.95)
9V	Pre	220	14.5 (10.2–19.9)	0.07 (0.06–0.07)	208	20.7 (15.4–26.8)	0.07 (0.06–0.08)	200	18.5 (13.4–24.6)	0.06 (0.05–0.07)	211	21.3 (16.0–27.5)	0.07 (0.06–0.08)
	Post-pri	222	98.6 (96.1–99.7)	1.57 (1.40–1.76)	214	99.1 (96.7–99.9)	1.77 (1.58–1.97)	210	99.0 (96.6–99.9)	1.42 (1.27–1.59)	218	100 (98.3–100)	2.27 (2.05–2.51)
	Pre-bst	213	94.8 (90.9–97.4)	0.76 (0.68–0.85)	202	98.0 (95.0–99.5)	0.77 (0.69–0.87)	198	97.0 (93.5–98.9)	0.70 (0.63–0.77)	207	93.7 (89.5–96.6)	0.53 (0.48–0.58)
	Post-bst	214	100 (98.3–100)	4.14 (3.70–4.62)	203	100 (98.2–100)	4.36 (3.93–4.84)	202	100 (98.2–100)	3.68 (3.32–4.09)	209	100 (98.3–100)	5.83 (5.26–6.46)
14	Pre	219	77.6 (71.5–83.0)	0.57 (0.48–0.68)	209	76.6 (70.2–82.1)	0.55 (0.46–0.65)	201	75.1 (68.6–80.9)	0.47 (0.39–0.56)	207	78.3 (72.0–83.7)	0.58 (0.48–0.70)
	Post-pri	222	99.5 (97.5–100)	4.19 (3.72–4.71)	214	100 (98.3–100)	4.45 (3.95–5.00)	210	100 (98.3–100)	4.21 (3.72–4.77)	218	99.5 (97.5–100)	4.20 (3.68–4.80)
	Pre-bst	214	94.9 (91.0–97.4)	1.30 (1.11–1.53)	204	99.0 (96.5–99.9)	1.45 (1.28–1.64)	201	96.0 (92.3–98.3)	1.12 (0.97–1.30)	209	95.7 (92.0–98.0)	1.66 (1.44–1.93)
	Post-bst	213	99.5 (97.4–100)	6.17 (5.45–6.98)	203	100 (98.2–100)	6.52 (5.80–7.33)	201	99.0 (96.5–99.9)	5.75 (5.07–6.51)	209	100 (98.3–100)	10.05 (8.97–11.25)
18C	Pre	219	32.4 (26.3–39.1)	0.11 (0.09–0.13)	209	34.9 (28.5–41.8)	0.12 (0.10–0.14)	201	34.8 (28.3–41.8)	0.12 (0.10–0.14)	210	35.2 (28.8–42.1)	0.11 (0.09–0.13)
	Post-pri	222	99.1 (96.8–99.9)	2.84 (2.45–3.28)	214	98.6 (96.0–99.7)	2.56 (2.21–2.96)	210	98.1 (95.2–99.5)	2.56 (2.19–2.98)	219	100 (98.3–100)	3.17 (2.87–3.51)
	Pre-bst	212	95.8 (92.1–98.0)	0.76 (0.67–0.86)	200	91.0 (86.1–94.6)	0.68 (0.60–0.77)	195	94.9 (90.8–97.5)	0.74 (0.65–0.84)	207	95.7 (91.9–98.0)	0.59 (0.54–0.65)
	Post-bst	213	100 (98.3–100)	7.65 (6.79–8.61)	203	100 (98.2–100)	7.20 (6.39–8.11)	201	99.5 (97.3–100)	8.00 (7.06–9.06)	209	100 (98.3–100)	6.01 (5.45–6.63)
19F	Pre	219	55.7 (48.9–62.4)	0.22 (0.18–0.26)	211	59.7 (52.8–66.4)	0.24 (0.20–0.29)	202	52.5 (45.3–59.5)	0.22 (0.18–0.26)	213	58.2 (51.3–64.9)	0.23 (0.19–0.29)
	Post-pri	223	100 (98.4–100)	3.65 (3.20–4.16)	214	98.6 (9.60–99.7)	3.31 (2.91–3.76)	210	97.6 (94.5–99.2)	3.68 (3.15–4.30)	218	100 (98.3–100)	3.07 (2.83–3.34)
	Pre-bst	212	95.8 (92.1–98.0)	1.11 (0.97–1.28)	199	97.0 (93.6–98.9)	1.11 (0.96–1.29)	196	94.9 (90.8–97.5)	1.10 (0.95–1.29)	207	89.4 (84.4–93.2)	0.50 (0.44–0.57)
	Post-bst	213	100 (98.3–100)	8.67 (7.72–9.73)	203	100 (98.2–100)	8.50 (7.55–9.59)	203	100 (98.2–100)	8.22 (7.40–9.13)	209	100 (98.3–100)	6.40 (5.77–7.11)
23F	Pre	219	24.2 (18.7–30.4)	0.07 (0.06–0.09)	208	17.8 (12.8–23.7)	0.07 (0.06–0.08)	199	20.6 (15.2–26.9)	0.07 (0.06–0.09)	210	24.3 (18.6–30.7)	0.08 (0.06–0.09)
	Post-pri	222	81.1 (75.3–86.0)	0.62 (0.52–0.73)	214	81.3 (75.4–86.3)	0.69 (0.57–0.83)	210	83.8 (78.1–88.5)	0.72 (0.61–0.86)	218	94.5 (90.6–97.1)	1.59 (1.38–1.84)
	Pre-bst	214	84.6 (79.0–89.1)	0.51 (0.44–0.58)	205	84.4 (78.7–89.1)	0.54 (0.47–0.62)	198	86.4 (80.8–90.8)	0.49 (0.43–0.56)	208	72.6 (66.0–78.5)	0.34 (0.29–0.39)
	Post-bst	214	99.1 (96.7–99.9)	3.09 (2.73–3.49)	203	99.0 (96.5–99.9)	3.31 (2.93–3.73)	201	100 (98.2–100)	2.98 (2.65–3.35)	209	99.5 (97.4–100)	6.49 (5.69–7.39)
6A	Pre	222	26.1 (20.5–32.4)	0.09 (0.07–0.10)	210	27.1 (21.3–33.7)	0.08 (0.07–0.10)	204	23.5 (17.9–30.0)	0.08 (0.06–0.09)	215	34.0 (27.7–40.7)	0.11 (0.09–0.14)
	Post-pri	222	38.3 (31.9–45.0)	0.14 (0.12–0.17)	214	88.3 (83.2–92.3)	1.12 (0.93–1.34)	208	30.3 (24.1–37.0)	0.12 (0.10–0.14)	218	99.5 (97.5–100)	2.05 (1.81–2.32)
	Pre-bst	211	55.0 (48.0–61.8)	0.23 (0.19–0.27)	196	94.4 (90.2–97.2)	0.89 (0.78–1.01)	194	53.1 (45.8–60.3)	0.22 (0.18–0.26)	205	90.7 (85.9–94.3)	0.64 (0.56–0.73)
	Post-bst	212	91.0 (86.4–94.5)	1.07 (0.90–1.27)	203	100 (98.2–100)	7.94 (6.99–9.02)	200	88.0 (82.7–92.2)	0.91 (0.76–1.09)	209	100 (98.3–100)	9.31 (8.41–10.3)
19A	Pre	218	46.3 (39.6–53.2)	0.17 (0.14–0.21)	208	41.8 (35.0–48.8)	0.17 (0.14–0.20)	202	46.5 (39.5–53.7)	0.18 (0.15–0.22)	206	50.0 (43.0–57.0)	0.19 (0.16–0.24)
	Post-pri	222	98.6 (96.1–99.7)	1.63 (1.43–1.86)	214	95.8 (92.2–98.1)	1.18 (1.03–1.36)	209	47.4 (40.4–54.4)	0.18 (0.15–0.22)	219	99.5 (97.5–100)	2.67 (2.39–3.00)
	Pre-bst	212	76.9 (70.6–82.4)	0.46 (0.39–0.54)	199	73.9 (67.2–79.8)	0.36 (0.31–0.42)	197	51.3 (44.1–58.4)	0.18 (0.15–0.21)	208	76.4 (70.1–82.0)	0.42 (0.35–0.49)
	Post-bst	214	99.5 (97.4–100)	5.35 (4.67–6.13)	203	99.0 (96.5–99.9)	4.46 (3.83–5.20)	201	86.1 (80.5–90.5)	1.11 (0.91–1.35)	209	100 (98.3–100)	7.06 (6.25–7.98)

N, number of infants with available results in each group; %, percentage of infants with antibody concentration ≥0.2 μg/mL; GMC, geometric mean concentration; CI, confidence interval; Pre, pre-vaccination; Post-pri, 1 month post-dose 3; Pre-bst, pre-booster vaccination; Post-bst, 1 month post-booster vaccination.

Table 2
Percentages of children with pneumococcal serotype-specific OPA titres ≥8 and OPA GMTs*, by timepoint (according-to-protocol cohort for immunogenicity).

		11vPHiD-CV			12vPHiD-CV			PHiD-CV			PCV13		
		N	% (95% CI)	GMT (95% CI)	N	% (95% CI)	GMT (95% CI)	N	% (95% CI)	GMT (95% CI)	N	% (95% CI)	GMT (95% CI)
1	Post-pri	105	38.1 (28.8–48.1)	13.2 (9.6–18.2)	105	44.8 (35.0–54.8)	15.6 (11.4–21.1)	98	40.8 (31.0–51.2)	13.6 (9.9–18.6)	105	61.0 (50.9–70.3)	26.4 (19.3–36.0)
	Post-bst	99	85.9 (77.4–92.0)	192.4 (129.0–287.1)	97	87.6 (79.4–93.4)	192.4 (133.3–277.5)	96	88.5 (80.4–94.1)	216.8 (148.3–316.9)	101	88.1 (80.2–93.7)	207.6 (145.8–295.6)
4	Post-pri	103	95.1 (89.0–98.4)	527.3 (401.5–692.4)	105	99.0 (94.8–100)	609.0 (492.8–752.5)	99	99.0 (94.5–100)	616.7 (503.2–756.0)	104	100 (96.5–100)	540.1 (444.7–656.1)
	Post-bst	96	100 (96.2–100)	1455.3 (1208.9–1751.9)	96	100 (96.2–100)	1650.5 (1360.9–2001.9)	95	100 (96.2–100)	1550.5 (1230.2–1954.1)	100	100 (96.4–100)	1972.2 (1586.3–2451.9)
5	Post-pri	102	82.4 (73.6–89.2)	43.0 (32.6–56.9)	104	91.3 (84.2–96.0)	46.7 (36.8–59.3)	98	82.7 (73.7–89.6)	40.5 (30.4–54.0)	105	87.6 (79.8–93.2)	57.2 (44.3–74.0)
	Post-bst	99	93.9 (87.3–97.7)	134.5 (100.3–180.4)	96	97.9 (92.7–99.7)	133.3 (105.2–168.8)	96	94.8 (88.3–98.3)	133.4 (100.5–177.1)	100	100 (96.4–100)	269.9 (216.2–337.0)
6B	Post-pri	101	92.1 (85.0–96.5)	478.3 (345.2–662.7)	104	94.2 (87.9–97.9)	603.2 (436.9–832.8)	96	93.8 (86.9–97.7)	622.6 (444.2–872.7)	103	96.1 (90.4–98.9)	742.3 (533.9–1031.8)
	Post-bst	98	96.9 (91.3–99.4)	681.4 (520.3–892.5)	96	97.9 (92.7–99.7)	1246.4 (963.1–1613.0)	95	98.9 (94.3–100)	694.6 (546.5–882.6)	100	100 (96.4–100)	1727.9 (1406.2–2123.4)
7F	Post-pri	104	100 (96.5–100)	3515.0 (2787.1–4433.0)	103	100 (96.5–100)	4472.3 (3463.6–5774.9)	98	100 (96.3–100)	3424.1 (2631.9–4454.8)	104	100 (96.5–100)	9737.9 (7540.5–12575.8)
	Post-bst	96	100 (96.2–100)	8362.9 (6977.1–10023.9)	96	100 (96.2–100)	7516.4 (6223.0–9078.7)	96	100 (96.2–100)	7880.8 (6408.6–9691.3)	97	100 (96.3–100)	16592.6 (13909.7–19792.9)
9V	Post-pri	105	100 (96.5–100)	1212.9 (953.6–1542.6)	105	100 (96.5–100)	1629.0 (1293.0–2052.4)	98	99.0 (94.4–100)	1469.9 (1178.3–1833.6)	104	100 (96.5–100)	1614.5 (1283.9–2030.2)
	Post-bst	99	100 (96.3–100)	3406.9 (2758.2–4208.1)	97	100 (96.3–100)	3616.1 (2838.1–4607.5)	93	100 (96.1–100)	3260.6 (2620.1–4057.6)	98	100 (96.3–100)	8470.4 (6692.4–10720.8)
14	Post-pri	105	97.1 (91.9–99.4)	1000.8 (743.1–1347.9)	104	100 (96.5–100)	1699.1 (1313.8–2197.3)	97	99.0 (94.4–100)	1417.4 (1059.6–1896.0)	103	99.0 (94.7–100)	2034.4 (1513.4–2734.8)
	Post-bst	99	100 (96.3–100)	2038.4 (1594.3–2606.2)	96	100 (96.2–100)	2519.9 (1960.2–3239.6)	94	100 (96.2–100)	2285.1 (1845.9–2828.9)	100	100 (96.4–100)	2772.6 (2218.6–3464.9)
18C	Post-pri	105	81.0 (72.1–88.0)	100.9 (67.7–150.4)	102	84.3 (75.8–90.8)	131.5 (86.9–198.8)	98	81.6 (72.5–88.7)	72.0 (47.0–110.4)	102	93.1 (86.4–97.2)	145.7 (102.6–206.8)
	Post-bst	97	95.9 (89.8–98.9)	914.8 (621.8–1345.9)	95	96.8 (91.0–99.3)	781.2 (536.3–1137.8)	93	97.8 (92.4–99.7)	912.0 (605.4–1374.1)	97	99.0 (94.4–100)	610.7 (421.3–885.1)
19F	Post-pri	102	86.3 (78.0–92.3)	144.2 (101.8–204.3)	102	94.1 (87.6–97.8)	201.4 (147.2–275.4)	96	90.6 (82.9–95.6)	210.4 (143.6–308.2)	103	89.3 (81.7–94.5)	66.0 (49.8–87.5)
	Post-bst	95	97.9 (92.6–99.7)	523.9 (382.9–716.8)	96	96.9 (91.1–99.4)	565.3 (406.4–786.6)	96	99.0 (94.3–100)	759.6 (554.3–1040.8)	98	95.9 (89.9–98.9)	438.0 (312.7–613.7)
23F	Post-pri	104	90.4 (83.0–95.3)	989.6 (652.9–1499.8)	104	94.2 (87.9–97.9)	1377.9 (951.5–1995.3)	98	93.9 (87.1–97.7)	1097.3 (742.1–1622.4)	104	99.0 (94.8–100)	5136.4 (3829.2–6889.8)
	Post-bst	97	100 (96.3–100)	2562.9 (2016.3–3257.6)	96	99.0 (94.3–100)	2923.6 (2248.9–3800.9)	95	100 (96.2–100)	2600.0 (1896.8–3563.9)	97	100 (96.3–100)	24350.4 (18303.2–32395.5)
6A	Post-pri	100	48.0 (37.9–58.2)	37.4 (22.9–60.9)	103	96.1 (90.4–98.9)	1292.6 (940.3–1777.0)	94	50.0 (39.5–60.5)	36.5 (22.6–59.0)	103	99.0 (94.7–100)	2832.0 (2212.8–3624.4)
	Post-bst	95	65.3 (54.8–74.7)	116.8 (67.9–201.0)	93	100 (96.1–100)	3436.7 (2716.0–4348.5)	92	71.7 (61.4–80.6)	146.4 (87.6–244.6)	98	100 (96.3–100)	5200.7 (4134.9–6541.3)

OPA, opsonophagocytic activity; N, number of infants with available results in each group; %, percentage of infants with OPA titre ≥8; GMT, geometric mean titre; CI, confidence interval; Post-pri, 1 month post-dose 3; Post-bst, 1 month post-booster vaccination.
Note: *Results for serotype 19A are not available to date, due to technical issues. Results using a newly-validated OPA assay will be disclosed when available.

Table 3
Percentages of infants with anti-protein D antibody concentrations ≥100 EL.U/mL and antibody GMCs, by timepoint (according-to-protocol cohort for immunogenicity).

	11vPHiD-CV		12vPHiD-CV		PHiD-CV		PCV13	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Pre	112	11.6 (6.3–19.0)	104	8.7 (4.0–15.8)	101	13.9 (7.8–22.2)	107	9.3 (4.6–16.5)
Post-pri	112	99.1 (95.1–100)	106	100 (96.6–100)	103	99.0 (94.7–100)	106	17.9 (11.2–26.6)
Pre-bst	108	93.5 (87.1–97.4)	102	95.1 (88.9–98.4)	101	94.1 (87.5–97.8)	106	23.6 (15.9–32.8)
Post-bst	108	99.1 (94.9–100)	100	100 (96.4–100)	101	100 (96.4–100)	104	28.8 (20.4–38.6)
	N	GMC (95% CI)	N	GMC (95% CI)	N	GMC (95% CI)	N	GMC (95% CI)
Pre	112	57.0 (53.1–61.3)	104	55.5 (51.7–59.6)	101	60.5 (54.5–67.1)	107	55.0 (51.7–58.4)
Post-pri	112	1430.1 (1194.2–1712.7)	106	1194.2 (1017.7–1401.3)	103	1344.8 (1116.4–1619.9)	106	64.4 (57.7–71.9)
Pre-bst	108	445.9 (365.0–544.7)	102	447.6 (363.4–551.2)	101	460.0 (376.2–562.4)	106	70.9 (61.8–81.3)
Post-bst	108	1866.0 (1535.7–2267.4)	100	1835.5 (1511.5–2229.0)	101	2128.4 (1777.1–2549.2)	104	77.8 (67.1–90.1)

N, number of infants with available results; %, percentage of infants with anti-protein D antibody concentrations ≥100 EL.U/mL; EL.U, ELISA units; GMC, geometric mean concentration; CI, confidence interval; Pre, pre-vaccination; Post-pri, 1 month post-dose 3; Pre-bst, pre-booster vaccination; Post-bst, 1 month post-booster vaccination.

doses in the investigational groups and 5.6–9.0% of doses in the comparator groups.

Throughout the study, 154 SAEs were reported in 117 children: 29 children in the 11vPHiD-CV group, 26 in the 12vPHiD-CV group, 38 in the PHiD-CV group and 24 in the PCV13 group (Table 4). Four SAEs were considered by the investigator to be causally related to vaccination: 2 in the 12vPHiD-CV group (pyrexia occurring in 2 different children, 1 day post-dose 1), 1 in the 11vPHiD-CV group (head injury), and 1 in the PHiD-CV group (pyrexia on the day of dose 2). All reported SAEs were resolved by study end except for 3: retinoblastoma in the 11vPHiD-CV group, hypotonia in the PHiD-CV group, and pneumonia in the 12vPHiD-CV group (resolved with sequelae). No fatal events were reported.

4. Discussion

This study showed that the immune responses induced by the investigational 11vPHiD-CV and 12vPHiD-CV vaccines were non-inferior to the licensed comparator vaccines (PHiD-CV or PCV13) following a 3-dose primary series in infants, by meeting pre-defined serological criteria recommended by the WHO [13] for the vast majority of serotypes (9/11 for 11vPHiD-CV and 10/12 for12vPHiD-CV). Also, immune responses to 10 serotypes common with PHiD-CV in both investigational vaccines were comparable to those induced by PHiD-CV, in terms of antibody concentrations and their functionality post-primary vaccination.

In our study, for serotype 19A, the non-inferiority criterion was met in terms of the percentage of infants with antibody concentration ≥0.2 μg/mL, but not in terms of antibody GMC ratios. Nevertheless, according to the WHO recommendations, meeting 1 of the 2 alternative serological criteria for non-inferiority is considered acceptable, and assessment of pneumococcal vaccines should also be made on a serotype to serotype basis, by taking into account the burden of disease associated with each serotype, together with any available effectiveness data [13]. For serotype 6A, pre-specified non-inferiority criteria were not met for 12vPHiD-CV. However, following primary vaccination, at least 96% of children had OPA titres ≥8 against serotype 6A in the groups receiving 12vPHiD-CV and PCV13 (overlapping 95% CIs). Moreover, all children vaccinated with 12vPHiD-CV had OPA titres ≥8 post-booster vaccination. Although neither of the 2 alternative serological non-inferiority criteria recommended by the WHO was met for 6A, the functionality of elicited antibodies as assessed by OPA was previously observed to better reflect effectiveness against IPD than antibody levels for several pneumococcal serotypes, including 6A [12] or 19A [14].

The addition of 19A and 6A serotype-specific CRM_{197}-conjugates to PHiD-CV did not seem to impact negatively the immune responses against the 10 common serotypes; the immune response elicited by 11vPHiD-CV and 12vPHiD-CV appeared similar to that induced by PHiD-CV, and was in line with previous reports on PHiD-CV co-administered with routine paediatric vaccines [15]. However, antibody GMCs for serotype 6B were higher post-booster dose in the 12vPHiD-CV group when compared with the PHiD-CV group. This may be explained by cross-reacting antibodies against 6A, despite – or maybe due to – the 2 capsular polysaccharides being conjugated to different protein carriers (protein D for 6B and CRM_{197} for 6A). Since immune responses to PHiD-CV for serotype 6B are usually lower than for the other serotypes [2], the difference in carrier might play an important role towards enhancing cross-reactivity. We did not make a similar observation for 19A and 19F, also conjugated to different protein carriers (19F to TT and 19A to CRM_{197}), but responses to 19F were in the high ranges for both vaccines.

Eight months after completion of the primary series, antibody concentrations were similar among the 3 PHiD-CV groups for each of the 10 common pneumococcal serotypes. A trend for higher percentages of toddlers with antibody concentrations ≥0.2 μg/mL and higher antibody GMCs was observed in our study in the 3 PHiD-CV groups compared to a study with a similar target population, in which PHiD-CV was co-administrated with DTPa-HBV-IPV/Hib, according to the same schedule [16].

Future development of higher-valent PCVs is a challenging task. Different approaches are being pursued, such as the addition of more serotypes to multivalent PCVs or the development of serotype-independent vaccines [17,18] using well-conserved proteins [19–22]. The emergence of non-vaccine serotypes [23–27] may be addressed by the addition of new serotypes in the vaccine composition, as done for the 2 investigational formulations containing serotypes 19A and 6A (for 12vPHiD-CV), especially since serotype 19A remains an important cause of IPD [7,28–31] and its multi-drug resistance makes it more difficult to control [32]. However, the prevalence and impact of emerging serotypes vary by region, age, and time after PCV introduction. This complicates determining which serotypes should be included into a higher-valency PCV [33].

The polysaccharide/carrier ratio in PCVs is also important and it has been discussed to impact the immune response to pneumococcal antigens and co-administered vaccines [9]. Co-administration of DTPa-HBV-IPV/Hib with PHiD-CV has been shown to increase anti-polyribosylribitol-phosphate antibody GMCs, compared to co-administration with the 7-valent PCV (PCV7) [34,35], probably due to the different nature and dosage of carrier proteins [9]. PHiD-CV includes 3 distinct proteins as carriers, and its efficacy and effectiveness was demonstrated in clinical [2] and post-marketing studies, with the latter indicating that protection against IPD extends to the vaccine-related serotype 19A [4,36,37]. Our study showed that more serotypes can be added to PHiD-CV without impacting the immune response against vaccine serotypes.

Table 4
Incidence of solicited adverse events reported within 4 days post-vaccination and unsolicited adverse events reported within 31 days post-vaccination, following the 3-dose primary series (overall/dose) and booster vaccination (total vaccinated cohort).

	11vPHiD-CV		12vPHiD-CV		PHiD-CV		PCV13	
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Primary vaccination								
Solicited AEs	N = 717		N = 697		N = 681		N = 706	
Pain	269	37.5 (34.0–41.2)	280	40.2 (36.5–43.9)	258	37.9 (34.2–41.6)	250	35.4 (31.9–39.1)
Grade 3	32	4.5 (3.1–6.2)	21	3.0 (1.9–4.6)	28	4.1 (2.7–5.9)	15	2.1 (1.2–3.5)
Redness	261	36.4 (32.9–40.0)	270	38.7 (35.1–42.5)	241	35.4 (31.8–39.1)	239	33.9 (30.4–37.5)
Grade 3	5	0.7 (0.2–1.6)	3	0.4 (0.1–1.3)	4	0.6 (0.2–1.5)	2	0.3 (0.0–1.0)
Swelling	184	25.7 (22.5–29.0)	205	29.4 (26.1–32.9)	158	23.2 (20.1–26.6)	157	22.2 (19.2–25.5)
Grade 3	5	0.7 (0.2–1.6)	12	1.7 (0.9–3.0)	14	2.1 (1.1–3.4)	6	0.8 (0.3–1.8)
Drowsiness	372	51.9 (48.2–55.6)	351	50.4 (46.6–54.1)	322	47.3 (43.5–51.1)	327	46.3 (42.6–50.1)
Grade 3	17	2.4 (1.4–3.8)	15	2.2 (1.2–3.5)	19	2.8 (1.7–4.3)	23	3.3 (2.1–4.8)
Irritability/fussiness	419	58.4 (54.7–62.1)	430	61.7 (58.0–65.3)	393	57.7 (53.9–61.5)	378	53.5 (49.8–57.3)
Grade 3	40	5.6 (4.0–7.5)	34	4.9 (3.4–6.8)	42	6.2 (4.5–8.2)	27	3.8 (2.5–5.5)
Loss of appetite	217	30.3 (26.9–33.8)	229	32.9 (29.4–36.5)	219	32.2 (28.7–35.8)	199	28.2 (24.9–31.7)
Grade 3	4	0.6 (0.2–1.4)	8	1.1 (0.5–2.2)	7	1.0 (0.4–2.1)	10	1.4 (0.7–2.6)
Fever	256	35.7 (32.2–39.3)	241	34.6 (31.0–38.2)	258	37.9 (34.2–41.6)	235	33.3 (29.8–36.9)
Grade 3	2	0.3 (0.0–1.0)	6	0.9 (0.3–1.9)	6	0.9 (0.3–1.9)	2	0.3 (0.0–1.0)
Unsolicited AEs	N = 718		N = 708		N = 685		N = 712	
Any	174	24.2 (21.1–27.5)	166	23.4 (20.4–26.7)	186	27.2 (23.9–30.7)	168	23.6 (20.5–26.9)
Grade 3	15	2.1 (1.2–3.4)	10	1.4 (0.7–2.6)	8	1.2 (0.5–2.3)	6	0.8 (0.3–1.8)
Any related	4	0.6 (0.2–1.4)	6	0.8 (0.3–1.8)	10	1.5 (0.7–2.7)	7	1.0 (0.4–2.0)
Grade 3	0	0.0 (0.0–0.5)	2	0.3 (0.0–1.0)	0	0.0 (0.0–0.5)	1	0.1 (0.0–0.8)
Booster vaccination								
Solicited AEs	N = 235		N = 224		N = 219		N = 231	
Pain	112	47.7 (41.1–54.3)	123	54.9 (48.1–61.5)	119	54.3 (47.5–61.1)	110	47.6 (41–54.3)
Grade 3	13	5.5 (3.0–9.3)	16	7.1 (4.1–11.3)	18	8.2 (4.9–12.7)	8	3.5 (1.5–6.7)
Redness	109	46.4 (39.9–53.0)	117	52.2 (45.5–58.9)	108	49.3 (42.5–56.1)	107	46.3 (39.8–53.0)
Grade 3	5	2.1 (0.7–4.9)	10	4.5 (2.2–8.1)	7	3.2 (1.3–6.5)	5	2.2 (0.7–5.0)
Swelling	84	35.7 (29.6–42.2)	88	39.3 (32.8–46.0)	89	40.6 (34.1–47.5)	85	36.8 (30.6–43.4)
Grade 3	8	3.4 (1.5–6.6)	7	3.1 (1.3–6.3)	5	2.3 (0.7–5.2)	7	3.0 (1.2–6.1)
Drowsiness	109	46.4 (39.9–53.0)	100	44.6 (38–51.4)	84	38.4 (31.9–45.1)	96	41.6 (35.1–48.2)
Grade 3	9	3.8 (1.8–7.1)	6	2.7 (1.0–5.7)	4	1.8 (0.5–4.6)	2	0.9 (0.1–3.1)
Irritability/fussiness	140	59.6 (53.0–65.9)	136	60.7 (54.0–67.2)	137	62.6 (55.8–69.0)	129	55.8 (49.2–62.4)
Grade 3	14	6.0 (3.3–9.8)	14	6.3 (3.5–10.3)	12	5.5 (2.9–9.4)	9	3.9 (1.8–7.3)
Loss of appetite	80	34.0 (28.0–40.5)	85	37.9 (31.6–44.7)	83	37.9 (31.4–44.7)	61	26.4 (20.8–32.6)
Grade 3	6	2.6 (0.9–5.5)	3	1.3 (0.3–3.9)	9	4.1 (1.9–7.7)	7	3.0 (1.2–6.1)
Fever	80	34.0 (28.0–40.5)	72	32.1 (26.1–38.7)	68	31.1 (25.0–37.6)	75	32.5 (26.5–38.9)
Grade 3	4	1.7 (0.5–4.3)	3	1.3 (0.3–3.9)	4	1.8 (0.5–4.6)	2	0.9 (0.1–3.1)
Unsolicited AEs	N = 237		N = 226		N = 222		N = 234	
Any	69	29.1 (23.4–35.3)	68	30.1 (24.2–36.5)	74	33.3 (27.2–40.0)	53	22.6 (17.5–28.6)
Grade 3	6	2.5 (0.9–5.4)	4	1.8 (0.5–4.5)	5	2.3 (0.7–5.2)	6	2.6 (0.9–5.5)
Any related	7	3.0 (1.2–6.0)	1	0.4 (0.0–2.4)	5	2.3 (0.7–5.2)	2	0.9 (0.1–3.1)
Grade 3	1	0.4 (0.0–2.3)	0	0.0 (0.0–1.6)	0	0.0 (0.0–1.6)	0	0.0 (0.0–1.6)
Children with reported SAEs throughout the study								
Any	29		26		38		24	
Any related	1		2		1		0	

n (%), number (percentage) of doses followed by at least one AE; CI, confidence interval; AE, adverse event; N, number of documented doses; SAE, serious adverse event.
Note: Grade 3 events were defined as "cried when limb was moved/spontaneously painful" for pain at injection site, "diameter > 30 mm" for redness and swelling, "rectal temperature > 40 °C" for fever, "not eating at all" for loss of appetite, and "preventing normal activity" for all other AEs.
All solicited local reactions were considered causally related to vaccination. The causality of all other AEs was assessed by the investigator.

The results presented here will contribute to further advances in the development of PCVs. Both investigational vaccines showed a reactogenicity profile very similar to that observed for PHiD-CV. AE incidence was comparable among groups receiving PHiD-CV formulations and corresponded to previously published results [38]. However, adding more serotypes may also trigger an increase in reactogenicity, as previously shown for a 15-valent PCV [8], and a potential interference with the immune responses to other paediatric vaccines [9].

The study's main strength was its design, with sufficient power to demonstrate the 2 co-primary confirmatory objectives of immunological non-inferiority. Potential limitations of the study were the lack of evaluation of T-cell responses and of the immune responses to co-administered vaccines to assess interference with the investigational vaccines. No statistical analyses were carried out to compare the 2 licensed vaccines. OPA was only evaluated in a subset of participants; therefore, these results should be interpreted with caution.

5. Conclusions

The investigational 11vPHiD-CV and 12vPHiD-CV vaccines given to infants as a 3 + 1 vaccination schedule showed immune responses to the 10 PHiD-CV serotypes which were at least non-inferior to those elicited by the licensed PHiD-CV. The 6A and 19A conjugates in 11vPHiD-CV and 12vPHiD-CV did not appear to negatively alter the immunogenicity of the 10 conjugates or protein D. Despite non-inferiority criteria not being met for both IgG and functional antibodies for serotypes 19A and 6A, the percentages of children with antibody concentrations over the pre-

specified threshold were high following primary vaccination. Both investigational vaccines showed acceptable reactogenicity profiles, similar to that of PHiD-CV.

6. Trademark statement

Synflorix and *Infanrix hexa* are trademarks of the GSK group of companies. *Prevnar 13/Prevenar 13* and *NeisVac-C* are trademarks of Pfizer Inc.

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Conflict of interest

DB and MT are employees of the GSK group of companies; KD was employed by the GSK group of companies; DB and KD hold shares of the GSK group of companies. For the conduct of the study: FCM, JMM and LS received personal fees from GSK group of companies and RP received grants from GSK group of companies; outside the submitted work: JMM reports personal fees from GSK group of companies, Pfizer and Sanofi Pasteur, LS reports grants from Novartis, Pfizer and Sanofi Pasteur, and grants from GSK group of companies in the past; RP reports grants from GSK group of companies, Novartis and Sanofi Pasteur, TJ reports personal fees from Pfizer. All other authors declare no conflict of interest.

Author's contribution

COR, DB, JB, KD, MT, and RP designed the study. ACM, COR, FCM, JB, JMMA, KD, LS, MH, MMV, RP, RR, and TJ acquired the data. COR, DB, JB, JMMA, KD, LS, MMV, MT, and RP analyzed the data. ACM, COR, FCM, JMMA, KD, LS, MH, RP, JB, RR, and TJ contributed to the conduct of the study. All authors reviewed and revised the manuscript, and approved the final manuscript as submitted.

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