Immunogenicity and Safety of 13-Valent Pneumococcal Conjugate Vaccine (PCV13) Formulated with 2-Phenoxyethanol in Multidose Vials Given with Routine Vaccination in Healthy Infants: An Open-Label Randomized Controlled Trial

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Running title: Multidose vial presentation of PCV13

Abbreviations: * 2-PE=2-phenoxyethanol; AE=adverse event; DMC=data monitoring committee; e-diary=electronic diary; GMC=geometric mean concentration; GMR=geometric mean ratio; GMT=geometric mean titer; IgG=immunoglobulin G; MDV=multidose vial;

MRC=Medical Research Council; OPA=opsonophagocytic activity; PCV=pneumococcal conjugate vaccine; PCV13=13-valent pneumococcal conjugate vaccine; SAE=serious adverse event; SDS=single-dose syringe; SDV=single-dose vial; WHO=World Health Organization.

Abstract

Background. This open-label randomized controlled trial in infants compared safety, tolerability, and immunogenicity of the 13-valent pneumococcal conjugate vaccine (PCV13) formulated with the preservative 2-phenoxyethanol (2-PE) in a multidose vial (MDV) to the current PCV13 without 2-PE in a single-dose syringe (SDS).

Methods. Gambian infants were randomized 1:1 to receive PCV13 as either MDV or SDS at ages 2, 3, and 4 months. Serotype-specific antipneumococcal antibody responses and opsonophagocytic activity ([OPA]; subset) were measured at age 5 months. Noninferiority was declared if the lower bound of the 97.5% CI for the difference (MDV-SDS) in proportions of subjects achieving IgG concentrations ≥0.35 ug/mL (primary endpoint) was greater than –10%. IgG geometric mean concentrations (GMCs) were noninferior if the lower limit of the two-sided 97.5% CI of the geometric mean ratio (MDV vs SDS) was greater than 0.5. Reactogenicity and other adverse events were collected.

Results. 500 participants were randomized and vaccinated; 489 (MDV: n=245; SDS: n=244) completed the trial. Noninferiority of MDV was demonstrated for all serotypes as measured by percentage of subjects achieving antibody responses above ≥0.35 ug/mL. IgG GMCs (coprimary endpoint) also demonstrated noninferiority of MDV; OPA results supported these findings. Safety and tolerability were comparable between groups.

Conclusions. PCV13 in MDV was safe and immunogenic when administered according to the routine schedule to infants. MDV was noninferior to SDS for all 13 pneumococcal serotypes. Comparable immunogenicity and safety profiles of PCV13 MDV and SDS suggest PCV13 MDV can help optimize vaccination in resource-limited settings. (ClinicalTrials.gov NCT01964716 https://clinicaltrials.gov/ct2/show/NCT01964716)

Keywords: pneumococcal conjugate vaccine; 2-phenoxyethanol; multidose vials; safety; immunogenicity

Introduction

The prevention of pneumococcal disease remains a major international public health priority due to high disease burden and associated mortality in children, especially in developing countries [1-3]. Pneumococcal conjugate vaccines (PCVs) are proven to prevent overall pneumococcal disease by decreasing disease burden and nasopharyngeal carriage caused by serotypes included in the vaccines [4-8]. In many parts of Africa, obstacles still exist that slow the wider uptake of PCVs, including available vaccine preparations. The 13-valent PCV (PCV13), which includes the largest number of serotypes in its formulation, is currently only available in single-dose vials (SDV) and syringes (SDS). Pneumococcal conjugate vaccines, including PCV13 SDV, have been prequalified by the World Health Organization (WHO) for use in the developing world [9]. Most vaccines used routinely in Africa are formulated in multidose vials (MDV) to maximize cold-chain storage efficiency, and serve as an important resource for vaccine introduction in resource-limited countries [10,11]. In 2010 the manufacturer of PCV13 (Pfizer Inc, New York, NY) entered into an agreement with the GAVI Alliance (formerly the Global Alliance for Vaccines and Immunization) aiming to increase access to PCV13 in GAVI-eligible countries [12]. To meet the supply needs of this program, the manufacturer developed a formulation containing the preservative 2-phenoxyethanol (2-PE), a phenolic derivative currently used as a preservative in other commercially available multidose vial presentations of pediatric vaccines [13]. This 4-dose MDV presentation would help optimize vaccine delivery and facilitate sustainable coverage.

General concerns regarding vaccines in multidose vials include contamination risk and potential for wastage. PCV13 formulated with 2-PE as a preservative meets stringent pharmacopeia class B requirements for antimicrobial suppression that were previously accepted by the WHO. In addition, the multidose vial can be stored refrigerated and is

acceptable for use up to 28 days after initial dose removal. The PCV13 MDV presentation was recently prequalified by the WHO [14], licensed by the European Medicines Evaluation Agency [15], and licensed in India based on data from this clinical trial. The MDV presentation will be crucial in sustaining PCV delivery across resource-limited settings and maintaining the protection from disease that PCV13 already provides.

We present here an open-label randomized vaccine trial conducted in The Gambia to compare the safety, tolerability, and immunogenicity of PCV13 with 2-PE presented in a multidose vial (PCV13 MDV) to that of PCV13 without 2-PE presented in a single-dose syringe (PCV13 SDS).

Methods

Trial design and population

This phase 3, open-label randomized controlled trial (ClinicalTrials.gov, NCT01964716) was conducted between January and September, 2014, in The Gambia at the Medical Research Council (MRC) Unit Fajara. Participants were enrolled at the routine Expanded Programme on Immunization clinic at the Fajikunda Major Health Centre in Western Gambia. The trial was conducted per ethical principles derived from the Declaration of Helsinki and in compliance with International Conference on Harmonisation and Good Clinical Practice guidelines. The trial protocol and relevant documents were reviewed and approved by the National Regulatory Authority and the Gambian Government/MRC Joint Ethics Committee. Written informed consent was obtained from parents of each participant before enrollment and before any trial-related procedure was performed.

The primary objective was to demonstrate noninferiority of immune responses induced by PCV13 MDV compared with PCV13 SDS as measured by serotype-specific immunoglobulin

G (IgG) concentrations 1 month after infant series completion. Safety profiles of each formulation were measured by rates of local reactions, systemic events, and adverse events (AEs). The secondary objective was to assess immune responses induced by PCV13 MDV relative to PCV13 SDS as measured by serotype-specific opsonophagocytic activity (OPA) in a subset of subjects.

Healthy infants aged 42 to 70 days weighing 3.5 kg or more at enrollment were eligible to participate. Infants with known or suspected immune deficiency or suppression, severe acute or chronic medical conditions, neurologic disorders, known major or congenital malformations, any contraindication to vaccination with pneumococcal conjugate vaccine, previous vaccination with pneumococcal vaccine, or a history of culture-proven invasive disease caused by *Streptococcus pneumoniae* were excluded from the trial.

Randomization

In this open-label trial, participants were randomly assigned 1:1 to receive 3 doses of either PCV13 MDV or SDS. Randomization was performed using sequential allocation to trial groups based on a randomization sequence prepared by the sponsor, and provided as individual randomization envelopes.

Trial vaccines and vaccination schedule

PCV13 contains saccharides from pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F individually conjugated to nontoxic diphtheria toxin cross-reactive material 197. Each 0.5-mL dose contains 2.2 μg of each saccharide, except for 4.4 μg of 6B, 5 mM succinate buffer, 0.02% polysorbate 80, and 0.125 mg aluminum as aluminum phosphate. PCV13 MDVs also contain 4 mg of 2-phenoxyethanol (2-PE, the concentration of which is within the range of 2-PE concentrations used in other licensed vaccines presented in MDV formulations) per 0.5-mL dose. Four doses of PCV13 (2.0 mL) are contained within

each MDV; for this trial, only 1 dose was used from each vial to allow for 1:1 vaccine accountability (1 vial to 1 subject) in a clinical trial conducted per Good Clinical Practice guidelines. This study compared responses to PCV13 with and without 2-PE, which has already been proven an effective preservative [16].

Participants received 1 dose (0.5 mL) of PCV13 MDV or SDS at approximately 2, 3, and 4 months of age per the Gambian immunization schedule, into the left anterolateral thigh. A range of 42 to 70 days of age was allowed for the 2-month visit, with subsequent visits 28 to 42 days following the previous visit. Other injectable vaccines routinely administered at this age (pentavalent vaccine containing diphtheria, whole-cell pertussis, tetanus, *Haemophilus influenzae* type b, and hepatitis B virus antigens) were given into the contralateral limb at the same time as PCV13. Children also received oral rotavirus and polio vaccines according to local guidelines.

Safety assessments

An experienced physician independent of the trial was available onsite and served as a local safety monitor to provide support for any potential safety issues. The sponsor also provided a data monitoring committee (DMC) independent of the trial site to periodically review safety data. Local reactions and systemic events were monitored for at least 30 minutes after each vaccination and from days 2 to 6 after each vaccination (day 1 being the day of vaccination); events were recorded in electronic diaries (e-diaries) by trained field workers during daily home visits. Local reactions included redness, swelling, and tenderness at the PCV13 injection site. Systemic events included fever (temperature ≥38.0°C), changes in appetite, sleep, and irritability; antipyretic use was also documented. If any local or systemic event persisted at day 6 and/or antipyretic use continued at day 6, field workers continued daily visits and completed the e-diary until resolution of either. Persistent fever or development of

other symptoms triggered a referral to the safety nurse and trial physician. A rapid diagnostic test for malaria parasitemia was conducted whenever a temperature reading ≥38.0°C was obtained. Any other AEs and serious AEs (SAEs) occurring between the signing of the informed consent form and the postvaccination blood draw were recorded. The relationship between AEs and the trial vaccine received was characterized as related or not related by the trial physicians.

Immunogenicity assessments

One venous blood sample (up to 5 mL) was collected 1 month after dose 3. Blood samples were transported to the MRC laboratory within 4 hours of collection, and serum was separated, barcoded, stored at −80°C and shipped to the sponsor for analysis. For all participants, a standardized enzyme-linked immunosorbent assay measured the concentration of serotype-specific IgG to the 13 pneumococcal vaccine serotypes [17-19].

Functional antibodies to the 13 serotypes were assessed by OPA assays [20,21] and were performed in a randomly selected subset of samples to ensure approximately 100 valid OPA results per serotype per group. To ensure 100 valid and determinate results for each serotype per treatment group, 160 subjects were randomly chosen from each treatment group. Invalid or indeterminate results were excluded from analysis, and samples with insufficient blood volume were not tested.

Statistical analysis

The WHO has established criteria for licensing new PCV formulations, which must demonstrate noninferiority to a current formulation for mean IgG concentrations and proportion of vaccinees achieving IgG concentrations ≥0.35 μg/mL, the accepted correlate of protection against invasive pneumococcal disease, all measured 1 month after primary series completion [22-24].

The primary endpoint for each vaccine group was the proportion of participants achieving a serotype-specific IgG concentration ≥0.35 μg/mL 1 month after dose 3. The coprimary endpoint was the serotype-specific IgG geometric mean concentration (GMC) one month after dose 3. The WHO [25] guidance calls for control of the type 1 error rate to be pre-specified for multiple endpoints. As there are 2 primary comparisons (GMC or % responder), a Bonferroni correction was applied (split the 5% type 1 error rate evenly for comparison of each serotype). Therefore, 97.5% CIs were used for multiple primary comparisons. For the primary endpoint, noninferiority for a serotype (MDV relative to SDS) was achieved if the lower limit of the two-sided 97.5% CI of difference in proportions (MDV−SDS) was greater than −10%. For IgG GMCs, noninferiority for a serotype was claimed if the lower limit of the two-sided 97.5% CI of the geometric mean ratio (GMR) (MDV relative to SDS) was greater than 0.5. The overall noninferiority of immune response of the PCV13 MDV to the PCV13 SDS was declared if noninferiority for either the primary or the coprimary endpoint was demonstrated for all 13 serotypes.

Exact, unconditional, 2-sided, 95% CIs on the proportion were computed using the F distribution. The differences in proportions for the vaccine groups were calculated with 97.5% CIs for IgG. Log transformation was used for GMRs. The OPA analysis for each vaccine group calculated the serotype-specific OPA geometric mean titers (GMTs) for each pneumococcal serotype 1 month after dose 3. The evaluable immunogenicity population was the primary analysis population, and included infants who received all assigned vaccine doses, adhered to protocol requirements, had ≥1 valid and determinate assay result, and had no major protocol violations. The safety analysis included all subjects who received ≥1 dose of PCV13.

Sample size

Sample size was based on simulations for proportions of responders with IgG antibody concentrations ≥0.35 µg/mL and for ratios of the geometric mean IgG concentrations for the MDV group relative to the SDS group. The variance-covariance input matrix and the mean vector for generating the random samples from the multiple-normal distribution were based on immunogenicity data from a previous Pfizer trial [26]. One thousand studies with 200 participants per group were generated for the simulations. The sample size was chosen to meet the WHO criteria [25], with Type-I error controlled by Bonferroni's method for GMC and responder hypotheses (97.5% CIs were used for testing). Using these criteria, the trial had ≥90% power to achieve the criteria from the simulation. Estimating a dropout rate of 20%, 500 participants (250 per group) were recommended for enrollment.

Results

Recruitment occurred between January 9 and May 19, 2014, and the last study visit was completed on September 1, 2014. Of 526 participants assessed for eligibility, 500 were enrolled, randomized, and vaccinated with either PCV13 MDV or SDS (250 per group) concomitantly with routine vaccines **(Figure 1)**. Overall, 489 (97.8%) participants completed the blood draw 1 month after dose 3 and were included in the evaluable immunogenicity population (245 and 244 in the PCV13 MDV and SDS groups, respectively). Demographic characteristics of the evaluable immunogenicity population were similar between the vaccine groups **(Table 1)**. Safety was assessed in all 500 participants who received ≥1 dose of trial vaccine. Characteristics of participants in the safety population were comparable to those in the evaluable immunogenicity population.

Immunogenicity

Pneumococcal IgG Concentrations ≥0.35 μg/mL

The numbers of participants in each trial arm achieving a pneumococcal IgG concentration ≥0.35μg/mL are compared in **Table 2.** More than 95% of children achieved IgG concentrations ≥0.35 μg/mL 1 month after dose 3 for each of the 13 serotypes in both vaccine groups, and the noninferiority criterion was met for this endpoint.

Pneumococcal IgG Geometric Mean Concentrations

One month after dose 3, GMCs were similar in both vaccine groups for the majority of serotypes. For this coprimary endpoint, noninferiority between the PCV13 MDV group and the PCV13 SDS group was demonstrated for all 13 serotypes **(Table 3)**.

Pneumococcal OPA Geometric Mean Titers

The OPA GMTs for all serotypes were determined for a subset of subjects in each vaccine group (MDV, 156–160 subjects; SDS, 155–160 subjects). GMTs were similar in both groups for the majority of serotypes, except serotype 3, for which titers were statistically significantly lower in the MDV group, and serotype 18C, for which titers were statistically significantly higher in the MDV group **(Table 4)**. All lower limits of the 95% CIs of OPA GMRs comparing MDV to SDS were greater than 0.5 except for serotype 14, which was slightly lower (ratio 0.7; 95% CI [0.48, 1.08]) **(Table 4)**. Reverse cumulative distribution curves showing OPA titers for each PCV13 serotype 1 month after dose 3 indicate that levels were similar across the full range of OPA titers for the majority of serotypes in both vaccine groups **(Supplementary Figure 1)**.

Safety

Local reactions and systemic events after each vaccination were comparable between vaccine groups, were mainly mild, and are summarized in **Table 5**. Local reactions were reported mainly on day 2 (roughly 24 hours after vaccination) and generally lasted <72 hours. Proportions of participants reporting redness and swelling at the vaccination site were low in both groups after any dose. No participant experienced a severe local reaction. For all doses, fever rates were comparable in both groups and generally low (1.2%–3.6%), and no participant experienced a fever >40°C. Although documented fever was rare, antipyretic medication was used in up to 23.2% of participants and was similar in both vaccine groups. Other systemic events were generally mild or moderate and were reported in similar proportions in both groups.

The AEs reported reflected anticipated illnesses in this age group and did not differ between groups (49.2% and 50.8% for PCV13 MDV and PCV13 SDS, respectively). The most frequently reported individual AEs were upper respiratory tract infection, viral diarrhea, and dermatitis, which were reported by similar proportions in the MDV group (23.2%, 7.6%, and 6.0%) and SDS group (20.0%, 12.0%, and 8.8%). There were also 3 related AEs of pyrexia (1 event in PCV13 MDV, 2 events in PCV13 SDS) that occurred on the day of vaccination (and therefore were not captured in the e-diary). One sudden infant death occurred in the PCV13 MDV group on day 20 after dose 3; this SAE was considered unrelated to trial vaccines.

Discussion

This trial compared the currently licensed PCV13 SDS presentation with a novel MDV preparation containing 2-PE in Gambian infants. Results confirmed noninferiority of the new formulation for all 13 serotypes for the primary outcome measures. Specifically, proportions

of participants achieving antipneumococcal IgG antibody concentrations ≥0.35 µg/mL were noninferior for MDV compared to SDS, as were IgG GMCs. Additionally, functional antibody assessed using OPA was similar between groups. No safety concerns were raised with the new formulation.

Substituting PCV13 SDS with a preparation containing multiple doses would have considerable advantages regarding logistics associated with vaccine delivery to remote areas, but equivalent safety and immunogenicity records are paramount for WHO prequalification and introduction. More than 95% of participants achieved concentrations above the WHO-defined threshold for protection for all 13 serotypes, and no major differences were observed between vaccine groups based on predefined noninferiority criteria. Minor differences in GMCs noted for serotype 18C and serotype 3 between vaccine groups are not likely to be of clinical significance. Results from OPA assays confirmed that IgG concentrations were associated with functional antibody, and GMTs were similar between groups for the majority of serotypes.

These results are likely generalizable, as the current trial setting is representative of other areas where MDV would be used.

Solicited local and systemic reactions and AEs were generally few and mild, with no differences between vaccine arms. No new safety issues were detected, suggesting that safety profiles of MDV and SDS are at least similar. Reactogenicity was low in both groups when compared to previous studies conducted elsewhere using PCV [27]. One potential explanation for low reactogenicity is the initial day of assessment being approximately 24 hours after vaccination, meaning reactions limited to the day of vaccination and resolving before day 2 could have been missed. However, this would only include reactions lasting <1 day, which are likely to be mild. Related adverse events on vaccination days were also low

and similar between groups. Other vaccine trials in this setting using similar reporting methods and times have also reported low vaccine reactogenicity [28]. The recording of reactogenicity data in the e-diary from day 2 following vaccination may partially explain the disparity between proportions of participants reporting antipyretic use (13.8%–23.2%) and those with documented pyrexia (≤3.6%), as pyrexia may have developed after field workers departed on day 1 but before their return visit on day 2. Moreover, antipyretics may have been used for pyrexia perceived by parents rather than actual pyrexia.

The AEs noted were similar between trial groups and were generally consistent with conditions common in this age group. One SAE occurred in the MDV group compared with none in the SDS group, but this fatal SAE occurring 20 days after dose 3 was considered unrelated to vaccination following review by the local safety monitor and DMC. Considering infant mortality in The Gambia [29], unexplained deaths in this age group are unsurprising; overall mortality in the trial was very low.

In conclusion, the immune response induced by PCV13 formulated with 2-PE in multidose vials was noninferior to the immune response induced by PCV13 without 2-PE in single-dose syringes when given at approximately 2, 3, and 4 months of age with routine pediatric vaccinations in healthy infants. Therefore, PCV13 with 2-PE likely induces an immune response adequate to protect against pneumococcal disease, similar to that induced by PCV13 without 2-PE. The comparable immunogenicity and safety profiles of PCV13 MDV and PCV13 SDS support use of PCV13 MDV in places where the SDS may pose unique challenges. Availability of PCV13 MDV would help ensure vaccine sustainability for infants in resource-limited settings.

Conflict of Interest Statement

BK has previously received funding from Pfizer Inc, GlaxoSmithKline, Novartis, PATH, the United Kingdom Department for International Development, Medical Research Council, and the Wellcome Trust. OTI, BC, RBM, MO, and AR have received funding for this trial from Pfizer Inc. FL, JZL, NLN, KUJ, AG, KJC, and DAS are employees of Pfizer Inc and hold stock in the company.

Acknowledgments

The authors acknowledge the contributions of the trial communities and participants, the field and quality assurance teams led by Basiru Sanyang, Abdou Gibba, Philip Mendy, Jerreba Darboe, and Assan Sanyang. We also acknowledge the Medical Research Council's Clinical Trial Support Office led by Dr Jenny Mueller, the Research Support team led by Elizabeth Batchilly and Adrameh Gaye, the local safety monitor Dr Muhammed Afolabi, and the DMC. This trial was supported by Pfizer Inc, which was involved in data collection, data interpretation, and writing of the manuscript. Additional editorial support was provided by Jill E. Kolesar, PhD, of Complete Healthcare Communications, LLC, and was funded by Pfizer Inc.

Author Contribution Statements

All authors approved and agreed to submit the final article for publication.

OTI, FL, NLN, KUJ, AG, KJC, DAS, BK, and AR conceived the trial. OTI, RBM, MO, BC, BK, and AR were involved in subject recruitment and data acquisition. JZL was responsible for statistical analyses. OTI drafted the manuscript with support from AR and BK. All authors participated in data interpretation and manuscript development, including critical review of drafts and approval of the final submitted manuscript. OTI, BK, and AR are the

guarantors, and confirm all authors had full access to all data, and assume final responsibility for the decision to submit the manuscript for publication.

Funding Statement and Role of the Sponsor

This study was sponsored by Pfizer Inc. Authors employed by Pfizer were involved in the study design, collection, interpretation, and analysis of data, and in the preparation of the manuscript. The MRC Unit The Gambia receives core funding from the UK Medical Research Council for generic support, including clinical trials activities.

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Tables

Table 1. Demographic Characteristics of the Population Evaluable for Immunogenicity

Characteristics	Vaccine Group (as Randomized) PCV13 MDV N[a]=245	PCV13 SDS N[a]=244	Total N[a]=489
Sex, n (%)			
Female	127 (51.8)	128 (52.5)	255 (52.1)
Male	118 (48.2)	116 (47.5)	234 (47.9)
Race, n (%)			
Black	245 (100.0)	244 (100.0)	489 (100.0)
Ethnic Group, n (%)			
Mandinka	112 (45.7)	110 (45.1)	222 (45.4)
Jola	42 (17.1)	47 (19.3)	89 (18.2)
Fula	35 (14.3)	27 (11.1)	62 (12.7)
Wolof	30 (12.2)	25 (10.2)	55 (11.2)
Sarahule	8 (3.3)	11 (4.5)	19 (3.9)
Other	18 (7.3)	24 (9.8)	42 (8.6)
Age at enrollment, days			
Mean (SD)	57.2 (8.6)	56.8 (8.7)	57.0 (8.7)
Median	58.0	56.0	57.0
Min, Max	43.0, 71.0	43.0, 71.0	43.0, 71.0
Weight, kg			
Mean (SD)	5.0 (0.7)	4.9 (0.7)	4.9 (0.7)
Median	4.9	4.8	4.8
Min, max	3.5, 7.8	3.5, 6.7	3.5, 7.8

PCV13 MDV=13-valent pneumococcal conjugate vaccine formulated with 2-PE in multidose vials; PCV13 SDS= 13-valent pneumococcal conjugate vaccine formulated without 2-PE in single-dose syringes.

[a]Number of participants in the vaccine group, or total sample. These values are used as denominators for percentages.

Table 2. Participants Achieving a Pneumococcal IgG Antibody Concentration ≥0.35 µg/mL 1 Month After Dose 3 (Evaluable Immunogenicity Population)

	Vaccine Group (as Randomized)									
	PCV13 MDV				PCV13 SDS					
Serotype	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	Difference[d]	(97.5% CI[e])
1	245	243	99.2	(97.1, 99.9)	244	244	100.0	(98.5, 100.0)	−0.8	(–3.4, 1.2)
3	245	242	98.8	(96.5, 99.7)	243	242	99.6	(97.7, 100.0)	−0.8	(–3.7, 1.6)
4	245	244	99.6	(97.7, 100.0)	244	243	99.6	(97.7, 100.0)	0.0	(–2.3, 2.4)
5	245	235	95.9	(92.6, 98.0)	244	237	97.1	(94.2, 98.8)	−1.2	(–5.4, 2.8)
6A	243	234	96.3	(93.1, 98.3)	244	238	97.5	(94.7, 99.1)	−1.2	(–5.3, 2.6)
6B	245	233	95.1	(91.6, 97.4)	244	232	95.1	(91.6, 97.4)	0.0	(–4.7, 4.7)
7F	245	244	99.6	(97.7, 100.0)	244	244	100.0	(98.5, 100.0)	−0.4	(–2.7, 1.6)
9V	245	240	98.0	(95.3, 99.3)	244	240	98.4	(95.9, 99.6)	−0.4	(–3.8, 2.8)
14	245	239	97.6	(94.7, 99.1)	244	240	98.4	(95.9, 99.6)	−0.8	(–4.3, 2.5)
18C	245	243	99.2	(97.1, 99.9)	244	239	98.0	(95.3, 99.3)	1.2	(–1.6, 4.5)
19A	245	244	99.6	(97.7, 100.0)	244	241	98.8	(96.4, 99.7)	0.8	(–1.6, 3.6)
19F	245	237	96.7	(93.7, 98.6)	244	237	97.1	(94.2, 98.8)	−0.4	(–4.4, 3.5)
23F	245	235	95.9	(92.6, 98.0)	244	234	95.9	(92.6, 98.0)	0.0	(–4.3, 4.4)

IgG=immunoglobulin G; PCV13 MDV=13-valent pneumococcal conjugate vaccine formulated with 2-PE in multidose vials; PCV13 SDS= 13-valent pneumococcal conjugate vaccine formulated without 2-PE in single-dose syringes.

[a]Number of participants with a valid and determinate IgG concentration to the given serotype.

[b]Number of participants with an antibody concentration ≥0.35 µg/mL for the given serotype.

[c]Exact 2-sided confidence interval (Clopper and Pearson) based on the observed proportion of participants.

[d]Difference in proportions, PCV13 MDV−PCV13 SDS, expressed as a percentage.

[e]Exact 2-sided CI (based on Chan and Zhang [30]) for the difference in proportions, PCV13 MDV−PCV13 SDS, expressed as a percentage.

Table 3. Comparison of Pneumococcal IgG GMCs (µg/mL) 1 Month After Dose 3 (Evaluable Immunogenicity Population)

	Vaccine Group (as Randomized)							
	PCV13 MDV			PCV13 SDS				
Serotype	n[a]	GMC[b]	(95% CI[c])	n[a]	GMC[b]	(95% CI[c])	Ratio[d]	(97.5% CI[e])
1	245	4.59	(4.11, 5.12)	244	4.45	(4.01, 4.93)	1.03	(0.87, 1.22)
3	245	1.38	(1.29, 1.49)	243	1.74	(1.62, 1.87)	0.79	(0.71, 0.90)
4	245	5.30	(4.84, 5.81)	244	5.28	(4.76, 5.85)	1.00	(0.86, 1.18)
5	245	2.00	(1.79, 2.22)	244	1.98	(1.79, 2.20)	1.01	(0.85, 1.19)
6A	243	2.25	(2.02, 2.50)	244	2.19	(1.96, 2.44)	1.03	(0.86, 1.22)
6B	245	3.42	(2.91, 4.02)	244	3.24	(2.77, 3.78)	1.06	(0.82, 1.36)
7F	245	3.92	(3.59, 4.27)	244	4.18	(3.83, 4.55)	0.94	(0.82, 1.08)
9V	245	2.83	(2.56, 3.13)	244	2.75	(2.49, 3.04)	1.03	(0.87, 1.21)
14	245	4.78	(4.06, 5.63)	244	4.96	(4.27, 5.77)	0.96	(0.75, 1.24)
18C	245	3.47	(3.17, 3.79)	244	2.72	(2.46, 3.00)	1.28	(1.09, 1.49)
19A	245	6.49	(5.70, 7.38)	244	6.44	(5.66, 7.32)	1.01	(0.82, 1.24)
19F	245	5.19	(4.59, 5.86)	244	5.00	(4.43, 5.63)	1.04	(0.85, 1.26)
23F	245	2.61	(2.30, 2.97)	244	2.17	(1.92, 2.46)	1.20	(0.98, 1.48)

GMC=geometric mean concentration; IgG=immunoglobulin G; PCV13 MDV=13-valent pneumococcal conjugate vaccine formulated with 2-PE in multidose vials; PCV13 SDS= 13-valent pneumococcal conjugate vaccine formulated without 2-PE in single-dose syringes.

[a]Number of participants with a valid and determinate antibody concentration for the specified serotype.

[b]GMCs were calculated using all participants with available data for the specified blood draw.

[c]CIs are back transformations of a CI based on the Student *t* distribution for the mean logarithm of the concentrations.

[d]Ratio of GMCs, PCV13 MDV to PCV13 SDS, was calculated by back transforming the mean difference between the vaccine groups on the logarithmic scale.

[e]CIs for the ratio are back transformations of a CI based on the Student *t* distribution for the mean difference of the logarithms of the measures (PCV13 MDV–PCV13 SDS).

Table 4. Comparison of Pneumococcal OPA GMTs 1 Month After Dose 3 (Evaluable Immunogenicity Population)[a]

	Vaccine Group (as Randomized)							
	PCV13 MDV			PCV13 SDS				
Serotype	n[b]	GMT[c]	(95% CI[d])	n[b]	GMT[c]	(95% CI[d])	Ratio[e]	(95% CI[f])
1	159	48	(39.0, 58.0)	160	52	(43.2, 62.6)	0.9	(0.70, 1.20)
3	160	97	(87.3, 108.8)	160	122	(110.1, 135.7)	0.8	(0.69, 0.93)
4	159	1666	(1412.3, 1966.3)	159	1492	(1285.2, 1732.3)	1.1	(0.89, 1.39)
5	160	79	(67.7, 92.4)	159	80	(69.1, 92.6)	1.0	(0.80, 1.22)
6A	160	1690	(1460.5, 1955.9)	160	1968	(1698.5, 2279.3)	0.9	(0.70, 1.06)
6B	156	1990	(1611.7, 2456.9)	155	2014	(1639.1, 2475.4)	1.0	(0.74, 1.33)
7F	159	2891	(2565.4, 3258.5)	160	3450	(3014.7, 3947.9)	0.8	(0.70, 1.00)
9V	158	709	(600.5, 836.2)	160	706	(597.0, 835.3)	1.0	(0.79, 1.27)
14	157	567	(415.4, 773.5)	160	786	(607.8, 1015.3)	0.7	(0.48, 1.08)
18C	159	2792	(2387.5, 3264.8)	160	1605	(1352.0, 1904.4)	1.7	(1.38, 2.19)
19A	160	305	(256.2, 362.9)	160	329	(284.8, 379.8)	0.9	(0.74, 1.16)
19F	158	430	(357.6, 517.1)	159	470	(391.4, 565.3)	0.9	(0.71, 1.18)
23F	159	918	(729.0, 1156.4)	160	998	(810.6, 1229.6)	0.9	(0.67, 1.25)

GMT=geometric mean titer; OPA=opsonophagocytic activity; PCV13 MDV=13-valent pneumococcal conjugate vaccine formulated with 2-PE in multidose vials; PCV13 SDS=13-valent pneumococcal conjugate vaccine formulated without 2-PE in single-dose syringes.

[a]OPA assays were performed on the blood sample taken 1 month after dose 3 in a subset of randomly selected participants from each group.

[b]Number of participants with a valid and determinate antibody titer for the specified serotype.

[c]GMTs were calculated using all participants with available data for the specified blood draw.

[d]CIs are back transformations of a CI based on the Student *t* distribution for the mean logarithm of the titers.

[e]Ratio of GMTs, PCV13 MDV to PCV13 SDS, was calculated by back transforming the mean difference between the vaccine groups on the logarithmic scale.

[f]CIs for the ratio are back transformations of a CI based on the Student *t* distribution for the mean difference of the logarithms of the measures (PCV13 MDV–PCV13 SDS).

524 **Table 5. Subjects Reporting Local Reactions, Systemic Events, and Antipyretic Medication Use on Days 2–6**

Condition Reported	Dose 1		Dose 2		Dose 3	
	PCV13 MDV % (n[a]/N[b])	PCV13 SDS % (n[a]/N[b])	PCV13 MDV % (n[a]/N[b])	PCV13 SDS % (n[a]/N[b])	PCV13 MDV % (n[a]/N[b])	PCV13 SDS % (n[a]/N[b])
Local Reaction						
Tenderness[c]						
Any	16.9 (42/248)	18.8 (47/250)	13.7 (34/248)	13.0 (32/247)	15.0 (37/246)	14.5 (35/241)
Mild	12.9 (32/248)	14.8 (37/250)	10.9 (27/248)	11.3 (28/247)	12.2 (30/246)	13.3 (32/241)
Moderate	5.2 (13/248)	5.6 (14/250)	2.8 (7/247)	2.0 (5/247)	3.7 (9/246)	1.7 (2/241)
Severe	0.0 (0/248)	0.0 (0/250)	0.0 (0/247)	0.0 (0/247)	0.0 (0/246)	0.0 (0/241)
Swelling[d]						
Any	0.4 (1/248)	0.0 (0/250)	0.8 (2/247)	0.0 (0/247)	0.0 (0/246)	0.0 (0/241)
Mild	0.4 (1/248)	0.0 (0/250)	0.8 (2/247)	0.0 (0/247)	0.0 (0/246)	0.0 (0/241)
Moderate	0.0 (0/248)	0.0 (0/250)	0.4 (1/247)	0.0 (0/247)	0.0 (0/246)	0.0 (0/241)
Severe	0.0 (0/248)	0.0 (0/250)	0.0 (0/247)	0.0 (0/247)	0.0 (0/246)	0.0 (0/241)
Redness[d]						
Any	0.4 (1/248)	0.0 (0/250)	0.8 (2/247)	0.0 (0/247)	0.0 (0/246)	0.0 (0/241)
Mild	0.4 (1/248)	0.0 (0/250)	0.8 (2/247)	0.0 (0/247)	0.0 (0/246)	0.0 (0/241)
Moderate	0.0 (0/248)	0.0 (0/250)	0.0 (0/247)	0.0 (0/247)	0.0 (0/246)	0.0 (0/241)
Severe	0.0 (0/248)	0.0 (0/250)	0.0 (0/247)	0.0 (0/247)	0.0 (0/246)	0.0 (0/241)
Systemic Event						
Fever[e]						
≥38°C	3.6 (9/248)	2.8 (7/250)	2.8 (7/247)	2.8 (7/247)	1.2 (3/246)	3.3 (8/241)
≥38°C but ≤39°C	3.6 (9/248)	2.8 (7/250)	2.8 (7/247)	2.8 (7/247)	1.2 (3/246)	2.9 (7/241)
>39°C but ≤40°C	0.0 (0/248)	0.0 (0/250)	0.4 (1/247)	0.0 (0/247)	0.0 (0/246)	0.4 (1/241)
>40°C	0.0 (0/248)	0.0 (0/250)	0.0 (0/247)	0.0 (0/247)	0.0 (0/246)	0.0 (0/241)
Decreased appetite[f]						
Any	6.9 (17/248)	10.4 (26/250)	11.3 (28/247)	7.3 (18/247)	9.8 (24/246)	8.3 (20/242)
Moderate	6.9 (17/248)	10.4 (26/250)	11.3 (28/247)	7.3 (18/247)	9.8 (24/246)	7.9 (19/242)
Severe	0.0 (0/248)	0.0 (0/250)	0.0 (0/247)	0.0 (0/247)	0.0 (0/246)	0.4 (1/241)
Irritability[g]						
Any	41.4 (103/249)	37.2 (93/250)	37.5 (93/248)	33.6 (83/247)	33.7 (83/246)	37.9 (92/243)
Mild	34.5 (86/249)	30.8 (77/250)	30.2 (75/248)	27.1 (67/247)	28.9 (71/246)	30.6 (74/242)

Moderate	7.7 (19/248)	6.8 (17/250)	9.3 (23/247)	6.9 (17/247)	6.1 (15/246)	7.4 (18/242)
Severe	0.0 (0/248)	0.0 (0/250)	0.0 (0/247)	1.2 (3/247)	0.4 (1/246)	2.1 (5/241)
Increased sleep[h]						
Any	6.5 (16/248)	5.6 (14/250)	9.7 (24/247)	5.7 (14/247)	4.9 (12/246)	5.0 (12/241)
Mild	4.4 (11/248)	4.0 (10/250)	8.1 (20/247)	4.9 (12/247)	4.1 (10/246)	4.6 (11/241)
Moderate	2.4 (6/248)	1.6 (4/250)	1.6 (4/247)	0.4 (1/247)	0.8 (2/246)	0.4 (1/241)
Severe	0.0 (0/248)	0.0 (0/250)	0.0 (0/247)	0.4 (1/247)	0.4 (1/246)	0.0 (0/241)
Use of antipyretic medication	22.2 (55/248)	23.2 (58/250)	18.5 (46/248)	17.4 (43/247)	13.8 (34/246)	14.9 (36/241)

PCV13 MDV=13-valent pneumococcal conjugate vaccine formulated with 2-PE in multidose vials; PCV13 SDS=13-valent pneumococcal conjugate vaccine formulated without 2-PE in single-dose syringes.

[a]Number of subjects reporting the reaction.

[b]Number of subjects reporting yes for at least 1 day or no for all days.

[c]Tenderness was categorized as mild (hurts if gently touched), moderate (hurts if gently touched with crying), or severe (causes limitation of limb movement).

[d]Swelling and redness were measured by caliper (each caliper unit representing 0.5 cm) and categorized as mild (0.5–2.0 cm), moderate (2.1–7.0 cm) or severe (>7.0 cm).

[e]Fever severity was categorized as: 38°C–39°C, 39.1°C–40°C, and >40°C.

[f]Loss of or decreased appetite defined as moderate (decreased oral intake), or severe (refusal to feed).

[g]Irritability defined as mild (easily consolable), moderate (requiring increased attention) or severe (inconsolable, crying that cannot be comforted).

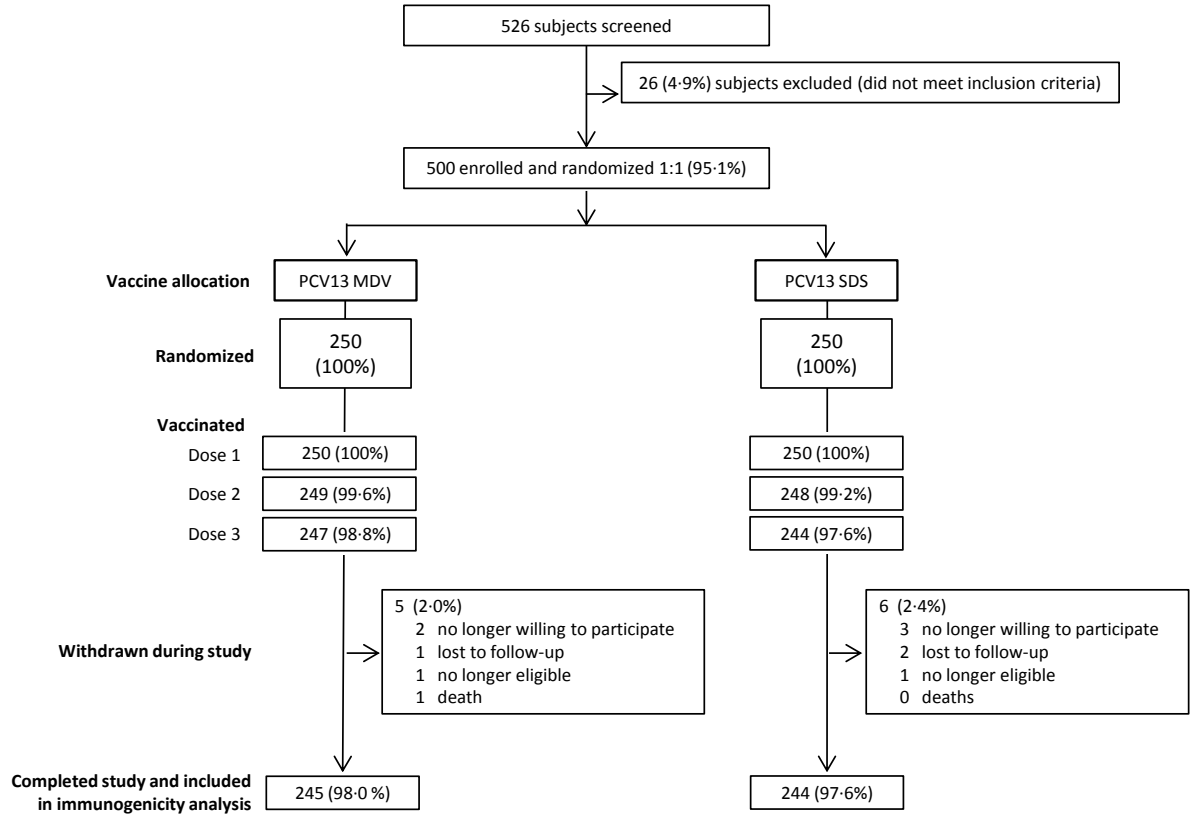
[h]Increased sleep defined as drowsiness, mild (increased or prolonged sleeping bouts), moderate (slightly subdued, interfering with daily activity) or severe (disabling, not interested in usual daily activity).

Figure Legend

Figure 1. CONSORT diagram. All 26 ineligible participants were excluded for failure to meet inclusion criteria or for meeting exclusion criteria: 14 (54%) weighed less than 3.5 kg, 5 (20%) suffered from an intercurrent illness and would have been too old for enrollment after the allowable window of 5 days after completing antibiotic therapy, 3 (11%) had underlying congenital anomalies, and 2 (7.5%) each were not available for the entire trial period, or had received previous pneumococcal vaccination.

MDV=multidose vials; PCV13=13-valent pneumococcal conjugate vaccine; SDS=single-dose syringe.

Figure 1.


526 subjects screened
26 (4·9%) subjects excluded (did not meet inclusion criteria)
500 enrolled and randomized 1:1 (95·1%)
Vaccine allocation
PCV13 MDV
PCV13 SDS
Randomized
250 (100%)
250 (100%)
Vaccinated
Dose 1
250 (100%)
250 (100%)
Dose 2
249 (99·6%)
248 (99·2%)
Dose 3
247 (98·8%)
244 (97·6%)
Withdrawn during study
5 (2·0%)
2 no longer willing to participate
1 lost to follow-up
1 no longer eligible
1 death
6 (2·4%)
3 no longer willing to participate
2 lost to follow-up
1 no longer eligible
0 deaths
Completed study and included in immunogenicity analysis
245 (98·0 %)
244 (97·6%)

Supplementary Figure 1. Reverse Cumulative Distribution Curve of Pneumococcal OPA Antibody Titers 1 Month After PCV13 Dose 3, Evaluable Immunogenicity Population.