ORIGINAL ARTICLE

Fractional Doses of Pneumococcal Conjugate Vaccine — A Noninferiority Trial

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ABSTRACT

BACKGROUND

Pneumococcal conjugate vaccines are an expensive component of the routine immunization schedule. Fractional-dose regimens may be one option to increase the sustainability of the vaccine program.

METHODS

We assessed whether the immunogenicity of fractional doses of the 10-valent and 13-valent pneumococcal conjugate vaccines (PCV10 [GSK] and PCV13 [Pfizer], respectively) would be noninferior to that of the full doses and analyzed the prevalence of vaccine-serotype carriage. We randomly assigned healthy infants in Kenya to one of seven equal-sized trial groups. Participants in groups A through F were assigned to receive either a fractional or full dose of PCV10 or PCV13, administered as two primary doses plus one booster dose. In group A, participants received a full dose of PCV13; group B, a 40% dose of PCV13; group C, a 20% dose of PCV13; group D, a full dose of PCV10; group E, a 40% dose of PCV10; and group F, a 20% dose of PCV10. Participants in the seventh group (group G) received a full dose of PCV10 as three primary doses without a booster. Immunogenicity was assessed 4 weeks after the primary series of doses and 4 weeks after the booster dose. Noninferiority could be declared 4 weeks after the primary series if the difference in the percentage of participants with a threshold response was not more than 10% and 4 weeks after administration of the booster if the ratio of the geometric mean concentration (GMC) of IgG was more than 0.5. A vaccine dose was prespecified as noninferior if it met the noninferiority criterion for at least 8 of the 10 vaccine types in the PCV10 groups or at least 10 of the 13 vaccine types in the PCV13 groups. Carriage was assessed when participants were 9 months and 18 months of age.

RESULTS

In the per-protocol analysis, 40% of a full dose of PCV13 met the noninferiority criterion for 12 of 13 serotypes after the primary series and for 13 of 13 serotypes after the booster. The immunogenicity of the 20% dose of PCV13 and of the 40% and 20% doses of PCV10 was not noninferior to that of the full doses. Vaccine serotype-type carriage prevalence was similar across the PCV13 groups at 9 months and 18 months of age.

CONCLUSIONS

In a three-dose schedule (two primary doses and a booster), 40% doses of PCV13 were noninferior to full doses for all included serotypes. Lower doses of PCV13 and PCV10 did not meet the criteria for noninferiority. (Funded by the Bill and Melinda Gates Foundation and others; ClinicalTrials.gov number, NCT03489018; Pan African Clinical Trial Registry number, PACTR202104717648755.)

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Pneumococcal conjugate vaccines have proved to be highly effective in reducing vaccine-type pneumococcal disease.[1-3] Since 2010, Gavi, the Vaccine Alliance, has funded introduction of pneumococcal conjugate vaccines in 47 low- and lower-middle-income countries. However, even at a subsidized cost of $2.00 to $3.30 per dose (in U.S. dollars), the pneumococcal vaccine program is the most expensive component of the routine immunization schedule in many of these countries.[4] The World Health Organization (WHO) recommends the administration of a primary series of doses when infants are 6 to 8 weeks, 10 to 12 weeks, and 14 to 20 weeks of age (a three prime–no booster schedule), or two primary doses at 6 to 8 weeks and 14 to 16 weeks of age with a booster at least 6 months after the second dose (a two prime–one booster schedule).[5] The sustainability of the pneumococcal vaccine program is in question in countries that are transitioning out of Gavi support and taking on the full cost of procuring the vaccine. Furthermore, for middle-income countries that are ineligible for Gavi support, a reduction in the cost of the pneumococcal conjugate vaccine may enable vaccine introduction in areas where it is currently unaffordable.

Fractional doses of antigen have been shown to induce immune responses that are noninferior to full doses in trials of vaccines against *Haemophilus influenzae* type b,[6-10] *Neisseria meningitidis*,[11] yellow fever,[12-15] and polio.[16-20] A systematic review[21] identified one early trial of a pentavalent pneumococcal conjugate vaccine that showed serotype-specific immune responses that reached the threshold of protection (≥0.35 μg per milliliter; established after later efficacy trials) after a dose of just 0.5 μg of antigen, without an adjuvant. This dose equates to 23% of the current dose in the 13-valent pneumococcal conjugate vaccine (PCV13 [Prevnar13]), produced by Pfizer, and 50% of the dose in the 10-valent pneumococcal conjugate vaccine (PCV10 [Synflorix]), produced by GSK (Table 1),[22] although the two vaccines have different carrier proteins and conjugation methods.[23,24]

We aimed to assess whether the serotype-specific immunogenicity of fractional doses (20% or 40%) of PCV10 or PCV13, administered in the two prime–one booster schedule, would be noninferior to the immunogenicity of full doses. In

Table 1. Available Vaccine Formulations and Proposed Fractional Doses of PCV10 and PCV13.*

Serotype	PCV13, Full Dose	PCV13, 40% Dose	PCV13, 20% Dose	PCV10, Full Dose	PCV10, 40% Dose	PCV10, 20% Dose
	serotype-specific saccharide dose (μg)					
1	2.20	0.88	0.44	1.00	0.40	0.20
3	2.20	0.88	0.44	—	—	—
4	2.20	0.88	0.44	3.00	1.20	0.60
5	2.20	0.88	0.44	1.00	0.40	0.20
6A	2.20	0.88	0.44	—	—	—
6B	4.40	1.76	0.88	1.00	0.40	0.20
7F	2.20	0.88	0.44	1.00	0.40	0.20
9V	2.20	0.88	0.44	1.00	0.40	0.20
14	2.20	0.88	0.44	1.00	0.40	0.20
18C	2.20	0.88	0.44	3.00	1.20	0.60
19A	2.20	0.88	0.44	—	—	—
19F	2.20	0.88	0.44	3.00	1.20	0.60
23F	2.20	0.88	0.44	1.00	0.40	0.20

* The pneumococcal conjugate vaccines that were studied were the PCV10 (GSK) and PCV13 (Pfizer). The saccharide in PCV10 is conjugated to nontypable *Haemophilus influenzae* protein D, tetanus toxoid (ST18C), or diphtheria toxin (ST19F). The saccharide in PCV13 is conjugated to CRM197 carrier protein.

addition, we planned to assess the prevalence of vaccine-serotype carriage.

METHODS

TRIAL DESIGN AND PARTICIPANTS

In this randomized trial, we evaluated infants at nine health facilities in Kilifi and Mombasa counties in Kenya. PCV10, in a three prime–no booster schedule, was introduced as part of the Kenyan Expanded Program on Immunization in 2011. In 2017, among children 12 to 23 months of age, coverage of the third dose was 89%.[25] In 2016, there were 3.2 cases of vaccine-type invasive pneumococcal disease per 100,000 person-years in children younger than 5 years of age.[2]

In anticipation of a potential change in the immunization schedule, we designed the trial to deliver pneumococcal conjugate vaccine in a two prime–one booster schedule, with the two primary doses administered when infants were 6 weeks and 14 weeks of age and the booster dose administered with the first dose of the measles vaccine when infants were 9 months of age. Coverage for the first dose of the measles vaccine was approximately 78% in 2017.[26] Healthy infants were randomly assigned to one of seven trial groups when they were 6 to 8 weeks of age and received follow-up until 18 months of age. Six trial groups received the pneumococcal conjugate vaccine in a two prime–one booster schedule; in group A, participants received a full dose of PCV13; group B, a 40% dose of PCV13; group C, a 20% dose of PCV13; group D, a full dose of PCV10; group E, a 40% dose of PCV10; and group F, a 20% dose of PCV10. Participants in the seventh trial group (group G) received PCV10 in a three prime–no booster schedule to bridge the findings to the existing dose and schedule in Kenya (Fig. 1). All vaccine doses were procured commercially through distributors approved by the Kenyan Pharmacy and Poisons Board, with the use of funds provided by the Gates Foundation. The details of the trial design are provided in the trial protocol available (with the statistical analysis plan) with the full text of this article at NEJM.org.

TRIAL PROCEDURES

Community health volunteers identified households with newborn infants and invited the caregivers to the health facility to receive information about the trial. We recruited any healthy infant (i.e., an infant with no acute febrile illness on the day of enrollment) who was 6 to 8 weeks of age and eligible for vaccination in the routine immunization program but had not yet received the first dose of pneumococcal conjugate vaccine. Infants who were older than 8 weeks of age were excluded from the trial. Less than 5% of the mothers of infants in the trial had human immunodeficiency virus (HIV) infection at the time of enrollment; infants were eligible for enrollment regardless of HIV status.

Each infant was randomly assigned with equal probability to one of the seven trial groups with the use of sequentially numbered, sealed envelopes that contained computer-generated randomization codes in block sizes of 14, which were prepared in advance by an independent statistician. Parents of participants in groups A through F were unaware of the group assignments. Other than the team administering the vaccine, all other trial personnel were also unaware of the group assignments until the end of the trial. Blinding of the regimen for group G was not possible. A research nurse prepared PCV10 or PCV13 at a dose of 0.5 ml as a full dose, 0.2 ml as a 40% dose, or 0.1 ml as a 20% dose and administered the vaccine intramuscularly in the right anterolateral thigh muscle with a syringe that had the contents masked. Participants received other immunizations according to the routine schedule.

The first dose of the primary series was administered at the time of enrollment (visit 1), with the second and third doses administered approximately 28 days (visit 2) and 56 days (visit 3) later, according to the infant's assigned schedule. Four weeks after visit 3, when the infants were approximately 18 weeks of age, a blood sample was obtained from all infants. At approximately 9 months of age (visit 5), a single nasopharyngeal swab specimen was obtained from all participants, and infants in groups A through F received a third, booster dose of PCV10 or PCV13. Four weeks after the administration of the booster dose (visit 6), a blood sample was obtained from all participants in groups A through F. Finally, at approximately 18 months of age (visit 7), a nasopharyngeal swab specimen was obtained from all participants. A member of the trial team, who was unaware of the group assignments, assessed each participant

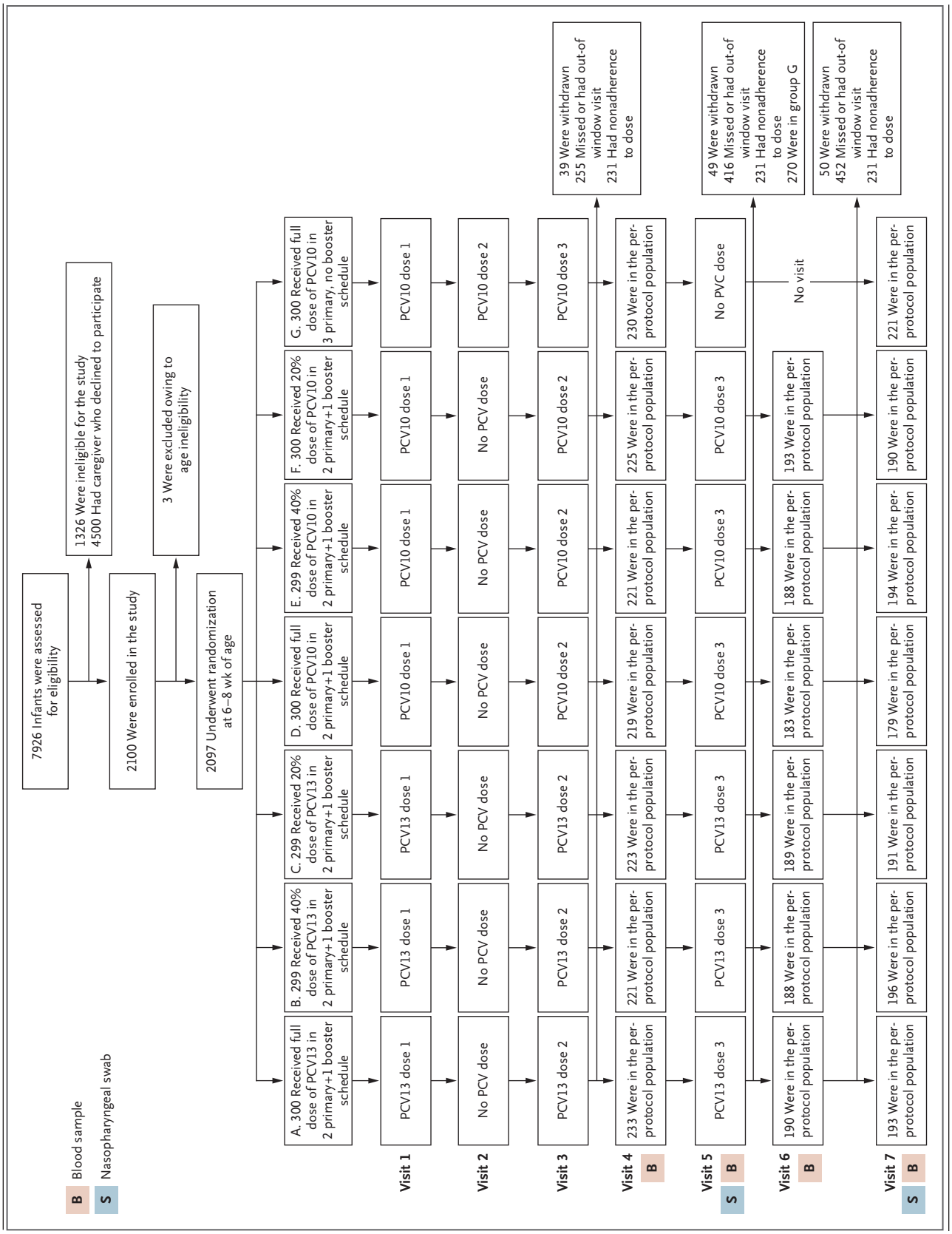

Figure 1 (facing page). Screening, Enrollment, Randomization, Administration of Vaccine, and Follow-up.

Withdrawals from the trial include withdrawals initiated by parents or investigators, deaths, and ineligibility for the trial determined after randomization. Participants who missed visits or had out-of-window visits include participants who had missed or out-of-window vaccination or sampling visits and those whose samples were missing owing to failed venipuncture. Visit 4 and visit 6 had to occur 28 days after the last pneumococcal conjugate vaccine (PCV) dose. Nonadherence refers to infants who received full doses outside the trial activities (predominantly during the pause in research activities during the Covid-19 pandemic) and 13 errors related to randomization and vaccination. Half the participants in groups A through F were randomly assigned to provide blood samples at visits 4 and 6, and the other half were assigned to provide samples at visits 4, 5, 6, and 7. Visit 1 occurred on day 0, visit 2 occurred on day 28 (±7 days), visit 3 occurred on day 56 (±7 days), visit 4 occurred 28 days after visit 3 (±7 days), visit 5 occurred on day 228 (+3 months or –2 weeks), visit 6 occurred 28 days after visit 5 (±7 days), and visit 7 occurred on day 502 (±14 days).

7 days after the administration of each dose for injection-site abscesses.

Adverse events and serious adverse events were defined in accordance with the International Council on Harmonisation Good Clinical Practice guidelines. Adverse events were treated by the trial nurses stationed at each facility, who were aware of the group assignments. All serious adverse events were treated by a trial clinician at the hospital.

TRIAL OVERSIGHT

Approvals were obtained from the Kenyan Medical Research Institute Scientific and Ethics Review Unit and the London School of Hygiene and Tropical Medicine ethics committee. Written informed consent was obtained from at least one caregiver of all the infants who were enrolled in the trial. An independent data and safety monitoring committee provided trial oversight. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

LABORATORY METHODS

A maximum of 2 ml of whole blood was obtained by means of venipuncture and transported to the Kenya Medical Research Institute (KEMRI)–Wellcome Trust Research Programme (KWTRP) laboratory at a temperature of 2 to 8°C; serum was separated within 48 hours after arrival at the laboratory. Serologic analysis was conducted at the WHO reference laboratory for pneumococcal serology at the Great Ormond Street Institute of Child Health, University College London. Serum samples were tested for IgG to vaccine-type capsular polysaccharides by means of an enzyme-linked immunosorbent assay. In addition, a subgroup of 50 randomly selected samples that were obtained 1 month after the administration of the booster were tested for functional antibody with the use of the multiplexed opsonophagocytic killing assay.[27] Samples were analyzed for IgG to all vaccine serotypes, except for the samples from the routine immunization group (full dose of PCV10 in the three primary–no booster schedule), which were assayed for seven vaccine serotypes because of funding constraints.

Single nasopharyngeal swabs, obtained when participants were 9 months and 18 months of age, were placed in 1 ml of transport medium (skim milk, tryptone, glucose, and glycerin) and sent to the KWTRP laboratory for processing with standard methods.[28,29] A primary culture was prepared on blood agar with gentamicin, and one colony on the plate was selected at random for serotyping by means of latex agglutination and confirmatory Quellung reaction. A polymerase-chain-reaction (PCR) assay was performed for quality-control purposes on 10% of the samples and as a confirmatory test for samples that had ambiguous or negative Quellung tests. Vaccine-serotype carriage was defined as the identification of a vaccine serotype by means of latex agglutination and confirmatory Quellung reaction.[29]

STATISTICAL ANALYSIS

The statistical analysis plan prespecified that noninferiority would be determined with the use of the lower limit of a one-sided 95% confidence interval (i.e., the equivalent of a two-sided 90% confidence interval). The analyses presented here use more-stringent two-sided 95% confidence intervals to be consistent with the noninferiority analyses of the immunogenicity of PCV13 used in licensure studies.[30,31] In all the fractional and full-dose groups, noninferiority could be declared 4 weeks after the administration of the booster dose if the lower limit of the 95% confidence interval for the ratio (fractional doses:full

doses) of the geometric mean concentration (GMC) of IgG was more than 0.5. At 4 weeks after the primary series, when participants were approximately 18 weeks of age, infants were considered to have had a protective response if the serotype-specific IgG antibody concentration was at least 0.35 μg per milliliter[32]; noninferiority could be declared if the lower limit of the 95% confidence interval for the difference in the percentage of participants with a response (fractional-dose group vs. full-dose group) was more than –10%.[30] A vaccine dose was prespecified as noninferior if it met the noninferiority criterion for at least 8 of the 10 vaccine types in the PCV10 groups or at least 10 of the 13 vaccine types in the PCV13 groups.

Analyses were restricted to the per-protocol population, which comprised participants who underwent randomization in groups A through G, had completed their assigned schedule with their assigned vaccine dose, and had at least one blood sample obtained within the specified window (±7 days for immunogenicity analyses) or at least one carriage sample obtained within the specified window (±7 days for carriage analyses). For the noninferiority analyses of immunogenicity, the widths of the confidence intervals have not been adjusted for multiplicity and should not be used in place of hypothesis testing. For the secondary analysis of carriage, the widths of the confidence intervals around the risk differences have not been adjusted for multiplicity and should not be used in place of hypothesis testing.

The required sample size for the trial was calculated to ensure sufficient power for the noninferiority analyses at two time points: after the administration of the primary series and after the administration of the booster.[33] In order to declare noninferiority after the primary series with 90% power, we estimated that we would need to enroll 300 infants per group, assuming serotype-specific response rates that were based on previous literature[34-38] and a 5% loss to follow-up. This sample size would provide the trial with more than 99% power to declare noninferiority in the postbooster analyses, with the assumption that the GMCs would be similar to those that have been reported in South African children.[38]

RESULTS

TRIAL POPULATION

From March 2019 through November 2021, a total of 2100 infants were enrolled in the trial; 673 of the 2100 participants (32%) had been enrolled by March 2020, at which point trial activities were paused until October 2020 because of the coronavirus disease 2019 (Covid-19) pandemic; 1427 infants were enrolled from October 2020 through November 2021 (Fig. 1). Owing to the disruption of follow-up in 2020, a total of 1572 of the 2100 participants (75%) were included in the per-protocol analysis at 18 weeks of age. For the postbooster immunogenicity analysis, 1131 of the 1797 participants (63%) who were assigned to the two prime–one booster schedules were included in the per-protocol analysis (Tables S1A and S1B in the Supplementary Appendix, available at NEJM.org). For the carriage prevalence analyses, 1439 participants (69%) were included in the per-protocol analysis at 9 months of age and 1364 (65%) at 18 months of age (Tables S1C and S1D). The characteristics of the participants in the per-protocol analysis with respect to sex, HIV exposure (maternal HIV status), infant weight at enrollment, breast-feeding status at 10 months of age, and the timing of their booster dose were balanced across the groups (Table S2). The distribution of infants according to sex and ethnic group in the per-protocol population at 10 months of age was representative of the Kilifi population[25,39] (Table S2E).

IMMUNOGENICITY AFTER THE PRIMARY SERIES

As compared with two full doses of PCV13, two doses of PCV13 at 40% of the full dose met the noninferiority criterion for 12 of 13 serotypes, exceeding the prespecified 10 of 13 serotypes required to establish noninferiority; the 20% dose of PCV13 was noninferior for only 7 of 13 serotypes. The 40% and 20% doses of PCV10 were both noninferior to two full doses of PCV10 for 7 of 10 serotypes, which did not meet the prespecified 8 of 10 serotypes required to establish noninferiority (Fig. 2). In addition, a primary series of two full doses of PCV10 was noninferior to a primary series of three full doses of PCV10 for 6 of the 7 serotypes assayed (Table S3).

IMMUNOGENICITY AFTER THE BOOSTER DOSE

Among participants assigned to receive PCV13 in a two prime–one booster schedule, 40% of a full dose met the noninferiority criterion for 13 of 13 serotypes after the booster dose, exceeding the prespecified 10 of 13 serotypes required to establish noninferiority; the 20% dose was noninferior for 6 of 13 serotypes. Among participants assigned to receive PCV10 in a two prime–one booster schedule, 40% of a full dose met the noninferiority criterion for 6 of 10 serotypes after the booster dose, which did not meet the prespecified 8 of 10 serotypes required to establish noninferiority; the 20% dose was noninferior for only 1 of the 10 serotypes (Fig. 3). In the subgroup of participants who had a sample assayed for opsonophagocytic function, the proportion of samples with geometric mean titers greater than 8 was high in all groups and serotypes. Additional details on immunogenicity after the booster dose are provided in Table S4.

CARRIAGE PREVALENCE

When participants were assessed at 9 months of age, the carriage prevalence of PCV10 serotypes ranged from 4.4 to 8.6% in the seven trial groups. When assessed at 18 months of age, the PCV13-serotype carriage ranged from 16 to 19% among participants in the PCV13 groups; in the PCV10 groups on a two prime–one booster schedule, PCV10-serotype carriage ranged from 3 to 11%. At 18 months of age, 9.5% of the participants in the full-dose PCV10 group (three primes–no booster) carried PCV10 serotypes (Table 2 and Table S5).

SAFETY

No injection-site abscesses were recorded. A total of 61 cases of nonsevere pneumonia and 65 serious adverse events were recorded, which were evenly distributed across the groups (Table S6).

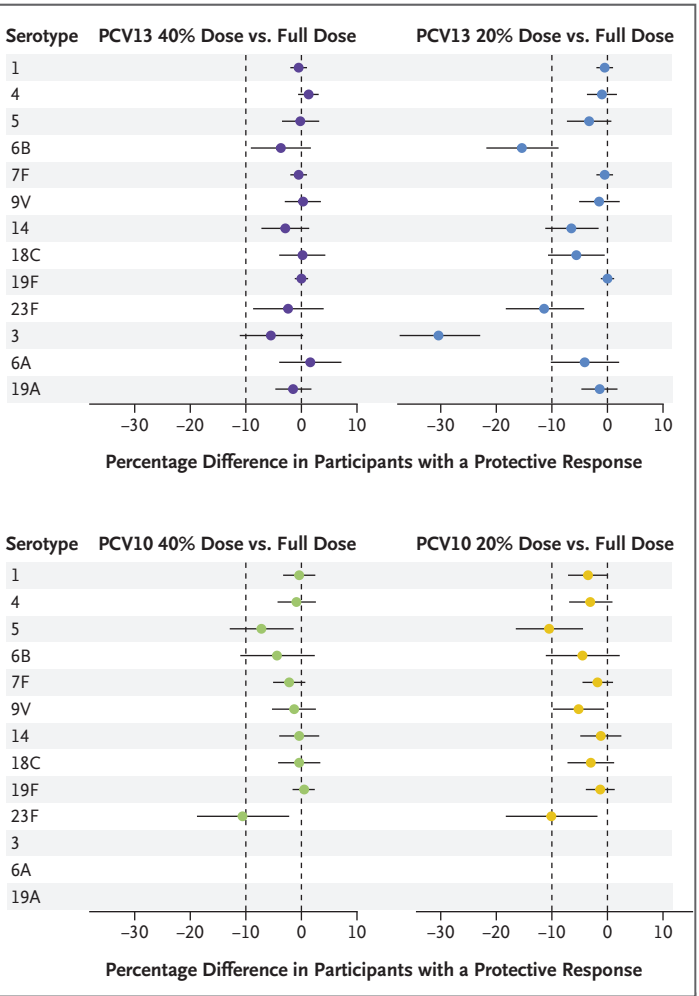

Figure 2. Difference in Percentage of Participants with a Protective Immune Response after the Primary Series.

Shown are the differences in the protective immune response at 4 weeks after completion of the primary series (when the infants were 18 weeks of age) between participants who received two fractional doses of PCV13 and those who received two full doses of PCV13, and between participants who received two fractional doses of PCV10 and those who received two full doses of PCV10. Horizontal bars indicate 95% confidence intervals (see also Table S3B in the Supplementary Appendix). The widths of confidence intervals have not been adjusted for multiplicity and should not be used in place of hypothesis testing.

DISCUSSION

In a two prime–one booster schedule, a 40% dose of PCV13 was noninferior to a full dose for IgG responses after both the primary series and the booster dose at peak immune-response time points. However, when PCV13 was administered in lower doses (20% of a full dose), the immunogenicity was not noninferior to a full dose. Prevalence of vaccine-serotype carriage was similar across the PCV13 groups when the participants were 9 and 18 months of age. The per-protocol populations for the noninferiority analyses were smaller than planned, which most likely reduced the precision with which we could estimate the ratios of the proportion of participants with a

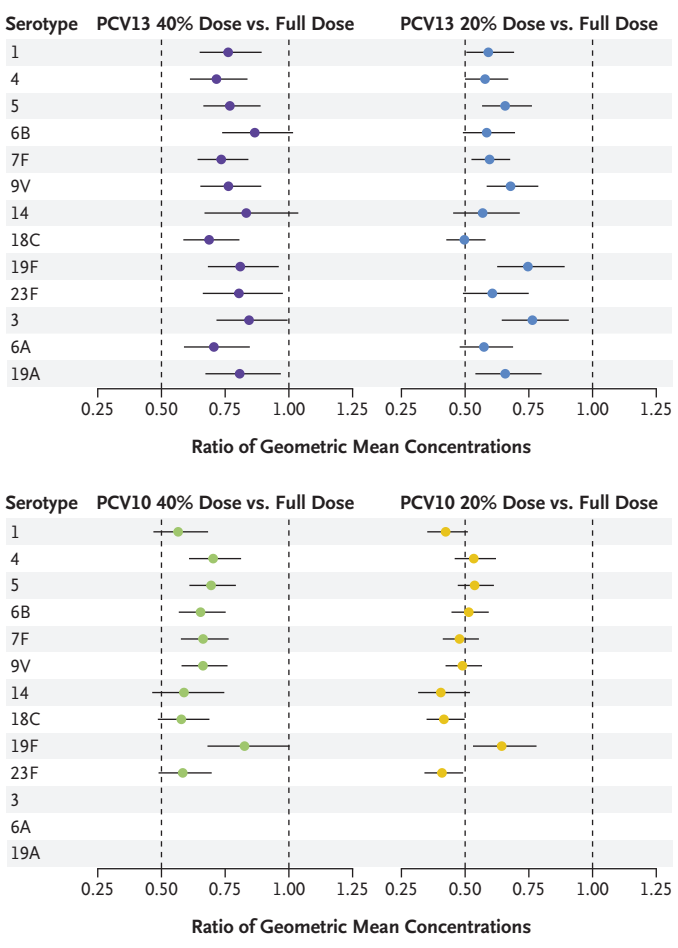

Figure 3. Ratio (Fractional Dose:Full Dose) of Geometric Mean Concentrations of IgG after the Booster.

The booster was administered when the infants were approximately 9 months of age; the immunogenicity assessment was performed 4 weeks later, when the infants were approximately 10 months of age. Horizontal bars indicate 95% confidence intervals (see also Table S4B). The widths of confidence intervals have not been adjusted for multiplicity and should not be used in place of hypothesis testing.

response and of GMCs. The 20% dose of PCV13 narrowly missed meeting the noninferiority criteria for some serotypes.

Fractional dose schedules of PCV10 failed to meet noninferiority criteria for immunogenicity and showed higher vaccine-serotype carriage prevalence at 18 months of age than the full-dose schedule. These results align with a dose–response relationship across products: full-dose PCV13, full-dose PCV10, and a 40% dose of PCV13 contain at least 0.88 μg of saccharide, whereas the 20% dose of PCV13 and the 40% and 20% doses of PCV10 contain less than 0.88 μg (Table 1). When administered in a schedule of two full primary doses, the immunogenicity of PCV10 was noninferior to three full primary doses of PCV10 among 6 of the 7 serotype-specific responses that were assayed (all except ST23F) at 18 weeks of age. A lower vaccine-serotype carriage prevalence was observed at 18 months of age in participants assigned to the two prime–one booster schedule than in those assigned to the three prime–no booster schedule.

The government of Kenya has announced that it aims to fully finance its routine immunization program by 2030. In 2022, the country switched from the PCV10 produced by GSK ($3.05 per dose [in U.S. dollars]) to a lower-cost alternative ($2.00 per dose) produced by Serum Institute of India (SII). The off-label use of a three-dose schedule of a 40% dose of PCV13 ($1.10 per dose) represents a more affordable option that could reduce the annual cost of purchasing the vaccine, from $9 million to $5 million (at the current costs, assuming no vaccine wastage) for an annual birth cohort of 1.5 million children. In addition, 4-dose vials of PCV13 contain a preservative that enables multidose vials to be used for up to 28 days after the first puncture. It would be feasible, therefore, to implement a 40%-dose policy immediately by reclassifying the present 4-dose vials of PCV13 as 10-dose vials of 40% doses (0.2 ml per dose).

The doses of saccharide in the SII PCV10 are similar to those in PCV13; however, because of differences in the manufacturing processes, we cannot assume that our findings are generalizable to the SII PCV10. At the time the trial was designed, only the PCV10 produced by GSK and the PCV13 produced by Pfizer were available, so we could not evaluate fractional doses of the SII PCV10, nor could we evaluate the newer 15-valent and 20-valent pneumococcal conjugate vaccines.

We used noninferiority criteria that are used routinely in vaccine licensure studies for the evaluation of immunogenicity after the primary series and booster. However, the end points in this trial were serologic, not clinical, end points. There is some evidence that the threshold of protection against invasive pneumococcal disease varies by serotype[40] and that correlates of protection against carriage are substantially higher than those against invasive disease.[41] Whether the lower, albeit noninferior, immunogenicity of a 40% dose of PCV13 would influence protection against car-

Table 2. Carriage Prevalence at 9 and 18 Months of Age.*

Serotype	PCV13, Full Dose 2p+1 Schedule	PCV13, 40% Dose 2p+1 Schedule	PCV13, 20% Dose 2p+1 Schedule	PCV10, Full Dose 2p+1 Schedule	PCV10, 40% Dose 2p+1 Schedule	PCV10, 20% Dose 2p+1 Schedule	PCV10, Full Dose 3p+0 Schedule
				number/total number (percent)			
At 9 months of age							
PCV13 serotypes	37/207 (17.9)	49/210 (23.3)	43/206 (20.9)	49/198 (24.7)	49/203 (24.1)	61/209 (29.2)	52/206 (25.2)
PCV10 serotypes	10/207 (4.8)	16/210 (7.6)	13/206 (6.3)	10/198 (5.1)	12/203 (5.9)	18/209 (8.6)	9/206 (4.4)
3/6A/19A	27/207 (13.0)	33/210 (15.7)	30/206 (14.6)	39/198 (19.7)	37/203 (18.2)	43/209 (20.6)	43/206 (20.9)
6A/19A	20/207 (9.7)	28/210 (13.3)	25/206 (12.1)	33/198 (16.7)	26/203 (12.8)	38/209 (18.2)	35/206 (17.0)
Any serotype	174/207 (84.1)	173/210 (82.4)	168/206 (81.6)	158/198 (79.8)	167/203 (82.3)	178/209 (85.2)	173/206 (84.0)
At 18 months of age							
PCV13 serotypes	34/193 (17.6)	37/196 (18.9)	31/191 (16.2)	34/179 (19.0)	53/194 (27.3)	52/190 (27.4)	52/221 (23.5)
PCV10 serotypes	10/193 (5.2)	17/196 (8.7)	13/191 (6.8)	6/179 (3.4)	11/194 (5.7)	20/190 (10.5)	21/221 (9.5)
3/6A/19A	24/193 (12.4)	20/196 (10.2)	18/191 (9.4)	28/179 (15.6)	42/194 (21.6)	32/190 (16.8)	31/221 (14.0)
6A/19A	19/193 (9.8)	13/196 (6.6)	10/191 (5.2)	22/179 (12.3)	32/194 (16.5)	23/190 (12.1)	20/221 (9.0)
Any serotype	149/193 (77.2)	149/196 (76.0)	129/191 (67.5)	133/179 (74.3)	140/194 (72.2)	137/190 (72.1)	160/221 (72.4)

* PCV13 was administered as two primary doses plus one booster dose (the 2p+1 schedule). PCV10 was administered either in the 2p+1 schedule or as three primary doses and no booster (the 3p+0 schedule).

riage acquisition or against pneumococcal disease is unclear. We did not detect increased vaccine-serotype carriage prevalence during our trial; however, our trial population was under substantial indirect protection conferred by the high coverage of PCV10 in the routine immunization system. Furthermore, the effect of a 40% dose on the durability of immunity is unknown; follow-up over several years will reveal whether the rate of antibody waning over time will differ among the groups.

None of the participants acquired HIV infection during the trial; however, a small number of participants were exposed to the virus. The trial was not designed to determine whether infants with HIV infection would mount a protective immune response with a schedule that uses a 40% dose of PCV13. In Kenya, it is estimated that 0.9% of infants have HIV infection.[42]

In a two prime–one booster schedule, 40% doses of PCV13 generated immune responses that were noninferior to those with full doses. No difference in vaccine-type carriage prevalence was observed after full or 40% doses of PCV13. The long-term effects on the duration of immunity and carriage transmission associated with switching to a 40% PCV13 schedule are unclear, and the findings in this trial cannot be generalized to HIV-positive populations. However, an off-label, three-dose schedule with 40% doses of PCV13 is a less costly alternative to a full-dose pneumococcal vaccine program in low- and lower-middle-income countries that are transitioning out of Gavi support and in middle-income countries that are not eligible for Gavi support.

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APPENDIX

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