Immunogenicity and safety of a 10-valent pneumococcal conjugate vaccine administered as a 2 + 1 schedule to healthy infants in The Gambia: a single-centre, double-blind, active-controlled, randomised, phase 3 trial

Ikechukwu Adigweme, Ahmed Futa, Ebrima Saidy-Jah, Bassey Edem, Edem Akpalu, Tida Dibbasey, Vistasp Sethna, Rajeev Dhere, Beate Kampmann, Christopher Bengt, Jake Sirr, Nancy Hosken, David Goldblatt, Kalpana Antony, Mark R Alderson, Steve Lamola, Ed Clarke**

Summary

Background Three pneumococcal conjugate vaccines (PCVs) are currently licensed and WHO prequalified for supply by UN agencies. Here, we aimed to investigate the safety and immunogenicity of SIIPL-PCV compared with PHiD-CV and PCV13, when administered to infants according to a 2+1 schedule.

Methods This single-centre, double-blind, active-controlled, randomised, phase 3 trial was done in Medical Research Council Unit The Gambia at the London School of Hygiene & Tropical Medicine clinical trial facilities within two government health centres in the western region of The Gambia. Healthy, PCV-naive infants aged 6–8 weeks were enrolled if they weighed at least 3·5 kg and had no clinically significant health complaints, as determined by history and clinical examination. Eligible infants were randomly assigned (1:1:1) to receive either SIIPL-PCV, PHiD-CV, or PCV13 using permuted blocks of variable size. Parents and the trial staff assessing all study outcomes were masked to vaccine group. The first PCV vaccine was given with other routine Expanded Programme on Immunization vaccines when infants were aged 6–8 weeks (visit 1). At visit 2, routine vaccines alone (without a PCV) were administered. At visit 3, the second dose of the PCV was administered alongside other routine vaccines. At visit 4, a blood sample was collected. Visits 1–4 took place at intervals of 4 weeks. The booster PCV was administered at age 9–18 months (visit 5), with final follow-up 4 weeks after the booster (visit 6). The primary immunogenicity outcome compared the serotype-specific IgG geometric mean concentrations (GMCs) generated by SIIPL-PCV with those generated by PHiD-CV and PCV13, 4 weeks after the booster. We used descriptive 95% CIs without adjustment for multiplicity. Immunogenicity analyses were done in the per protocol population (defined as all children who received all the assigned study vaccines, who had an immunogenicity measurement available, and who had no protocol deviations that might interfere with the immunogenicity assessment). This trial was registered with the Pan African Clinical Trials Registry, PACTR201907754270299, and ClinicalTrials.gov, NCT03896477.

Findings Between July 18 and Nov 14, 2019, 745 infants were assessed for study eligibility. Of these, 85 infants (11%) were ineligible and 660 (89%) were enrolled and randomly assigned to receive SIIPL-PCV (n=220), PHiD-CV (n=220), or PCV13 (n=220). 602 infants (91%) were included in the per protocol immunogenicity population. The median age at vaccination was 46 days (range 42–56). 342 infants (52%) were female and 318 (48%) were male. Post-booster serotype-specific IgG GMCs generated by SIIPL-PCV ranged from 1·54 µg/mL (95% CI 1·38–1·73) for serotype 5 to 12·46 µg/mL (11·07–14·01) for serotype 6B. Post-booster GMCs against shared serotypes generated by PHiD-CV ranged from 0·80 µg/mL (0·72–0·88) for serotype 5 to 17·31 µg/mL (14·83–20·20) for serotype 19F. Post-booster GMCs generated by PCV13 ranged from 2·04 µg/mL (1·86–2·24) for serotype 5 to 15·54 µg/mL (13·71–17·60) for serotype 6B. Post-booster IgG GMCs generated by SIIPL-PCV were higher than those generated by PHiD-CV for seven of the eight shared serotypes (1, 5, 6B, 7F, 9V, 14, and 23F). The GMC generated by serotype 19F was higher after PHiD-CV. The SIIPL-PCV to PHiD-CV GMC ratios for shared serotypes ranged from 0·64 (95% CI 0·52–0·79) for serotype 19F to 2·91 (2·47–3·44) for serotype 1. The serotype 1 GMC generated by SIIPL-PCV was higher than that generated by PCV13, whereas serotype 5, 6A, 19A, and 19F GMCs were higher after PCV13. The SIIPL-PCV to PCV13 GMC ratios ranged from 0·72 (0·60–0·87) for serotype 19A to 1·44 (1·23–1·69) for serotype 1.

Interpretation SIIPL-PCV was safe and immunogenic when given to infants in The Gambia according to a 2+1 schedule. This PCV is expected to provide similar protection against invasive and mucosal pneumococcal disease to the protection provided by PCV13 and PHiD-CV, for which effectiveness data are available. Generating post-implementation data on the impact of SIIPL-PCV on pneumococcal disease endpoints remains important.

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*Joint senior authors

Medical Research Council Unit The Gambia at the London School of Hygiene & Tropical Medicine, Banjul, The Gambia (I Adigweme MBBS, A Futa MD, E Saidy-Jah MBChB, B Edem MBBCh, E Akpalu MD, T Dibbasey MBChB, Prof B Kampmann PhD, E Clarke MBChB); **The Vaccine Centre, London School of Hygiene & Tropical Medicine, London, UK** (Prof B Kampmann, E Clarke); **Serum Institute of India, Pune, India** (V Sethna MBBS, R Dhere PhD); **Great Ormond Street Institute of Child Health Biomedical Research Centre, University College London, London, UK** (C Bengt, J Sirr BSc, Prof D Goldblatt MBChB); **PATH, Seattle, WA, USA** (N Hosken PhD, K Antony BSc, M R Alderson PhD, S Lamola MD)

Correspondence to: Dr Ed Clarke, Medical Research Council Unit The Gambia at the London School of Hygiene & Tropical Medicine, PO Box 273, Banjul, The Gambia **ed.clarke@lshtm.ac.uk**

Research in context

Evidence before this study

We searched PubMed for articles published in English from database inception to July 20, 2022, using the search terms "pneumococcal conjugate vaccin*", "pneumococcal vaccin*", "Prevnar*", "Synflorix", "Pneumosil", "PCV13", "PHiD-CV", "SIIPL-PCV", "immun*", "meta-analysis", "systematic review", "randomized controlled trial", "clinical trial", "efficacy", "effectiveness", "impact", and "safety", with Boolean operators. Three pneumococcal conjugate vaccines (PCVs) are licensed and WHO prequalified for purchase by Gavi and other UN agencies. PHiD-CV and PCV13 are immunogenic and effective at reducing vaccine serotype invasive pneumococcal disease, pneumonia, and acute otitis media when given as a 2+1 schedule. Despite differences in valency, no significant differences in the effectiveness of the two vaccines have been shown against disease endpoints. However, differences in the schedules and the way the vaccines were introduced, including whether catch-up campaigns were used, limits the strength of this conclusion. Both vaccines are safe. SIIPL-PCV was licensed and WHO prequalified after it was shown that the vaccine is safe and immunologically non-inferior to PHiD-CV following a three-dose primary series (weeks 6, 10, and 14).

Added value of this study

This study is the first to examine the immunogenicity and safety of SIIPL-PCV when given as a 2+1 schedule and to directly compare the three currently licensed PCVs. We showed that SIIPL-PCV is safe and highly immunogenic. Post-booster IgG geometric mean concentrations (GMCs) and opsonophagocytic activity (OPA) geometric mean titre (GMT) responses generated by SIIPL-PCV were higher than those generated by PHiD-CV for seven of the eight shared serotypes (1, 5, 6B, 7F, 9V, 14, and 23F), whereas responses generated by serotype 19F were higher after PHiD-CV. Serotype 1 GMC generated by SIIPL-PCV was higher than that generated by PCV13, whereas serotype 5, 6B, 19A, and 19F GMCs were higher after PCV13. Comparing SIIPL-PCV with PCV13, post-primary seroresponse rates were higher for serotype 23F after SIIPL-PCV and for serotype 6A after PCV13. Post-primary seroresponse rates were higher for five shared serotypes (1, 5, 6B, 14, and 23F) after SIIPL-PCV than those generated after PHiD-CV. The distribution of antibody concentrations was similar between SIIPL-PCV and PCV13. IgG GMC and OPA GMT booster responses were generated against all serotypes after SIIPL-PCV.

Implications of all the available evidence

Our immunogenicity and safety data support the use of SIIPL-PCV according to a 2+1 schedule. The vaccine is expected to have similar effectiveness to PCV13 and PHiD-CV, although generating data on the impact of the vaccine following introduction into national schedules remains of high importance.

Introduction

Pneumonia remains the leading cause of under-5 mortality after the neonatal period worldwide, and of all under-5 mortality in sub-Saharan Africa. It is estimated to have caused more than 800 000 deaths in this age group in 2017.[1] *Streptococcus pneumoniae* is the most common cause of pneumonia-associated morbidity and mortality. More than 300 000 children die from pneumococcal pneumonia, meningitis, and other invasive pneumococcal diseases each year.[2] Most of these deaths occur in low-income and middle-income countries (LMICs).[2]

Pneumococcal conjugate vaccines (PCVs) are highly effective at preventing serotype-specific pneumococcal disease, and their introduction has led to substantial reductions in morbidity and mortality associated with pneumococcal infection—including in The Gambia.[3,4] PCVs are recommended by WHO for inclusion in childhood immunisation programmes from age 6 weeks, either as a three-dose primary series without a booster (3+0 schedule) or a two-dose primary series with a booster at age 9–18 months (2+1 schedule).[4] No substantial advantage of one schedule over the other has been shown in preventing invasive pneumococcal disease, pneumonia, or nasopharyngeal pneumococcal carriage. However, data allowing such comparisons are scarce and confounded by differences in the duration of PCV use and in baseline disease rates.[4] Nonetheless, 2+1 schedules generate higher antibody titres after the third dose. Thus, 2+1 schedules have a theoretical advantage over 3+0 schedules in maintaining direct protection in the second year of life and beyond, and in generating indirect protection. Currently, 61 countries (mostly in sub-Saharan Africa) use a 3+0 schedule and 60 countries (including most of Europe, north Africa, and South America) use a 2+1 schedule.

Three PCVs are currently licensed and WHO prequalified for supply by UN agencies. The 10-valent PHiD-CV (Synflorix; GlaxoSmithKline, Brentford, UK) has been available since 2009, and the 13-valent PCV13 (Prevenar 13; Pfizer, New York, NY, USA) since 2010. Both PCVs reduce vaccine-type pneumococcal disease and provide indirect protection in the non-vaccinated population. Despite the difference in valency and immunogenicity,[5–7] the effect of these two vaccines on pneumonia and invasive pneumococcal disease is similar, although robust surveillance data (particularly from sub-Saharan Africa) are rare.[4,8] A second 10-valent PCV (SIIPL-PCV; Pneumosil; Serum Institute of India, Pune, India) targeting pneumococcal serotypes most prevalent in LMICs was licensed and WHO prequalified in 2019, on the basis of data from The Gambia showing

immunological non-inferiority to PHiD-CV when given as a three-dose primary series.[9,10]

This study is the first head-to-head comparison of the safety and immunogenicity of SIIPL-PCV with PHiD-CV and PCV13, when administered to infants as two primary doses and one booster dose (2+1 schedule).

Methods

Study design and participants

This single-centre, double-blind, active-controlled, randomised, phase 3 trial was done in Medical Research Council (MRC) Unit The Gambia at the London School of Hygiene & Tropical Medicine (LSHTM) clinical trial facilities within two government health centres in the western region of The Gambia. Healthy, PCV-naive infants aged 6–8 weeks were enrolled if they weighed at least 3·5 kg and had no clinically significant health complaints, as determined by history and clinical examination. Full inclusion and exclusion criteria are shown in the appendix (pp 1–3). All parents provided written informed consent. The study was approved by The Gambia Government–MRC Joint Ethics Committee, the LSHTM Research Ethics Committee, Western Institutional Review Board, and the Gambian Medicines Control Agency.

Randomisation and masking

Eligible infants were randomly assigned (1:1:1) to receive either SIIPL-PCV, PHiD-CV, or PCV13 using a predefined randomisation scheme. An independent biostatistician generated randomisation sequences using permuted blocks of variable size. Vaccine assignments were allocated to sequentially numbered, sealed, opaque, tamper-evident envelopes. Unmasked nurses conducted randomisation and administered the vaccines using identical syringes but were not involved in the assessment of any study endpoints. Parents and all other trial staff were masked to the treatment allocation.

Procedures

The first vaccination, during which one of the three PCVs (SIIPL-PCV, PHiD-CV, or PCV13) was given alongside other routine Expanded Programme on Immunization vaccines, took place during visit 1 when infants were aged 6–8 weeks. At visit 2, routine vaccines alone (without a PCV) were administered. At visit 3, the second dose of the PCV was administered alongside other routine vaccines. At visit 4, a blood sample was collected for the post-primary vaccine immunogenicity assessment. Visits 1–4 took place at intervals of 4 weeks. A pre-booster blood sample was collected from all infants. An initial window of age 9–10 months was specified for the booster vaccination; however, at the start of the COVID-19 pandemic, this window was extended to reduce clinic attendances and home visits and to ensure adherence with national and institutional infection control guidance, while remaining in line with WHO recommendations for PCV administration.[4] Therefore, the booster vaccine was administered when infants were aged 9–18 months instead (visit 5). A final blood sample for post-booster vaccine immunogenicity was collected 4 weeks after the booster (visit 6; appendix p 4).

A single 0·5 mL dose of SIIPL-PCV contains 2 µg of serotype 1, 5, 6A, 7F, 9V, 14, 19A, 19F, and 23F polysaccharides plus 4 µg of serotype 6B polysaccharide, all individually conjugated to a recombinant non-toxic diphtheria cross-reactive material 197 (CRM_{197}) protein and adsorbed onto aluminium phosphate. SIIPL-PCV vaccine lot numbers 209Y7003AZ and 209Y7001C were used. A single 0·5 mL dose of PHiD-CV contains 1 µg of serotype 1, 5, 6B, 7F, 9V, 14, and 23F polysaccharides plus 3 µg of serotype 4 polysaccharide, all individually conjugated to a recombinant non-typeable *Haemophilus influenzae* protein D, 3 µg of serotype 18C polysaccharide conjugated to tetanus toxoid, and 3 µg of serotype 19F polysaccharide conjugated to diphtheria toxoid, adsorbed onto aluminium phosphate. PHiD-CV vaccine lot number ASPNB206AA was used. A single 0·5 mL dose of PCV13 contains 2·2 µg of serotype 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, and 23F polysaccharides and 4·4 µg of serotype 6B polysaccharide, all conjugated to CRM_{197} and adsorbed onto aluminium phosphate. PCV13 vaccine lot number Y02163 was used.

See Online for appendix

Infants concomitantly received routine vaccinations as part of the Expanded Programme on Immunization, according to the schedule (appendix p 5), except for those who had the booster vaccination delayed due to the COVID-19 pandemic. In this group, the routine vaccines due at age 9 months were administered on time, whereas the PCV was administered as soon as restrictions allowed. Parenteral vaccines were administered by intramuscular injection into the anterolateral aspect of the thigh using 23G, 25 mm needles.

At visits 4, 5, and 6, 3·0 mL blood samples were collected, and serum was separated and stored at temperatures lower than –70°C before immunogenicity testing. PCV immunogenicity was evaluated by the WHO Pneumococcal Serology Reference Laboratory (UCL Great Ormond Street Institute of Child Health, London, UK) using a validated ELISA to quantify pneumococcal IgG concentrations and a validated multiplex opsonophagocytic activity (OPA) assay to assess functional immune responses.[9]

Solicited injection-site (tenderness, erythema, and induration) and systemic (cutaneous rash, axillary temperature, irritability, drowsiness, and decreased appetite) adverse events were recorded after each study vaccination and once per day for 6 days during home visits conducted by trained field workers. Unsolicited adverse events were assessed, managed, and recorded by study clinicians throughout the study. Solicited adverse events were graded for severity as 1–4 (appendix p 6). Unsolicited adverse events were categorised using

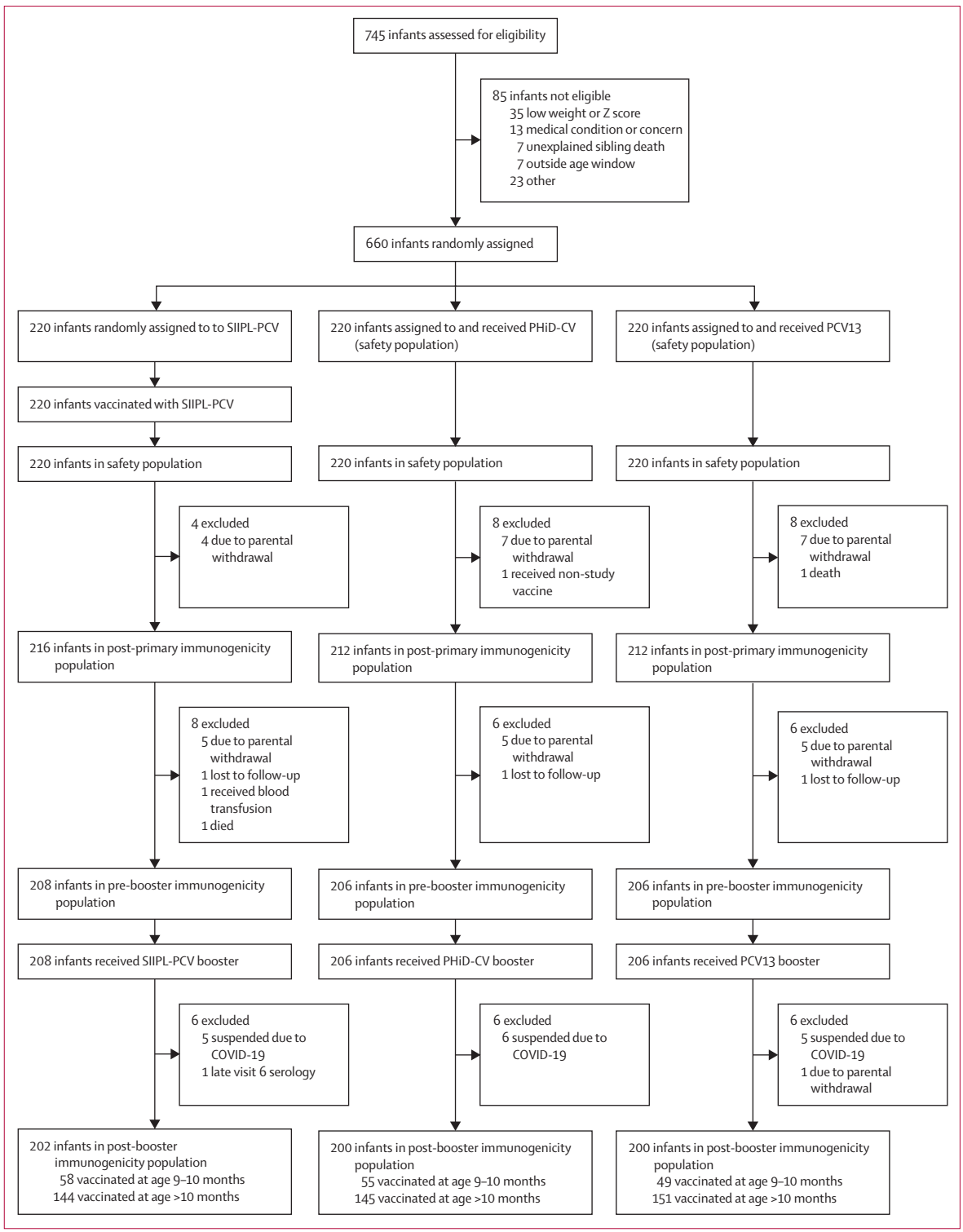


Figure 1: **Trial profile**
PCV=pneumococcal conjugate vaccine.

Medical Dictionary for Regulatory Activities preferred terms, graded from 1 (mild) to 5 (death), and assessed for relatedness to the study vaccine.

Outcomes

The primary immunogenicity outcome compared the serotype-specific IgG geometric mean concentrations

(GMCs) generated by SIIPL-PCV with those generated by PHiD-CV and PCV13, 4 weeks after the booster (visit 6). Secondary immunogenicity outcomes included examining the serotype-specific OPA IgG geometric mean titre (GMT) measured post-primary vaccination (visit 4), pre-booster (visit 5), and post-booster (visit 6); and the serotype-specific IgG seroresponse rates (defined as the percentage of participants with an IgG of ≥0·35 µg/mL or ≥1·0 µg/mL [only at visit 6]) and OPA seroresponse rates (defined as the percentage of participants with a reciprocal OPA titre of ≥8) at visits 4, 5, and 6. Booster responses, defined as the ratio of the serotype-specific IgG GMC or OPA GMT measured post-booster immunisation (visit 6) relative to the same serotype-specific endpoints measured post-primary immunisation (visit 4) were additional secondary endpoints. Safety outcomes were the number and severity of solicited local and systemic adverse events until day 6 after each vaccination; and the number, severity, and relatedness of all unsolicited adverse events from the first vaccination (visit 1) until age 9 months and from the booster vaccination (visit 5) until the 4 weeks follow-up visit (visit 6). The number, severity, and relatedness of serious adverse events were collected throughout the study period.

	SIIPL-PCV (n=220)	PHiD-CV (n=220)	PCV13 (n=220)
Age at vaccination 1, days	46 (42–56)	46 (42–56)	46 (42–56)
Age at booster vaccination, months	13 (9–15)	13 (9–16)	14 (9–15)
Sex			
Female	125 (57%)	108 (49%)	109 (50%)
Male	95 (43%)	112 (51%)	111 (50%)
African race	220 (100%)	220 (100%)	220 (100%)
Ethnicity			
Mandinka	109 (50%)	118 (54%)	124 (56%)
Wolof	21 (10%)	17 (8%)	22 (10%)
Fula	26 (12%)	25 (11%)	25 (11%)
Jola	28 (13%)	31 (14%)	15 (7%)
Other	36 (16%)	29 (13%)	34 (15%)
Infant weight, kg	4·7 (3·5–5·9)	4·7 (3·5–6·8)	4·7 (3·5–6·7)
Infant length, cm	55·5 (50·7–59·2)	55·5 (50·0–62·5)	55·4 (49·5–61·3)
Primary cooking fuel			
Wood or charcoal	218 (99%)	219 (99%)	219 (99%)
Gas or electricity	2 (<1%)	1 (<1%)	1 (<1%)
Primary water source			
Private tap, well, or borehole	168 (76%)	180 (82%)	178 (81%)
Community tap, well, or borehole	52 (24%)	40 (18%)	42 (19%)

Data are n (%) or median (range). Percentages might not equal 100% due to rounding. PCV=pneumococcal conjugate vaccine.

Table 1: **Baseline characteristics of all infants who received at least one vaccine dose**

Statistical analysis

The study was designed to provide descriptive data on the immunogenicity and safety of SIIPL-PCV when delivered as a 2+1 schedule, alongside comparator data for PHiD-CV and PCV13. The sample size was determined to generate parameter estimates of sufficient precision to guide policy and regulatory decisions. Coefficients of variation based on previously published data for SIIPL-PCV in the same population were used.[9,10] Descriptive 95% CIs without adjustment for multiplicity were calculated throughout. A sample size of 220 participants per group was expected to generate 95% CIs with an upper boundary no more than 16% higher and a lower boundary no more than 14% lower than the serotype-specific GMCs. The sample size also gave an 89% chance of observing a given safety event occurring in the population at a rate of 1%.

Having confirmed the log-normality assumption was appropriate, 95% CIs around serotype-specific GMCs, GMTs, GMC ratios, and GMT ratios were calculated using normal distribution for $\log_{10}$ transformed antibody concentrations or titres. Asymptotic Wald 95% CIs were calculated for seroresponse rates. CIs for differences in seroresponse rates were calculated using the Miettinen–Nurminen likelihood score method. The trial was not powered to detect differences between the three vaccines. However, for the purposes of descriptive comparison, CIs for GMC and GMT ratios that excluded 1 and CIs for difference in seroresponse rates that excluded 0 were considered to indicate meaningful differences.

Immunogenicity analyses were done in the per protocol population (defined as all children who received all the assigned study vaccines, who had an immunogenicity measurement available, and who had no protocol deviations that might interfere with the immunogenicity assessment).

Differences in the proportions of participants with solicited and unsolicited adverse events were assessed using Cochran–Mantel–Haenszel tests stratified by site or using Fisher's exact test, as appropriate based on the number of comparisons. All participants who received at least one dose of the study vaccine and provided safety data were included in the safety analysis. Statistical analyses were performed with SAS-STAT software (version 14.1). A data safety monitoring board reviewed the safety data and trial conduct throughout the study. This trial was registered with the Pan African Clinical Trials Registry, PACTR201907754270299, and ClinicalTrials.gov, NCT03896477.

Role of the funding source

This work was supported by a Bill & Melinda Gates Foundation [INV-006923] grant to PATH. Under the grant conditions of the Foundation, a Creative Commons Attribution 4.0 Generic License has already been assigned to the author accepted manuscript version that might arise from this submission. The funder of the study had no role in data collection, data analysis, data interpretation, or writing of the report.

Results

Between July 18 and Nov 14, 2019, 745 infants were assessed for study eligibility (figure 1). Of these,

	IgG GMC (μg/mL)							OPA GMT						
	n	SIIPL-PCV (95% CI)	n	PHiD-CV (95% CI)	n	PCV13 (95% CI)	SIIPL-PCV to PHiD-CV ratio (95% CI)	SIIPL-PCV to PCV13 ratio (95% CI)	n	SIIPL-PCV (95% CI)	n	PHiD-CV (95% CI)	n	PCV13 (95% CI)	SIIPL-PCV to PHiD-CV ratio (95% CI)	SIIPL-PCV to PCV13 ratio (95% CI)
1	201	8·45 (7·54–9·48)	197	2·90 (2·57–3·28)	200	5·87 (5·26–6·56)	2·91 (2·47–3·44)	1·44 (1·23–1·69)	50	631·29 (467·98–851·59)	50	282·35 (190·44–418·60)	49	429·13 (310·99–592·14)	2·24 (1·37–3·64)	1·47 (0·95–2·27)
5	202	1·54 (1·38–1·73)	199	0·80 (0·72–0·88)	200	2·04 (1·86–2·24)	1·93 (1·66–2·25)	0·76 (0·65–0·88)	50	885·98 (662·20–1185·37)	50	484·66 (361·73–649·38)	50	703·15 (556·01–889·24)	1·83 (1·22–2·75)	1·26 (0·87–1·82)
6A*	201	9·56 (8·26–11·05)	195	0·60 (0·50–0·71)	199	10·95 (9·57–12·54)	16·03 (12·84–20·03)	0·87 (0·72–1·06)	50	3651·54 (2593·53–5141·16)	45	53·86 (25·10–115·56)	50	6464·88 (5120·52–8162·19)	67·80 (30·54–150·48)	0·56 (0·38–0·85)
6B	202	12·46 (11·07–14·01)	200	4·96 (4·44–5·53)	200	15·54 (13·71–17·60)	2·51 (2·14–2·95)	0·80 (0·68–0·95)	50	3931·21 (2969·79–5203·89)	50	1294·61 (929·52–1803·11)	50	6013·88 (4130·89–8752·29)	3·04 (1·98–4·66)	0·65 (0·41–1·04)
7F	202	6·66 (5·96–7·44)	200	3·15 (2·87–3·45)	200	6·31 (5·75–6·93)	2·11 (1·83–2·44)	1·05 (0·91–1·22)	50	7053·37 (5904·91–8425·18)	50	4401·18 (3593·44–5390·50)	50	8288·88 (6756·83–10 168·30)	1·60 (1·23–2·09)	0·85 (0·65–1·11)
9V	202	3·46 (3·08–3·88)	200	2·45 (2·21–2·72)	200	3·87 (3·47–4·32)	1·41 (1·21–1·65)	0·89 (0·76–1·05)	50	1408·68 (1092·33–1816·64)	49	845·47 (631·39–1132·13)	50	2464·43 (1957·36 to 3102·85)	1·67 (1·14–2·44)	0·57 (0·41–0·80)
14	202	8·28 (6·97–9·82)	200	5·02 (4·22–5·97)	200	9·17 (8·06–10·45)	1·65 (1·29–2·10)	0·90 (0·73–1·12)	50	2622·36 (1845·88–3725·47)	50	1381·52 (883·30–2160·74)	50	3131·96 (2245·73–4367·91)	1·90 (1·08–3·33)	0·84 (0·52–1·35)
19A*	200	8·82 (7·65–10·15)	199	2·39 (1·97–2·89)	199	12·21 (10·83–13·76)	3·69 (2·91–4·67)	0·72 (0·60–0·87)	50	1620·76 (1200·51–2188·13)	50	305·46 (177·87–524·57)	50	3679·06 (2920·79–4634·19)	5·31 (2·88–9·77)	0·44 (0·30–0·64)
19F	200	11·11 (9·70–12·73)	194	17·31 (14·83–20·20)	197	14·99 (13·25–16·96)	0·64 (0·52–0·79)	0·74 (0·62–0·89)	50	1384·38 (937·18–2044·98)	50	2541·40 (1666·99–3874·49)	50	2094·57 (1410·71–3109·94)	0·54 (0·31–0·96)	0·66 (0·38–1·14)
23F	202	4·95 (4·28–5·73)	200	2·16 (1·92–2·44)	198	4·97 (4·34–5·69)	2·29 (1·89–2·76)	1·00 (0·82–1·22)	50	2998·53 (2272·86–3955·89)	50	1427·66 (1110·72–1835·05)	50	5687·60 (3891·57–8312·54)	2·10 (1·45–3·04)	0·53 (0·33–0·84)

n denotes the number of infants with a reportable result, according to serotype and assay. GMC=geometric mean concentration. GMT=geometric mean titre. OPA=opsonophagocytic activity. PCV=pneumococcal conjugate vaccine. *Serotypes not included in PHiD-CV.

Table 2: **Post-booster serotype-specific IgG GMC and OPA GMT**

85 infants (11%) were ineligible and 660 (89%) were enrolled and randomly assigned to receive SIIPL-PCV (n=220), PHiD-CV (n=220), or PCV13 (n=220). 602 infants (91%) were included in the per-protocol immunogenicity population. All enrolled infants were included in the safety population. The median age at vaccination was 46 days (range 42–56). 125 infants (57%) in the SIIPL-PCV group, 108 (49%) in the PHiD-CV group, and 109 (50%) in the PCV13 group were female. 95 (43%) infants in the SIIPL-PCV group, 112 (51%) in the PHiD-CV group, and 111 (50%) in the PCV13 group were male. There were no other noteworthy differences in anthropometric or sociodemographic variables between groups (table 1).

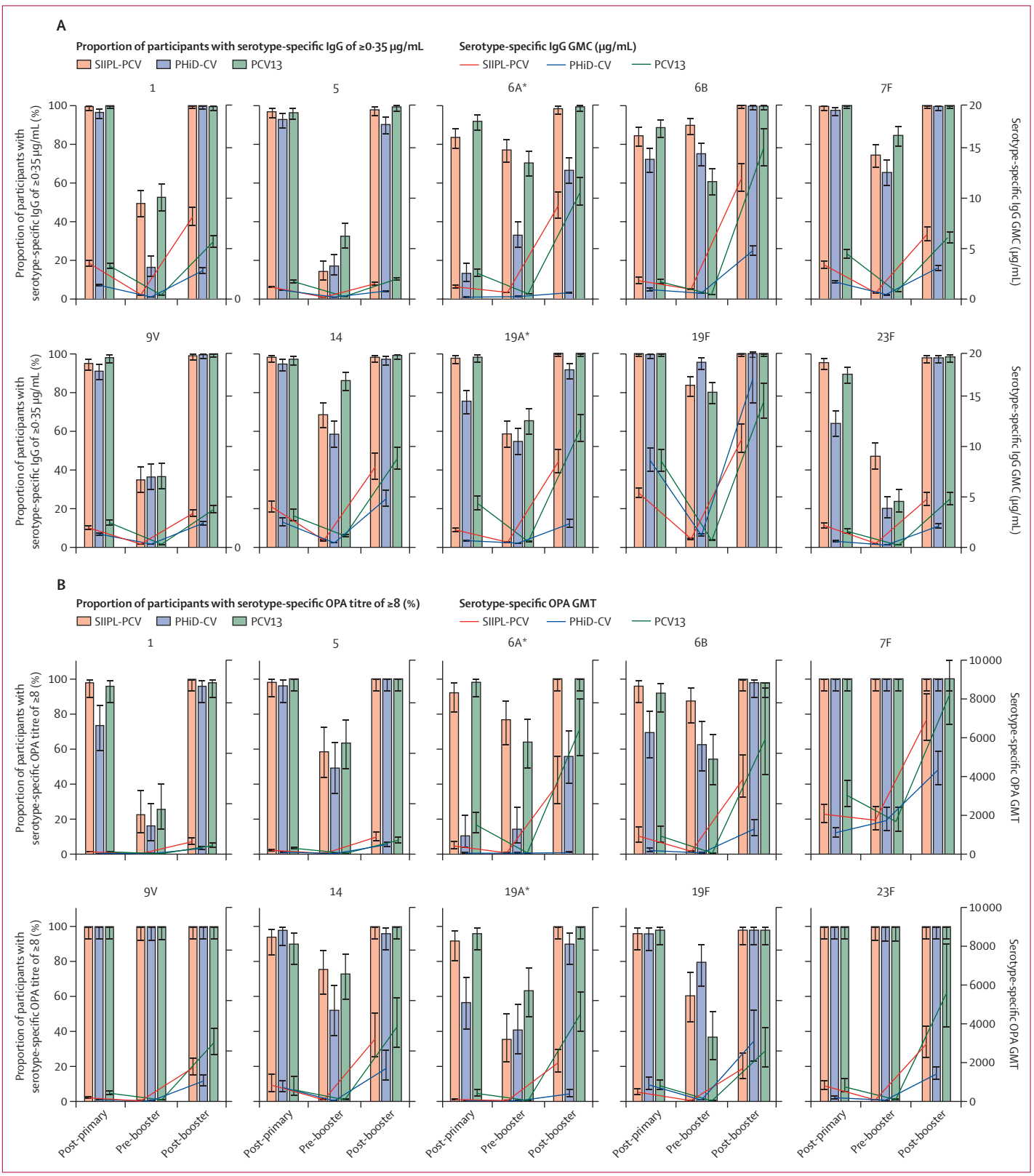
Post-booster serotype-specific IgG GMCs generated by SIIPL-PCV ranged from 1·54 μg/mL (95% CI 1·38–1·73) for serotype 5 to 12·46 μg/mL (11·07–14·01) for serotype 6B (table 2; figure 2A). Post-booster GMCs against shared serotypes generated by PHiD-CV ranged from 0·80 μg/mL (0·72–0·88) for serotype 5 to 17·31 μg/mL (14·83–20·20) for serotype 19F. The cross-reactive responses generated by serotype 6B in PHiD-CV was 0·60 μg/mL (0·50–0·71) against serotype 6A. The cross-reactive response generated by serotype 19F in PHiD-CV was 2·39 μg/mL (1·97–2·89) against 19A. Post-booster GMCs generated by PCV13 ranged from 2·04 μg/mL (1·86–2·24) for serotype 5 to 15·54 μg/mL (13·71–17·60) for serotype 6B.

Post-booster IgG GMCs generated by SIIPL-PCV were higher than those generated by PHiD-CV for seven of the eight shared serotypes (1, 5, 6B, 7F, 9V, 14, and 23F; table 2; appendix p 11). The GMC generated by serotype 19F was higher after PHiD-CV. The SIIPL-PCV to PHiD-CV GMC ratios for shared serotypes ranged from 0·64 (95% CI 0·52–0·79) for serotype 19F to 2·91 (2·47–3·44) for serotype 1. The serotype 1 GMC generated by SIIPL-PCV was higher than that generated by PCV13, whereas serotype 5, 6B, 19A, and 19F GMCs were higher after PCV13. The SIIPL-PCV to PCV13 GMC ratios ranged from 0·72 (0·60–0·87) for serotype 19A to 1·44 (1·23–1·69) for serotype 1.

Post-booster OPA GMT responses had a similar pattern to the IgG GMC responses (table 2; figure 2B). The OPA GMTs generated by SIIPL-PCV were higher than those generated by PHiD-CV for seven shared serotypes (1, 5, 6B, 7F, 9V, 14, and 23F) and for cross-reactive serotypes 6A and 19A. Post-booster OPA GMT to serotype 19F was higher after PHiD-CV than after SIIPL-PCV. The SIIPL-PCV to PHiD-CV GMT ratios for

Figure 2: **Serotype-specific IgG and OPA rates and antibody concentrations or titres according to visit**

Bars show 95% CIs. (A) Serotype-specific IgG rates and IgG GMCs. (B) Serotype-specific OPA rates and GMTs. GMC=geometric mean concentration. GMT=geometric mean titre. OPA=opsonophagocytic activity. PCV=pneumococcal conjugate vaccine. *Serotypes not included in PHiD-CV.


A
Proportion of participants with serotype-specific IgG of ≥0·35 µg/mL
SIIPL-PCV
PHiD-CV
PCV13
Serotype-specific IgG GMC (µg/mL)
SIIPL-PCV
PHiD-CV
PCV13
1
5
6A*
6B
7F
9V
14
19A*
19F
23F
Proportion of participants with serotype-specific IgG of ≥0·35 µg/mL (%)
Serotype-specific IgG GMC (µg/mL)
B
Proportion of participants with serotype-specific OPA titre of ≥8 (%)
Serotype-specific OPA GMT
Post-primary
Pre-booster
Post-booster

	IgG seroresponse rates (≥0·35 µg/mL)							IgG GMC						
	n/N	SIIPL-PCV (95% CI)	n/N	PHiD-CV (95% CI)	n/N	PCV13 (95% CI)	SIIPL-PCV – PHiD-CV difference (95% CI)	SIIPL-PCV – PCV13 difference (95% CI)	n	SIIPL-PCV (95% CI)	n	PHiD-CV (95% CI)	n	PCV13 (95% CI)	SIIPL-PCV to PHiD-CV ratio (95% CI)	SIIPL-PCV to PCV13 ratio (95% CI)
1	215/216	99·5% (97·5 to 100·0)	204/212	96·2% (92·7 to 98·4)	212/212	100·0% (98·3 to 100·0)	3·3% (0·8 to 6·9)	−0·5% (−2·6 to 1·3)	216	3·63 (3·32 to 3·98)	212	1·36 (1·23 to 1·51)	212	3·40 (3·10 to 3·74)	2·66 (2·32 to 3·05)	1·07 (0·94 to 1·22)
5	209/216	96·8% (93·4 to 98·7)	195/212	92·0% (87·5 to 95·3)	204/212	96·2% (92·7 to 98·4)	4·8% (0·4 to 9·6)	0·5% (−3·3 to 4·4)	216	1·19 (1·10 to 1·28)	212	0·87 (0·79 to 0·96)	212	1·81 (1·62 to 2·01)	1·36 (1·21 to 1·54)	0·66 (0·57 to 0·75)
6A*	180/216	83·3% (77·7 to 88·1)	27/211	12·8% (8·6 to 18·1)	194/212	91·5% (86·9 to 94·9)	70·5% (63·2 to 76·6)	−8·2% (−14·6 to −1·9)	216	1·19 (1·00 to 1·41)	211	0·14 (0·13 to 0·16)	212	2·62 (2·24 to 3·08)	8·50 (6·92 to 10·43)	0·45 (0·36 to 0·57)
6B	183/216	84·7% (79·2 to 89·2)	151/212	71·2% (64·6 to 77·2)	187/210	89·0% (84·0 to 92·9)	13·5% (5·7 to 21·3)	−4·3% (−10·9 to 2·1)	216	1·82 (1·48 to 2·23)	212	0·91 (0·75 to 1·10)	210	1·75 (1·49 to 2·07)	2·00 (1·51 to 2·65)	1·04 (0·80 to 1·35)
7F	215/216	99·5% (97·5 to 100·0)	206/212	97·2% (93·9 to 99·0)	212/212	100·0% (98·3 to 100·0)	2·4% (−0·1 to 5·6)	−0·5% (−2·6 to 1·3)	216	3·46 (3·09 to 3·88)	212	1·73 (1·55 to 1·92)	212	4·67 (4·19 to 5·20)	2·01 (1·72 to 2·34)	0·74 (0·63 to 0·87)
9V	205/216	94·9% (91·1 to 97·4)	193/212	91·0% (86·4 to 94·5)	208/212	98·1% (95·2 to 99·5)	3·9% (−1·0 to 9·1)	−3·2% (−7·2 to 0·3)	216	1·93 (1·74 to 2·16)	212	1·31 (1·17 to 1·46)	212	2·56 (2·28 to 2·88)	1·48 (1·27 to 1·73)	0·76 (0·64 to 0·89)
14	213/216	98·6% (96·0 to 99·7)	202/212	95·3% (91·5 to 97·7)	206/212	97·2% (93·9 to 99·0)	3·3% (0·1 to 7·2)	1·4% (−1·5 to 4·8)	216	4·03 (3·50 to 4·64)	212	2·58 (2·18 to 3·04)	212	3·27 (2·70 to 3·96)	1·56 (1·26 to 1·94)	1·23 (0·97 to 1·56)
19A*	211/216	97·7% (94·7 to 99·2)	158/210	75·2% (68·8 to 80·9)	207/212	97·6% (94·6 to 99·2)	22·4% (16·5 to 28·9)	0·0% (−3·2 to 3·4)	216	1·75 (1·57 to 1·96)	210	0·65 (0·57 to 0·73)	212	4·38 (3·73 to 5·15)	2·71 (2·30 to 3·20)	0·40 (0·33 to 0·49)
19F	216/216	100·0% (98·3 to 100·0)	208/209	99·5% (97·4 to 100·0)	211/211	100·0% (98·3 to 100·0)	0·5% (−1·3 to 2·7)	0·0% (−1·8 to 1·8)	216	5·45 (4·94 to 6·01)	209	8·86 (7·71 to 10·17)	211	9·06 (7·97 to 10·30)	0·62 (0·52 to 0·73)	0·60 (0·51 to 0·71)
23F	207/216	95·8% (92·2 to 98·1)	134/212	63·2% (56·3 to 69·7)	190/212	89·6% (84·7 to 93·4)	32·6% (25·7 to 39·7)	6·2% (1·4 to 11·5)	216	2·21 (1·92 to 2·56)	212	0·57 (0·48 to 0·68)	212	1·64 (1·39 to 1·93)	3·87 (3·11 to 4·83)	1·35 (1·09 to 1·68)

Infants with a reportable result, according to serotype and assay. GMC=geometric mean concentration. PCV=pneumococcal conjugate vaccine. *Serotypes not included in PHiD-CV.

Table 3: **Post-primary vaccination IgG seroresponse rates and IgG GMC**

shared serotypes ranged from 0·54 (95% CI 0·31–0·96) for serotype 19F to 3·04 (1·98–4·66) for serotype 6B. Post-booster OPA GMTs to serotypes 6A, 9V, 19A, and 23F were higher after PCV13 than after SIIPL-PCV. The SIIPL-PCV to PCV13 GMT ratios ranged from 0·44 (0·30–0·64) for serotype 19A to 1·47 (0·95–2·27) for serotype 1.

Post-booster seroresponse rates (IgG ≥0·35 µg/mL) were 97·5% or higher for all serotypes after SIIPL-PCV and PCV13, with no significant differences between the two vaccines (figure 2A; appendix p 12). The seroresponse rates to PHiD-CV were 97·5% or higher for the shared serotypes (1, 6B, 7F, 9V, 14, 19F, and 23F), except for serotype 5, for which the seroresponse rate was 89·8% (95% CI 84·9 to 93·8). At least 94·6% of participants had an IgG concentration of 1·0 µg/mL or higher to all serotypes, except serotype 5, after SIIPL-PCV and PCV13 (appendix p 14). The seroresponse rate to serotype 5 at the threshold of 1·0 µg/mL was 68·8% (61·9 to 75·1) after SIIPL-PCV and 87·5% (82·1 to 91·7) after PCV13. Differences in seroresponse (≥1·0 µg/mL) rates between SIIPL-PCV and PCV13 ranged from 1·0% (–2·1 to 4·4) for serotype 1 to –18·7% (–26·6 to –10·8) for serotype 5. Among the shared serotypes in PHiD-CV between 37·7% (30·9 to 44·8) for serotype 5 and 96·9% (93·4 to 98·9) for serotype 19F had an IgG concentration of 1·0 µg/mL or higher. Differences in seroresponse between SIIPL-PCV and PHiD-CV ranged from 1·6% (–1·6 to 5·3) for serotype 19F to 31·1% (21·6 to 40·1) for serotype 5 (appendix p 14). Post-booster OPA seroresponse rates (≥8) were 98·0% or higher against all serotypes after SIIPL-PCV and PCV13 and 96% or higher against all shared serotypes after PHiD-CV (figure 2B; appendix p 18).

Post-primary IgG seroresponse rates (≥0·35 µg/mL) were 94·9% or higher for all serotypes, except 6A and 6B, after SIIPL-PCV; 96·2% or higher for all serotypes, except 6A, 6B, and 23F, after PCV13; and 91·0% or higher for all shared serotypes, except 6B and 23F, after PHiD-CV (table 3). Comparing SIIPL-PCV with PCV13, the post-primary seroresponse rate was higher for serotype 23F after SIIPL-PCV (difference of 6·2% [95% CI 1·4 to 11·5]) and for serotype 6A after PCV13 (difference of –8·2% [–14·6 to –1·9]). Comparing SIIPL-PCV with PHiD-CV, the post-primary seroresponse rates were higher for five shared serotypes (1, 5, 6B, 14, and 23F) after SIIPL-PCV. For all shared serotypes, the difference ranged from 0·5% (–1·3 to 2·7) for serotype 19F to 32·6% (25·7 to 39·7) for serotype 23F.

Post-primary IgG GMCs were higher for seven of the eight shared serotypes (1, 5, 6B, 7F, 9V, 14, and 23F) after SIIPL-PCV than after PHiD-CV and higher for serotype 19F after PHiD-CV (table 3). The IgG GMCs were higher for six of the ten shared serotypes (5, 6A, 7F, 9V, 19A, and 19F) after PCV13 than after SIIPL-PCV. The IgG GMC was higher for serotype 23F after SIIPL-PCV than after PCV13. The IgG GMCs were similar for the remaining serotypes.

Post-primary OPA seroresponse rates (≥8) were 91·8% or higher for all ten serotypes after SIIPL-PCV and 90·0% or higher after PCV13. There were no notable differences in the OPA seroresponse rates between SIIPL-PCV and PCV13 (appendix p 19). The OPA seroresponse rate after PHiD-CV was 69·4% (95% CI 54·6–81·8) for serotype 6B and 73·5% (58·9–85·1) for serotype 1. Both rates were lower than the seroresponses generated by SIIPL-PCV. The OPA seroresponse rates were 95·9% or higher for the remaining six shared serotypes (5, 7F, 9V, 14, 19F, and 23F) after PHiD-CV and were similar to the responses generated by SIIPL-PCV. Post-primary OPA GMTs were higher for seven of the eight shared serotypes (1, 5, 6B, 7F, 9V, 19F, and 23F) after SIIPL-PCV than after PHiD-CV and were similar for serotype 14 (appendix p 21). The OPA GMTs were also higher for six of the ten serotypes (5, 6A, 7F, 9V, 19A, and 19F) after PCV13 than after SIIPL-PCV. The responses were similar for the remaining four serotypes.

Pre-booster vaccination, the IgG seroresponse rates (≥0·35 µg/mL) were between 13·7% (95% CI 9·3–19·1) for serotype 5 and 89·9% (85·0–93·6) for serotype 6B after SIIPL-PCV; between 24·9% (19·1–31·4) for serotype 23F and 86·3% (80·9–90·7) for serotype 14 after PCV13; and between 16·4% (11·6–22·3) for serotype 5 and 95·1% (91·2–97·6) for serotype 19F after PHiD-CV (appendix p 22). For serotypes 6B and 23F, the IgG seroresponse rates (≥0·35 µg/mL) were higher after SIIPL-PCV than after PCV13, whereas for serotypes 5, 7F, and 14 the rates were higher after PCV13. The seroresponse rates were similar for the remaining five serotypes. For five shared serotypes (1, 6B, 7F, 14, 23F), the IgG seroresponse rates were higher after SIIPL-PCV than after PHiD-CV, whereas for serotype 19F the rate was higher after PHiD-CV. Percentages were similar for the remaining two shared serotypes (5 and 9V). For serotypes 6A, 6B, and 23F the pre-booster IgG GMCs were higher after SIIPL-PCV than after PCV13, whereas the IgG GMCs were higher for serotypes 5, 7F, and 14 after PCV13 (appendix p 23). Among the shared serotypes, pre-booster IgG GMCs were higher after SIIPL-PCV than after PHiD-CV for serotypes 1, 6B, 7F, 14, and 23F and for cross-reactive serotypes 6A and 19A, whereas the IgG GMC was higher for serotype 19F after PHiD-CV.

Pre-booster OPA seroresponse rates (≥8) were between 22·4% for serotype 1 and 100·0% for serotypes 7F, 9V, and 23F after SIIPL-PCV; between 25·5% for serotype 1 and 100·0% for serotypes 7F, 9V, and 23F after PCV13; and, among shared serotypes, between 16·0% for serotype 1 and 100·0% for serotypes 7F, 9V, and 23F after PHiD-CV (appendix p 24). For serotypes 6B and 19F, the OPA seroresponse rates were higher after SIIPL-PCV than after PCV13, whereas for serotype 19A, the rate was higher after SIIPL-PCV. OPA seroresponse rates were similar for the remaining seven serotypes. For two shared serotypes 6B and 14, the OPA seroresponse rate was higher after SIIPL-PCV than after PHiD-CV. In line with the IgG seroresponses the reverse was true for serotype 19F. The percentages were similar for the remaining five shared serotypes.

For serotype 6B, pre-booster OPA GMT was higher after SIIPL-PCV than after PCV13, whereas the GMT was higher for serotype 19A after PCV13 (appendix p 25). Among shared serotypes, pre-booster OPA GMTs were higher after SIIPL-PCV than after PHiD-CV for serotypes 6B, 14, and the cross-reactive serotype 6A, whereas the OPA GMT was higher for serotype 19F after PHiD-CV.

Finally, there was an IgG and OPA booster response to all serotypes after SIIPL-PCV and PCV13 (appendix p 26). There was an IgG booster response to all serotypes, except serotype 5, and an OPA booster response to all serotypes after PHiD-CV.

There were no notable vaccine-related safety concerns during the study. At least one injection-site reaction was observed in 72 (33%) of 220 participants after SIIPL-PCV, 63 (29%) after PCV13, and 84 (38%) after PHiD-CV (table 4). Most of these were mild tenderness (216 [33%] of 660) and all resolved with no more than

	SIIPL-PCV (n=220)	PHiD-CV (n=220)	PCV13 (n=220)
Solicited adverse events			
Injection-site adverse events			
Any injection-site adverse event	72 (33%)	84 (38%)	63 (29%)
Tenderness	70 (32%)	83 (38%)	61 (28%)
Erythema or redness	1 (<1%)	3 (1%)	1 (<1%)
Induration or swelling	3 (1%)	5 (2%)	1 (<1%)
Systemic adverse events			
Any systemic adverse event	160 (73%)	167 (76%)	160 (73%)
Grade ≥3	3 (1%)	0	2 (<1%)
Fever	98 (45%)	105 (48%)	108 (49%)
Grade ≥3	3 (1%)	0	2 (1%)
Cutaneous rash*	16 (7%)	7 (3%)	6 (3%)
Grade ≥3	0	0	0
Irritability	105 (48%)	110 (50%)	101 (46%)
Grade ≥3	0	0	0
Drowsiness	12 (5%)	15 (7%)	18 (8%)
Grade ≥3	0	0	0
Decreased appetite	25 (11%)	18 (8%)	28 (13%)
Grade ≥3	0	0	0
Unsolicited adverse events			
Number of adverse events	630	615	554
Participants with an adverse event	198 (90%)	197 (90%)	189 (86%)
Number of serious adverse events	14	11	8
Participants with a serious adverse event	12 (5%)	10 (5%)	7 (3%)
Number of participants with a vaccine-related serious adverse event	0	0	0

Data are n (%). PCV=pneumococcal conjugate vaccine. *There was a significant difference between groups in the number of participants who had a cutaneous rash (p=0·036; according to the Cochran–Mantel–Haenszel test stratified by site).

Table 4: **Participants reporting solicited and unsolicited adverse events**

simple analgesia. There were no grade 3 severe injection-site reactions. Around three-quarters of participants in each group had at least one systemic adverse event. More participants had a cutaneous rash of grade 3 or higher after SIIPL-PCV (16 [7%]) than after PHiD-CV (seven [3%]) or PCV13 (six [3%]), all of which resolved without intervention. Three (1%) participants had grade 3 or higher fever (>39°C) after SIIPL-PCV and two (1%) after PCV13. There were no other systemic adverse events of grade 3 or higher. At least one unsolicited adverse event occurred in 189 (86%) participants after PCV13, 197 (90%) after PHiD-CV, and 198 (90%) after SIIPL-PCV. Upper respiratory tract infections (453 events in 322 [49%] of 660 participants) and diarrhoea (188 events in 155 [23%] participants) were the most common unsolicited adverse events (appendix p 28). 33 serious adverse events occurred in total (12 [5%] of 220 infants after SIIPL-PCV, ten [5%] after PHiD-CV, and seven [3%] after PCV13 vaccination), none of which were thought to be related to vaccination (appendix p 30; table 4). One participant in the SIIPL-PCV group died after a diagnosis of intussusception and one in the PCV13 group died after an atrioventricular canal defect diagnosis; neither were judged to be related to vaccination.

Discussion

This phase 3 trial provides immunogenicity and safety data to support the use of SIIPL-PCV, according to a two-dose primary vaccination followed by a booster (2+1) schedule. This study is the first direct comparison of all three WHO prequalified PCVs. SIIPL-PCV induced robust post-booster and post-primary IgG and OPA antibody responses. Post-booster IgG GMC and OPA GMT responses generated by SIIPL-PCV were higher than after PHiD-CV for seven of eight shared serotypes (1, 5, 6B, 7F, 9V, 14, and 23F), with serotype 19F being higher after PHiD-CV. The serotype 1 IgG GMC was higher after SIIPL-PCV than after PCV13, whereas the IgG GMC and OPA GMT were higher after PCV13 for four serotypes (5, 6A, 19A, and 19F).

PHiD-CV and PCV13 are effective at reducing vaccine-type invasive pneumococcal disease, pneumonia, and acute otitis media when administered as a 2+1 schedule.[11–13] Based on these data, the effect of SIIPL-PCV on disease and carriage endpoints is expected to be similar. After at least two doses of PCV13, an effectiveness of 85% (95% CI 37–96) against PCV13 vaccine-type invasive pneumococcal disease was reported in HIV-negative infants in South Africa.[14] Similar effectiveness was shown in HIV-exposed but uninfected infants and in malnourished infants, although the effectiveness in HIV-positive infants did not reach significance.[14] After at least one dose of PCV13, effectiveness against PCV13 vaccine-type invasive pneumococcal disease ranged from 66% (52–76) in children aged between 2 months and 9 years in the UK to 86% (62–95) in children aged 2–59 months in Canada.[15–18] Given the absence of consistent protection against serotype 3 generated by PCV13, effectiveness estimates consistently increase when invasive pneumococcal disease caused by this serotype is excluded.[16,18] After at least one dose of PHiD-CV, an effectiveness of 92% (58–100) against PHiD-CV vaccine-type invasive pneumococcal disease was reported in Finland.[19] In the Canadian study,[15] the protection conferred by at least one dose of PHiD-CV against PHiD-CV serotypes plus serotype 6A was 97% (84–99), whereas the effectiveness against PCV13 vaccine types was 84% (65–93), similar to the 86% efficacy conferred by PCV13.

The serotypes 6A and 19A IgG and OPA responses generated by SIIPL-PCV were lower than those generated by PCV13, which provides protection against both serotypes.[20] Nonetheless, after the SIIPL-PCV booster, more than 96% of participants had an IgG concentration of 1·00 µg/mL or higher and 100% had a reciprocal OPA titre of 8 or higher against both serotypes. This higher IgG threshold might predict protection, particularly against mucosal disease and carriage, more consistently than an IgG concentration of 0·35 µg/mL.[21,22] Furthermore, the responses to SIIPL-PCV were considerably higher than the cross-reactive responses to serotypes 6B and 19F generated by PHiD-CV. Data on the cross-protection conferred by PHiD-CV against serotype 6A are scarce. Case-control and indirect cohort studies[23,24] conducted in Brazil did not show statistically significant cross-protection against this serotype. In contrast, a population-based study in Finland[25] showed sustained protection against serotype 6A at 6 years after vaccination. A population-based study in Sweden also showed evidence of cross-protection against this serotype.[26]

Studies examining cross-protection against serotype 19A conferred by PHiD-CV are heterogeneous. The serotype is the most frequently isolated from children younger than 5 years with pneumococcal meningitis in countries using the PHiD-CV vaccine.[27] However, case-control and independent cohort studies in Brazil showed significant protection against 19A disease.[23,24] Additionally, a case-control study conducted in Canada[15] reported 71% (95% CI 24–89) effectiveness with PHiD-CV against serotype 19A and 74% (11–92) effectiveness with PCV13. In Finland, PHiD-CV introduction resulted in a significant reduction in serotype 19A invasive pneumococcal disease after 3 years, although this result was not sustained at 6 years[25] and cross-protection was not shown against this serotype in a population-based study in Sweden.[26] Nonetheless, taken together we expect that SIIPL-PCV administered as a 2+1 schedule will provide similar protection against serotype 6A and 19A to that provided by PCV13.

Cross-protection against serotype 6C generated by serotype 6A in PCV13 has previously been reported. An indirect cohort study in the UK showed an effectiveness of 70·0% (95% CI 2·0 to 91·8) against serotype 6C after at least one dose of PCV13 and an

effectiveness of 94·3% (64·9 to 99·1) on completion of a 2+1 schedule.[18] An effectiveness of 80·0% (–100·0 to 98·2), albeit non-significant, was also reported in a case-control study in Australia.[28] Serotype 6C has become the leading cause of invasive pneumococcal disease in countries using PHiD-CV, suggesting an absence of significant cross-protection provided by serotype 6B in PHiD-CV.[27] Given the similar IgG antibody distribution generated by PCV13 and SIIPL-PCV and high OPA GMT generated against serotype 6A by SIIPL-PCV, the vaccine might also provide cross-protection against serotype 6C, although further post-implementation effectiveness studies are required.

Finally, the robust serotype 1 IgG and OPA antibody responses generated by SIIPL-PCV which were similar to or higher than those generated by PCV13 post-primary and post-booster vaccination, support the use of the vaccine in prospective or reactive vaccination campaigns aimed at epidemic control of this serotype.[29] The introduction of PCV13 according to a 3+0 schedule, with restricted catch-up campaigns in Ghana and Central African Republic, has not prevented serotype 1 outbreaks. However, this introduction has shifted the age distribution of cases upwards, which is consistent with the generation of direct protection but limited indirect protection.[29] The introduction of an infant 2+1 schedule in South Africa resulted in a decrease in cases of serotype 1 invasive pneumococcal disease in people younger than 65 years, suggesting broader indirect protection from this schedule.[30] The magnitude of serotype 1 responses generated by the 2+1 schedule of SIIPL-PCV suggests the vaccine will generate similar direct and indirect protection against this serotype, and will be particularly suitable for epidemic control.

This trial had several strengths. This study is the first to directly compare the three PCVs that are currently WHO prequalified. Thus, we provide data for countries, particularly in sub-Saharan Africa and other similar settings, which are needed to support decisions regarding future PCV and scheduling choices. The consistency of the IgG and OPA antibody responses strengthens the findings and suggests they are likely to translate into vaccine effectiveness. Furthermore, despite the impact of the COVID-19 pandemic, per protocol follow-up was maintained for 91% of participants until blood sample collection after the booster. This trial also had several limitations. Although the antibody data are reassuring, the impact of SIIPL-PCV against invasive and mucosal disease endpoints when administered as a 2+1 schedule needs to be monitored after implementation. Additionally, the trial was not powered to detect differences between the three vaccines, so differences in seroresponse rates and antibody concentrations should be interpreted with caution. Furthermore, any differences should not be extrapolated to indicate expected differences in protection.

In conclusion, SIIPL-PCV was safe and immunogenic when given to infants in The Gambia according to a 2+1 schedule. Based on these data, the vaccine has been introduced in India and is expected to have a similar effectiveness on invasive and mucosal pneumococcal disease to that shown by PCV13 and PHiD-CV, when administered according to the same schedule. The importance of countries generating data on the effectiveness and impact of SIIPL-PCV after introduction is emphasised.

Contributors

SL, MRA, and EC contributed to the trial design. EC, IA, SL, and KA oversaw trial planning and implementation. IA, AF, BE, ES-J, TD, EA, BK, and NH coordinated trial planning and implementation. IA, AF, BE, ES-J, TD, EA, BK, EC, and DG collected the data. SL, EC, MRA, DG, RD, and VS interpreted the data. All authors approved the final manuscript. All authors had full access to all the data in the study and accept responsibility to submit for publication. EC and SL have accessed and verified all the data in the study.

Declaration of interests

RD and VS are employees of Serum Institute of India and received funding from the Bill & Melinda Gates Foundation for this trial. A grant from PATH paid some or all salaries of IA, AF, BE, ES-J, TD, EA, and EC. SL, MRA, NH, and KA received grant funding from the Bill & Melinda Gates Foundation for the conduct of this trial. DG conducts contract and collaborative research and advised the vaccine manufacturers (GlaxoSmithKline, Merck, and Sanofi Pasteur). EC is part of a data safety monitoring board for Pfizer, unrelated to pneumococcal vaccines. BK contributed to advisory boards and conducted clinical vaccine trials sponsored by GlaxoSmithKline and Pfizer. All other authors declare no competing interests.

Data sharing

Individual participant data will be shared after deidentification and made available from 3 months to 3 years after publication. Clinical documents including the study protocol, statistical analysis plan, and informed consent form will be available immediately after publication. Researchers who provide a scientifically sound proposal to the corresponding author and sign a data access agreement will receive access to individual participant data. Proposals will be reviewed and approved by the funder, investigator, and collaborators based on scientific merit.

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