The antibody response following a booster with either a 10- or 13-valent pneumococcal conjugate vaccine in toddlers primed with a 13-valent pneumococcal conjugate vaccine in early infancy

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Keypoints:

A PCV-10 booster was generally less immunogenic than a PCV-13 booster in PCV-13 primed children. It may be more appropriate to give a PCV-13 booster to PCV-13 primed children although the clinical significance of these findings remains unclear.

Abstract

Background Both the 13- and 10-valent pneumococcal conjugate vaccines (PCV-13 and PCV-10) are immunogenic and effective against vaccine-type pneumococcal disease when given to young children. However, limited data are available regarding the interchangeability of these two vaccines.

Methods UK children (n=178) who had previously been vaccinated with PCV-13 at 2 and 4 months were randomized 1:1 to receive a booster of either PCV-13 or PCV-10 at 12 months of age. PCV-13 vaccine-type anti-polysaccharide serum IgG concentrations and opsonophagocytic assay (OPA) titers were measured before and at 1 and 12 months following vaccination. The primary objective was to assess non-inferiority of PCV-10 compared to PCV-13.

Results For 8 out of the PCV-10 serotypes at least 97% of participants in both groups had IgG concentrations ≥0.35 μg/ml at 1 month after vaccination; inferior responses were seen for serotypes 5 and 9V following a booster dose of PCV-10 compared with PCV-13. Post-booster geometric mean IgG concentrations and OPA titers were significantly superior for most serotypes in PCV-13 compared with PCV-10 recipients whereas similar or inferior responses were seen for serotypes 4, 18C and 19F.

Conclusions In PCV-13 primed infants, a booster dose of PCV-10 is generally less immunogenic than a PCV-13 booster. For the 3 serotypes in PCV-10 with higher antigen content and/or conjugation to a diphtheria or tetanus toxoid carrier protein, higher or similar booster responses were seen in PCV-10 and PCV13 recipients. Although these findings suggest that responses are generally better with a PCV13 booster among PCV-13 primed children, the clinical significance of these differences in immunogenicity remains unclear.

Introduction

The encapsulated bacterium *Streptococcus pneumoniae* commonly causes respiratory infections and may also cause severe infections such as meningitis and sepsis. Pneumococcal protein-polysaccharide conjugate vaccines (PCVs) were first routinely used in childhood immunization programs in children in the USA in 2000 and introduced as a 7-valent vaccine (PCV-7) into the UK infant immunization schedule in 2006, successfully reducing the burden of invasive pneumococcal disease in both countries (IPD) [1-3]. Newer PCVs with extended serotype coverage became available in 2009 including either an additional 3 (PCV-10) or 6 (PCV-13) serotypes. Both vaccines are immunogenic and effective against IPD when given to young children in a series of 3-4 vaccine doses [3-6]. Although both PCV-10 and PCV-13 share 10 serotypes, they differ substantially in the concentrations of polysaccharides, the method of conjugation, and the type and concentrations of the carrier proteins [7].

There are several potential advantages of interchanging PCVs and using PCV-10 in PCV-13 primed children. The use of a novel carrier protein such as nontypeable *Haemophilus influenzae* (NTHi)-derived protein D in PCV-10, which is not closely related to an antigen included in any concurrently or previously administered routine vaccine minimizes the risk of interference related to the carrier protein although the effect is usually seen in primary vaccination [8]. This in turn may enhance immune responses against the contained pneumococcal serotypes. In PCV-10, most serotypes are conjugated to protein D, which has the potential to induce responses that may protect children against NTHi disease through an immune response generated by the carrier protein [9, 10]. Interchanging PCVs may help to improve our understanding of vaccine immunobiology, addressing unanswered questions in relation to the interaction of conjugate vaccines with the immune system [11] and the poor booster responses with certain serotypes [7].

This study aimed to investigate the potential of an alternative booster vaccine to be given to 12-month old children who have been primed with PCV-13 in infancy. IgG concentrations and OPA titers for PCV-13 serotypes were assessed before, 1 and 12 months following the booster. The safety and reactogenicity of the 12-month booster was assessed using diary cards containing parental reports of local and systemic reactions following vaccination.

Methods

Participants, recruitment and design

The study was a randomized controlled clinical trial, which was open-labeled for participants and clinical trial staff, but blinded for laboratory staff. Ethical approval was obtained from the Oxfordshire Research Ethics Committee (reference number 11/SC/0473) and the study was registered on Clinicaltrials.gov (registration number NCT01443416). Participants were recruited primarily by information booklets mailed out via the UK National Health Application and Infrastructure Services who are responsible for the central NHS patient database. Potential study participants were healthy 12 month (range 50-58 week) old children at the time of enrolment, who were available for the entire study period and had received all primary vaccines according to the UK routine immunization schedule including 2 immunizations of PCV-13 at less than 6 months of age with a gap of at least 6 weeks between the two vaccinations. Absolute and temporary exclusion criteria are summarized in Table S1. Following written informed consent, study participants were randomly allocated to receive a booster dose at 12 months of either PCV-13 (Prevenar 13®, Pfizer) or PCV-10 (Synflorix™, GSK Biologicals).

Vaccines and interventions

Most serotypes contained in PCV-10 are conjugated individually to protein D (total dose 9-16 µg), a recombinant form of a lipoprotein of non-typeable *H. influenzae*; serotypes 18C and 19F polysaccharides are conjugated to tetanus toxoid (5-10 µg) and diphtheria toxoid (3-6 µg), respectively (Table 1). PCV-13 contains saccharides from pneumococcal serotypes 3, 6A, and 19A in addition to PCV-10 serotypes, individually conjugated to cross-reacting material (CRM_{197}, total dose of around 34 µg) (Table 1). Both vaccines (0.5 ml) were administered intramuscularly using a 0.6 x 25 mm 23 gauge needle into the anterolateral aspect of either thigh. Combined *Haemophilus influenzae* type b/group C meningococcal vaccine and measles, mumps and rubella vaccine were given at 13 months but did not form part of the study evaluation.

Laboratory measurements

Serum was separated within 24 hours at the study site and stored at -20 °C. Antibody measurements were performed at the WHO pneumococcal reference laboratory at University College London. Serum

concentrations of total anticapsular immunoglobulin G (IgG) for PCV-13 serotypes were identified by ELISA method after absorption with C polysaccharide-containing cell wall extract and 22F polysaccharide, and expressed as µg/ml. Opsonophagocytic assay (OPA) titers against PCV-13 serotypes were measured using a multiplex opsonophagocytic assay [12]. The lower limit of quantitation (LLOQ) for all serotypes as established during the validation was 0.150 µg/ml for IgG concentrations measured by ELISA and 8 for OPA titers. Values below the LLOQ were replaced with 0.075 µg/ml and 4, respectively.

Statistical analysis

Data were log-transformed prior to analysis and group summaries presented as geometric means with associated two-sided, 95% confidence intervals (CI). In addition, the geometric mean fold-rise for the serotype-specific antibody measurements was derived from the exponent of the within-person difference between the log-transformed individual assay result before and after the booster dose. The proportion of study participants achieving thresholds of 0.35 µg/ml for IgG concentrations, or 8 for OPA titers were calculated within each group and confidence intervals computed using the binomial exact method. Similar analyses were performed to calculate proportions and 95% CI for rates of local and systemic reactions. Chi-squared test (or Fisher's exact tests when expected counts were less than 5) were used to compare proportions of participants between groups. Two-sample t-tests or analysis of covariance was used to compare the continuous variables with adjustment for baseline values where appropriate. Comparisons between the two groups were carried out based on treatment allocation. Statistical analysis was performed using SAS version 9.2 (SAS Institute Inc., USA) and R [13].

Study objectives

The primary objective of this study was to assess whether PCV-10 is non-inferior to PCV-13 using proportions of participants with IgG concentrations ≥0.35 µg/ml for PCV-10 serotypes PCV-10, one month following booster vaccination at 12 months of age with PCV-10 or PCV-13. Non-inferiority of PCV-10 would be shown if the confidence interval for the difference between groups (PCV-10 – PCV-13) did not include values less than -10% (non-inferiority margin). The sample size of 84 participants in each of the vaccine groups was calculated to allow assessment of non-inferiority with a margin of 10% using 80% power and 2.5% significance level allowing for a 15% drop-out rate.

During the course of the study, blood samples for less than 85% of participants were available at 13 months of age, therefore more study participants were recruited following amendment of the protocol. The Intention to treat (ITT) population for immunogenicity consisted of all participants receiving a dose of PCV-10 or PCV-13 and providing a blood sample at age 13 months. Participants with pre-defined deviations from protocol were removed from the per-protocol (PP) population. The PP population was used for primary non-inferiority analysis, with a sensitivity analysis performed on the ITT population. All other analyses were conducted on an ITT population; secondary objectives reported here included the immunogenicity and reactogenicity of the booster. Other secondary objectives that will be reported separately were the assessment of immediate pain at time of injection of the PCV booster and the investigation of antigen-specific peripheral blood memory B cells in response to vaccination.

Results

178 children aged 11-13 months, from the Oxfordshire region, were recruited and randomized in a 1:1 ratio into 2 groups to receive one dose of either PCV-10 or PCV-13 at 12 months of age. Figure 1 shows the number of participants and their flow through the study. Baseline demographics of randomized participants are shown in Table 2.

One child was enrolled at age 11 months and 5 days, below the minimum age for inclusion, and was therefore excluded from the PP population (Figure 1), but included in the ITT population. There were a number of protocol deviations related to the timing of visits, none of which were thought to significantly affect any of the outcome measures. Hence, none of these study participants were excluded from the PP population. There were 5 serious adverse events (febrile illness, suspected meningococcal sepsis, viral gastroenteritis, viral wheeze, febrile convulsion) reported during the study none of which were considered related to study vaccines and all participants recovered.

At baseline, there were significantly higher IgG GMC seen in the PCV-10 compared with the PCV-13 group for serotypes 19F and 19A (Figure 2). For serotype-specific geometric mean OPA titers (GMT), group differences were found only for serotype 3 with a significantly higher OPA GMT in PCV-10 compared with PCV-13 recipients (Figure 3).

Non-inferiority assessment of PCV-10 as an alternative 12-month booster (PP population)

Table 3 shows the results of the primary endpoint analysis. IgG responses to serotypes 5 and 9V in the PCV-10 group were inferior to the PCV-13 group at 13 months when proportions of participants with serotype-specific IgG concentrations ≥0.35 μg/ml were compared between groups.

Short-term antibody response to a booster dose of PCV-10 compared with PCV-13 (ITT population)

One month following the booster vaccine, at least 97% of participants in each group had IgG concentrations ≥0.35 μg/ml for the serotypes they were vaccinated against with the exception of serotypes 5 and 9V in the PCV-10 group. For these 2 serotypes, which are common to both PCV-10 and PCV-13, the proportions of participants with serotype-specific IgG above the threshold were significantly higher in PCV-13 compared with PCV-10 recipients (Figure S1 & Table S2). In addition, these proportions were also higher in the PCV-13 group for 2 out of the 3 serotypes only included in PCV-13, namely serotypes 3 and 6A but not serotype 19A (Figure S1 & Table S2).

Post-booster IgG GMC were significantly higher in the PCV-13 compared with the PCV-10 group for the majority of serotypes common to both vaccines (1, 5, 6B, 7F, 9V, 14, and 23F) as well as for the serotypes only included in PCV-13 (3, 6A, and 19A) whereas GMCs were significantly higher in PCV-10 compared with PCV-13 recipients only for serotypes 4, 18C and 19F (Figure 2 & Table S4).

An analysis of covariance model that adjusted for baseline values, age, sex and ethnicity was used to investigate changes from baseline in IgG concentrations between groups. Significant increases in IgG concentrations were observed in both groups for all serotypes between 12 and 13 months of age and group differences from adjusted and unadjusted analyses were similar to differences observed in analysis of 13-month values alone (Table S6).

Serotype-specific functional antibodies were assessed by OPA for all PCV-13 serotypes. One month following the booster, at least 98% of participants had titers ≥8 and there were no observable group differences, for all PCV-10 serotypes except for serotypes 1, 5 and 9V; for these serotypes the proportion of participants with OPA titers ≥8 was higher in the PCV-13 than PCV-10 group. These proportions were also higher for all 3 serotypes (3, 6A, and 19A) only contained in PCV-13 (Table S7 & Figure S2).

Significantly higher post-booster GMT were seen in the PCV-13 than the PCV-10 group for most serotypes common to both vaccines as well as for all 3 serotypes only included in PCV-13. For

serotypes 4 and 18C there were no significant differences between the groups and for serotype 19F, the OPA response was significantly higher in the PCV-10 than the PCV-13 group (Figure 3 & Table S9).

For both study groups significant increases in OPA titers for all serotypes with the exception of serotype 3 in the PCV-10 group were seen between 12 and 13 months of age (Table S11). Analyses of change from baseline to 13 months in OPA titers with adjustment for baseline values, age, sex and ethnicity, gave similar results to unadjusted analyses of 13 month values although group differences in immunogenicity for serotypes 1 and 19F were no longer observed (Table S11).

One-year antibody persistence following a booster dose of PCV-10 compared with PCV-13 (ITT population)

Group differences in proportions above the IgG or OPA thresholds were observed for a number of serotypes at 24 months of age, i.e. 12 months following the booster. These proportions were similarly greater for both measurements for PCV-13 compared with PCV-10 recipients for serotypes 6B, 7F and 6A and lower for serotype 19F (Figures S1 and S2).

When persistence of IgG concentrations and OPA titers were assessed at 24 months of age, significant differences remained between the groups. IgG GMCs and OPA GMTs were greater in PCV-13 compared with PCV-10 recipients for serotypes 6B, 7F, 9V, and 6A whereas both measurements were significantly higher in the PCV-10 compared with the PCV-13 group for serotype 19F (Figures 2 & 3; Tables S5 & S10).

When analyses of change from baseline to 24 months adjusted for baseline antibody, age, sex and ethnicity, group differences were similar to unadjusted analyses (Tables S12 & S13) with a significant decline in serotype-specific IgG antibodies and OPA titers from 13 to 24 months for all serotypes except for OPA titers against serotype 3 in the PCV-10 group (not shown).

Reactogenicity

The reactogenicity profile of the booster vaccination was similar regardless of whether participants had received PCV-10 or PCV-13 (Table S14). Local reactions such as redness, hardness, and swelling were either absent or mild in most cases. Moderate or severe localized pain was reported by almost 13% of parents of study participants across both groups; irritability, drowsiness and decreased appetite

were recorded in 53%, 29% and 29% of participants of both groups combined, respectively (Table S15). Low-grade fever (38-39°C) was noted in 4% of participants and 4 children (2%) had a temperature of >39°C in the first 4 days following booster vaccination (Table S15). The majority of these reported adverse effects of vaccination were short-lived lasting 1-3 days (Table S16).

Discussion

This is the first study to investigate the interchangeability of PCV-10 and PCV-13 as a 12-month booster in children primed with PCV-13. A robust antibody response was induced by both vaccines at one year of age when administered to PCV-13 primed children. For the primary objective, PCV-10 was non-inferior to PCV-13 for 8 of the PCV-10 serotypes. However, there were 22% and 10% ~~less~~ fewer ~~study participants~~toddlers with IgG concentrations ≥0.35 µg/ml against serotypes 5 and 9V, respectively, in the PCV-10 than the PCV-13 group (Table 3), possibly representing a clinically relevant difference.

When post-booster serotype-specific IgG GMC and OPA GMT were considered, PCV-13 was more immunogenic for the majority of serotypes common to both vaccines. There are no published large head-to-head clinical trials comparing PCV-10 and PCV-13. In a recent small study in which children were vaccinated with either PCV-10 or PCV-13 at 2, 3, 4 and 11 months of age, serotype-specific IgG, plasma and memory B cells against serotypes 1, 6B, 7F, and 19F were investigated and compared between the groups before and 7-9 days following the booster dose [14]. This study showed statistically superior post-booster IgG responses in the PCV-13 group to one (19F) out of the 4 serotypes common to both vaccines. These findings are in contrast to our study in which responses to serotype 19F were lower in PCV-13 recipients using both IgG levels and OPA titers as read-out at 1 and 12 months following the booster. In the aforementioned study by van Westen et al., post-booster responses were measured in a considerably smaller group of children at 7-9 days rather than 1 month following vaccination, which may explain this difference.

In our study, only responses against serotypes 4, 18C, and 19F were consistently similar or statistically superior (19F) at 13 months in the PCV-10 compared with the PCV-13 group. Interestingly, these 3 serotypes are contained in PCV-10 in a higher concentration than the other serotypes (3 µg vs. 1 µg) and also compared with the same serotypes in PCV-13 (3 µg vs. 2.2 µg). In addition, PCV-10 serotypes 18C and 19F are conjugated to a non-protein D carrier protein – tetanus and diphtheria toxoid, respectively – and both these antigens are included in previously administered routine childhood vaccines. This may also partly explain the better antibody response to these two serotypes compared with other serotypes in PCV-10 recipients as priming would have already happened through

these other vaccines. Although there are no immunogenicity studies directly comparing PCV-10 with PCV-13, antibody responses to PCV-10 have previously been compared with those elicited by PCV-7 [15]. Vesikari *et al*. showed that post-booster antibody responses in participants who had exclusively received either vaccine were superior in the PCV-7 group for the majority of PCV-7 serotypes with the exception of serotypes 18C (similar) and 19F (inferior) indicating that PCV-7 is generally more immunogenic than PCV-10. In the same study, antibody responses were largely similar between the group of children who had exclusively received PCV-7 and those who had been primed with PCV-7 followed by a booster dose of PCV-10 [15]. These findings suggest that similar antibody responses can be achieved when switching from one PCV to another containing similar capsular serotypes despite a difference in carrier proteins. However, Vesikari et al. also demonstrated that there were markedly lower antibody responses to serotypes 1, 5, and 7F (not included in PCV-7) in children in the PCV-7/PCV-10 compared with the PCV-10/PCV-10 group [15] indicating that serotype-specific priming even when performed with a different vaccine and carrier protein is essential for obtaining sufficiently high booster responses. In a case-control study performed in Canada the effectiveness against all IPD caused by PCV-13 serotypes of a mixed PCV schedule consisting of 2 doses of PCV-10 followed by one dose of PCV-13 was similar to alternative schedules in which children were only vaccinated with PCV-10 or PCV-13 [4]. These findings suggest that interchanging PCVs does not *per se* result in inferior protection compared with schedules using a single type of PCV although the combination of priming with PCV-13 and boosting with PCV-10 was not assessed in this study.

For the three serotypes that are exclusive to PCV-13 (3, 6A and 19A), not only PCV-13 but also PCV-10 recipients showed an increased antibody response following booster vaccination, which may represent generation of cross-reactive antibodies through vaccination with the related serotypes 6B and 19F. Not surprisingly, the antibody responses against these 3 serotypes were greatly lower in the PCV-10 compared with the PCV-13 group (Figures 2 and 3).

In the present study, antibody persistence up to 1 year following the booster was assessed using both serotype-specific IgG antibody concentrations and OPA titers against PCV-13 serotypes. Over the 12-month period following the booster, there was a rapid decline in antibody in both groups. IgG levels and OPA titers at 24 months were largely determined by the amount of antibody detected 1 month

post-booster at 13 months of age, which has been previously demonstrated where the same PCV was used for both priming and boosting [16]. These findings suggest that boosting with a different vaccine containing the same capsular serotypes, albeit conjugated to different carrier proteins, induces an immune response that is not only driven by short-lived extrafollicular B cells but also the generation of long-lived plasma cells, a hallmark of immune memory.

Conclusions

Our study showed that a booster dose of PCV-10 at 12-month of age is generally less immunogenic than a PCV-13 booster in PCV-13 primed children. Post-booster antibody responses that were similar or superior in the PCV-10 group were seen for serotypes 4, 18C and 19F, which are contained in PCV-10 with higher antigen content and/or conjugation to a diphtheria or tetanus toxoid carrier protein. The clinical significance of the observed differences in immunogenicity remains unknown although our findings suggest that it may be more appropriate to give a PCV-13 booster to PCV-13 primed children. Further studies in children primed with PCV-10 and then boosted with PCV-13 are needed to expand our understanding and the clinical implications of interchangeable PCV schedules.

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Conflicts of interest

AJP has previously conducted studies on behalf of Oxford University funded by vaccine manufacturers, including the present study, but ~~currently does not~~no longer undertakes new ~~undertake~~ industry funded clinical trials. AJP chairs the UK Department of Health's (DH) Joint Committee on Vaccination and Immunisation (JCVI); the views expressed in this manuscript do not necessarily reflect the views of JCVI or DH.

M.D.S. acts as chief or principal investigators for clinical trials conducted by the University of Oxford, sponsored by vaccine manufacturers, but receives no personal payments from them. M.D.S. has participated in advisory boards and industry sponsored symposia for vaccine manufacturers, but receives no personal payments for this work. M.D.S. and J.T. have received financial assistance from vaccine manufacturers to attend scientific conferences. The other authors have no financial conflicts of interest.

Authorship contributions

Study concept and design: J.T., M.D.S., and A.J.P. Acquisition of data: J.T., D.G. Statistical analysis: S.J., J.T, and M.V. Interpretation of the data: J.T., M.D.S, and A.J.P. Drafting of the manuscript: J.T. Critical revision of the manuscript for important intellectual content: all authors.

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Table 1 Pneumococcal polysaccharide concentrations and serotype-specific carrier proteins contained in PCV-10 and PCV-13.

Serotype	**PCV-10*** Dose of polysaccharide (μg)	Carrier protein	**PCV-13**** Dose of polysaccharide (μg)	Carrier protein
1	1	Protein D	2.2	CRM_{197}
4	**3**	Protein D	2.2	CRM_{197}
5	1	Protein D	2.2	CRM_{197}
6B	1	Protein D	**4.4**	CRM_{197}
7F	1	Protein D	2.2	CRM_{197}
9V	1	Protein D	2.2	CRM_{197}
14	1	Protein D	2.2	CRM_{197}
18C	**3**	**Tetanus toxoid**	2.2	CRM_{197}
19F	**3**	**Diphtheria toxoid**	2.2	CRM_{197}
23F	1	Protein D	2.2	CRM_{197}
3			2.2	CRM_{197}
6A			2.2	CRM_{197}
19A			2.2	CRM_{197}

*contains 0.5 mg aluminium phosphate
**contains 5mM succinate buffer and 0.125 mg aluminum phosphate

Table 2 Baseline demographics by group.

	PCV-10 (n = 87)		**PCV-13 (n = 90)**	
	N	(%)	N	(%)
Age (Months)				
Mean (SD) [Min-Max]	12.6 (0.4) [11.1-13.3]		12.7 (0.4) [11.7-13.5]	
Sex				
Male	46	(52.9)	58	(64.4)
Female	41	(47.1)	32	(35.6)
Ethnicity				
White Caucasian/ European	78	(89.7)	74	(82.2)
Other	9	(10.3)	15	(16.7)
Unknown	0	0	1	(1.1)

Table 3 Proportion of participants with IgG antibody concentrations ≥0.35 μg/ml by serotype and vaccine group at 13 months and difference between groups (PP population).

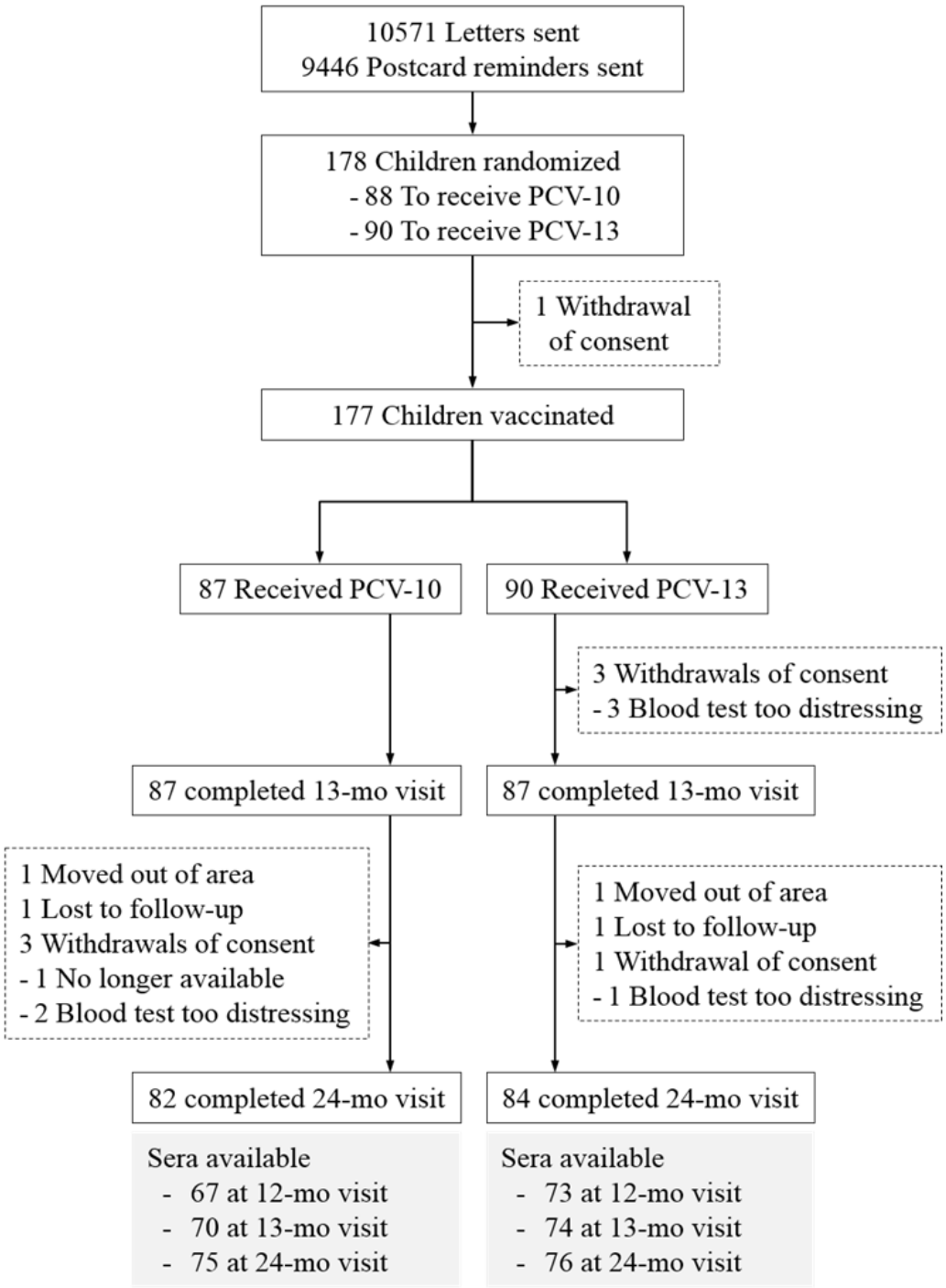
	PCV-10 (n = 69)			**PCV-13 (n = 74)**			**PCV-10 – PCV-13**	
Serotype	N	Proportion IgG ≥0.35 μg/ml (95% CI)		N	Proportion IgG ≥0.35 μg/ml (95% CI)		Difference (95% CI)	
1	69	0.986	(0.922, 1.000)	74	0.987	(0.927, 1.000)	-0.001	(-0.040, 0.038)
4	69	1.000	(0.948, 1.000)	74	0.987	(0.927, 1.000)	0.014	(-0.013, 0.040)
5	**69**	**0.739**	**(0.619, 0.837)**	**74**	**0.960**	**(0.886, 0.992)**	**-0.220**	**(-0.336, -0.105)**
6B	69	0.971	(0.899, 0.997)	73	1.000	(0.951, 1.000)	-0.029	(-0.070, 0.012)
7F	69	0.986	(0.922, 1.000)	74	1.000	(0.951, 1.000)	-0.015	(-0.043, 0.014)
9V	**69**	**0.884**	**(0.784, 0.949)**	**74**	**0.987**	**(0.927, 1.000)**	**-0.102**	**(-0.184, -0.021)**
14	69	1.000	(0.948, 1.000)	74	1.000	(0.951, 1.000)	0.000	(0.000, 0.000)
18C	69	1.000	(0.948, 1.000)	74	0.973	(0.906, 0.997)	0.027	(-0.011, 0.065)
19F	69	1.000	(0.948, 1.000)	74	0.987	(0.927, 1.000)	0.014	(-0.013, 0.040)
23F	63	1.000	(0.943, 1.000)	74	1.000	(0.951, 1.000)	0.000	(0.000, 0.000)

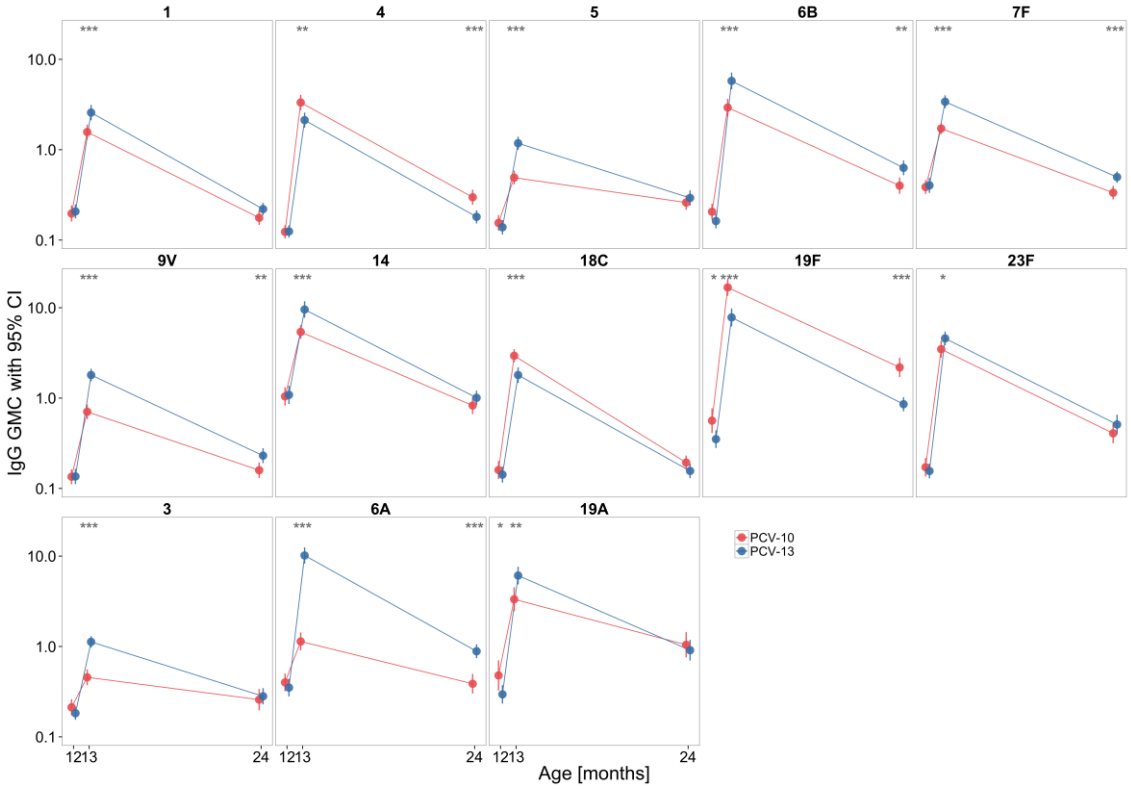
Figure legends

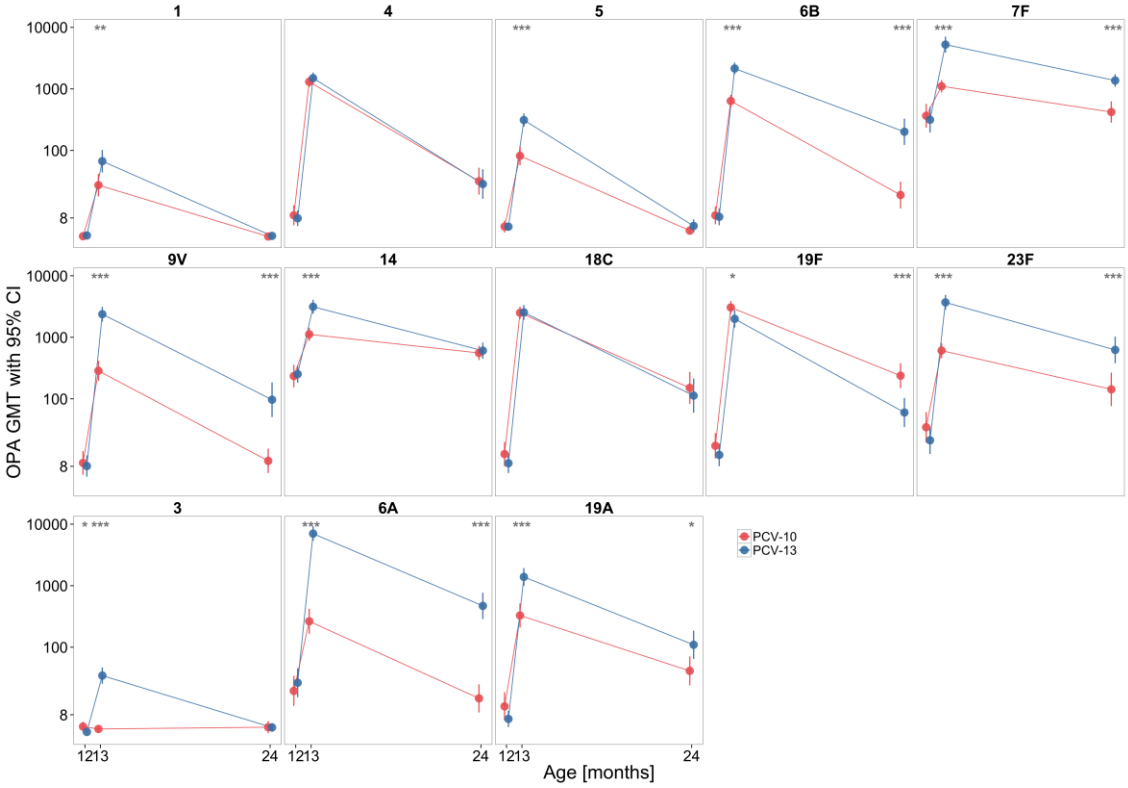
Figure 1 CONSORT diagram showing the flow through the study. One study participant receiving PCV-10 was excluded from the analysis of the primary objective because of major protocol violation resulting in n = 69 in the PCV-10 group at the 13-mo visit.

Figure 2 Serotype-specific IgG geometric mean concentrations by serotype and vaccine group at all 3 study time points. Groups were compared using independent samples t-tests using log_{10}-transformed data with Satterthwaite's correction for unequal variances and stars indicate the associated p-value (*** <.001; ** <.01; * <.05).

Figure 3 Serotype-specific geometric mean OPA titers by serotype and vaccine group at all 3 study time points. Groups were compared using independent samples t-tests using log_{10}-transformed data with Satterthwaite's correction for unequal variances and stars indicate the associated p-value (*** <.001; ** <.01; * <.05).


10571 Letters sent
9446 Postcard reminders sent
178 Children randomized
- 88 To receive PCV-10
- 90 To receive PCV-13
1 Withdrawal of consent
177 Children vaccinated
87 Received PCV-10
90 Received PCV-13
3 Withdrawals of consent
- 3 Blood test too distressing
87 completed 13-mo visit
87 completed 13-mo visit
1 Moved out of area
1 Lost to follow-up
3 Withdrawals of consent
- 1 No longer available
- 2 Blood test too distressing
1 Moved out of area
1 Lost to follow-up
1 Withdrawal of consent
- 1 Blood test too distressing
82 completed 24-mo visit
84 completed 24-mo visit
Sera available
- 67 at 12-mo visit
- 70 at 13-mo visit
- 75 at 24-mo visit
Sera available
- 73 at 12-mo visit
- 74 at 13-mo visit
- 76 at 24-mo visit


1
4
5
6B
7F
9V
14
18C
19F
23F
3
6A
19A
IgG GMC with 95% CI
10.0
1.0
0.1
PCV-10
PCV-13
1213
24
Age [months]


1
4
5
6B
7F
9V
14
18C
19F
23F
3
6A
19A
OPA GMT with 95% CI
10000
1000
100
8
PCV-10
PCV-13
1213
24
Age [months]