

Immunogenicity and safety of a novel ten-valent pneumococcal conjugate vaccine in healthy infants in The Gambia: a phase 3, randomised, double-blind, non-inferiority trial



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Summary

Background An affordable pneumococcal conjugate vaccine (PCV) is needed to ensure sustainable access in low-income and middle-income countries. This trial examined the immunogenicity and safety of a novel ten-valent PCV (SIIP-PCV) containing serotypes 1, 5, 6A, 6B, 7F, 9V, 14, 19A, 19F, and 23F compared with the pneumococcal polysaccharide protein D-conjugate vaccine (PHiD-CV; Synflorix; GlaxoSmithKline; Brentford, UK).

Methods In this single-centre, randomised, double-blind, phase 3, non-inferiority trial in The Gambia, healthy, PCV-naïve infants aged 6–8 weeks were enrolled and assigned using permuted block randomisation to receive one of three lots of SIIP-PCV or to PHiD-CV in a ratio of 2:2:2:3. Parents and all staff assessing study outcomes were masked to group assignment. Vaccines (0.5 mL SIIP-PCV or 0.5 mL PHiD-CV) were administered at ages 6, 10, and 14 weeks by intramuscular injection. Primary immunogenicity outcomes, measured at age 18 weeks, were serotype-specific IgG geometric mean concentrations (GMCs) and seroresponse rates (IgG \geq 0.35 μ g/mL). Lot-to-lot equivalence (objective 1) was shown if the upper and lower bounds of the two-sided 95% CI around the GMC ratio for each pairwise lot-to-lot comparison was between the 0.5 and 2.0 equivalence margins for all ten serotypes. The immunogenicity of SIIP-PCV was defined as being non-inferior to that of PHiD-CV (objective 2) if, for at least seven of the ten serotypes in SIIP-PCV, the lower bound of the 97.5% CI for the GMC ratio was greater than 0.5, or the lower bound of the 97.5% CI for differences in seroresponse rate was greater than –10%. The GMC and seroresponse rates to serotypes 6A and 19A, which are not in PHiD-CV, were compared with those of the serotype in PHiD-CV that had the lowest seroresponse rate. Non-inferiority of the immune responses to antigens in the co-administered Expanded Programme on Immunization (EPI) vaccines (objective 3) was declared if the lower bound of the 95% CI for the difference between SIIP-PCV and PHiD-CV in seroresponse rates, or GMC ratios for pertussis antigens, was greater than –10% (or 0.5 for pertussis antigens) for all vaccine antigens. Safety data were assessed according to treatment received at the first visit in infants who received at least one dose of study vaccine and for whom at least some post-vaccination safety data were available. The primary immunogenicity analysis was in the per-protocol immunogenicity population, which included infants who received all study vaccines and had immunogenicity measurements after vaccination and no major protocol deviations. This trial is registered at ClinicalTrials.gov (NCT03197376).

Findings Between June 21, 2017, and Jan 29, 2018, 2250 infants were enrolled and randomly assigned to receive SIIP-PCV (n=1503; 502 to lot 1, 501 to lot 2, and 500 to lot 3) or PHiD-CV (n=747). 1458 (97.0%) infants assigned to SIIP-PCV and 724 (96.9%) assigned to PHiD-CV were included in the per-protocol primary immunogenicity analysis. Lot-to-lot equivalence was shown, with the lowest lower bound of the 95% CI for the GMC ratio being 0.52 (for serotype 6B in lot 2 vs lot 3) and the highest upper bound being 1.69 (for serotype 6B in lot 1 vs lot 2). SIIP-PCV was non-inferior to PHiD-CV in terms of immunogenicity: the lower bound of the 97.5% CI for the GMC ratio was greater than 0.5 (the lowest being 0.67 for serotype 19F) and the lower bound of the 97.5% CI for the difference in seroresponse rate was greater than –10% (the lowest being –2.2% for serotype 6B) for all ten serotypes in SIIP-PCV. The lowest seroresponse rate after PHiD-CV was to serotype 6B (76.7% [95% CI 73.4–79.7]). This serotype was therefore used for the comparisons with serotype 6A and 19A in SIIP-PCV. Non-inferiority of immune responses to the EPI vaccines after co-administration with SIIP-PCV compared with after co-administration with PHiD-CV was shown for all vaccine antigens included in the primary series. The lowest lower bound of the 95% CI for the difference in seroresponse rates was –7.1% for rotavirus antibody and for the GMC ratio for pertussis antigens was 0.62 for anti-pertussis toxoid. 1131 (75.2%) of 1503 infants in the SIIP-PCV group and 572 (76.6%) of 747 in the PHiD-CV group had at least one unsolicited adverse event. 36 (2.4%) participants in the SIIP-PCV group and 18 (2.4%) in the PHiD-CV group had a serious adverse event; none were considered related to vaccination. In infants who were selected to have solicited adverse events recorded, injection-site induration after primary vaccinations occurred in 27 (4.9%) of 751 infants who received SIIP-PCV versus 34 (9.4%) of 364 who received PHiD-CV (p=0.0032). There were no other notable differences in the safety profiles of the

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two vaccines. One infant in the SIIPL-PCV group and two in the PHiD-CV group died during the study. The deaths were not considered to be related to study vaccination or study participation.

Interpretation The immunogenicity of SIIPL-PCV was non-inferior to that of PHiD-CV, for which efficacy and effectiveness data against pneumococcal disease are available. The vaccine is safe and can be co-administered with routine EPI vaccines. The data generated in this trial have supported the licensure and pre-qualification of SIIPL-PCV, making the vaccine available for introduction into national immunisation programmes. Generating post-implementation data confirming vaccine impact remains important.

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Introduction

Pneumonia is the leading cause of under-5 mortality beyond the neonatal period worldwide, and the leading

cause of all under-5 mortality in sub-Saharan Africa. It caused an estimated 900 000 deaths worldwide in this age group in 2015.^{1,2} *Streptococcus pneumoniae* is the most

Research in context

Evidence before this study

We searched PubMed to identify articles published before April 1, 2020, using the following search terms with appropriate Boolean operators: "pneumococcal conjugate vaccin*", "pneumococcal vaccin*", "immun*", "meta-analysis", "systematic review", "randomized controlled trial", "clinical trial", "efficacy", "effectiveness", "impact", and "safety". Only three pneumococcal conjugate vaccines (PCVs) from two manufacturers in high-income countries had been licensed and WHO prequalified for purchase by Gavi-eligible countries before this study: the first-generation seven-valent vaccine (Prevenar, Pfizer) and two second-generation vaccines, including the pneumococcal polysaccharide protein D-conjugate vaccine (PHiD-CV; Synflorix, GSK), ten-valent PCV, and the 13-valent PCV (Prevenar 13, Pfizer). All three vaccines are safe on the basis of both randomised controlled trials (RCTs) and post-licensure pharmacovigilance data. Meta-analyses of RCTs indicate that the pooled efficacy of PCVs against vaccine-type invasive pneumococcal disease (IPD) is at least 80%, and against all IPD (vaccine type and non-vaccine type) is around 60%. The pooled efficacy of the vaccines against radiologically confirmed pneumonia is about 30% and against clinical pneumonia is between 5% and 10%. The vaccines reduce the incidence of pneumococcal acute otitis media after administration in infancy by between around a quarter and a half, whereas their effect on all-cause and recurrent acute otitis media is uncertain. An effect of the vaccines on all-cause mortality has also been shown in some RCTs, including a trial done in The Gambia, although meta-analyses have not shown a significant effect of the PCVs on this endpoint overall. Effectiveness data generated after vaccine licensure are heterogenous according to study design, schedule, and setting. The effectiveness of the vaccines against vaccine-type IPD ranges from about 75% to almost 100%. The vaccines reduced radiologically confirmed pneumonia by between a third and two-thirds and clinical pneumonia by less than a fifth in some studies and by more than two-thirds in others. No substantial differences in effectiveness between the

two second-generation vaccines on disease endpoints have been shown. PHiD-CV, the reference vaccine used in this trial, was licensed on the basis of non-inferiority of the serotype-specific IgG seroresponse rates generated by the vaccine to those generated by the seven-valent PCV. However, the vaccine has subsequently been shown to have an efficacy of 100% against vaccine-type IPD and of 18% against community-acquired pneumonia in RCTs and to have significant effects on pneumococcal disease endpoints in post-licensure effectiveness studies, including studies done in sub-Saharan Africa.

Added value of this study

The candidate ten-valent PCV, SIIPL-PCV, includes the dominant pneumococcal serotypes causing disease in low-income and middle-income countries. The vaccine met the criteria set out in the WHO Technical Report Series for the clinical assessment of PCVs and the target product profile, which defines the specifications new PCVs must meet to secure future purchase for Gavi-eligible countries. After a three-dose primary series, given at ages 6, 10, and 14-weeks, the immunogenicity of SIIPL-PCV was non-inferior to that of PHiD-CV. The vaccine can be co-administered with routine EPI vaccines and has a similar safety profile to that of PHiD-CV. A robust response to a booster dose of the vaccine given at age 9 months and high functional opsonophagocytic activity antibody titres both after the primary vaccinations and after the booster vaccination were also demonstrated.

Implications of all the available evidence

Based on these data, SIIPL-PCV has been prequalified by WHO. The vaccine is therefore available to Gavi-eligible countries and for purchase by the UN and other agencies. The addition of SIIPL-PCV to the pool of available PCVs is expected to accelerate PCV rollout and ensure programme sustainability, further reducing vaccine-preventable pneumococcal disease worldwide. Demonstration of non-inferiority and the comparable distribution of antibody concentrations suggests SIIPL-PCV will have a similar effect on pneumococcal disease to PHiD-CV.

common cause of pneumonia-associated morbidity and mortality. More than 300 000 children die from pneumococcal pneumonia, meningitis, and other invasive pneumococcal diseases (IPDs) each year.³ Most of these deaths occur in a small number of low-income and middle-income countries (LMICs).^{2,3} There are more than 90 serotypes of *S pneumoniae*, but a relatively small number are responsible for the majority of disease, and there are important geographical differences in their distributions.⁴

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 where this trial was conducted.^{5,6} However, PCVs are available from only two manufacturers and are unaffordable for many low-income countries without financial support from Gavi, the Vaccine Alliance.⁷ The organisation is expected to spend more than 40% of its budget on PCVs between 2016 and 2020, equivalent to US\$2.8 billion.⁸ Pricing also places considerable financial burden on middle-income countries ineligible for, or transitioning from, Gavi support.⁷ Consequently, the availability of an additional safe, effective, more affordable PCV that targets serotypes most prevalent in LMICs is expected to enhance programme sustainability in those settings where the disease burden is highest.⁷

The ten-valent candidate PCV developed by Serum Institute of India (SIIP-PCV) includes the dominant disease-causing serotypes in Africa, Asia, and Latin America (1, 5, 6A, 6B, 7F, 9V, 14, 19A, 19F, and 23F) and offers similar coverage to the licensed PCVs in these regions.⁴ In phase 1/2 trials done in The Gambia and India, SIIP-PCV had a reassuring safety profile in adults, toddlers, and infants. The vaccine was immunogenic for all ten serotypes in the three age-groups, including when co-administered with Expanded Programme on Immunization (EPI) vaccines.^{9,10}

This phase 3 trial was designed to meet the criteria specified in the WHO Technical Report Series for the clinical assessment of PCVs, alongside the target product profile for the advanced market commitment for PCVs, which defines the specifications new vaccines must meet to secure purchase for Gavi-supported countries.^{11,12} The study had three primary immunogenicity objectives. First, to establish the equivalence of the immune responses generated by three lots of SIIP-PCV. The three lots (manufacturing batches) were produced at commercial scale, based on a plan approved by the WHO before the start of the study. Second, to show non-inferiority of the immune response induced by SIIP-PCV compared with the immune response induced by the pneumococcal polysaccharide protein D-conjugate vaccine (PHiD-CV; Synflorix; GlaxoSmithKline; Brentford, UK), a licensed ten-valent PCV. Third, to confirm the non-inferiority of the immune responses generated by routine EPI vaccines

when co-administered with SIIP-PCV compared with PHiD-CV as part of the primary series.

Given the value an additional PCV is expected to bring to the global market, and the high efficacy of the available vaccines, the primary immunogenicity analyses were for non-inferiority. PHiD-CV, rather than the 13-valent PCV (Prevenar13, Pfizer [PCV13]), was used as the reference vaccine. The choice was made because the efficacy of PHiD-CV against IPD, pneumonia, and otitis media in infants and children has been established in randomised controlled trials done in Europe and South America.^{13,14} The vaccine has also been shown to be highly effective at preventing IPD and pneumonia in infants in Kenya—also based on a 6-week, 10-week, and 14-week schedule.^{15,16} Thus, confirmation that SIIP-PCV has non-inferior immunogenicity to PHiD-PCV supports the expected effect of the vaccine on IPD, for which an immunological correlate of protection exists.¹² Descriptive comparisons allow the protection the vaccine is expected to confer against other pneumococcal disease endpoints to be estimated. Furthermore, although the post-primary seroconversion rates and effect on vaccine-type IPD are consistently high after both vaccines, the IgG geometric mean concentrations (GMCs) generated by PHiD-CV tend to be lower than those generated by PCV13.^{17–20}

Methods

Study design and participants

This was a single-centre, randomised, double-blind, phase 3, non-inferiority trial. Healthy, PCV-naïve infants aged 6–8 weeks were enrolled at Medical Research Council (MRC) clinical trial facilities within three government health centres (Faji Kunda Health Centre, Brikama Health Centre, and Bundung Maternal and Child Health Hospital) in the peri-urban western region of The Gambia. To be eligible, infants had to weigh at least 3.5 kg and have no clinically relevant health conditions. Full inclusion and exclusion criteria are in the appendix (pp 1–3). All parents provided written informed consent before any study-related procedures took place.

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Approval was obtained from The Gambia Government/MRC joint ethics committee, the Western Institutional Review Board, and the Gambian Medicines Control Agency.

Randomisation and masking

Eligible infants were assigned to receive either one of three lots of SIIP-PCV or PHiD-CV in a 2:2:2:3 ratio using a predefined randomisation scheme. As part of the randomisation scheme, half of the infants in each group were selected to provide solicited adverse event data after the vaccinations at weeks 6, 10, and 14. An independent biostatistician generated randomisation sequences using

See Online for appendix

permuted blocks with randomly selected block sizes. Vaccine assignments were printed on the inside of sequentially numbered, sealed, opaque, tamper-evident envelopes. Randomisation was done by unmasked nurses by opening the next envelope in sequence. The same nurses then drew up and administered the vaccines using identical syringes, but they were not involved in any other participant-related procedures or endpoint assessments. Parents and all other trial staff were masked to group assignment.

Procedures

The first primary vaccination visit (visit 1) took place when the infants were aged 6–8 weeks. Two further primary vaccination visits (visit 2 and visit 3) and a follow-up immunogenicity visit (visit 4; post-primary visit) took place at 4-week intervals. The first 675 infants were also enrolled to receive a booster vaccination at age 9 months (visit 5) and a final follow-up immunogenicity visit (visit 6; post-booster visit) 4 weeks later (appendix, p 4).

A single 0.5 mL dose of SIIPL-PCV (Serum Institute of India, Pune, India) contains 2 µg each of serotypes 1, 5, 6A, 7F, 9V, 14, 19A, 19F, and 23F polysaccharide and 4 µg of serotype 6B polysaccharide, all individually conjugated to recombinant non-toxic diphtheria cross-reactive material-197 protein and adsorbed onto aluminium phosphate. Lots 209Y7001AZ, 209Y7002AZ, and 209Y7003AZ were used. A single 0.5 mL dose of PHiD-CV (GlaxoSmithKline, Brentford, UK) contains 1 µg each of serotypes 1, 5, 6B, 7F, 9V, 14, and 23F polysaccharide and 3 µg of serotype 4 polysaccharide, all individually conjugated to recombinant non-typable *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, all adsorbed onto aluminium phosphate. Lot XSPNA828BB was used.

Infants concomitantly received the routine EPI vaccinations according to the schedule in The Gambia (appendix p 5). Parenteral vaccines were administered by intramuscular injection into the anterolateral aspect of the thigh using 23G, 25 mm needles.

The first 450 infants in the SIIPL-PCV group and the first 225 infants in the PHiD-CV group who had sufficient blood volumes were included in the analysis of EPI vaccine responses. The first 250 infants in both the SIIPL-PCV and PHiD-CV groups were included in the analysis of opsonophagocytic activity (OPA) at visit 4 and the first 100 infants in both the SIIPL-PCV and PHiD-CV groups were included in the analysis of OPA responses at visit 6. At visit 4 and visit 6, 5.0 mL blood samples were collected and serum was separated and stored at –70°C for immunogenicity testing. PCV immunogenicity was assessed by the WHO Pneumococcal Serology Reference Laboratory (Great Ormond Street Institute of Child Health Biomedical Research Centre, London, UK) using a validated ELISA to quantify pneumococcal

IgG concentrations and a validated multiplex OPA assay to assess functional responses.^{21,22} IgG concentrations to each component of the co-administered diphtheria, tetanus, whole-cell pertussis, hepatitis B, *H influenzae* type b (Hib) vaccine, and to the measles and rubella vaccine, and IgA concentrations to rotavirus, were measured by ELISA. Neutralising antibody titres were measured for polioviruses types 1, 2, and 3 and yellow fever virus (appendix p 6).

Solicited injection-site (tenderness, erythema, and induration) and systemic (cutaneous rash, axillary temperature, irritability, drowsiness, and decreased appetite) adverse events were recorded after each primary vaccination in all infants and, in those infants randomly selected to have solicited adverse events collected, daily for the next 6 days through home visits. Solicited adverse events were collected from all participants after the booster vaccination. Parents were also asked to contact the study team with any health-related concerns, and their infants were then seen by a study clinician who provided any necessary treatment and recorded all unsolicited adverse events.

Solicited adverse events were graded for severity from grade 1 to grade 4 (appendix p 7). Unsolicited adverse events were categorised using Medical Dictionary for Regulatory Activities preferred terms, graded from grade 1 (mild) to grade 5 (resulted in death), and assessed for relatedness to study vaccine by the investigator.

Outcomes

For the assessment of lot-to-lot equivalence (objective 1), we assessed serotype-specific GMCs. The primary outcome measures for PCV immunogenicity (objective 2) were the serotype-specific IgG GMCs and seroresponse rates. The seroresponse rate was defined as the proportion of infants with serotype-specific IgG concentrations of at least 0.35 µg/mL, which is the reference concentration for assessment of vaccine efficacy against IPD.¹² The primary outcome measures for EPI vaccine immunogenicity (objective 3), other than for pertussis, were seroresponse rates. The primary outcome measures for pertussis vaccine immunogenicity were GMCs of anti-pertussis toxoid IgG and anti-fimbriae 2/3 IgG. All primary outcomes were assessed at the primary visit.

Secondary outcome measures were the OPA seroresponse rates, defined as the proportion of infants with an OPA titre of at least 8, and OPA geometric mean titres (GMTs); both were measured at the post-primary visit. Another secondary outcome was the ratio of IgG GMCs and OPA GMTs measured at the post-booster visit to those measured at the post-primary visit. Secondary outcome measures for measles, rubella, and yellow fever immunogenicity were seroresponse rates at the post-booster visit (appendix p 6).

Safety outcomes were the number and severity of solicited adverse events during the 7 days after each vaccination and the number, severity, and relatedness to study vaccine of adverse events and serious adverse

events throughout the study. A data safety monitoring board reviewed safety data and trial conduct throughout the trial, first meeting after about a quarter of participants had received one dose of the study vaccine.

Statistical analysis

The estimated required sample size of 2250 infants was calculated on the basis of an iterative process allowing for up to 10% participant attrition from the per-protocol population. Based on achieving the lot-to-lot equivalence objective, data for all three lots of SIPL-PCV were to be combined in the analysis of further objectives. The overall power to achieve the three primary objectives was calculated as the product of the individual powers and was about 94%. The collection of solicited adverse event data on half the infants was judged to provide sufficient power to detect clinically significant differences in these event rates (appendix pp 8–13).

All three primary immunogenicity objectives had to be attained individually for the trial to achieve its overall aim. The equivalence and non-inferiority margins used were aligned with those used to support licensure of the already available PCVs.^{23–25} To achieve lot-to-lot equivalence, the upper and lower bounds of the two-sided 95% CIs around the GMC ratios for each of the three pairwise lot-to-lot comparisons (eg, $GMC_{lot1} : GMC_{lot2}$) had to be between the 0.5 and 2.0 equivalence margins for all ten serotypes. No adjustment for multiplicity was made given the requirement to show equivalence for all comparisons.

The trial was not designed to establish non-inferiority for the immune responses induced by individual serotypes in SIPL-PCV, but rather to show the non-inferiority of the immune response induced by SIPL-PCV compared with that induced by PHiD-CV. For SIPL-PCV to be non-inferior to PHiD-CV, at least one of the following had to be achieved for seven of the ten serotypes included in SIPL-PCV: the lower bound of the two-sided 97.5% CI around the GMC ratio ($GMC_{SIPL-PCV} : GMC_{PHiD-CV}$) for the serotype had to be greater than 0.5 or the lower bound of the 97.5% CI around the difference in the seroresponse rates ($seroresponse\ rate_{SIPL-PCV} - seroresponse\ rate_{PHiD-CV}$) had to be greater than -10%. 97.5% CIs were used to adjust for the two endpoints by which non-inferiority could be established. As recommended by the WHO Technical Report Series, GMCs and seroresponse rates for serotypes 6A and 19A, the non-matched serotypes in SIPL-PCV, were compared with data for the serotype in PHiD-CV

with the lowest seroresponse rate.¹² As a secondary objective, the superiority of the seroresponse rates and GMCs to serotypes 6A and 19A induced by SIPL-PCV, compared with the crossreactive responses to the same serotypes generated by PHiD-CV, were tested. The trial was not otherwise designed to draw conclusions regarding individual serotypes. However, for the eight serotypes shared by both vaccines, we considered CIs around

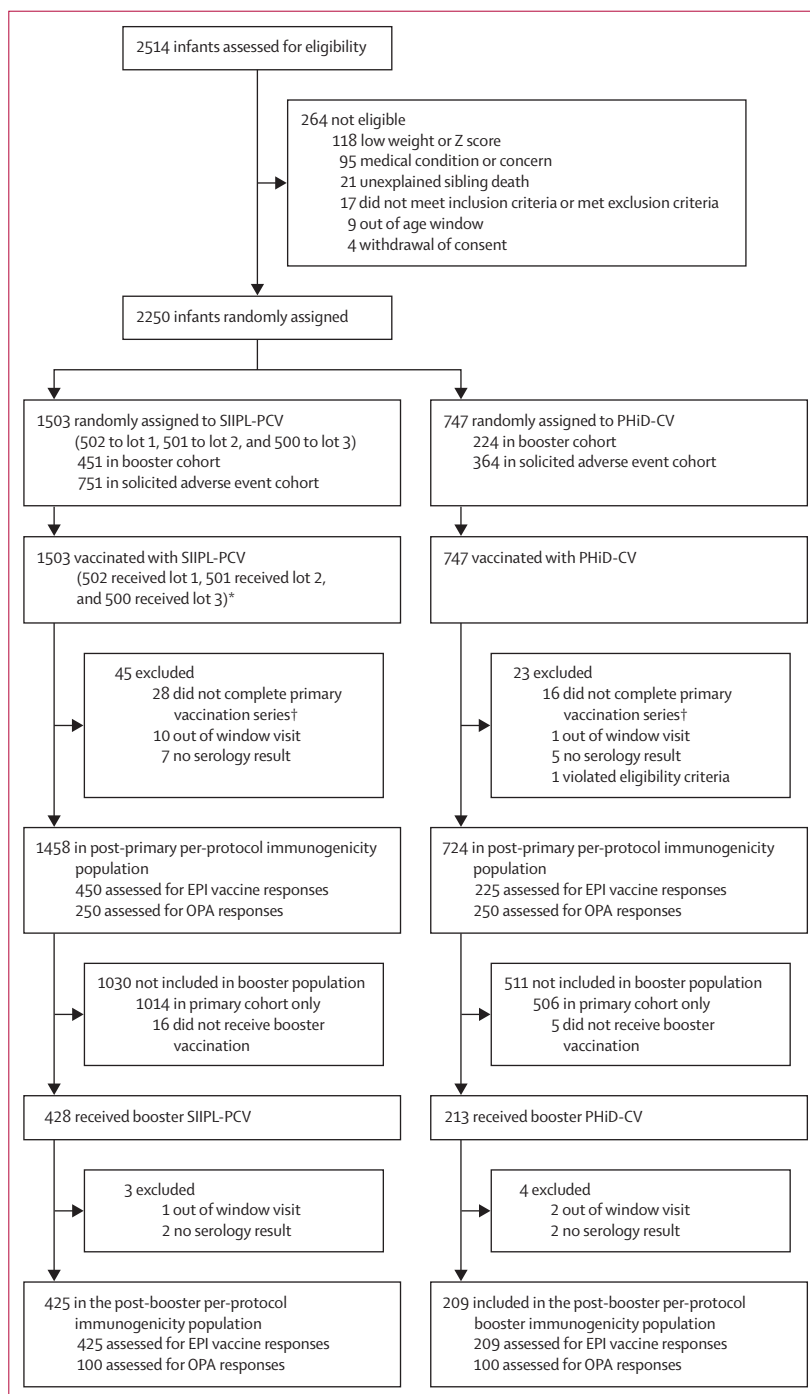


Figure 1: Trial profile

SIPL-PCV=Serum Institute of India candidate ten-valent pneumococcal conjugate vaccine. PHiD-CV=pneumococcal polysaccharide protein D-conjugate vaccine (Synflorix). EPI=Expanded Programme on Immunization. OPA=opsonophagocytic activity. *Data for the three lots were combined in all further analyses once lot-to-lot equivalence had been confirmed. †Of these infants, seven in the SIPL-PCV group and six in the PHiD-CV group were also assigned to the booster populations.

| | SIIP-PCV (n=1503) | PHiD-CV (n=747) |
|----------------------------------|----------------------|--------------------|
| Age at vaccination 1, days | 46 (42–56) | 46 (42–56) |
| Sex | | |
| Female | 738 (49.1%) | 347 (46.5%) |
| Male | 765 (50.9%) | 400 (53.5%) |
| Race | | |
| African | 1502 (99.9%) | 747 (100%) |
| Other | 1 (0.1%) | 0 |
| Ethnicity | | |
| Mandinka | 777 (51.7%) | 397 (53.1%) |
| Wolof | 156 (10.4%) | 61 (8.2%) |
| Fula | 186 (12.4%) | 86 (11.5%) |
| Jola | 180 (12.0%) | 100 (13.4%) |
| Other | 203 (13.5%) | 103 (13.8%) |
| Weight, kg | 4.7 (3.4–6.9) | 4.6 (3.5–6.5) |
| Length, cm | 55.5 (47.7–63.4) | 55.4 (49.8–61.5) |
| Primary cooking fuel source | | |
| Wood or charcoal | 1491 (99.2%) | 734 (98.3%) |
| Other | 12 (0.8%) | 13 (1.7%) |
| Primary water source | | |
| Private tap, well, or borehole | 958 (63.7%) | 473 (63.3%) |
| Community tap, well, or borehole | 545 (36.3%) | 274 (36.7%) |

Data are median (range) or n (%). PHiD-CV=pneumococcal polysaccharide protein D-conjugate vaccine (Synflorix). SIIP-PCV=Serum Institute of India candidate ten-valent pneumococcal conjugate vaccine.

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

seroresponse differences that excluded 0 and around GMC or GMT ratios that excluded 1 to be meaningful differences for the purpose of descriptive comparison. To show non-inferiority of the immune responses to the co-administered EPI vaccines, the lower limit of the two-sided 95% CI around the difference in seroresponse rates (EPI-seroresponse rate_{SIIP-PCV} – EPI-seroresponse rate_{PHiD-CV}) for diphtheria, tetanus, hepatitis B, Hib, polioviruses types 1, 2, and 3, and rotavirus had to be greater than –10%. To show non-inferiority of the immune responses to pertussis, the lower bounds of the 95% CIs around the GMC ratios for anti-pertussis toxoid and anti-fimbriae 2/3 IgG (eg, anti-pertussis toxoid GMC_{SIIP-PCV}:anti-pertussis toxoid GMC_{PHiD-CV}) had to be greater than 0.5. All EPI responses had to be non-inferior to achieve this primary objective and therefore no adjustment for multiplicity was required.

All CIs around differences in seroresponse rates were calculated using the Miettinen-Nurminen likelihood ratio score method. Having confirmed the normality assumption was appropriate, CIs around GMC ratios were calculated on the basis of a normal distribution for the log₁₀-transformed antibody concentrations or titres.

Differences in the proportions of participants with solicited and unsolicited adverse events were assessed using Cochran-Mantel-Haenszel tests, stratified by field

site, or using Fisher's exact tests, as appropriate based on the number of comparisons being made. Observed differences in safety parameters were also assessed for medical relevance.

Primary immunogenicity analyses were done on a per-protocol basis, in infants who received all primary doses of study vaccine and had post-dose immunogenicity measurements available with no major protocol deviations. Safety data were assessed according to treatment received at the first visit in infants who received at least one dose of study vaccine and for whom at least some post-vaccination safety data were available.

Statistical analyses were done with SAS/STAT software version 9.4. The trial is registered at ClinicalTrials.gov (NCT03197376).

Role of the funding source

The Bill & Melinda Gates Foundation funded PATH to conduct this study. PATH was involved in all stages of the study conduct, data analysis, and interpretation. All authors had full access to all the data in the study and were responsible for the decision to submit for publication.

Results

Between June 21, 2017, and Jan 29, 2018, 2514 infants were assessed for eligibility (figure 1). Of these, 2250 (89.5%) infants were enrolled, of whom 1503 (66.8%) were randomly assigned to receive one of the three lots of SIIP-PCV (502 to lot 1, 501 to lot 2, and 500 to lot 3) and 747 (33.2%) were randomly assigned to receive PHiD-CV. 2182 (97.0%) of 2250 infants, including 1458 (97.0%) of 1503 infants in the SIIP-PCV group and 724 (96.9%) of 747 infants in the PHiD-CV group, were eligible for inclusion in the per-protocol population for assessment of the primary immunogenicity objectives. The first 675 infants also received a booster dose of their assigned vaccine at age 9 months (451 in the SIIP-PCV group and 224 in the PHiD-CV group). Within this group, 634 (93.9%) were eligible for inclusion in the per-protocol population for assessment of booster responses. The median age at the first study vaccination was 46 days (range 42–56 days). There were no noteworthy differences in anthropometric or sociodemographic characteristics between groups at baseline (table 1).

Based on pneumococcal serotype-specific IgG GMCs assessed at the post-primary visit, the prespecified lot-to-lot equivalence criteria were met for all pairwise lot-to-lot comparisons, for all ten serotypes (appendix pp 14–15). The lowest lower bound of the 95% CI for the GMC ratio was 0.52 (for serotype 6B in lot 2 vs lot 3) and the highest upper bound was 1.69 (for serotype 6B in lot 1 vs lot 2). Thus, lot-to-lot equivalence was confirmed (objective 1) and data for the three lots were combined for further analyses.

Seroresponse rates at the post-primary visit ranged from 99.7% (95% CI 99.3–99.9) for serotype 1 to 78.7%

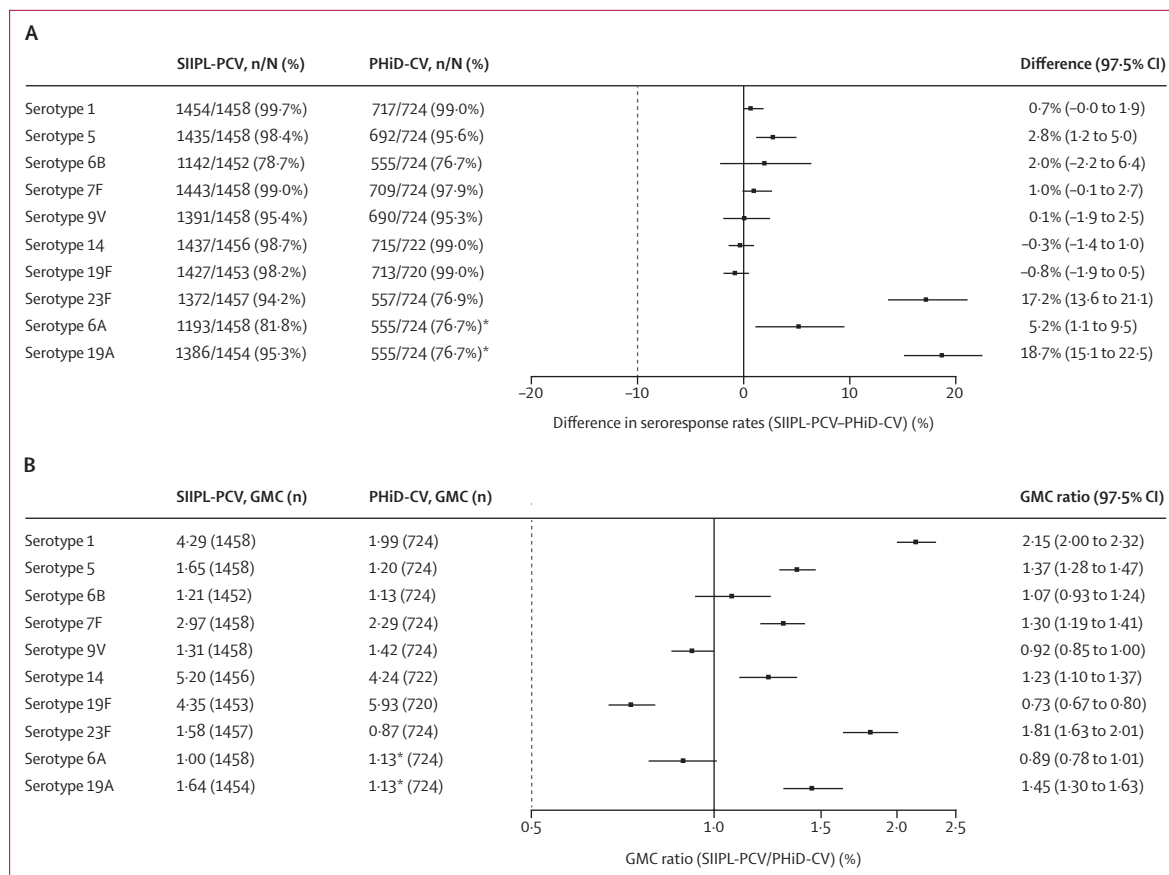


Figure 2: Non-inferiority analysis for seroresponse rates (A) and GMCs (B) 4 weeks after the three-dose primary vaccination series

The dotted lines show the non-inferiority margins. GMC=geometric mean concentration. PHiD-CV=pneumococcal polysaccharide protein D-conjugate vaccine (Synflorix). SIPL-PCV=Serum Institute of India candidate ten-valent pneumococcal conjugate vaccine.*For serotypes 6A and 19A (which are not included in PHiD-CV), seroresponse rates and GMCs for the SIPL-PCV group were compared with those for the serotype in the PHiD-CV group with the lowest seroresponse rate (ie, serotype 6B).

(76.5–80.7) for serotype 6B after SIPL-PCV, and from 99.0% (98.0–99.6) for serotype 1 to 76.7% (73.4–79.7) for serotype 6B after PHiD-CV (figure 2A; appendix p 16). The seroresponse rate to serotype 6B was the lowest among the eight shared serotypes after PHiD-CV, and therefore serotype 6B was used as the comparator for serotypes 6A and 19A. The lower bound of the 97.5% CI for the difference in seroresponse rates was above -10% for all eight shared serotypes and by comparison to serotype 6B for serotypes 6A and 19A (figure 2A; appendix p 16). Among the shared serotypes, seroresponse rates for serotypes 5 and 23F were higher after SIPL-PCV than after PHiD-CV (97.5% CIs exclude 0; figure 2A; appendix p 16).

The post-primary GMCs after SIPL-PCV ranged from 5.20 µg/mL (95% CI 4.92–5.50) for serotype 14 to 1.00 µg/mL (0.95–1.06) for serotype 6A, whereas the GMCs after PHiD-CV ranged from 5.93 µg/mL (5.50–6.39) for serotype 19F to 0.87 µg/mL (0.80–0.95) for serotype 23F. The lower bound of the 97.5% CI for the GMC ratio was above 0.5 for all eight shared

serotypes and by comparison to serotype 6B for serotypes 6A and 19A (figure 2B; appendix p 16). Additionally, among the shared serotypes, the GMCs for serotypes 1, 5, 7F, 14, and 23F were higher after SIPL-PCV than after PHiD-CV (97.5% CIs exclude 0; figure 2B; appendix p 16). The GMC was higher for serotype 19F after PHiD-CV than after SIPL-PCV. Thus, on the basis of seroresponse rates and GMCs, the overall non-inferiority of the immune response to SIPL-PCV compared with PHiD-CV was confirmed (objective 2). The seroresponse rates and GMCs to serotypes 6A and 19A in SIPL-PCV were also superior to the cross-reactive responses to serotypes 6B and 19F generated by PHiD-CV (appendix p 18).

Seroresponse rates to tetanus, diphtheria, hepatitis B, Hib, and polio were high irrespective of whether the vaccines were co-administered with SIPL-PCV or PHiD-CV (table 2). Rotavirus seroresponse rates were 27.3% (95% CI 23.2–31.7) after co-administration with SIPL-PCV and 27.1% (21.4–33.4) after co-administration with PHiD-CV. For all antigens, the lower bound of the

| | SIIP-PCV | PHiD-CV | Difference (95% CI) |
|--|--------------------------------|--------------------------------|----------------------|
| EPI vaccine seroresponse after primary vaccination* | | | |
| Anti-diphtheria toxoid ≥ 0.1 IU/mL | 100% (99.2 to 100; 447/447) | 100% (98.4 to 100; 225/225) | 0.0% |
| Anti-tetanus toxoid ≥ 0.1 IU/mL | 100% (99.2 to 100; 447/447) | 100% (98.4 to 100; 225/225) | 0.0% |
| Anti-hepatitis B surface antigen concentration ≥ 10 mIU/mL | 100% (99.2 to 100; 447/447) | 99.6% (97.6 to 100; 224/225) | 0.4% (-0.4 to 2.5) |
| Anti-polyribosylribitol phosphate (<i>Haemophilus influenzae</i> type b) concentration ≥ 0.15 μ g/mL | 98.7% (97.1 to 99.5; 441/447) | 99.6% (97.6 to 100; 224/225) | -0.9% (-2.5 to 1.2) |
| Anti-polio neutralising antibody titre > 8 | | | |
| Type 1 | 99.8% (98.8 to 100; 446/447) | 100% (98.4 to 100; 225/225) | -0.2% (-1.3 to 1.5) |
| Type 2 | 83.7% (79.9 to 87.0; 374/447) | 80.9% (75.1 to 85.8; 182/225) | 2.8% (-3.2 to 9.3) |
| Type 3 | 97.8% (95.9 to 98.9; 437/447) | 98.7% (96.2 to 99.7; 222/225) | -0.9% (-3.0 to 1.8) |
| Anti-rotavirus antibody concentration ≥ 20 U/mL | 27.3% (23.2 to 31.7; 122/447) | 27.1% (21.4 to 33.4; 61/225) | 0.2% (-7.1 to 7.1) |
| Post-primary EPI vaccine GMC† | | | |
| Anti-pertussis toxoid, IU/mL | 50.95 (43.13 to 60.20; 447) | 61.82 (49.58 to 77.09; 225) | 0.82 (0.62 to 1.09)‡ |
| Anti-fimbriae 2/3, IU/mL | 317.97 (275.91 to 366.45; 447) | 324.87 (267.34 to 394.78; 225) | 0.98 (0.77 to 1.25)‡ |
| EPI vaccine seroresponse after booster vaccination* | | | |
| Anti-measles IgG ≥ 150 mIU/mL | 89.6% (86.4 to 92.4; 381/425) | 88.0% (82.8 to 92.1; 183/208) | 1.7% (-3.3 to 7.4) |
| Anti-rubella IgG ≥ 4 IU/mL | 99.1% (97.6 to 99.7; 421/425) | 98.1% (95.2 to 99.5; 204/208) | 1.0% (-0.9 to 4.0) |
| Anti-yellow fever neutralising antibody titre ≥ 8 | 99.1% (97.6 to 99.7; 420/424) | 96.6% (93.2 to 98.6; 201/208) | 2.4% (0.2 to 5.9) |

References to the assays used are in the appendix (p 5). EPI=Expanded Programme on Immunization. GMC=geometric mean concentration. IU=international units. PHiD-CV=pneumococcal polysaccharide protein D-conjugate vaccine (Synflorix). SIIP-PCV=Serum Institute of India candidate ten-valent pneumococcal conjugate vaccine. *Data are % (95% CI; number of infants with seroresponse/total number of infants). †Data are GMC (95% CI; total number of infants). ‡Data are GMC ratio (95% CI).

Table 2: Antibody responses to EPI vaccines after co-administration with SIIP-PCV or PHiD-CV

| | OPA seroresponse* | | | OPA GMTs | | |
|---------------|-------------------------------|--------------------------------|----------------------|--------------------------------|--------------------------------|---------------------|
| | SIIP-PCV† | PHiD-CV† | Difference (95% CI) | SIIP-PCV‡ | PHiD-CV‡ | GMT ratio (95% CI) |
| Serotype 1 | 92.7% (88.7 to 95.6; 229/247) | 75.5% (69.7 to 80.7; 188/249) | 17.2% (11.0 to 23.6) | 85.2 (71.3 to 101.7; 247) | 27.6 (23.0 to 33.1; 249) | 3.09 (2.40 to 3.98) |
| Serotype 5 | 98.8% (96.5 to 99.8; 244/247) | 96.0% (92.7 to 98.1; 239/249) | 2.8% (-0.0 to 6.2) | 161.3 (139.9 to 186.0; 247) | 115.9 (98.9 to 136.0; 249) | 1.39 (1.12 to 1.72) |
| Serotype 6B | 95.9% (92.6 to 98.0; 233/243) | 86.5% (81.6 to 90.5; 212/245) | 9.4% (4.5 to 14.6) | 913.5 (746.0 to 1118.7; 243) | 467.7 (365.3 to 598.7; 245) | 1.95 (1.42 to 2.69) |
| Serotype 7F | 100% (98.5 to 100.0; 247/247) | 99.6% (97.8 to 100.0; 249/250) | 0.4% (-1.1 to 2.2) | 1833.7 (1612.3 to 2085.5; 247) | 1586.8 (1392.6 to 1807.9; 250) | 1.16 (0.96 to 1.39) |
| Serotype 9V | 100% (98.5 to 100.0; 242/242) | 100% (98.5 to 100.0; 249/249) | 0.0% | 141.7 (113.4 to 177.2; 242) | 376.8 (324.0 to 438.1; 249) | 0.38 (0.29 to 0.49) |
| Serotype 14 | 97.1% (94.2 to 98.8; 237/244) | 98.0% (95.3 to 99.3; 242/247) | -0.8% (-4.0 to 2.2) | 1019.3 (816.5 to 1272.5; 244) | 1102.6 (878.6 to 1383.9; 247) | 0.92 (0.67 to 1.27) |
| Serotype 19F | 96.8% (93.7 to 98.6; 239/247) | 98.4% (96.0 to 99.6; 246/250) | -1.6% (-4.9 to 1.2) | 594.3 (510.0 to 692.5; 247) | 895.4 (785.0 to 1021.4; 250) | 0.66 (0.54 to 0.81) |
| Serotype 23F | 100% (98.5 to 100.0; 246/246) | 100% (98.5 to 100.0; 243/243) | 0.0% | 767.2 (649.0 to 907.1; 246) | 253.1 (197.1 to 325.0; 243) | 3.03 (2.25 to 4.09) |
| Serotype 6A§ | 97.2% (94.3 to 98.9; 240/247) | 14.9%¶ (10.7 to 20.1; 36/241) | 82.2% (76.7 to 86.6) | 1317.2 (1109.4 to 1563.9; 247) | 7.1¶ (5.8 to 8.6; 241) | 186 (144 to 241) |
| Serotype 19A§ | 92.3% (88.3 to 95.3; 228/247) | 39.0%¶ (32.7 to 45.5; 92/236) | 53.3% (46.0 to 60.1) | 148.6 (121.4 to 182.0; 247) | 11.1¶ (9.2 to 13.4; 236) | 13.4 (10.2 to 17.7) |

OPA=opsonophagocytic activity. GMTs=geometric mean titres. PHiD-CV=pneumococcal polysaccharide protein D-conjugate vaccine (Synflorix). SIIP-PCV=Serum Institute of India's candidate ten-valent pneumococcal conjugate vaccine. *Seroresponse was defined as OPA titres of at least 8. †Data are proportion of infants with seroresponse (95% CI; number of infants with seroresponse/total number of infants). ‡Data are GMT (95% CI; total number of infants). §Serotypes not included in PHiD-CV. ¶Cross-reactive responses to serotype 6B and 19F in PHiD-CV.

Table 3: Opsonophagocytic activity 4 weeks after the three-dose primary vaccination series

95% CI for the difference in seroresponse rates was greater than -10%. Responses to pertussis in the SIIP-PCV group were non-inferior to those in the PHiD-CV group on the basis of GMC ratios. Therefore,

non-inferiority of the immune responses to all EPI vaccines after co-administration with SIIP-PCV compared with co-administration with PHiD-CV during the primary series (objective 3) was demonstrated.

| | SI IPL-PCV | | | PHiD-CV | | | Post-booster SI IPL-PCV:PHiD-CV GMC ratio (95% CI) |
|---------------|-----------------------------|-----------------------------|---------------------|------------------------------|------------------------------|---------------------|--|
| | Post-primary IgG GMC | Post-booster IgG GMC | GMC ratio (95% CI) | Post-primary IgG GMC | Post-booster IgG GMC | GMC ratio (95% CI) | |
| Serotype 1 | 4.05 (3.76 to 4.36; 424) | 5.71 (5.25 to 6.21; 424) | 1.41 (1.31 to 1.52) | 2.12 (1.88 to 2.38; 208) | 2.47 (2.19 to 2.80; 208) | 1.17 (1.06 to 1.28) | 2.34 (2.02 to 2.71) |
| Serotype 5 | 1.49 (1.39 to 1.59; 424) | 1.31 (1.21 to 1.41; 424) | 0.88 (0.81 to 0.95) | 1.26 (1.14 to 1.38; 207) | 0.84 (0.76 to 0.93; 207) | 0.67 (0.61 to 0.74) | 1.57 (1.38 to 1.79) |
| Serotype 6B | 1.29 (1.13 to 1.48; 422) | 8.32 (7.70 to 8.99; 422) | 6.43 (5.70 to 7.26) | 1.15 (0.94 to 1.41; 208) | 4.44 (4.00 to 4.93; 208) | 3.85 (3.23 to 4.59) | 1.89 (1.65 to 2.15) |
| Serotype 7F | 3.12 (2.89 to 3.37; 424) | 6.36 (5.87 to 6.89; 424) | 2.04 (1.89 to 2.19) | 2.49 (2.22 to 2.79; 208) | 4.07 (3.67 to 4.52; 208) | 1.63 (1.47 to 1.82) | 1.57 (1.37 to 1.80) |
| Serotype 9V | 1.29 (1.20 to 1.39; 423) | 1.80 (1.67 to 1.94; 423) | 1.39 (1.29 to 1.50) | 1.43 (1.28 to 1.60; 208) | 2.08 (1.87 to 2.31; 208) | 1.46 (1.31 to 1.62) | 0.87 (0.76 to 0.99) |
| Serotype 14 | 5.06 (4.57 to 5.62; 419) | 6.84 (6.08 to 7.68; 419) | 1.35 (1.21 to 1.51) | 3.86 (3.25 to 4.57; 203) | 4.67 (3.92 to 5.55; 203) | 1.21 (1.03 to 1.42) | 1.48 (1.21 to 1.82) |
| Serotype 19F | 4.16 (3.85 to 4.48; 414) | 6.18 (5.70 to 6.71; 414) | 1.49 (1.36 to 1.63) | 6.31 (5.51 to 7.24; 203) | 9.79 (8.77 to 10.92; 203) | 1.55 (1.38 to 1.75) | 0.63 (0.55 to 0.73) |
| Serotype 23F | 1.65 (1.50 to 1.80; 423) | 4.11 (3.75 to 4.50; 423) | 2.50 (2.29 to 2.72) | 0.94 (0.80 to 1.11; 208) | 2.15 (1.90 to 2.44; 208) | 2.29 (1.98 to 2.65) | 1.91 (1.63 to 2.24) |
| Serotype 6A* | 1.09 (0.98 to 1.22; 423) | 4.86 (4.40 to 5.38; 423) | 4.46 (4.01 to 4.96) | 0.12† (0.11 to 0.14; 208) | 0.42† (0.36 to 0.50; 208) | 3.49 (2.97 to 4.11) | 11.6 (9.67 to 14.0) |
| Serotype 19A* | 1.50 (1.37 to 1.64; 421) | 3.97 (3.63 to 4.33; 421) | 2.64 (2.40 to 2.91) | 0.26† (0.23 to 0.31; 204) | 0.95† (0.79 to 1.15; 204) | 3.60 (2.99 to 4.33) | 4.22 (3.52 to 5.06) |

Data are GMC (95% CI; total number of infants) unless otherwise indicated. Serotype-specific IgG GMCs were measured 4 weeks after the three-dose primary vaccination series and 4 weeks after the booster dose at age 9 months. GMC=geometric mean concentration. PHiD-CV=pneumococcal polysaccharide protein D-conjugate vaccine (Synflorix). SI IPL-PCV=Serum Institute of India candidate ten-valent pneumococcal conjugate vaccine. *Serotypes not included in PHiD-CV. †Cross-reactive responses to serotype 6B and 19F in PHiD-CV.

Table 4: Serotype-specific IgG responses after the primary vaccination series and booster dose

Post-primary OPA seroresponse rates ranged from 92.3% (88.3–95.3) for serotype 19A to 100.0% (95% CI 98.5–100.0) for serotypes 7F, 9V, and 23F after SI IPL-PCV, and from 75.5% (69.7–80.7) for serotype 1 to 100.0% (98.5–100.0) for serotypes 9V and 23F after PHiD-CV (table 3). Among the shared serotypes, the OPA seroresponse rates for serotypes 1 and 6B were higher after SI IPL-PCV than after PHiD-CV. Compared with after PHiD-CV, OPA GMTs after SI IPL-PCV were higher for serotypes 1, 5, 6B, and 23F and lower for serotypes 9V and 19F.

In both groups, a significant booster response was demonstrated for all serotypes except serotype 5 on the basis of IgG GMC ratios (table 4), and for all serotypes on the basis of OPA GMT ratios (appendix p 19). Among the shared serotypes, post-booster IgG GMCs were higher in the SI IPL-PCV group than the PHiD-CV group for serotypes 1, 5, 6B, 7F, 14, and 23F and were higher in the PHiD-CV group than the SI IPL-PCV group for serotypes 9V and 19F (table 4). The OPA GMTs were higher in the SI IPL-PCV group than the PHiD-CV group for serotypes 1, 6B, 7F, 14, and 23F (appendix p 19).

The distributions in serotype-specific IgG concentrations after both vaccines were similar, as shown by the reverse cumulative distribution curves, which generally ran in parallel after both primary and booster vaccination (appendix p 20). The variability in

serotype 6B concentrations after the primary vaccination series was high compared with that in the other serotypes, but this was consistent between groups and was reduced after booster vaccination. Among the shared serotypes, variability in OPA titres after primary vaccination was relatively greater for serotype 1 after PHiD-CV and for serotype 9V after SI IPL-PCV (appendix p 20). These differences were reduced after booster vaccination.

Among the infants randomly selected to have solicited adverse events collected, 377 (50.2%) of 751 in the SI IPL-PCV group and 203 (55.8%) of 364 in the PHiD-CV group had at least one solicited injection-site reaction after any primary series vaccination (table 5). All injection-site adverse events were mild (grade 1) to moderate (grade 2). Induration rates were significantly higher with PHiD-CV (9.3%) than with SI IPL-PCV (4.9%). There were no other significant differences between groups.

About two-thirds of participants in each group (496 [66.0%] in the SI IPL-PCV group and 240 [65.9%] in the PHiD-CV group) had at least one solicited systemic reaction after any primary series vaccination (table 5). Of these, fever was the most frequent and was observed in more than half of the participants in both groups. Altogether, five (0.7%) of 751 participants had any grade 3 systemic reaction after SI IPL-PCV compared with four (1.1%) of 364 after PHiD-CV. The rates of local and systemic reactions were lower after the booster

| | Three-dose primary vaccination series | | Booster vaccination | |
|--------------------------------------|---------------------------------------|-----------------|---------------------|-----------------|
| | SIIPL-PCV (n=751) | PHiD-CV (n=364) | SIIPL-PCV (n=428) | PHiD-CV (n=213) |
| Injection-site adverse event* | | | | |
| Any | 377 (50.2%) | 203 (55.8%) | 35 (8.2%) | 15 (7.0%) |
| Tenderness | 369 (49.1%) | 193 (53.0%) | 33 (7.7%) | 13 (6.1%) |
| Erythema or redness | 33 (4.4%) | 19 (5.2%) | 0 | 0 |
| Induration or swelling | 37 (4.9%)† | 34 (9.3%)† | 5 (1.2%) | 4 (1.9%) |
| Systemic adverse event | | | | |
| Any | 496 (66.0%) | 240 (65.9%) | 51 (11.9%) | 29 (13.6%) |
| Grade ≥3 | 5 (0.7%) | 4 (1.1%) | 0 | 0 |
| Cutaneous rash | 40 (5.3%) | 19 (5.2%) | 4 (0.9%) | 2 (0.9%) |
| Grade ≥3 | 0 | 1 (0.3%) | 0 (0.0%) | 0 |
| Fever (≥37.5°C)‡ | 391 (52.1%) | 187 (51.4%) | 24 (5.6%) | 16 (7.5%) |
| Grade ≥3 (≥39.1°C) | 3 (0.4%) | 2 (0.5%) | 1 (0.2%) | 0 |
| Irritability | 240 (32.0%) | 109 (29.9%) | 13 (3.0%) | 6 (2.8%) |
| Grade ≥3 | 2 (0.3%) | 0 | 0 | 0 |
| Drowsiness | 48 (6.4%) | 21 (5.8%) | 10 (2.3%) | 5 (2.3%) |
| Grade ≥3 | 1 (0.1%) | 0 | 1 (0.2%) | 0 |
| Decreased appetite | 47 (6.3%) | 26 (7.1%) | 3 (0.7%) | 2 (0.9%) |
| Grade ≥3 | 2 (0.3%) | 1 (0.3%) | 0 | 0 |

Data are n (%). Solicited adverse event grading was completed as per appendix p 7. SIIPL-PCV=Serum Institute of India candidate ten-valent pneumococcal conjugate vaccine. PHiD-CV=pneumococcal polysaccharide protein D-conjugate vaccine (Synflorix). *No grade 3 or worse solicited injection site adverse events occurred in the study. †p=0.0032 (Cochran-Mantel-Haenszel test stratified on field site); no other differences were significant. ‡Temperature measured in the axilla.

Table 5: Participants with solicited adverse events in the 7 days from the day of vaccination

vaccination than after the primary vaccinations. There were no notable differences in type or frequency of solicited systemic adverse events between groups at any point.

More than three-quarters of infants in each group (1131 [75.2%] of 1503 in the SIIPL-PCV group and 572 [76.6%] of 747 in the PHiD-CV group) had at least one unsolicited adverse event (appendix p 22). 36 (2.4%) participants in the SIIPL-PCV group and 18 (2.4%) in the PHiD-CV group had a serious adverse event (appendix p 23); none were considered related to vaccination. Three infants died during the study: one in the SIIPL-PCV group from serotype 10A pneumococcal meningitis and two in the PHiD-CV group from pneumonia. The deaths were not considered to be related to the study vaccine or protocol.

Discussion

This phase 3 trial was designed to show that SIIPL-PCV meets the specifications set out in the WHO Technical Report Series for the clinical assessment of PCVs and the target product profile, which defines the criteria that new PCVs must meet to secure purchase for Gavi-supported countries.^{11,26} All three primary immunogenicity objectives and the safety objectives were met. First, the three lots of SIIPL-PCV assessed were immunologically equivalent on the basis of GMC ratios. Second, the immunogenicity of SIIPL-PCV was non-inferior to that of PHiD-CV. All eight of the matched serotypes in the

two vaccines met the criteria for defining non-inferiority on the basis of both seroresponse rates and GMC ratios. Responses to serotypes 6A and 19A, the non-matched serotypes in SIIPL-PCV, achieved the same criteria when compared with serotype 6B, the serotype with the lowest seroresponse rate in the PHiD-CV group. Booster responses were generated for all serotypes except serotype 5 after both SIIPL-PCV and PHiD-CV on the basis of IgG GMCs, and for all serotypes on the basis of OPA GMTs. Third, the study demonstrated non-inferiority of the immune responses induced by the EPI vaccines after co-administration with SIIPL-PCV compared with after co-administration with PHiD-CV. Finally, SIIPL-PCV had a similar safety and tolerability profile to PHiD-CV.

In a double-blind, randomised, controlled trial in South America, the efficacy of PHiD-CV was 100% (95% CI 74–100) against vaccine-type IPD, 18% (5–29) against bacterial community-acquired pneumonia, and 68% (17–87) against vaccine-type acute otitis media.¹³ In a study in Finland, infants received PHiD-CV according to a 3+1 schedule that was similar to the one used in this trial, and the effectiveness of the vaccine was 100% (83–100) against vaccine-type IPD.¹⁴ Additionally, a clear reduction in IPD incidence after PHiD-CV introduction was reported in Kenya.¹⁶ The adjusted incidence rate ratio, comparing the periods before and after vaccine introduction, for vaccine-type IPD was 0.08 (95% CI 0.03–0.22), and for all IPD (ie, vaccine and non-vaccine type) it was 0.32 (0.17–0.60). The adjusted incidence rate ratio for radiologically confirmed pneumonia was 0.52 (0.32–0.86), and for clinically defined pneumonia it was 0.73 (0.54–0.97).¹⁵ The introduction of PHiD-CV into the routine immunisation schedule at ages 6, 10, and 14 weeks in Kenya was accompanied by a catch-up campaign targeting children younger than 5 years, which is likely to have accelerated vaccine effects. Nonetheless, the data indicate that PHiD-CV confers protection against both invasive and mucosal pneumococcal disease after an infant schedule in a low-income, sub-Saharan African setting that is similar to The Gambia.^{15,16}

On the basis of the finding of non-inferior immunogenicity, we expect that SIIPL-PCV will be effective against IPD in infancy—the age group and endpoint for which the serological correlate has been established.^{26,27} The findings are further supported by the similar or higher OPA seroresponse rates generated by SIIPL-PCV, which might ultimately be a better correlate of protection against IPD than the serotype-specific IgG concentrations.²⁸ Correlates of protection against mucosal disease, including pneumonia and acute otitis media, have not been established, although the levels of serum antibody required are generally believed to be higher than those required to prevent IPD.²⁹ The non-inferiority of SIIPL-PCV compared with PHiD-CV based on GMC ratios, the closely aligned reverse cumulative distribution curves, the similar or higher OPA GMTs for the shared

serotypes, as well as the robust booster responses, suggest SIIPL-PCV will also affect mucosal pneumococcal disease, although studies should be done after implementation to demonstrate this.

Before efficacy data for PHiD-CV became available, the vaccine was assessed for immunological non-inferiority to the licensed seven-valent PCV (Prevenar; Pfizer), for which efficacy had already been established.²³ PHiD-CV was non-inferior to Prevenar for all shared serotypes except serotypes 6B and 23F, whereas the OPA seroresponse rates were similar for all serotypes. The efficacy of PHiD-CV against IPD caused by serotype 6B was 100% (95% CI 55–100) in the Finnish study; therefore, the lower antibody responses elicited by PHiD-CV than by Prevenar against this serotype have not had a demonstrable clinical impact.^{14,23} In our trial, the responses to serotypes 6B and 23F after SIIPL-PCV were higher than the responses after PHiD-CV, both after the primary vaccination series and the booster dose, supporting the expectation that SIIPL-PCV will be effective against these serotypes.

A limitation of using PHiD-CV as the comparator vaccine in this study is the consequent absence of matched responses for serotypes 6A and 19A in SIIPL-PCV. On the basis of the guidance set out in the WHO Technical Report Series, responses to the two serotypes were compared with responses to serotype 6B—the serotype with the lowest seroresponse rate following PHiD-CV. This approach tends to favour the new vaccine. Therefore, although the prespecified criteria for establishing non-inferiority of SIIPL-PCV compared with PHiD-CV were achieved, caution is warranted in interpreting these findings in isolation as the basis on which to predict efficacy against the two non-matched serotypes. Descriptive data from the phase 1/2 study of SIIPL-PCV done in The Gambia suggest the immunogenicity of the vaccine against these serotypes is somewhat lower than that of PCV13.⁹ Nonetheless, the IgG GMCs generated by SIIPL-PCV in our study were 1.00 µg/mL (95% CI 0.95 to 1.06) against serotype 6A and 1.64 µg/mL (1.57 to 1.72) against serotype 19A. The point estimates in both cases are greater than the serotype-specific correlates of protection estimated for the same serotypes, even though they are based on UK data (0.16 µg/mL [0.08 to 1.05] against serotype 6A and 1.00 µg/mL [0.60 to 2.47] against serotype 19A).³⁰ Additionally, in settings incorporating a booster dose of the vaccine into their schedule, serotypes 6B and 19F in PHiD-CV have been shown to provide a level of cross-protective immunity against IPD caused by serotypes 6A and 19A. In Brazil, the effectiveness of PHiD-CV against IPD caused by serotype 19A was 82.2% (95% CI 10.7 to 96.4), although no significant protection was demonstrated against serotype 6A in that setting (14.7% [−311.6 to 82.3]).^{31,32} In Canada, the effectiveness against serotype 19A was 76% (95% CI 7 to 94).³³ A population-based study in Finland

reported a non-significant reduction of 26% (95% CI −13 to 51) in serotype 19A IPD and a reduction of 95% (75 to 100) in serotype 6A IPD 6 years after introduction of PHiD-CV. Any protection against serotype 19A in this population appeared predominately in infants younger than 2 years.^{34,35} Thus, although the data on cross-protection are somewhat heterogenous, the IgG GMCs generated by SIIPL-PCV in this study were more than five-times higher and the OPA GMTs more than ten-times higher than the cross-reactive responses generated by PHiD-CV. Although follow-up studies are warranted, the data support the expected effect of SIIPL-PCV on serotype 6A and 19A IPD.

Immune responses to the EPI vaccines were non-inferior when the vaccines were co-administered with SIIPL-PCV compared with when they were co-administered with PHiD-CV. PHiD-CV is licensed for co-administration with all EPI vaccines that were assessed in this trial except yellow fever, for which no data are available. However, given the seroresponse rate to yellow fever when co-administered with SIIPL-PCV was greater than 99%, clinically significant differences in the yellow fever seroresponse rates after co-administration of the two vaccines are unlikely. At about 27%, the seroresponse rate to rotavirus was low irrespective of group, reflecting the generally low immunogenicity and efficacy of rotavirus vaccines in LMICs.³⁶

The tolerability and safety of SIIPL-PCV and PHiD-CV were compared on the basis of the occurrence of solicited and unsolicited adverse events. The proportion of children with injection-site swelling was lower after primary vaccination with SIIPL-PCV than after primary vaccination with PHiD-CV, but otherwise the safety profiles of the two vaccines were similar. Three infants died during the trial, unrelated to the trial vaccines or to trial participation. This number of deaths is somewhat lower than might have been predicted on the basis of a post-neonatal mortality rate of eight deaths per 1000 livebirths in urban regions of The Gambia.³⁷ It probably reflects the exclusion of infants with clinically significant health complaints identified at screening and the availability of a clinician to assess and provide care for enrolled participants throughout the trial.

The trial has several strengths. It was designed to meet the requirements established for a PCV to achieve WHO prequalification and used non-inferiority criteria that were aligned with those used in the pivotal phase 3 trials of the two licensed and prequalified second-generation PCVs.^{23,25} Based on the data presented, SIIPL-PCV achieved WHO prequalification in December, 2019, and is thus available to Gavi-supported countries and for purchase by UNICEF and other agencies. Data for the week 6, 10, and 14 schedule can reasonably be extrapolated to schedules starting later and having a wider dosing interval, making the results of the trial applicable to more relaxed schedules. The trial achieved high retention rates and few infants were excluded from the per-protocol population as a result of protocol deviations, ensuring a

high degree of confidence in the study findings. Conducting the study in The Gambia maximised the relevance of the data for similar LMICs, where the potential value of the vaccine is likely to be greatest. The eligibility criteria aimed to exclude infants with clinically significant underlying health complaints in order to maximise the probability of detecting genuine safety signals. Nonetheless, the findings are expected to be broadly applicable to the infant population. The equivalence margins used were at least as stringent as those used to support licensure of other PCVs and suggest an absence of meaningful differences between lots.^{23,24} Finally, although the limitations related to serotypes 6A and 19A have been noted, the use of PHiD-CV as the reference vaccine ensures that immunobridging for the other serotypes is directly to efficacy data generated in randomised controlled trials, which reduces the risk of the so-called biocreeper associated with the conduct of serial non-inferiority trials based on immunogenicity alone.³⁸

The trial has some additional limitations. First, although use of IgG seroresponse rates as a correlate of protection is well established and recommended by WHO, the marker has been defined on the basis of its value in predicting population-level protection from IPD in infancy. It does not account for potential serotype-specific differences in strain susceptibility to antibodies and does not a priori predict protection from mucosal disease.³⁰ The antibody distributions and functional antibody responses suggest SIIP-PCV will effect these disease endpoints. Nonetheless, the limitations of using any one serological marker in isolation to predict disease effect should be noted and the importance of generating robust post-implementation effectiveness data emphasised.

Since Rwanda and The Gambia became the first sub-Saharan African countries to introduce PCV into their national EPI schedules in 2009, there has been substantial progress in PCV rollout. Nonetheless, recent estimates suggest that more than 60% of children younger than 5-years remain unvaccinated globally, with the bulk of vaccine-preventable pneumococcal deaths occurring across Africa and southeast Asia.³ In all, PCVs are expected to have accounted for more than 40% of Gavi expenditure on vaccines between 2016 and 2020.⁸ Furthermore, although the price of available PCVs has decreased, countries that are no longer eligible for Gavi support, as well as middle-income countries that have delayed PCV introduction, face substantial financial constraints. The data generated in this trial have supported the licensure and WHO prequalification of SIIP-PCV and suggest the vaccine will have an impact on pneumococcal disease globally.

Contributors

SL, MRA, and EC contributed to trial design. EC, AB, SL, KA, and IA-L oversaw trial planning and implementation. AB, IA, MBH, AU, AF, MO, BE, DO, ES-J, CO, BK, and NH contributed to and coordinated trial planning and implementation. AB, IA, MBH, AU, AF, MO, DO, BE, ES-J,

CO, and DG contributed to data collection. DT analysed the data. SL, EC, MRA, BLI, DT, RD, and VS contributed to data interpretation. All authors provided input into the manuscript and approved the final manuscript. EC, SL, and DT accessed and verified the data underlying the study.

Declaration of interests

RD and VS are employees of Serum Institute of India and have received funding from the Bill & Melinda Gates Foundation. The grant from PATH paid some or all of the salaries of Medical Research Council personnel conducting the trial (EC, AB, IA, MBH, AU, AF, MO, DO, BE, ES-J, CO, and BK). Employees of PATH (SL, MRA, NH, KA, BLI, and IA-L) received grant funding from the Bill & Melinda Gates Foundation for the conduct of this trial. DG conducts contract and collaborative research with, and has advised, vaccine manufacturers GlaxoSmithKline, Merck, and Sanofi Pasteur. EC is part of a data safety monitoring board for Pfizer unrelated to pneumococcal vaccines. DT declares no competing interests.

Data sharing

The individual participant data that underlie the results reported in this Article, after deidentification (text, tables, figures, and appendices), will be shared on request. Individual participant data will be available beginning 3 months and ending 3 years after publication. Supporting clinical documents, including the study protocol, statistical analysis plan, and the informed consent form, will be available immediately after publication on request. Researchers who provide a scientifically sound proposal will be allowed access to the individual participant data. Proposals should be directed to the corresponding author. These proposals will be reviewed and approved by the funder, investigator, and collaborators on the basis of scientific merit. To gain access, data requesters will need to sign a data access agreement.

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