Title

Randomised controlled trial of the immunogenicity and reactogenicity of PCV10 versus PCV13 among infants in Ho Chi Minh City, Vietnam

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ABSTRACT

Background: Two pneumococcal conjugate vaccines (PCVs) are currently available, but there are few data to support the choice of vaccine. Here we report a head-to-head comparison of the immunogenicity and reactogenicity of PCV10 and PCV13 within a parallel, open-label randomised controlled trial in Vietnam.

Methods: 1201 healthy infants from two districts in Ho Chi Minh City were randomised to one of six infant PCV schedules using a computer-generated list: PCV10 in a 3+1, 3+0, 2+1 or two-dose schedule; PCV13 in a 2+1 schedule; or no infant PCV. One of two trial aims was to compare vaccination responses between PCV10 and PCV13. Blood samples collected between 2 and 18 months of age were analysed (blinded) for serotype-specific IgG and opsonophagocytic responses. The primary outcome was the percentage of infants with IgG ≥0·35μg/ml post-primary series for the ten shared serotypes. Trial registration: ClinicalTrials.gov NCT01953510.

Findings: There was no difference in the percentage of infants with IgG ≥0·35μg/ml at the 10% level following a two dose primary series of PCV10 or PCV13, with risk differences (95% CIs, PCV10-PCV13) of: serotype 1, -2.1 (-4.8, -0.1); serotype 4, -1.3 (-3.7, 0.6); serotype 5, -3.4 (-6.8, -0.4); serotype 6B, 15.6 (7.2, 23.7); serotype 7F, -1.3 (-3.7, 0.6); serotype 9V, -1.6 (-5.1, 1.7); serotype 14, 0.0 (-2.7, 2.9); serotype 18C, -2.1 (-5.3, 0.9); serotype 19F, 0.0 (-2.2, 2.3); and serotype 23F -11.6 (-18.2, -4.9). Two doses of PCV13 were also non-inferior to three doses of PCV10, with the risk difference (including 90% CI) less than 10% for 9/10 shared serotypes (all except 6B). The criteria for concluding no overall difference and non-inferiority (based on 7/10 serotypes) were both met.

Interpretation: This is the first trial to directly compare the post-primary series immunogenicity of PCV10 and PCV13 in a 2+1 schedule. Both vaccines are highly immunogenic and factors such as the comparative magnitude of the antibody responses, price, and the relative importance of different serotypes in different settings may influence the choice of vaccine.

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Evidence before this study

We searched PubMed to 31 August 2018 using search terms including but not limited to "10-valent pneumococcal conjugate vaccine" or "13-valent pneumococcal conjugate vaccine", and "immunogenicity". At the time this trial was designed there were no published studies on the comparative immunogenicity or PCV10 and PCV13. The licensure of each of these vaccines was based on demonstrating their immunological non-inferiority to PCV7. However, this in itself does not preclude differences between these two second-generation PCVs. Countries considering PCV introduction have little on which to base their decision other than the relative cost of the vaccines.

Added value of this study

This is the first study designed specifically to compare the post-primary series immunogenicity of the two currently licensed PCVs. Previously, published data have been limited to comparisons with PCV7 or, more recently, two trials of investigational vaccines that have included both PCV10 and PCV13 control groups, and one study of the booster response in a 3+1 schedule. This is the first published study to compare the vaccines in a lower-and-middle-income-country (LMIC) setting in a 2+1 schedule. This is the schedule increasingly used by LMICs and one of the WHO-recommended schedules. The results of this study will therefore have importance for high burden settings.

Implications of all the available evidence

The data from this randomised controlled trial in a LMIC support previous non-comparative data that both PCV10 and PCV13 are highly immunogenic in a 2+1 schedule, with similar reactogenicity. There are few differences between the two vaccines in relation to the 0.35μg/ml correlate of protection, but the geometric mean concentrations of antibody, both post-primary series and post-booster, tend to be higher following vaccination with PCV13. It is hard to assess whether these differences would translate to differing degrees of protection afforded by the two vaccines, particularly for mucosal disease where a higher concentration of antibody may be required for protection. Vietnam and other LMICs considering vaccine introduction may want to take into account the immunological differences we have shown, in the context of their own pneumococcal epidemiology.

INTRODUCTION

Streptococcus pneumoniae (pneumococcus) is a leading vaccine preventable cause of serious infection in young children, and was estimated to cause 294,000 deaths amongst children less than five years of age in 2015.[1] The greatest burden of disease and mortality is in lower and middle income countries (LMICs). There are currently two pneumococcal conjugate vaccines (PCVs) licensed for infant vaccination against pneumococcus. PCV13 (*Prevnar-13/Prevenar-13*; Pfizer) contains serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F. PCV10 (*Synflorix*, PhiD-CV; GlaxoSmithKline) contains ten of these serotypes (all except 3, 6A, and 19A), although there is evidence for some cross protection against serotype 6A and 19A disease.[2–4] Both PCV10 and PCV13 have been shown to be immunologically non-inferior to the first licensed PCV, PCV7,[5–7] but there are few data directly comparing the two vaccines, despite their availability for several years. There have been two European trials of investigational next-generation GSK pneumococcal vaccines that included control groups of both PCV10 and PCV13, administered in a 3+1 schedule at 2, 3, 4, and 12-15 months of age, with immunogenicity data post-primary series, pre-booster and post-booster.[8,9] There are two other trials with post-primary series immunogenicity data available on ClinicalTrials.gov: a trial of investigational protein-based pneumococcal vaccines in a 3+0 schedule from the Gambia that includes both PCV10 and PCV13 control groups (NCT01262872); and a trial from Mexico to evaluate mixed regimens that includes groups that received a two-dose primary series of either PCV10 or PCV13 (NCT01641133). There has also been a small, non-randomised study from the Netherlands that compared the booster response to PCV10 and PCV13 in a 3+1 schedule.[10] Broadly, these studies show that both vaccines are highly immunogenic post-primary series and post-booster. Serotype-specific geometric mean concentrations (GMCs) of IgG antibody following vaccination with PCV13 tend to be higher post-primary series, lower pre-booster, and higher post-booster, than those with PCV10, although these trends do not hold for all serotypes. Notably, of these studies, only the study of the booster response from the Netherlands was designed specifically to evaluate differences in the immunogenicity of the two vaccines.
Given the limited comparative data available to influence the choice of PCV, particularly from LMICs, we conducted a randomised controlled trial in Vietnam of different infant pneumococcal vaccination schedules that included a head-to-head comparison of PCV10 and PCV13 delivered in a 2+1 schedule, one of the schedules recommended by the World Health Organization (WHO).[11] The trial had two independent aims: to compare vaccination responses between PCV10 and PCV13; and to evaluate different schedules of PCV10. This manuscript presents results pertaining to the first aim.

METHODS

Study design

The parallel open-label randomised controlled trial "Evaluation of different infant vaccination schedules incorporating pneumococcal vaccination" (the Vietnam Pneumococcal Project) was designed to investigate simplified childhood vaccination schedules that are more appropriate for use in LMICs. The trial was conducted in two districts within Ho Chi Minh City. The protocol was approved by the Institutional Review Board at the Pasteur Institute of Ho Chi Minh City and ethical approval was obtained from the Human Research Ethics Committee of the Northern Territory Department of Health and Menzies School of Health Research, Australia, and the Ministry of Health Ethics Committee, Vietnam. The protocol for this trial has been published.[12]

Participants

Participants were enrolled at 2 months of age and followed up to 24 months of age. Details of the participant eligibility criteria and recruitment processes have been described previously.[12] A parent/legal guardian of each participant provided written informed consent.

Randomisation and masking

A computer-generated list of randomisation numbers was used in a block randomisation scheme, stratified by district. This was a single-blind trial with all laboratory-based outcome assessors blinded to the group allocation. Additional details of the randomisation and masking have been described previously.[12]

Procedures

Participants were randomly assigned to one of six infant vaccination schedules: PCV10 in a 3+1, 3+0, 2+1 or two-dose schedule (Groups A, B, C, and D, respectively); PCV13 in a 2+1 schedule (Group E); or a control group (Group F) that received no infant doses of PCV (Table 1). The control group is included to contribute data primarily for the secondary nasopharyngeal carriage outcomes, which will be presented elsewhere. Participants (from Groups A-E) provided a total of four blood samples over the course of the trial. The time-points for the collection of blood samples varied both between and within study groups, to enable more questions to be addressed within the confines of a maximum of four blood samples per participant (see Appendix, p1 for the full schedule of vaccines and samples). As such, blood samples from different PCV10 study groups contribute to analyses of the comparative immunogenicity of PCV10 and PCV13 at different time-points (Figure 1), and the number of samples varies by time-point.

Outcomes

In order to address the study aim to compare vaccination responses between PCV10 and PCV13, we planned to fully evaluate the immunogenicity of a 2+1 schedule (administered at 2, 4, and 9·5 months of age) in a head-to-head manner. We assessed serotype-specific IgG antibody levels to all 13 serotypes in PCV13 using a modified third-generation standardised ELISA[13] at the following time-points (Figure 1): pre-PCV (in Group A); four-weeks after one dose of PCV at 2 months of age

(in Group D and a subset of Group E); post-primary series (four-weeks after two doses of PCV at 2 and 4 months of age, in Groups C and E); pre-booster (at 9 months of age, in Groups C and E); post-booster (four-weeks after a booster dose of PCV at 9·5 months of age, in Groups C and E); and at 18 months of age (in a subset of Groups C and E). We also assessed the functional antibody response to all 13 serotypes by opsonophagocytic assay (OPA)[14] in a subset of participants, four-weeks post-primary series and four-weeks post-booster (in Groups C and E). The primary time-point was four-weeks post-primary series. At this time-point we also compared the two-dose primary series of PCV13 (Group E) with a three-dose primary series of PCV10 at 2, 3, and 4 months of age (Group A+B). This comparison was listed in the protocol as the primary outcome, as at the time the trial was designed the two-dose primary series was not an approved schedule for PCV10. Both comparisons are presented here.

ELISA results are presented as the percentage of children with protective levels of antibody (≥0·35µg/ml, the primary outcome) and the GMC of antibody. OPA results are presented as the percentage of children with Opsonisation Indices (OIs) ≥8 and the geometric mean OI (GMOI). The comparative reactogenicity of PCV10 and PCV13 was also evaluated. Reactogenicity assessments included erythema at the vaccination site(s) and axillary temperature on days 0-4 post-vaccination, as measured by the parent/caregiver and recorded on a parent-held diary card.

Statistical analyses

Primary comparisons between groups are presented as comparisons of the percentages of children with IgG ≥0·35µg/ml four-weeks post-primary series, the threshold used for comparing PCV formulations. For the head-to-head comparison of a two-dose primary series of PCV10 or PCV13, a 10% risk difference is considered clinically significant. Risk differences (PCV10-PCV13) with 95% confidence intervals (CIs) are calculated using the Newcombe-Score method. The null hypothesis for each of the shared serotypes is that the risk difference is between -10% and 10%, with the null hypothesis rejected if the 95% CI of the risk difference is entirely outside +/-10%. An overall difference is declared if at least seven of the ten individual null hypotheses are rejected in the same direction. Comparisons between a two-dose primary series of PCV13 and a three-dose primary series of PCV10 are assessed in terms of non-inferiority, based on a non-inferiority margin of a 10% risk difference as used by regulatory authorities. The null hypothesis for each of the shared serotypes is that the risk difference is greater than 10%, with the null hypothesis rejected if the upper bound of the 90% CI is less than 10% (equivalent to using a 5% one-sided test). An overall conclusion of non-inferiority is drawn if the null hypotheses are rejected for at least seven of the ten shared serotypes. The sample size provides 98% power for an overall conclusion on the difference between two doses of PCV10 and PCV13, and >99% power for an overall conclusion on the non-inferiority of two doses of PCV13 compared with three doses of PCV10. Details of the sample size calculations have been described previously.[12]

IgG levels between groups are also compared in terms of GMC ratios (PCV10/PCV13) with 95% CIs, and are described as higher in one group if the 95% CI excludes one. GMOIs are compared

using the Mann Whitney U-test. Reactogenicity rates between groups are compared using Fisher's Exact Test. One-sided p-values are used for comparisons with the control group, and two-sided p-values for comparisons between the PCV10 and PCV13 groups.

Statistical analyses were conducted in accordance with the protocol and the statistical analysis plan. All immunological analyses were performed on the per-protocol population. Primary analyses were repeated on the intention-to-treat population. Reactogenicity analyses were performed on the intention-to-treat population. Analyses were performed using Stata Statistical Software, Release 14 (StataCorp 2015, College Station, TX). The trial was overseen by an independent Data Safety and Monitoring Board and is registered at ClinicalTrials.gov (NCT01953510).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

1424 infants were screened between 30 September 2013 and 9 January 2015, with 1201 (84%) enrolled (Figure 1). The groups were balanced with respect to baseline characteristics (Table 1). Overall, 98% of participants completed their primary series vaccinations, 95% received their booster dose of PCV or were followed up to 9 months of age, and 91% were followed up to 18 months of age. Of the 108 participants withdrawn before 18 months, the reasons for withdrawal were: moved away and lost to follow up (51%); refusing a study procedure (21%); voluntary withdrawal (20%); and other (8%).

Post-primary series, the head-to-head comparison of two doses of PCV13 and PCV10 showed no evidence of a difference in the percentage of infants achieving serotype-specific IgG ≥0·35µg/ml at the 10% level, with the outer bound of the CI of the difference in percentage within +/-10% for all ten shared serotypes (Table 2 and Appendix, p2). In both groups, over 95% of participants had protective IgG levels to all serotypes except 6B (76·8% in the PCV10 group and 61·2% in the PCV13 group) and 23F (77·6% in the PCV10 group and 89·2% in the PCV13 group). Comparing the magnitude of the response (based on the ratio of GMCs), IgG GMCs were higher in the PCV10 group for serotypes 6B and 19F, and higher in the PCV13 group for the other eight shared serotypes (Table 2). We also showed that two doses of PCV13 were non-inferior to three doses of PCV10 in relation to the percentage of responders, with the upper bound of the CI of the difference in percentage less than 10% for nine of the ten-shared serotypes (Table 3 and Appendix, p2). The exception was serotype 6B, for which the percentage of participants achieving IgG ≥0·35µg/ml was 84·6% in the PCV10 group compared with 61·2% in the PCV13 group (risk difference 23·4%, 90% CI 17·0-29·6%). IgG GMCs were higher in the PCV10 group for serotypes 6B, 14, and 18C, and

higher in the PCV13 group for serotypes 1, 4, 5, and 9V. There were no differences in the conclusions between the results of the per-protocol and intention-to-treat analyses (Appendix, p3).
In addition to the post-primary series time-point, we directly compared responses to PCV10 and PCV13 four-weeks after a single dose, at 9 months of age, four-weeks post-booster, and at 18 months of age (Figure 2 and Appendix, p4-6). At 2 months of age, pre-PCV, the highest GMCs of antibody were seen for serotypes 14, 19F, 19A, and 6A, and 44-68% of participants had IgG levels ≥0·35μg/ml for these serotypes. Comparing pre- and post-PCV levels, a single dose of either PCV10 or PCV13 elicited no response to the shared serotypes 6B, 14, and 23F or to the non-PCV10 types 6A and 19A. Following a single dose, over 64% of participants had IgG levels ≥0·35μg/ml to serotypes 1, 4, 5, 7F, 14, and 19F in both groups, and to serotype 18C in the PCV13 group. Considering a 10% difference in the percentage of participants achieving IgG levels ≥0·35μg/ml as clinically significant, more participants had protective levels to serotype 19F in the PCV10 group and more to serotype 18C in the PCV13 group. Comparing the magnitude of the response (based on the ratio of GMCs), GMCs were higher in the PCV10 group for serotypes 1, 4, 5, 9V, and 19F, and higher in the PCV13 group for serotypes 7F and 18C.
At 9 months of age, five-months post-primary series, the majority of participants still had protective levels of antibody to most serotypes (75-100% in the PCV10 group and 69-99% in the PCV13 group). More participants had protective levels to serotype 6B in the PCV10 group and more to serotype 5 in the PCV13 group at the 10% level. GMCs were higher in the PCV10 group for serotypes 6B, 18C, 19F, and 23F, and higher in the PCV13 group for serotypes 1, 5 and 7F, 9V, and 14. Post-booster, the percentage of participants with IgG levels ≥0·35μg/ml in both groups was greater than 97% for all serotypes. In terms of GMCs, the same pattern was seen post-booster dose as post-primary series for most serotypes, with GMCs higher in the PCV10 group for serotype 19F and higher in the PCV13 group for serotypes 1, 5, 7F, 9V, 14, and 23F. In contrast to the post-primary series results, post-booster GMCs were higher in the PCV10 group for serotype 18C and higher in the PCV13 group for serotype 6B, with no difference between groups for serotype 4. At 18 months of age the percentage of participants with IgG levels ≥0·35μg/ml was still greater than 90% for serotypes 14 and 19F (both groups) and for serotype 6B (PCV10 group), and greater than 59% for all other serotypes. Differences in GMCs were only seen for serotypes 18C and 19F, with higher levels in the PCV10 group.
For the non-PCV10 serotypes (3, 6A, and 19A), a high percentage of PCV13-recipients responded with IgG ≥0·35μg/ml (over 94% and 99% of participants post-primary series and post-booster, respectively), although the GMC to serotype 3 was similar post-primary series and post-booster. PCV10 also elicited responses to serotypes 6A and 19A post-booster, with over 90% of participants achieving IgG ≥0·35μg/ml. GMCs to all three non-PCV10 serotypes were higher in the PCV13 group at all time-points, with the exception of serotype 6A at 3 months of age and serotype 19A at 18 months of age, for which there were no differences between the vaccine groups.

Differences in opsonophagocytic responses post-primary series, following vaccination with either PCV10 or PCV13, broadly reflected those seen in the IgG levels (Table 3). GMOIs were higher in the PCV10 group for serotypes 6B and 19F and higher in the PCV13 group for all other serotypes except 14 (Mann Whitney U-test). The percentages with an OI ≥8 also generally reflected the percentages with IgG ≥0·35µg/ml, with some exceptions. For serotype 1, over 97% of infants achieved IgG levels ≥0·35µg/ml, while the proportions achieving an OI ≥8 were 66·1% and 87·9% in the PCV10 and PCV13 groups, respectively. A similar pattern was seen for serotype 9V in the PCV10 group with only 80·6% achieving an OI ≥8. These two were the only serotypes with differences between the groups at the 10% level, with higher percentages in the PCV13 group. Post-booster, fewer differences were seen between groups. GMOIs were higher in the PCV10 group for serotype 19F and higher in the PCV13 group for serotypes 4, 6B, 7F, 9V, and 23F. Over 90% of participants achieved an OI ≥8 for the ten shared serotypes in both the PCV10 and PCV13 groups, including serotype 1, with no differences between groups at the 10% level.

PCV13 was immunogenic to each of the non-PCV10 serotypes following the primary series, with over 92% achieving OI ≥8, and increased responses were seen following the booster dose for serotypes 6A and 19A. As with the IgG responses, PCV10 generated little to no functional immunity post-primary series but substantial OPA responses to 6A and 19A were seen following the booster dose of PCV10.

Reactogenicity information was analysed at 2 and 4 months of age from the 2+1 PCV10, 2+1 PCV13 and control groups (Groups C, E, and F, respectively), and at 9·5 months of age from the 2+1 PCV10 and 2+1 PCV13 groups (Groups C and E, respectively; Table 4). Diary cards were collected from over 96% of participants vaccinated at each time-point. The incidences of erythema at the PCV vaccination site and at the *Infanrix-hexa* vaccination site were both low. There was no difference in the incidence of erythema between those vaccinated with PCV10 and PCV13 at any time-point, and the incidence of erythema at the PCV site was similar to that at the *Infanrix-hexa* site. Co-administration with either PCV10 or PCV13 also had no impact on the incidence of erythema at the *Infanrix-hexa* site. The incidence of axillary fever ≥37·5°C following vaccination with PCV ranged from 38·7-44·1%, and the incidence of severe fever from 3·8-9·6%. There was no difference in the incidence of fever or severe fever between PCV10 recipients and PCV13 recipients at any time-point. In the PCV13 group there was a higher incidence of severe fever at 4 and 9·5 months than at 2 months. The incidence of fever following coadministration of PCV and *Infanrix-hexa* was significantly higher than administration of *Infanrix-hexa* alone. 135 participants (from Groups A-F) were hospitalised over the course of the trial, in a total of 163 admissions. The most common reasons for hospitalisation were acute respiratory infection (ARI, 43%) and acute gastroenteritis (18%). The majority (94%) of hospitalisations were unrelated to vaccination, and all resolved without sequelae. There were no differences in the overall rates of hospitalisation or the rates of hospitalisation for ARI between groups. No participants were withdrawn as a result of harms and there were no deaths during the trial.

DISCUSSION

PCVs are now in use in national immunisation programmes in 142 countries. Increasingly, countries are adopting a 2+1 schedule, with a two dose primary series followed by a booster dose at or after 9 months of age. In this paper we present the results of the first head-to-head study comparing the two currently available PCVs in a 2+1 schedule, measuring both serotype-specific IgG (by ELISA) and functional antibody levels (by OPA) to all 13 serotypes in the vaccines.

Our findings reveal that the immunological advantage of one vaccine over the other varies by serotype and by time-point. The overall pattern that emerges is one in which PCV10 generally fares better for the shared serotypes after a single dose. After the two-dose primary series, responses to PCV13 are stronger, but wane similarly to PCV10 by 9 months of age. PCV13 produces stronger booster responses, but this effect is lost by 18 months.

Responses after a single dose allow us to judge protection in the interval between doses. This is important because many children will not present on time for the second dose, and also because 1+1 schedules are currently under consideration.[15] After a single dose there was no response to some serotypes (6B, 14, 23F, and non-PCV10 types 6A or 19A). However, for most other serotypes the majority of children responded beyond the critical level of 0·35μg/ml, consistent with the observation that there is some incomplete protection afforded to infants following a single dose. The magnitude of the response was greater with PCV10 for half of the shared serotypes.

Both vaccines produced strong responses post-primary series with over 95% of children responding to most serotypes (the exceptions being 6B and 23F, consistent with previous findings[16,17]), although the magnitude of the response was greater with PCV13 for eight of the shared serotypes. After the booster almost all children had protective levels of antibody, but again the magnitude of the response was greater with PCV13 for seven of the shared serotypes. The level of 0·35μg/ml was determined from a pooled analysis of data from efficacy trials, and was established as the basis for comparing new with existing PCVs post-primary series.[18] It is known that the true protective level of antibody varies geographically, by serotype and by disease type.[19–21] Applying a more conservative level of 1·0μg/ml to our data, post-primary series more participants in the PCV13 group had protective levels to serotypes 1 and 5 and more participants in the PCV10 group to serotype 6B at the 10% level, and post-booster more participants in the PCV13 group had protective levels to serotype 5 (Appendix, p6).

In general the OPA titres followed the ELISA titres and the proportions of infants protected by the IgG ≥0·35μg/ml and the OI ≥8 criteria were similar, but some important differences did emerge. With both vaccines, particularly PCV10, poor OPA responses to serotype 1 were seen post-primary series despite strong ELISA responses. This finding was reflected in the two European trials of investigational PCVs, in which 41% and 62% of participants had OI ≥8 in the PCV10

groups, and 61% and 84% in the PCV13 groups.[8,9] This disconnect between OPA and ELISA responses is corrected following the booster dose, providing immunological evidence for the importance of a booster dose in protecting against disease. This is an important finding for Africa where serotype 1 is an important cause of disease[22] and most countries employ a 3+0 schedule without a booster dose. Analysis of serotype 1 immunogenicity in the context of reduced-dose PCV10 schedules with or without a booster will be reported elsewhere as part of the evaluation of different PCV schedules (the other aim of this trial).

Both vaccines were strongly immunogenic against 19F; however responses were stronger following PCV10 at all time-points and by both ELISA and OPA. This contrasts with findings from the study in the Netherlands, in which PCV13 produced stronger 19F booster responses by ELISA than PCV10, although OPA responses were comparable.[10] Serotype 19F has persisted in both carriage[23] and disease[24] in the United States, despite over 15 years of vaccination, and has been the most common cause of vaccine failure in children.[25] In the original PCV7 efficacy trial, effectiveness against IPD and ear disease for serotype 19F was lower than for other serotypes (along with serotype 6B) despite good circulating antibody levels.[26] There is convincing evidence that the 19F component of PCV10 provides protection against 19A disease, but probably not carriage. The sharp rise in 19A disease following PCV7 introduction highlights important differences between the vaccines with respect to that type.[27]

PCV13 elicited strong responses to the non-PCV10 types, with over 94% of children responding post-primary series and over 99% post-booster. Interestingly, PCV13 produced only modest increases in IgG and OPA responses for serotype 3 post-booster compared with post-primary series, and these were considerably lower than those for other serotypes, a finding consistent with previous immunogenicity data.[17] The effectiveness of PCV13 against type 3 disease is in doubt.[28,29] Among PCV10 recipients we found modest immunogenicity to serotypes 6A and 19A after the booster-dose at 9 months, with over 90% of children achieving IgG ≥0·35μg/ml, although GMCs were significantly lower than those generated by PCV13. OPA responses were also poorer but did demonstrate considerable responses. These results support the finding from three experimental PCVs in the 1990s of low correlation between ELISA and OPA results for cross-reactive serotypes,[30] but are consistent with some degree of protection afforded by PCV10 against both 6A and 19A disease. As part of this trial we are evaluating the impacts of vaccination on pneumococcal carriage, which will elucidate the capacity for PCV10 to protect against carriage of serotypes 6A and 19A.

One of the limitations of this study is the use of immunological endpoints as opposed to disease outcomes. However, given that both PCV10 and PCV13 have been in routine use in many countries for a number of years with demonstrated effectiveness, a direct comparison of the two vaccines on this basis is appropriate, and is enhanced by the inclusion of functional OPAs in addition to the standard IgG antibody measurement by ELISA. Another limitation is the fact that this study involves assessing responses to multiple serotypes at several time-points, leading to the

likelihood that some of the observed differences arose by chance. This is a problem faced by all studies of PCVs. In order to compensate for this, we defined a single conclusion for the primary outcome, requiring a difference (or non-inferiority) in the percentage of participants with IgG ≥0·35µg/ml to be observed for seven of the ten shared serotypes. Beyond the primary outcome, our aim was to provide an overall description of the pattern of differences between PCV10 and PCV13. As such, no formal adjustments for multiple comparisons have been made but we have deliberately avoided reporting p-values. The inclusion of multiple outcomes in this study is also a strength. We have assessed the immunogenicity, with both ELISAs and OPAs, and reactogenicity of PCV10 and PCV13 in a 2+1 schedule, providing a comprehensive head-to-head comparison of these vaccines. For the reactogenicity assessments, a limitation of this study is the use of parent-held diary cards. However, the same potential issues of bias in self-reported symptoms apply to all study groups, and therefore would not impact the between-group comparisons. Furthermore, we reported a single measure for the occurrence of erythema and fever on days 0-4 post-vaccination to limit any effect of missing data; only 1% of diary cards were excluded from analysis due to lack of data.

In conclusion, both vaccines are highly immunogenic, consistent with their effectiveness, and show similar reactogenicity. The differences in immunogenicity described vary by serotype and time point. PCV13 tends to produce stronger responses post-primary series and post-booster, while PCV10 appears to produce stronger responses after a single dose. PCV10 produces reasonable responses to non-PCV10 types 6A and 19A, whilst PCV13 produces only modest responses to serotype 3. It has been argued that a higher antibody concentration is required to protect against mucosal disease than against IPD, but it is hard to assess if the observed differences in immunogenicity would translate to differing degrees of protection afforded by the two vaccines. Further analysis of data from this trial will compare B-cell memory induced by PCV10 and PCV13 and will evaluate the impact of the two vaccines on the carriage of vaccine serotypes, vaccine related serotypes and other serotypes, which may further tease out differences between the two vaccines.

Data sharing statement: The study protocol and informed consent form have been published and are freely available.[12] Data will be made publically available in accordance with the rules set out by the Bill and Melinda Gates Foundation.

Contributors

BT was involved with the design and day-to-day management of the trial, did the data analysis, and wrote the first draft of this manuscript with input from CDN and EKM. NTT, KB, and DYU were involved in the design, establishment, day-to-day management and implementation of the trial. VTTD was responsible for the ELISA assays. RAM was responsible for the OPA assays. PVL and

AB were involved in the design, and advised on and provided oversight of the immunology laboratory procedures. CDN advised on the statistical analyses and assisted with the Figures. TNH was involved in the design and establishment, and had overall responsibility for the conduct of the trial in Vietnam as Site Principal Investigator. EKM conceived the study, provided oversight for the conduct of the trial and data analysis, and had overall responsibility for all aspects of the trial as the Principal Investigator. All authors contributed to refinement of and approved this manuscript.

Declaration of interests

All authors receive salary support from grants from the National Health and Medical Research Council of Australia and/or the Bill and Melinda Gates Foundation. Non-financial support (in the form of PCV10 vaccine doses) and funding for opsonophagocytic assays are provided by GSK Biologicals SA. None of the authors have any other competing interests to declare.

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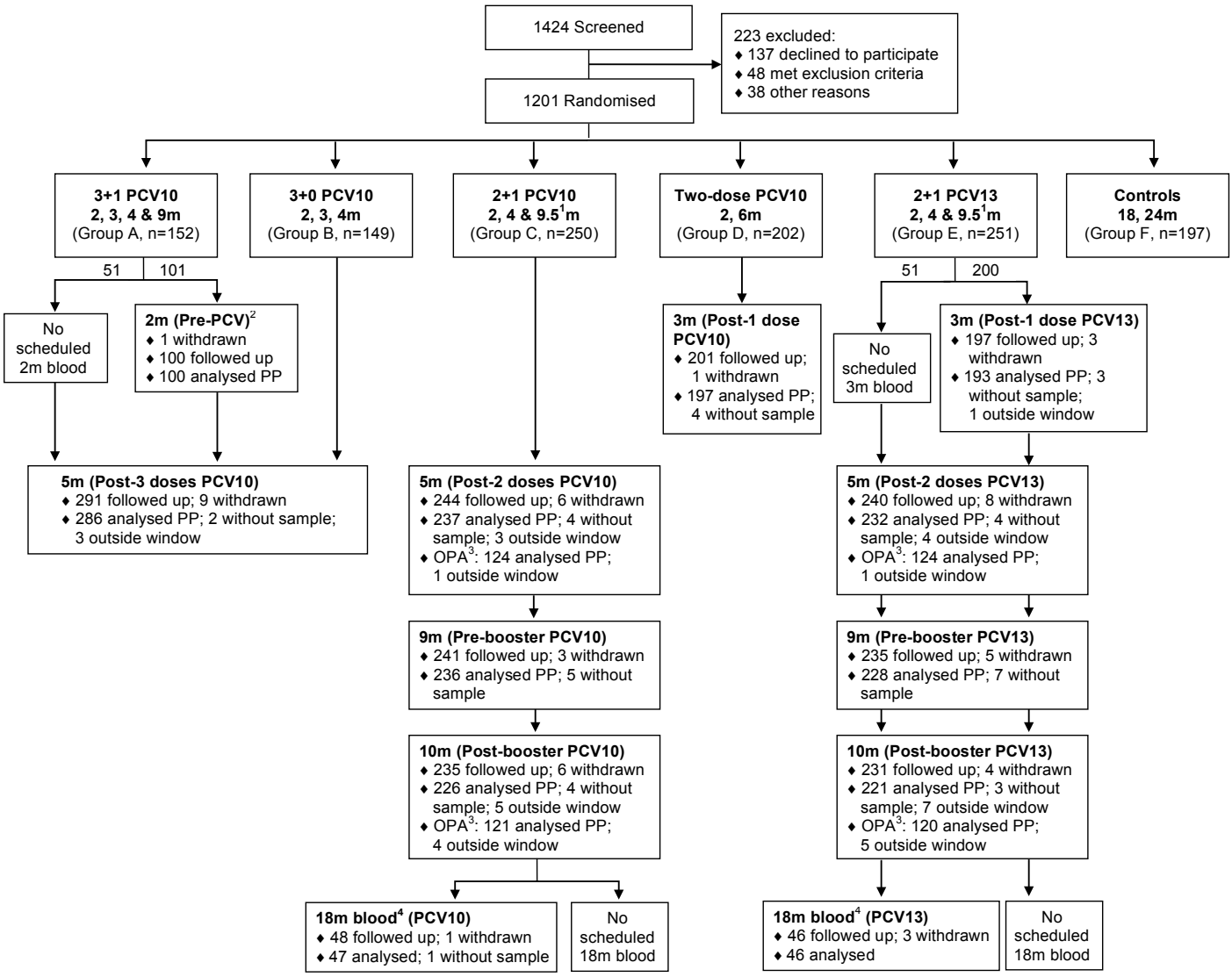
Figure 1: CONSORT diagram showing the blood samples contributing to the comparative analyses of PCV10 and PCV13



Footnotes:
[1] PCV (and *Infanrix-hexa*) were administered at 9·5 months in participants from groups C and E, as the Vietnam Ministry of Health does not permit co-administration of measles and *Infanrix-hexa* (see Appendix, page 1 for full schedules of PCV and co-administered vaccines).
[2] The 2-month blood sample from Group A provides pre-PCV data. Samples at this time-point were only collected from one study group, with the assumption that all groups are exchangeable at baseline as a result of randomisation.
[3] OPAs: 125 participants from groups C and E contributed to the OPA analyses, selected as the first 125 with both post-primary series and post-booster blood samples collected.
[4] The last 50 participants recruited per group provided a blood sample at 18 months of age, with the remainder providing a sample at an alternative time point (Appendix, page 1).
PP = per-protocol analysis. Samples collected outside the visit window (27-43 days post-vaccination) were included only in the intention-to-treat (ITT) analyses.
The most common reason for participants to be without a blood sample was that the nurse was unable to successfully find a vein (n=18, 49%).

Table 1: Baseline characteristics by study group

	Group A (n=152)	**Group B** (n=149)	**Group C** (n=250)	**Group D** (n=202)	**Group E** (n=251)	**Group F** (n=197)
Sex						
Male	66 (43%)	73 (49%)	135 (54%)	91 (45%)	127 (51%)	100 (51%)
Female	86 (57%)	76 (51%)	115 (46%)	111 (55%)	124 (49%)	97 (49%)
District						
4	68 (45%)	67 (45%)	112 (45%)	90 (45%)	111 (44%)	87 (44%)
7	84 (55%)	82 (55%)	128 (55%)	112 (55%)	140 (56%)	110 (56%)
Birthweight (g)*	3234 (424)	3212 (349)	3228 (370)	3234 (410)	3199 (357)	3208 (395)
Place of delivery						
Hospital	149 (98%)	149 (100%)	245 (98%)	194 (96%)	247 (99%)	192 (97%)
Other	3 (2%)	0 (0%)	4 (2%)	8 (4%)	3 (1%)	5 (3%)
Type of delivery						
Normal	89 (59%)	85 (57%)	160 (64%)	130 (64%)	151 (60%)	121 (61%)
Elective caesarean	30 (20%)	30 (20%)	43 (17%)	36 (18%)	57 (23%)	34 (17%)
Emergency caesarean	27 (18%)	30 (20%)	40 (16%)	34 (17%)	42 (17%)	41 (21%)
Other/unknown	6 (4%)	4 (3%)	7 (3%)	2 (1%)	1 (0.4%)	1 (1%)
Cigarette smoker in house						
No	57 (38%)	52 (35%)	81 (33%)	74 (37%)	86 (34%)	72 (37%)
Yes	95 (62%)	97 (65%)	168 (67%)	128 (63%)	165 (66%)	125 (63%)
Breastfeeding at enrolment						
No	41 (27%)	42 (28%)	55 (22%)	37 (18%)	56 (22%)	56 (29%)
Yes	110 (73%)	107 (72%)	195 (78%)	165 (82%)	194 (78%)	140 (71%)

Data are n(%) or mean(SD). * Birthweight data missing for 10 participants (1, 3, 3, 2, and 1 from Groups B, C, D, E, and F, respectively)

Table 2: Post-primary series immunogenicity. Percentage of participants with serotype-specific IgG ≥0·35µg/ml and GMCs four-weeks after: 2 doses of PCV10 at 2 and 4 months of age (Group C), 2 doses of PCV13 at 2 and 4 months of age (Group E), or 3 doses of PCV10 at 2, 3, and 4 months of age (Group A+B)

	% ≥0·35µg/ml (95% CI)					GMC (95% CI)				
	2 doses PCV10 (n=237)	2 doses PCV13 (n=232)	Risk difference (95% CI) (PCV10-PCV13)	3 doses PCV10 (n=286)	Risk difference (90% CI) (PCV10-PCV13)	2 doses PCV10 (n=237)	2 doses PCV13 (n=232)	GMC ratio (95% CI) (PCV10/PCV13)	3 doses PCV10 (n=286)	GMC ratio (95% CI) (PCV10/PCV13)
Shared serotypes										
1	97·9 (95·1, 99·3)	100 (98·4, 100)	-2·1 (-4·8, -0·1)	98·3 (96·0, 99·4)	-1·7 (-3·5, -0·3)	2·21 (1·97, 2·48)	4·88 (4·40, 5·42)	0·45 (0·39, 0·53)	2·79 (2·51, 3·10)	0·57 (0·49, 0·66)
4	98·7 (96·3, 99·7)	100 (98·4, 100)	-1·3 (-3·7, 0·6)	99·0 (97·0, 99·8)	-1·0 (-2·6, 0·3)	3·21 (2·87, 3·58)	4·82 (4·41, 5·26)	0·67 (0·58, 0·77)	3·85 (3·44, 4·31)	0·80 (0·69, 0·93)
5	95·8 (92·4, 98·0)	99·1 (96·9, 99·9)	-3·4 (-6·8, -0·4)	98·6 (96·5, 99·6)	-0·5 (-2·3, 1·3)	1·17 (1·07, 1·27)	2·20 (2·00, 2·41)	0·53 (0·47, 0·60)	1·81 (1·67, 1·97)	0·83 (0·73, 0·94)
6B	76·8 (70·9, 82·0)	61·2 (54·6, 67·5)	15·6 (7·2, 23·7)	84·6 (79·9, 88·6)	23·4 (17·0, 29·6)	0·80 (0·69, 0·92)	0·48 (0·42, 0·55)	1·65 (1·36, 1·99)	1·08 (0·95, 1·23)	2·24 (1·86, 2·69)
7F	98·7 (96·3, 99·7)	100 (98·4, 100)	-1·3 (-3·7, 0·6)	99·3 (97·5, 99·9)	-0·7 (-2·1, 0·5)	2·07 (1·89, 2·27)	3·33 (3·05, 3·63)	0·62 (0·55, 0·71)	3·04 (2·79, 3·32)	0·91 (0·81, 1·03)
9V	96·2 (92·9, 98·2)	97·8 (95·0, 99·3)	-1·6 (-5·1, 1·7)	99·3 (97·5, 99·9)	1·5 (-0·3, 3·7)	1·63 (1·47, 1·81)	3·27 (2·93, 3·65)	0·50 (0·43, 0·58)	2·47 (2·26, 2·71)	0·76 (0·66, 0·87)
14	98·3 (95·7, 99·5)	98·3 (95·6, 99·5)	0·0 (-2·7, 2·9)	100 (98·7, 100)	1·7 (0·4, 3·8)	5·86 (5·11, 6·73)	7·99 (6·82, 9·37)	0·73 (0·60, 0·90)	9·76 (8·79, 10·83)	1·22 (1·02, 1·47)
18C	96·6 (93·5, 98·5)	98·7 (96·3, 99·7)	-2·1 (-5·3, 0·9)	98·6 (96·5, 99·6)	-0·1 (-2·0, 1·9)	1·86 (1·64, 2·11)	3·14 (2·84, 3·48)	0·59 (0·50, 0·70)	3·87 (3·47, 4·30)	1·23 (1·06, 1·43)
19F	99·2 (97·0, 99·9)	99·1 (96·9, 99·9)	0·0 (-2·2, 2·3)	99·7 (98·1, 100)	0·5 (-0·8, 2·2)	9·54 (8·37, 10·87)	7·67 (6·78, 8·68)	1·24 (1·04, 1·49)	8·34 (7·52, 9·24)	1·09 (0·93, 1·27)
23F	77·6 (71·8, 82·8)	89·2 (84·5, 92·9)	-11·6 (-18·2, -4·9)	90·6 (86·6, 93·7)	1·3 (-3·0, 5·9)	0·89 (0·78, 1·02)	1·14 (1·01, 1·29)	0·78 (0·65, 0·94)	1·32 (1·18, 1·48)	1·16 (0·98, 1·37)
Additional PCV13-types										
3	5·9 (3·3, 9·7)	97·8 (95·0, 99·3)	-91·9 (-94·6, -87·3)	7·0 (4·3, 10·6)	-90·9 (-93·2, -87·2)	0·10 (0·09, 0·11)	1·53 (1·40, 1·68)	0·07 (0·06, 0·08)	0·11 (0·10, 0·12)	0·07 (0·06, 0·08)
6A	40·5 (34·2, 47·1)	94·8 (91·1, 97·3)	-54·3 (-60·8, -47·0)	50·3 (44·4, 56·3)	-44·5 (-49·7, -38·8)	0·31 (0·28, 0·35)	1·94 (1·69, 2·21)	0·16 (0·14, 0·19)	0·37 (0·34, 0·41)	0·19 (0·16, 0·22)
19A	70·5 (64·2, 76·2)	98·3 (95·6, 99·5)	-27·8 (-34·0, -21·8)	68·2 (62·4, 73·5)	-30·1 (-34·9, -25·3)	0·55 (0·49, 0·62)	3·82 (3·34, 4·36)	0·14 (0·12, 0·17)	0·56 (0·51, 0·62)	0·15 (0·12, 0·17)

Figure 2: Serotype-specific GMCs (lines) and percentage of participants achieving serotype-specific IgG ≥0·35µg/ml (bars) over time, for the ten shared serotypes and the three additional serotypes in PCV13, with 95% CIs.

Footnote
Sources of data: Group A at 2 months (pre-PCV); Group D (PCV10) and Group E (PCV13) at 3 months (post-one dose); and Group C (PCV10) and Group E (PCV13) at 5, 9, 10, and 18 months (post-two dose primary series, pre-booster, post-booster and at 18 months, respectively). Samples collected in a subset of participants at 18 months of age.

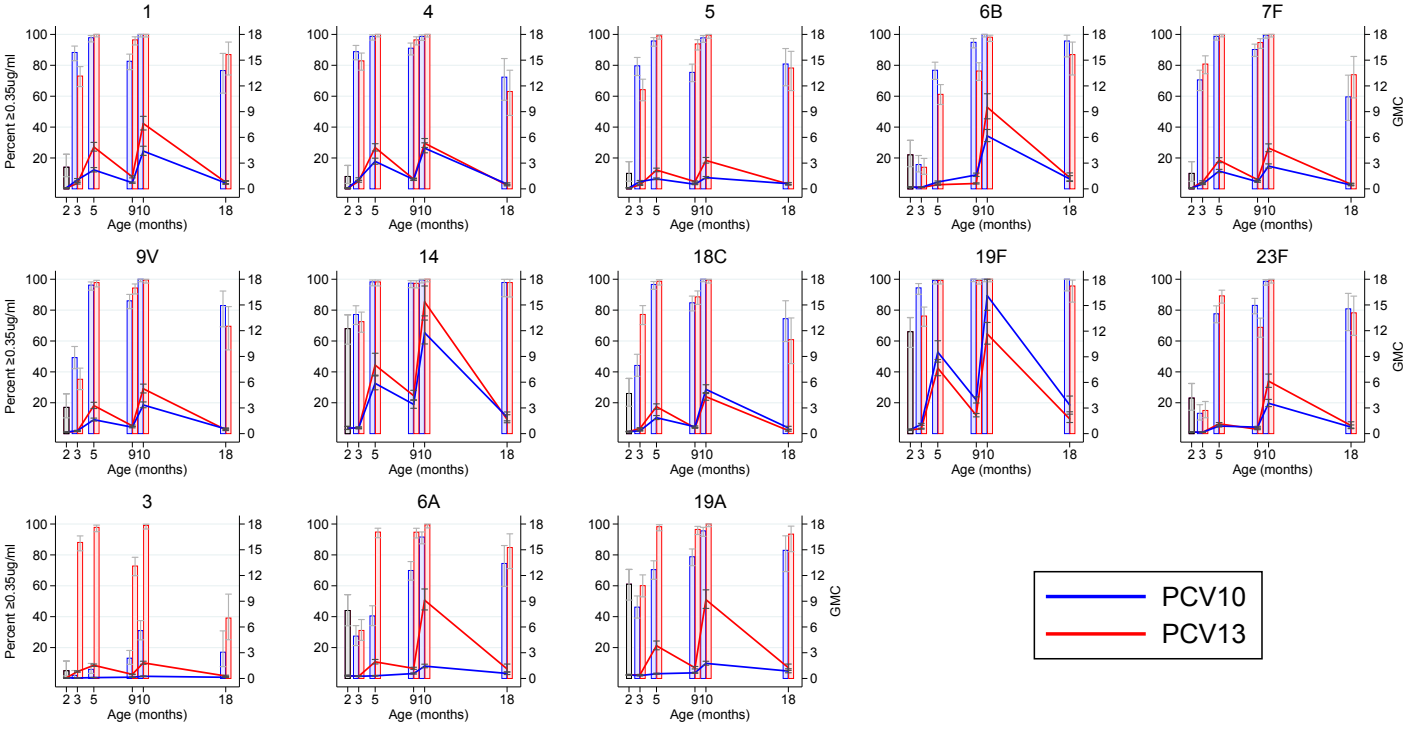

1
4
5
6B
7F
9V
14
18C
19F
23F
3
6A
19A
Percent ≥0.35ug/ml
GMC
Age (months)
2 3 5 9 10 18
0 3 6 9 12 15 18
0 20 40 60 80 100
PCV10
PCV13

Table 3: Functional antibody responses post-primary series and post-booster. Percentage of participants with serotype-specific OI ≥8 and GMOI four-weeks post-primary series and four-weeks post-booster dose, when given a 2+1 schedule of PCV10 or PCV13

	Post-primary series				Post-booster			
	% ≥8 (95% CI)		**GMOI** (95% CI)		**% ≥8** (95% CI)		**GMOI** (95% CI)	
	PCV10 (n=124)	PCV13 (n=124*)	PCV10 (n=124)	PCV13 (n=124*)	PCV10 (n=121)	PCV13 (n=120)	PCV10 (n=121)	PCV13 (n=120)
Shared serotypes								
1	66·1 (57·1, 74·4)	87·9 (80·8, 93·1)	22 (17, 28)	52 (40, 67)	90·9 (84·3, 95·4)	95·0 (89·4, 98·1)	145 (106, 198)	164 (127, 211)
4	100 (97·1, 100)	100 (97·1, 100)	922 (820, 1036)	1320 (1188, 1465)	99·2 (95·5, 100)	100 (97·0, 100)	1280 (1072, 1529)	1771 (1560, 2011)
5	97·6 (93·1, 99·5)	98·4 (94·3, 99·8)	351 (286, 430)	476 (394, 575)	98·3 (94·2, 99·8)	100 (97·0, 100)	768 (627, 941)	929 (802, 1076)
6B	71·8 (63·0, 79·5)	60·5 (51·3, 69·1)	59 (40, 86)	28 (20, 40)	96·7 (91·8, 99·1)	95·8 (90·5, 98·6)	299 (224, 399)	826 (592, 1153)
7F	96·8 (91·9, 99·1)	98·4 (94·3, 99·8)	250 (182, 343)	570 (418, 778)	100 (97·0, 100)	100 (97·0, 100)	484 (369, 636)	1231 (938, 1615)
9V	80·6 (72·6, 87·2)	99·2 (95·6, 100)	73 (52, 102)	267 (200, 357)	94·2 (88·4, 97·6)	99·2 (95·4, 100)	308 (217, 436)	742 (566, 974)
14	89·5 (82·7, 94·3)	93·5 (87·7, 97·2)	132 (92, 191)	220 (153, 316)	96·7 (91·8, 99·1)	96·7 (91·7, 99·1)	394 (293, 531)	454 (328, 628)
18C	88·7 (81·8, 93·7)	96·8 (91·9, 99·1)	124 (88, 175)	242 (189, 309)	99·2 (95·5, 100)	100 (97·0, 100)	732 (564, 950)	561 (446, 706)
19F	100 (97·1, 100)	99·2 (95·6, 100)	1217 (1078, 1375)	856 (728, 1008)	100 (97·0, 100)	98·3 (94·1, 99·8)	1579 (1380, 1807)	1095 (877, 1367)
23F	58·9 (49·7, 67·6)	76·6 (68·2, 83·7)	29 (21, 41)	53 (38, 75)	91·7 (85·3, 96·0)	100 (97·0, 100)	149 (109, 202)	689 (534, 890)
Additional PCV13-types								
3	0·0 (0·0, 2·9)	92·7 (86·6, 96·6)	4 (4, 4)	41 (34, 50)	3·3 (0·9, 8·2)	88·3 (81·2, 93·5)	4 (4, 5)	54 (43, 68)
6A	31·5 (23·4, 40·4)	97·6 (93·1, 99·5)	18 (12, 26)	1392 (1106, 1752)	66·9 (57·8, 75·2)	100 (97·0, 100)	118 (74, 189)	3847 (3311, 4468)
19A	35·5 (27·1, 44·6)	95·2 (89·8, 98·2)	9 (7, 11)	139 (106, 181)	61·2 (51·9, 69·9)	99·2 (95·4, 100)	25 (18, 34)	587 (461, 748)

* n=123 for serotype 3 - insufficient sera in one sample so serotype 3 not tested

Table 4: Reactogenicity. Percentage of participants reporting erythema at the vaccination site(s) and axillary fever, following vaccination at 2, 4, and 9·5 months of age

	2 months			4 months			9·5 months		
	n*	% any	% severe	n*	% any	% severe	n*	% any	% severe
Erythema (>30mm = severe)									
PCV10 site	244	9·4%	0·8%	235	11·1%	0·4%	218	8·7%	0·5%
PCV13 site	237	7·2%	0%	222	10·4%	0·5%	211	5·7%	0%
Infanrix-hexa site									
+ PCV10	244	5·3%	0·8%	236	8·9%	0·4%	222	5·9%	0·5%
+ PCV13	240	7·5%	0·4%	225	12·9%	0%	211	5·2%	0%
alone	192	5·7%	0%	188	8·0%	1·1%		n/a	
Fever (≥38·5°C = severe)									
PCV10 + *Infanrix-hexa*	237	43·9%	4·2%	235	43·4%	4·7%	225	38·7%	7·1%
PCV13 + *Infanrix-hexa*	236	41·5%	3·8%	227	44·1%	8·8%	219	40·6%	9·6%
Infanrix-hexa alone	186	18·8%	1·6%	187	9·6%	2·1%		n/a	

* A total of 1,809 diary cards were collected. 20 diary cards were excluded as they had no data recorded on erythema or fever. Otherwise, all available data contributed to the analysis. The maximum reported values for erythema and fever across days 0-4 were used.

Table S1: Schedule of vaccines and samples for infants enrolled into the Vietnam Pneumococcal Project

Group	2m	3m	4m	5m	6m	7m	9m	9·5m†	10m	12m	18m	19m	24m
A (3+1 PCV10)	Bld* NP PCV10 *Inf*	PCV10 *Inf*	PCV10 *Inf*	Bld	NP		Bld NP PCV10 MV		Bld	NP	Bld* NP MR	*Inf*	NP
B (3+0 PCV10)	NP PCV10 *Inf*	PCV10 *Inf*	PCV10 *Inf*	Bld	Bld NP		Bld* NP MV		Bld	NP	Bld* NP MR	*Inf*	NP
C (2+1 PCV10)	NP PCV10 *Inf*		PCV10 *Inf*	Bld	Bld * NP		Bld NP MV	PCV10 *Inf*	Bld	NP	Bld* NP MR	*Inf*	NP
D (2-dose PCV10)	NP PCV10 *Inf*	Bld	*Inf*		Bld NP PCV10 *Inf*	Bld	Bld* NP MV			NP	Bld* NP MR	*Inf*	NP
E (2+1 PCV13)	NP PCV13 *Inf*	Bld*	PCV13 *Inf*	Bld	NP		Bld NP MV	PCV13 *Inf*	Bld	NP	Bld* NP MR	*Inf*	NP
F (controls)	NP *Inf*	*Inf*	*Inf*		NP		NP MV			NP	Bld NP PCV10 *Inf*	Bld MR	NP PCV10 Bld

Bld = blood sample; NP = nasopharyngeal swab sample; *Inf* = *Infanrix-hexa* vaccine (DTP-Hib-HBV-IPV); MV = measles vaccine; MR = measles-rubella vaccine

* Each participant provides only one of these blood samples (the last 50 participants enrolled into groups A-E provide this sample at 18 months of age; the remainder provide it at the other time point)

† The Vietnam Ministry of Health does not permit co-administration of measles and *Infanrix-hexa*; therefore PCV and *Infanrix-hexa* were administered at 9·5 months in participants from groups C and E

Figure S1: Plots of the difference in the percentage of participants achieving serotype-specific IgG ≥0·35µg/ml four weeks post-vaccination for the ten shared serotypes, comparing: a) 2 doses of PCV13 and PCV10 at 2 and 4 months (Group E vs. Group C); and b) 2 doses of PCV13 at 2 and 4 months with 3 doses of PCV10 at 2, 3, and 4 months (Group E vs. Group A+B)

Footnote:
Plot a) shows 95% CIs for the two-sided tests of difference, whereas Plot b) shows 90% CIs for the one-sided test of non-inferiority. All CIs were calculated using the Newcombe Score method.

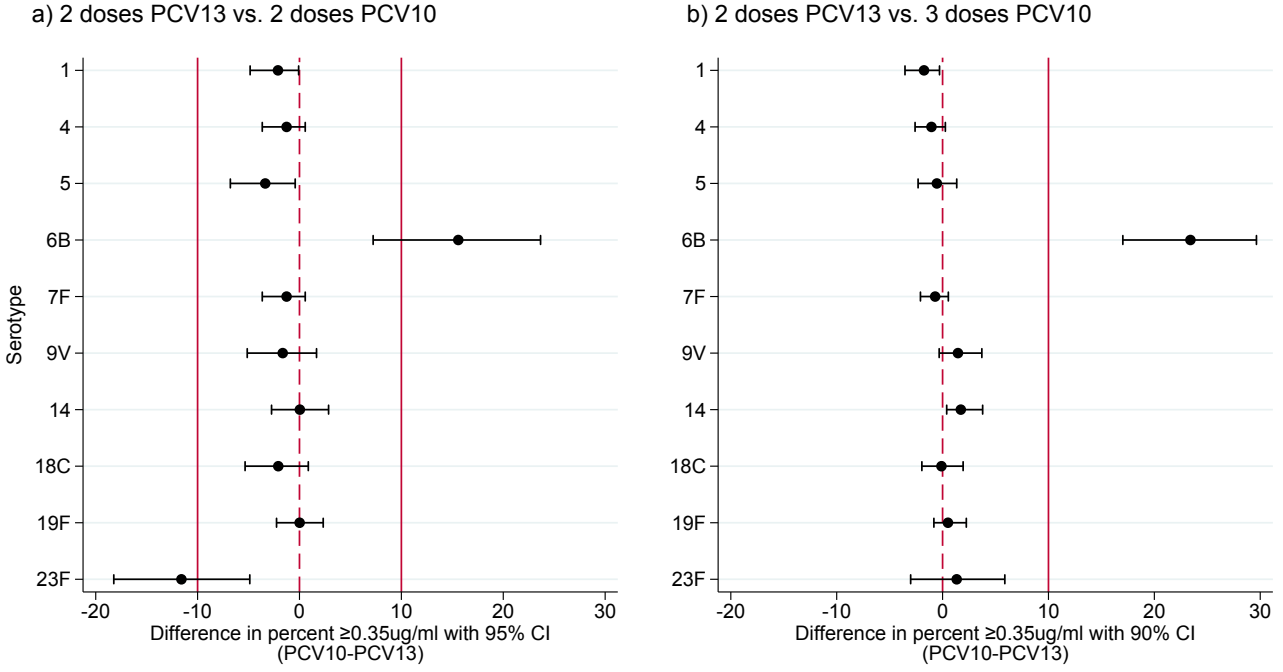

a) 2 doses PCV13 vs. 2 doses PCV10
b) 2 doses PCV13 vs. 3 doses PCV10
Serotype
1
4
5
6B
7F
9V
14
18C
19F
23F
-20
-10
0
10
20
30
Difference in percent ≥0.35ug/ml with 95% CI
(PCV10-PCV13)
Difference in percent ≥0.35ug/ml with 90% CI
(PCV10-PCV13)

Table S2: Post-primary series immunogenicity on the intention-to-treat population. Percentage of participants with serotype-specific IgG ≥0·35µg/ml and GMCs four-weeks after: 2 doses of PCV10 at 2 and 4 months of age (Group C), 2 doses of PCV13 at 2 and 4 months of age (Group E), or 3 doses of PCV10 at 2, 3, and 4 months of age (Group A+B)

	% ≥0·35µg/ml (95% CI)					GMC (95% CI)				
	2 doses PCV10 (n=240)	2 doses PCV13 (n=236)	Risk difference (95% CI) (PCV10-PCV13)	3 doses PCV10 (n=289)	Risk difference (90% CI) (PCV10-PCV13)	2 doses PCV10 (n=240)	2 doses PCV13 (n=236)	GMC ratio (95% CI) (PCV10/PCV13)	3 doses PCV10 (n=289)	GMC ratio (95% CI) (PCV10/PCV13)
Shared serotypes										
1	97.9 (95.2, 99.3)	100 (98.4, 100.0)	-2.1 (-4.8, -0.1)	98.3 (96.0, 99.4)	-1.7 (-3.5, -0.3)	2.22 (1.98, 2.48)	4.86 (4.38, 5.39)	0.46 (0.39, 0.53)	4.86 (4.38, 5.39)	0.57 (0.49, 0.66)
4	98.8 (96.4, 99.7)	100 (98.4, 100.0)	-1.3 (-3.6, 0.6)	99.0 (97.0, 99.8)	-1 (-2.6, 0.3)	3.21 (2.88, 3.58)	4.79 (4.39, 5.23)	0.67 (0.58, 0.77)	4.79 (4.39, 5.23)	0.8 (0.69, 0.93)
5	95.8 (92.5, 98.0)	99.2 (97.0, 99.9)	-3.3 (-6.7, -0.4)	98.6 (96.5, 99.6)	-0.5 (-2.3, 1.3)	1.17 (1.07, 1.27)	2.2 (2.01, 2.41)	0.53 (0.47, 0.60)	2.2 (2.01, 2.41)	0.83 (0.73, 0.94)
6B	77.1 (71.2, 82.2)	61.0 (54.5, 67.3)	16.1 (7.8, 24.1)	84.4 (79.7, 88.4)	23.4 (17.1, 29.6)	0.8 (0.70, 0.92)	0.49 (0.43, 0.55)	1.65 (1.37, 2.00)	0.49 (0.43, 0.55)	2.22 (1.84, 2.66)
7F	98.8 (96.4, 99.7)	100 (98.4, 100.0)	-1.3 (-3.6, 0.6)	99.3 (97.5, 99.9)	-0.7 (-2.1, 0.5)	2.07 (1.89, 2.26)	3.31 (3.03, 3.60)	0.63 (0.55, 0.71)	3.31 (3.03, 3.60)	0.92 (0.81, 1.04)
9V	96.3 (93.0, 98.3)	97.9 (95.1, 99.3)	-1.6 (-5.1, 1.6)	99.3 (97.5, 99.9)	1.4 (-0.3, 3.6)	1.63 (1.47, 1.81)	3.24 (2.91, 3.62)	0.5 (0.43, 0.58)	3.24 (2.91, 3.62)	0.76 (0.66, 0.88)
14	98.3 (95.8, 99.5)	98.3 (95.7, 99.5)	0 (-2.7, 2.8)	100 (98.7, 100.0)	1.7 (0.4, 3.7)	5.92 (5.17, 6.78)	7.83 (6.68, 9.18)	0.76 (0.61, 0.93)	7.83 (6.68, 9.18)	1.24 (1.03, 1.49)
18C	96.7 (93.5, 98.6)	98.7 (96.3, 99.7)	-2.1 (-5.3, 0.8)	98.6 (96.5, 99.6)	-0.1 (-1.9, 1.9)	1.87 (1.65, 2.12)	3.12 (2.82, 3.45)	0.6 (0.51, 0.70)	3.12 (2.82, 3.45)	1.24 (1.07, 1.44)
19F	99.2 (97.0, 99.9)	99.2 (97.0, 99.9)	0 (-2.2, 2.3)	99.7 (98.1, 100.0)	0.5 (-0.8, 2.2)	9.56 (8.40, 10.88)	7.6 (6.72, 8.59)	1.26 (1.05, 1.50)	7.6 (6.72, 8.59)	1.08 (0.92, 1.27)
23F	77.9 (72.1, 83.0)	89.4 (84.8, 93.0)	-11.5 (-18.1, -4.9)	90.3 (86.3, 93.5)	0.9 (-3.4, 5.4)	0.89 (0.78, 1.02)	1.14 (1.01, 1.29)	0.78 (0.65, 0.94)	1.14 (1.01, 1.29)	1.16 (0.98, 1.37)
Additional PCV13-types										
3	5.8 (3.2, 9.6)	97.9 (95.1, 99.3)	-92 (-94.7, -87.4)	97.9 (95.1, 99.3)	-91 (-93.3, -87.4)	0.1 (0.09, 0.11)	1.54 (1.41, 1.68)	0.07 (0.06, 0.08)	1.54 (1.41, 1.68)	0.07 (0.06, 0.08)
6A	40.8 (34.6, 47.3)	94.9 (91.3, 97.3)	-54.1 (-60.5, -46.8)	94.9 (91.3, 97.3)	-44.4 (-49.6, -38.8)	0.31 (0.28, 0.35)	1.94 (1.70, 2.22)	0.16 (0.14, 0.19)	1.94 (1.70, 2.22)	0.19 (0.16, 0.22)
19A	70 (63.8, 75.7)	98.3 (95.7, 99.5)	-28.3 (-34.5, -22.3)	98.3 (95.7, 99.5)	-30.5 (-35.2, -25.7)	0.55 (0.49, 0.61)	3.8 (3.33, 4.33)	0.14 (0.12, 0.17)	3.8 (3.33, 4.33)	0.15 (0.13, 0.17)

Table S3: Comparison of responses to a single dose of PCV10 or PCV13. Percentage of participants with serotype-specific IgG ≥0·35µg/ml and GMCs pre- and four-weeks post-one dose of PCV at 2 months of age

	% ≥0·35µg/ml (95% CI)				GMC (95% CI)			
	Pre-PCV (n=100)	Post-PCV10 (n=197)	Post-PCV13 (n=193)	Risk difference (95% CI) post-PCV (PCV10-PCV13)	Pre-PCV (n=100)	Post-PCV10 (n=197)	Post-PCV13 (n=193)	GMC ratio (95% CI) post-PCV (PCV10/PCV13)
Shared serotypes								
1	14·0 (7·9, 22·4)	88·3 (83·0, 92·5)	73·1 (66·2, 79·2)	15·3 (7·5, 22·9)	0·12 (0·10, 0·15)	1·05 (0·91, 1·20)	0·64 (0·56, 0·73)	1·64 (1·35, 1·99)
4	8·0 (3·5, 15·2)	88·8 (83·6, 92·9)	82·9 (76·8, 87·9)	5·9 (-1·0, 12·9)	0·09 (0·07, 0·10)	1·12 (0·98, 1·29)	0·88 (0·77, 1·00)	1·28 (1·06, 1·55)
5	10·0 (4·9, 17·6)	79·7 (73·4, 85·1)	64·2 (57·0, 71·0)	15·4 (6·5, 24·0)	0·11 (0·10, 0·13)	0·85 (0·74, 0·97)	0·46 (0·40, 0·53)	1·83 (1·51, 2·23)
6B	22·0 (14·3, 31·4)	15·7 (10·9, 21·6)	14·0 (9·4, 19·7)	1·7 (-5·4, 8·9)	0·21 (0·18, 0·24)	0·18 (0·16, 0·20)	0·17 (0·15, 0·19)	1·02 (0·87, 1·20)
7F	10·0 (4·9, 17·6)	70·6 (63·7, 76·8)	80·8 (74·6, 86·1)	-10·3 (-18·6, -1·7)	0·11 (0·09, 0·13)	0·57 (0·50, 0·66)	0·81 (0·70, 0·94)	0·71 (0·58, 0·86)
9V	17·0 (10·2, 25·8)	49·2 (42·1, 56·4)	35·2 (28·5, 42·4)	14·0 (4·2, 23·4)	0·18 (0·15, 0·20)	0·35 (0·31, 0·39)	0·28 (0·25, 0·31)	1·25 (1·07, 1·46)
14	68·0 (57·9, 77·0)	77·2 (70·7, 82·8)	72·5 (65·7, 78·7)	4·6 (-4·0, 13·2)	0·64 (0·49, 0·84)	0·69 (0·60, 0·78)	0·65 (0·55, 0·76)	1·06 (0·86, 1·30)
18C	26·0 (17·7, 35·7)	44·2 (37·1, 51·4)	77·2 (70·6, 82·9)	-33·0 (-41·7, -23·6)	0·24 (0·21, 0·28)	0·34 (0·30, 0·38)	0·62 (0·55, 0·70)	0·54 (0·46, 0·65)
19F	66·0 (55·8, 75·2)	94·4 (90·2, 97·2)	76·2 (69·5, 82·0)	18·3 (11·4, 25·2)	0·45 (0·39, 0·53)	1·09 (0·97, 1·21)	0·58 (0·53, 0·64)	1·87 (1·62, 2·16)
23F	23·0 (15·2, 32·5)	13·2 (8·8, 18·7)	15·0 (10·3, 20·9)	-1·8 (-8·8, 5·1)	0·19 (0·17, 0·23)	0·16 (0·14, 0·18)	0·15 (0·13, 0·17)	1·04 (0·88, 1·23)
Additional PCV13-types								
3	5·0 (1·6, 11·3)	2·0 (0·6, 5·1)	88·1 (82·7, 92·3)	-86·1 (-90·1, -79·9)	0·07 (0·06, 0·09)	0·06 (0·05, 0·07)	0·80 (0·72, 0·89)	0·07 (0·06, 0·09)
6A	44·0 (34·1, 54·3)	27·4 (21·3, 34·2)	31·1 (24·6, 38·1)	-3·7 (-12·6, 5·3)	0·32 (0·28, 0·37)	0·25 (0·23, 0·28)	0·25 (0·23, 0·28)	0·99 (0·87, 1·14)
19A	61·0 (50·7, 70·6)	46·2 (39·1, 53·4)	60·1 (52·8, 67·1)	-13·9 (-23·4, -4·0)	0·41 (0·36, 0·47)	0·33 (0·30, 0·37)	0·43 (0·38, 0·47)	0·79 (0·68, 0·91)

Table S4: Pre- and post-booster responses to a 2+1 schedule of PCV10 or PCV13. Percentage of participants with a) serotype-specific IgG ≥0·35µg/ml and b) GMCs, before and four-weeks after a booster dose of PCV at 9·5 months of age

a) Percentage of participants with serotype-specific IgG ≥0·35µg/ml (95% CI) before and four-weeks after a booster dose of PCV at 9·5 months of age

	PCV10		PCV13		Pre-booster risk difference (95% CI) (PCV10-PCV13)	Post-booster risk difference (95% CI) (PCV10-PCV13)
	Pre-booster (n=236)	Post-booster (n=226)	Pre-booster (n=228)	Post-booster (n=221)		
Shared serotypes						
1	82·6 (77·2, 87·2)	100 (98·4, 100)	96·5 (93·2, 98·5)	100 (98·3, 100)	-13·9 (-19·5, -8·5)	0 (-1·7, 1·7)
4	91·1 (86·7, 94·4)	98·7 (96·2, 99·7)	96·5 (93·2, 98·5)	100 (98·3, 100)	-5·4 (-10·0, -1·0)	-1·3 (-3·8, 0·6)
5	75·4 (69·4, 80·8)	97·8 (94·9, 99·3)	93·9 (89·9, 96·6)	99·5 (97·5, 100)	-18·4 (-24·8, -12·0)	-1·8 (-4·6, 0·7)
6B	94·9 (91·3, 97·3)	100 (98·4, 100)	76·3 (70·3, 81·7)	98·2 (95·4, 99·5)	18·6 (12·4, 24·9)	1·8 (-0·2, 4·6)
7F	90·3 (85·7, 93·7)	99·6 (97·6, 100)	94·7 (91·0, 97·3)	100 (98·3, 100)	-4·5 (-9·5, 0·4)	-0·4 (-2·5, 1·3)
9V	86·0 (80·9, 90·2)	100 (98·4, 100)	94·3 (90·4, 96·9)	99·5 (97·5, 100)	-8·3 (-13·8, -2·9)	0·5 (-1·3, 2·5)
14	97·5 (94·5, 99·1)	99·6 (97·6, 100)	97·4 (94·4, 99·0)	100 (98·3, 100)	0·1 (-3·1, 3·4)	-0·4 (-2·5, 1·3)
18C	84·7 (79·5, 89·1)	100 (98·4, 100)	88·6 (83·7, 92·4)	99·5 (97·5, 100)	-3·9 (-10·1, 2·4)	0·5 (-1·3, 2·5)
19F	100 (98·4, 100)	100 (98·4, 100)	99·1 (96·9, 99·9)	100 (98·3, 100)	0·9 (-0·8, 3·1)	0 (-1·7, 1·7)
23F	83·1 (77·6, 87·6)	98·7 (96·2, 99·7)	68·9 (62·4, 74·8)	99·5 (97·5, 100)	14·2 (6·4, 21·8)	-0·9 (-3·4, 1·4)
Additional PCV13-types						
3	13·1 (9·1, 18·1)	31·0 (25·0, 37·4)	72·8 (66·5, 78·5)	99·1 (96·8, 99·9)	-59·7 (-66·2, -51·8)	-68·1 (-73·8, -61·4)
6A	69·9 (63·6, 75·7)	91·6 (87·2, 94·9)	94·7 (91·0, 97·3)	99·5 (97·5, 100)	-24·8 (-31·3, -18·2)	-8·0 (-12·3, -4·3)
19A	78·8 (73·0, 83·8)	95·6 (92·0, 97·9)	96·5 (93·2, 98·5)	100 (98·3, 100)	-17·7 (-23·6, -11·9)	-4·4 (-8·0, -1·8)

b) GMCs (95% CI) before and four-weeks after a booster dose of PCV at 9·5 months of age

	PCV10		PCV13		Pre-booster GMC ratio (95% CI) (PCV10/PCV13)	Post-booster GMC ratio (95% CI) (PCV10/PCV13)
	Pre-booster (n=236)	Post-booster (n=226)	Pre-booster (n=228)	Post-booster (n=221)		
Shared serotypes						
1	0·71 (0·64, 0·79)	4·40 (3·91, 4·97)	1·40 (1·28, 1·53)	7·62 (6·86, 8·45)	0·51 (0·44, 0·58)	0·58 (0·49, 0·68)
4	1·09 (0·98, 1·22)	4·75 (4·20, 5·37)	1·14 (1·04, 1·24)	5·32 (4·82, 5·87)	0·96 (0·83, 1·11)	0·89 (0·76, 1·04)
5	0·54 (0·49, 0·59)	1·31 (1·20, 1·43)	0·85 (0·78, 0·92)	3·31 (3·00, 3·66)	0·63 (0·56, 0·72)	0·40 (0·35, 0·45)
6B	1·63 (1·44, 1·83)	6·17 (5·50, 6·92)	0·63 (0·56, 0·70)	9·51 (8·16, 11·09)	2·60 (2·21, 3·05)	0·65 (0·54, 0·78)
7F	0·83 (0·76, 0·91)	2·65 (2·41, 2·91)	1·07 (0·98, 1·17)	4·76 (4·33, 5·24)	0·78 (0·68, 0·88)	0·56 (0·49, 0·64)
9V	0·75 (0·68, 0·84)	3·34 (3·02, 3·69)	0·91 (0·83, 1·00)	5·23 (4·75, 5·77)	0·82 (0·72, 0·95)	0·64 (0·55, 0·73)
14	3·41 (2·96, 3·94)	11·76 (10·45, 13·24)	4·43 (3·89, 5·05)	15·37 (13·73, 17·21)	0·77 (0·63, 0·94)	0·77 (0·65, 0·90)
18C	0·81 (0·72, 0·90)	5·16 (4·68, 5·70)	0·67 (0·62, 0·73)	4·31 (3·89, 4·79)	1·19 (1·04, 1·37)	1·20 (1·04, 1·38)
19F	3·94 (3·59, 4·31)	16·16 (14·45, 18·08)	2·16 (1·97, 2·37)	11·68 (10·48, 13·02)	1·82 (1·60, 2·08)	1·38 (1·18, 1·62)
23F	0·76 (0·68, 0·86)	3·55 (3·15, 3·99)	0·51 (0·46, 0·57)	6·12 (5·40, 6·94)	1·49 (1·27, 1·75)	0·58 (0·49, 0·69)
Additional PCV13-types						
3	0·15 (0·13, 0·16)	0·25 (0·23, 0·29)	0·48 (0·45, 0·51)	1·82 (1·65, 2·01)	0·31 (0·27, 0·35)	0·14 (0·12, 0·16)
6A	0·57 (0·51, 0·65)	1·44 (1·25, 1·66)	1·18 (1·06, 1·31)	9·13 (7·99, 10·43)	0·49 (0·42, 0·57)	0·16 (0·13, 0·19)
19A	0·66 (0·60, 0·73)	1·76 (1·55, 2·00)	1·24 (1·11, 1·39)	9·18 (8·16, 10·33)	0·53 (0·46, 0·61)	0·19 (0·16, 0·23)

Table S5: Antibody levels at 18 months of age. Percentage of participants with serotype-specific IgG ≥0·35µg/ml (95% CI) and GMCs (95% CI) at 18 months of age, following a 2+1 schedule of PCV10 or PCV13 at 2, 4, and 9·5 months of age

	% ≥0·35µg/ml (95% CI)		Risk difference (95% CI)	GMC (95% CI)		GMC ratio (95% CI)
	PCV10 (n=47)	PCV13 (n=46)	(PCV10-PCV13)	PCV10 (n=47)	PCV13 (n=46)	(PCV10/PCV13)
Shared serotypes						
1	76·6 (62·0, 87·7)	87·0 (73·7, 95·1)	-10·4 (-25·8, 5·6)	0·68 (0·53, 0·87)	0·77 (0·61, 0·96)	0·88 (0·63, 1·23)
4	72·3 (57·4, 84·4)	63·0 (47·5, 76·8)	9·3 (-9·5, 27·3)	0·56 (0·45, 0·71)	0·43 (0·34, 0·54)	1·31 (0·96, 1·79)
5	80·9 (66·7, 90·9)	78·3 (63·6, 89·1)	2·6 (-13·8, 19·0)	0·61 (0·49, 0·74)	0·56 (0·44, 0·70)	1·09 (0·80, 1·47)
6B	95·7 (85·5, 99·5)	87·0 (73·7, 95·1)	8·8 (-3·4, 21·8)	1·15 (0·87, 1·54)	1·32 (0·93, 1·86)	0·88 (0·56, 1·36)
7F	59·6 (44·3, 73·6)	73·9 (58·9, 85·7)	-14·3 (-32·0, 4·7)	0·46 (0·35, 0·59)	0·53 (0·43, 0·66)	0·86 (0·62, 1·20)
9V	83·0 (69·2, 92·4)	69·6 (54·2, 82·3)	13·4 (-3·9, 29·9)	0·55 (0·45, 0·67)	0·45 (0·36, 0·58)	1·21 (0·89, 1·64)
14	97·9 (88·7, 99·9)	97·8 (88·5, 99·9)	0·0 (-9·1, 9·4)	1·94 (1·49, 2·52)	1·67 (1·27, 2·20)	1·16 (0·80, 1·69)
18C	74·5 (59·7, 86·1)	60·9 (45·4, 74·9)	13·6 (-5·3, 31·3)	0·67 (0·53, 0·86)	0·36 (0·28, 0·46)	1·85 (1·32, 2·61)
19F	100 (92·5, 100)	95·7 (85·2, 99·5)	4·3 (-3·8, 14·5)	3·36 (2·56, 4·40)	1·73 (1·31, 2·28)	1·94 (1·32, 2·86)
23F	80·9 (66·7, 90·9)	78·3 (63·6, 89·1)	2·6 (-13·8, 19·0)	0·77 (0·59, 1·01)	0·95 (0·65, 1·38)	0·81 (0·51, 1·29)
Additional PCV13-types						
3	17·0 (7·6, 30·8)	39·1 (25·1, 54·6)	-22·1 (-38·7, -3·8)	0·14 (0·11, 0·18)	0·29 (0·22, 0·38)	0·47 (0·33, 0·67)
6A	74·5 (59·7, 86·1)	84·8 (71·1, 93·7)	-10·3 (-26·2, 6·3)	0·59 (0·46, 0·76)	1·12 (0·75, 1·68)	0·53 (0·33, 0·84)
19A	83·0 (69·2, 92·4)	93·5 (82·1, 98·6)	-10·5 (-24·3, 3·2)	0·86 (0·66, 1·13)	1·26 (0·94, 1·68)	0·69 (0·46, 1·01)

Table S6: Percentage of participants with serotype-specific IgG ≥1.0µg/ml. Percentage of participants with serotype-specific IgG ≥1.0µg/ml (95% CI) four-weeks post-primary series and four-weeks post-booster, in a 2+1 schedule of PCV10 or PCV13 at 2, 4, and 9·5 months of age

	Post-primary series			Post-booster		
	PCV10 (n=237)	PCV13 (n=232)	Risk difference (95% CI) (PCV10-PCV13)	PCV10 (n=226)	PCV13 (n=221)	Risk difference (95% CI) (PCV10-PCV13)
Shared serotypes						
1	81.4 (75.9, 86.2)	97 (93.9, 98.8)	-15.5 (-21.2, -10.1)	92.5 (88.2, 95.6)	98.6 (96.1, 99.7)	-6.2 (-10.5, -2.4)
4	90.3 (85.8, 93.7)	98.7 (96.3, 99.7)	-8.4 (-12.9, -4.4)	95.1 (91.5, 97.5)	99.1 (96.8, 99.9)	-4 (-7.7, -0.8)
5	64.1 (57.7, 70.2)	84.9 (79.6, 89.3)	-20.8 (-28.2, -13.0)	65.5 (58.9, 71.7)	95.9 (92.4, 98.1)	-30.4 (-37.1, -23.6)
6B	42.2 (35.8, 48.8)	20.7 (15.7, 26.5)	21.5 (13.2, 29.4)	97.8 (94.9, 99.3)	94.6 (90.7, 97.2)	3.2 (-0.5, 7.2)
7F	86.9 (82.0, 90.9)	94.8 (91.1, 97.3)	-7.9 (-13.3, -2.7)	92.5 (88.2, 95.6)	99.1 (96.8, 99.9)	-6.6 (-10.9, -3.0)
9V	76.8 (70.9, 82.0)	91.8 (87.5, 95.0)	-15 (-21.5, -8.5)	96.5 (93.1, 98.5)	98.2 (95.4, 99.5)	-1.7 (-5.2, 1.5)
14	93.2 (89.3, 96.1)	93.5 (89.6, 96.3)	-0.3 (-5.0, 4.4)	99.1 (96.8, 99.9)	98.6 (96.1, 99.7)	0.5 (-2.0, 3.1)
18C	77.2 (71.3, 82.4)	93.1 (89.0, 96.0)	-15.9 (-22.2, -9.6)	99.6 (97.6, 100.0)	95.9 (92.4, 98.1)	3.6 (0.8, 7.1)
19F	95.4 (91.8, 97.7)	96.6 (93.3, 98.5)	-1.2 (-5.1, 2.6)	100 (98.4, 100.0)	99.1 (96.8, 99.9)	0.9 (-0.9, 3.2)
23F	50.2 (43.7, 56.7)	53.4 (46.8, 60.0)	-3.2 (-12.2, 5.8)	91.6 (87.2, 94.9)	96.4 (93.0, 98.4)	-4.8 (-9.5, -0.3)
Additional PCV13-types						
3	2.1 (0.7, 4.9)	77.6 (71.7, 82.8)	-75.5 (-80.5, -69.1)	9.7 (6.2, 14.4)	79.6 (73.7, 84.7)	-69.9 (-75.7, -62.5)
6A	10.5 (6.9, 15.2)	75 (68.9, 80.4)	-64.5 (-70.6, -57.0)	60.6 (53.9, 67.0)	97.7 (94.8, 99.3)	-37.1 (-43.7, -30.3)
19A	21.5 (16.5, 27.3)	89.2 (84.5, 92.9)	-67.7 (-73.5, -60.4)	73.5 (67.2, 79.1)	99.1 (96.8, 99.9)	-25.6 (-31.8, -19.8)