Title

Effect of reduced two-dose (1+1) schedule of 10 and 13-valent pneumococcal conjugate vaccines (Synflorix™ and Prevenar13™)) on nasopharyngeal carriage and serotype-specific immune response in the first two years of life: Results from an open-labelled randomized controlled trial in Indian children.

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Abstract

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Introduction: The World Health Organization recommends the administration of pneumococcal conjugate vaccines (PCV) in 3-dose schedules (3+0 or 2+1) for programmatic inclusion. Mature PCV programs have started considering a reduced dose (1+1) schedule as a cost-effective alternative for maintaining the direct and indirect impacts of the program as well as alleviating crowded immunization schedules. This study aimed to assess the effect of a reduced dose regime (1+1) of PCV10 and PCV13 along with 3-dose regimes on pneumococcal carriage and immunogenicity in the first two years of life in Indian children.

Methods: A total of 805 healthy Indian infants aged 6-8 weeks were randomized to 7 groups (n=115 per group). Six groups received Synflorix^{TM} (PCV10) or Prevenar13^{TM} (PCV13) in the following schedules: 3+0 (6, 10, and 14 weeks); 2+1 (6, 14 weeks, 9 months); 1+1 (14 weeks, 9 months) and the 7th group was a PCV-naïve control group. Nasopharyngeal swabs were collected at 6, 18 weeks, and 9, 10, 15, and 18 months of age. Venous blood samples were collected at 18 weeks, 9, 10, and 18 months of age for assessment of sero-specific IgG antibodies. Additionally, functional antibodies using an opsonophagocytic assay (OPA) were assessed at 10 and 18 months of age in a subset of participants.

Results: At 15 months of age, 1+1 schedule of PCV13 showed a significant reduction of 45% in vaccine-type (VT) carriage [OR=0.55 (95% CI; 0.31-0.97), p=0.038] as compared to the control which was comparable to 3-dose schedules. The 1+1 schedule of PCV10 showed a reduction of 38% with 10VT serotypes which was not significant [OR=0.62 (95% CI; 0.31-1.19), p=0.15]. The VT-carriage was further reduced at 18 months in all schedules of PCV13 and PCV10 (using 10VT+19A+6A). The immune responses at 18 weeks of age in those receiving a single primary dose were inferior as compared to 2+1 and 3+0 schedules for the majority of serotypes (except 1,3,4,5, and 6A). At 9 months of age, before the booster dose, these differences had largely disappeared. At 10 months of age, the immune response was comparable between 1+1 and 2+1 schedules and was superior to the 3+0 schedule for all serotypes for both PCV10 and PCV13. At 18 months, the persistent immune response was comparable for all the three schedules for PCV10 and PCV13.

Conclusion: The reduced dose schedule (1+1) of PCV10 and PCV13 results in significant VT-carriage reduction and immune protection in Indian children during the second year of life which is comparable to WHO-recommended 3-dose schedules.

Keywords

pneumococcal carriage, serotype-specific antibodies, pneumococcal conjugate vaccines, reduced dose regime

Word count – 4128

Introduction

Streptococcus pneumoniae is an important cause of childhood pneumonia and invasive pneumococcal disease (IPD) in India and worldwide(1,2). The World Health Organisation (WHO) has recommended the use of 3-dose regimes of pneumococcal conjugate vaccines (PCV10 or PCV13) in national childhood immunisation programs either as 3+0 (3 primary doses at 6, 10 and 14 weeks with no booster dose) or 2+1 (2 primary doses at 6 and 14 weeks with a booster dose at 9 months) (3). Widespread use of PCV in the health programs of high-and-middle-income countries has led to a substantial reduction in the IPD amongst vaccinated children through direct protection as well as amongst unvaccinated age groups through indirect (herd) protection(4).

Nasopharyngeal pneumococcal carriage (NPC) is a precondition for the development of pneumococcal pneumonia (3). Reduction in the nasopharyngeal carriage of vaccine serotypes (VT) has been documented with 3+1, 3+0, and 2+1 regimens of PCV which has resulted in a reduction in VT-IPD, reduced transmission, and herd protection (5). The presence of high titres of serotype-specific antibodies against PCV (>0.35 mcg/ml) has been shown to correlate with protection against IPD and is established as a threshold for licensure of PCV products (5–7).

While the inclusion of three primary doses may be associated with a reduced risk of breakthrough infections in the first year of life as compared to two primary doses(8), a two-dose primary series with a booster may offer better protection against colonisation and IPD from the second year of life onwards and herd protection to unvaccinated close contacts (9).

Recently, countries with mature PCV programs have shown that herd protection generated by sustained high coverage of PCV with a booster dose regardless of the number of priming doses, can keep VT-carriage in children at a low minimising transmission. This has led to the implementation of 1+1 schedule (1 primary dose with one booster) as a cost-effective alternative to the existing schedules of PCV for maintaining protection against pneumococcal disease at the community level while alleviating the currently crowded immunisation schedule (11,12). The United Kingdom recently switched to a 1+1 schedule based on the findings that post-booster responses with a 1+1 schedule were superior or equivalent to responses after a 2+1 schedule for the majority of the serotypes (13,14). A similar strategy is under consideration in South Africa(10,15). In Cuba, the evaluation of a novel strategy of pneumococcal vaccination is underway in which mass vaccination with high coverage of children aged 1-5 years is proposed to achieve herd protection followed by a reduced dose schedule in infants (16).

Currently, PCV is administered in a 2+1 schedule as part of the Indian national immunization program (17,18). A reduced dose schedule (1+1) of PCV seems an attractive and viable option for the long-term sustainability of the program considering the cost-effectiveness and ease of implementation once the PCV programs mature. However, there is a lack of evidence on the immunogenicity of the 1+1 schedule and its' impact on NPC in Indian children. The present study aims to assess these parameters using the 1+1 schedule and WHO-recommended 3-dose PCV schedules in Indian children.

Methods

Study Design and Population

This was a phase-IV, single-centre, randomized, open-labelled, parallel-arm clinical trial conducted at Vadu Rural Health Program of KEM Hospital Research Centre, Pune, India from July 2016 to May 2018 (http://ctri.nic.in/Clinicaltrials/login.php: CTRI/2016/06/007042).

Healthy infants aged 6-8 weeks were randomized to receive one of the following schedules for PCV: (1) PCV-13, 3+0 (primary vaccination at 6, 10 and 14 weeks with no booster vaccination); (2) PCV-13, 2+1 (primary vaccination at 6 and 14 weeks with a booster vaccination at 9 months); (3) PCV-13, 1+1 (primary single dose at 14 weeks and booster vaccination at 9 months); (4)PCV-10, 3+0; (5) PCV-10, 2+1; (6) PCV-10, 1+1; (7) PCV-naïve control group [n=115 for each group] [Figure 1]. Computer-generated randomization was done using block size of 7 and allocation concealment was done using sealed envelopes. The children received routine vaccines included in the national immunization program of India concomitantly. Healthy infants whose parents had provided written informed consent and those who were willing to comply with the study protocol and stay in the area for the study period were included in the study. Weight and height measurements were recorded for all children at baseline. Children with any significant malnutrition or other systemic illness or those who have received any blood product were excluded.

The study was conducted as per the principles of Good Clinical Practices, the Declaration of Helsinki, and Indian regulatory requirements. An approval from institutional ethics committee of KEM Hospital Research Centre, Pune was obtained before starting with the study. The study was conducted before rollout of PCV in the public health program of India and the study participants in the control group were offered two doses of the PCV13 vaccine after the study completion.

Study Vaccines

Prevenar13^{TM} (Pfizer) was administered to the study participants from PCV13 study groups which contains pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F. Synflorix™ (GlaxoSmithKline) was administered to the study participants from PCV10 study groups, which contains pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F. Both vaccines were administered in the dose of 0.5 ml intramuscularly on the anterolateral thigh.

Assessment of nasopharyngeal pneumococcal carriage

A single nasopharyngeal swab was collected from each participant at 6 and 18 weeks, 9, 10 15, and 18 months of age using nylon flocked swabs and were immediately inserted in skim milk, tryptone, glucose, and glycerine (STGG) medium. The samples were stored overnight at -80^{0}C at the field site and were transported the next day to the Department of Microbiology, KEM Hospital, Pune. Three 10-fold serial dilutions of the samples were made and a loopful (10 µl) of the preferred dilution was inoculated on sheep blood agar with gentamicin (5 µg/ml) and incubated for 18-24 hours at 37°C in CO_2-incubator for isolation of *Streptococcus pneumoniae* colonies. Bacterial colonies were identified by various biochemical methods, colony count was noted and serotyping was done by Quellung reaction (19). The laboratory

team was blinded to the study group allocation and was unaware of the PCV schedule received by the study participants. Additionally, antibiotic usage was assessed during all time points by questionnaire and urinary assay.

Immunogenicity assessment

Venous blood samples (volume up to 5 ml) were collected at four timepoints: one-month post-primary vaccination (18 weeks of age), just before booster vaccination (9 months of age), one-month post-booster vaccination (10 months of age), and in the second year of life (18 months) [Figure 1]. Sera were separated from the blood samples using aseptic precautions and were stored at -80^{0}C till further processing. The sera were shipped in coded batches to WHO pneumococcal reference laboratory at Institute of Child Health, University College London (ICH-UCL) for assessment of vaccine serotype-specific antibodies of *Streptococcus pneumoniae* for 13 serotypes using enzyme-linked immunosorbent assay (ELISA) (20). Percentage of children with SSIgG $\geq$0.35 mg/mL were considered as sero-responders (21). Functional immune responses using opsonophagocytic assays (OPA) were performed for all 13 serotypes in a randomly selected subset (20% of participants from each group maintaining anonymity) at 10 months and 18 months (22). The cut-off level of >=8 was used for opsonic titres(23).

Statistical analysis

The primary hypothesis was that 1+1 regime of PCV will result in significant reduction in the VT-carriage at 15 months of age as compared to the unvaccinated control group. Considering baseline VT-carriage of 50% (24), to detect at least a 50% relative reduction of VT-carriage at 15 months, 100 evaluable study participants were needed in each group at 80% power with a two-sided alpha of 0.05 using a Z-test. Adding 15% for dropouts, the total number of participants was 115 in each group.

The analysis was done on intention to treat and all available data points were used for the analysis. The NPC at all time points was expressed as a percentage. The number of participants with baseline pneumococcal carriage was compared amongst the study groups using Pearson's chi-square test. Additionally, the carriage was compared between individual study group and the control group at each timepoint in the study. The presence of at least one VT serotype (either dominant or subdominant in the case of multiple serotypes) was classified as the target state. All samples excluding the target state i.e. non-vaccine type (NVT), no growth, and non-typable samples were considered to be in reference state (25,26). The following three target states were considered for analysis: a) 13VT for PCV13 vaccine schedules; b) 10VT for PCV10 vaccine schedule; c) 10VT + 6A +19A for PCV10 vaccine schedules. The addition of 6A and 19A to 10 VT was considered for PCV10 schedules due to reported cross-reactivity of serotypes 6B and 19F with serotypes 6A and 19A, respectively(27). VT-carriage was compared between test and control groups using identical multiple logistic regression at each timepoint. Univariate logistic regression analysis was carried out to identify risk factors potentially associated with VT-carriage . These included baseline carriage, gender and antibiotic usage in the previous 15 days. The risk factors with p value of <= 0.25 at any timepoint were included in the final multiple logistic regression model. The reduction in VT-carriage (protection against VT colonisation) was estimated using the equation 1-OR (25,28).

For immunological endpoints, the percentages of infants reaching pre-defined immunologic cut-offs, antibody GMCs and OPA geometric mean titres (GMTs) were calculated with 95% confidence intervals (CIs). Equivalence of 3+0 and 2+1 versus 1+1 for each serotype was considered if both the upper and lower bounds of the 2-sided 95% CI of the GMC ratios (3+0/1+1) and (2+1/1+1) for a particular serotype was between 0.5 and 2.0. These equivalence margins are aligned with those used to support licensure of the available PCV(29). All the analysis was done using Stata version 15.0.

Results

Baseline demographics

A total of 944 children were screened of whom 805 were randomised to one of the study groups and 773 (96%) participants completed follow-up till the age of 18 months [Figure 2]. The baseline demographic characteristics were comparable across all the study groups. Baseline carriage of *Streptococcus pneumoniae* at 6 weeks was in the range of 16-27% and was comparable across the groups. The baseline carriage for 10VT serotypes was marginally lower in PCV10 1+1 group as compared to control (1.75%vs.7%, p= 0.053) [Table 1].

Primary Outcome: Pneumococcal carriage at 15 months of age

At 15 months of age i.e., 6 months after the booster dose, PCV13, 1+1 schedule demonstrated a significant reduction of 45% in carriage of 13VT types in comparison to the control group. [OR=0.55(95%CI; 0.31-0.97), p=0.038]. PCV10, 1+1 schedule showed a non-significant reduction of 38% for 10 VT serotypes and a nonsignificant reduction of 37% for 10VT+6A+19A serotypes. PCV13 2+1 schedule demonstrated a significant reduction of 55% in 13VT carriage [OR=0.45(95%CI;0.25-0.81), p=0.007]. PCV10 2+1 schedule demonstrated a significant 45% reduction in 10VT+6A+19A [OR=0.55, (95%CI;0.31-0.96),p=0.036]. PCV13 3+0 schedule showed a significant reduction of 54% in 13VT carriage [OR=0.46, (95%CI;0.26-0.82),p=0.008]. PCV10 3+0 schedule demonstrated a significant reduction 53% in 10VT+6A+19A [OR=0.47(95%CI,0.26-0.84),p=0.011].The 3-dose schedules of PCV10 didn't result in a significant reduction of 10VT-carriage as compared to the control [Table 2, Table 3 and Figure 3].

Pneumococcal carriage at 18 weeks, 9, 10, and 18 months of age

At 18 weeks i.e., one month after primary dosing, PCV13 3+0 schedule demonstrated a significant reduction of 49% as compared to the control group. PCV10 3+0 schedule showed a reduction of 38% and 50% for 10 VT and 10VT+6A+19A serotypes respectively which was significant for 10VT+6A+19A. The 2+1 and 1+1 schedules of PCV13 and PCV10 did not result in significantly lower VT-carriage compared to the control group.

At the age of 9 months i.e., 4.5 months after primary vaccination, PCV13 3+0 schedule showed a significant reduction of 45% in 13VT carriage. No other schedules showed significant VT-carriage reduction as compared to the control group.

At the age of 10 months i.e., one month after booster dose, no schedules of PCV13 or PCV10 showed significantly lower VT-carriage as compared to the control group.

At 18 months of age i.e., 9 months after booster dose, PCV13 1+1 schedule showed a significant reduction of 45% in VT-carriage as compared to the control group. PCV10 1+1 schedule showed 44% and 45% reduction for 10VT and 10VT+6A+19A which was significant for 10VT+6A+19A. The 2+1 and 3+0 schedules of PCV13 and PCV10 (for 10VT+6A+19A serotypes) demonstrated significantly lower VT-carriage. PCV10 schedules did not show significantly lower carriage for 10VT serotypes [Table 2, Table 3 and Figure 3].

Multiple serotypes were detected only in 3.68% (173 out of 4696) of the samples collected.

Immunogenicity outcomes

At 18 weeks of age i.e., one month after primary dosing, the 3+0 and 2+1 schedules of both vaccines were superior to the 1+1 schedule for most serotypes by all immune parameters, percent sero-responders, GMC titres, and GMC ratios, except for serotypes 1[GMC ratio for PCV10 and PCV13], 4[GMC ratio for PCV10 and PCV13], and 5 [GMC ratio for both PCV10 and PCV13], and 3 [GMC ratio for PCV13] [Figures 4a, 5a, 6a, 6e].

At 9 months of age i.e., 4.5 months after primary vaccination, the persistence of immune response was comparable across all the three schedules for PCV10 and PCV13 in terms of GMC ratio, except for the superiority of the 3+0 schedule of PCV10 for serotypes 6B, 14, and 18C [Figure 4b and 5b]. For both PCV10 and PCV13, the serotype-specific GMC levels were comparable amongst all schedules for most of the serotypes except 6B, 14, and 19F for PCV10 and serotype 14 for PCV13 [Figure 6b and 6f]. The percentage of sero-responders was numerically highest for the 3+0 schedule of PCV10 and PCV13 for all serotypes except 19F. Notably, for serotypes 5, 6A, 6B, 7F, 14, 18C, 19A, 19F, and 23F serotypes, the percentage of sero-responders in 2+1 and 1+1 groups increased at 9 months as compared to18 weeks, potentially indicating continued acquisition of these vaccine serotypes in lesser dose primary schedules [Table 3 and 4].

At 10 months of age i.e., one-month post-booster vaccination, the immune responses with 1+1 schedule of PCV10 and PCV13 were comparable to 2+1 schedule and were superior as compared to 3+0 for all the serotypes in terms of the GMC ratios and percentage sero-responders[Figure 4c, 5c and Table 3,4]. GMC levels were higher following booster vaccination, using the 1+1 schedule as compared to 2+1 schedule for serotypes 1, 4, 14, 19A, and 19F for both PCV10 and PCV13[Figure 6c and 6g]. OPA GMTs were higher for 1+1 schedule as compared to 2+1 for serotypes 1,4,5,6A,6C,14,18C,19F for PCV10 (8/13) and 1,3,4,5,14,18C,19A,19F,23F for PCV13 (9/13) [Table 5 and 6].

At 18 months of age, 1+1 and 2+1 schedules of both vaccines demonstrated higher sero-responders for all serotypes [Table 3 and 4], higher GMCs for all serotypes except 23F [with both vaccines], higher percent OPA responders for all serotypes, and higher OPA GMTs compared to the 3+0 schedules [Figure 4d, 5d, 6d, and 6h]. Of interest, the OPA GMTs for the 1+1 schedule were higher than those of the 2+1 schedule for 7 of the 10 serotypes in the PCV10 group (serotypes 4, 5, 6B, 7F, 9V, 19A, 23F) and for 4 of 13 serotypes in the PCV groups (serotypes 1, 5, 6A, 19F) [Table 5 and 6].

Discussion

The study results show that the 1+1 schedule of PCV10 and PCV13 can achieve a significant reduction in VT-carriage and adequate immune protection in Indian children in the second year of life which is comparable to the 3-dose schedules of PCV10 and PCV13. However, in the first year of life, this reduced dose schedule did not reduce VT-carriage in comparison to the 3+0 schedule and elicited an inferior immune response in comparison to either of the WHO-recommended 3-dose schedules.

Early and high nasopharyngeal acquisition of pneumococci was observed in our study participants which was consistent with previous Indian studies(24,30). The VT-carriage found in the control group was similar our earlier study results (31). Also, similar to previous studies, the overall pneumococcal carriage was not significantly altered after PCV vaccination(32,33). It is noteworthy that the 1+1 schedule of PCV exhibited significant VT-carriage reduction in the second year of life despite high carriage prevalence in a PCV-naïve population. Our findings regarding VT-carriage reduction in the first year of life are similar to the earlier published literature. The real-world data from Israel has shown that reduced-dose PCV schedules may confer lower protection against VT-carriage during the first year of life (34). A systematic review and meta-analysis of the short-term impact of each primary dose of PCV on VT-carriage showed that one vs two primary doses of PCV did not achieve significant VT-carriage reduction at 4-6 months of age. However, VT-carriage was significantly lower after 7 months(35).

The booster containing schedules of both PCV10 and PCV13 showed a significant reduction in VT-carriage at 15-18 months. Importantly, the non-booster containing the 3+0 schedule of PCV13 also showed significant VT-carriage reduction in the first year of life which continued until 18 months of age. These results are in agreement with the systematic review by Fleming-Dutra et al which showed that 3+0 and 2+1 schedules may achieve similar VT-carriage reduction in the second year of life(32). PCV10 schedules achieved significantly lower NPC for 10VT+6A+19A serotypes but not for 10VT serotypes indicating cross-protection offered by PCV10 against 6A and 19A serotypes in Indian children. Similarly, two head-to-head studies of PCV10 in Vietnam and Finland showed slightly better VT-carriage reduction with 2+1 schedule with no statistically significant difference between the 2+1 and 3+0 schedules (36,37). However, both these studies were conducted in low carriage settings. In the first year of life, 3+0 schedule of PCV10 and PCV13 achieved superior VT-carriage reduction as compared to the 2+1 and 1+1 schedules which were in agreement with the findings of a previous meta-analysis that during the first year of life, PCV 3+0 was the only dosing schedule to significantly reduce VT-carriage when compared to no PCV (32). The long-term VT-carriage reduction achieved by the 3+0 schedule could be due to very high titres of SSIgG antibodies induced by a greater number of doses preventing newer acquisition of vaccine serotypes during the period of maximum colonisation(32,35). However, in view of data from Australia demonstrating an increase in IPD in the second year of life with a 3+0 schedule (38) and increasing evidence that key transmitters are toddlers (39), it seems prudent that the booster-containing schedules may be better than ones without the booster.

The study results show that the reduced dose 1+1 schedule of both PCV10 and PCV13 offers good immunological protection in Indian infants following booster vaccination for most of the vaccine serotypes. Following booster vaccination, the GMC titers and the proportion of sero-responders associated with 1+1 were overall superior to the 3+0 schedule and comparable to the 2+1 schedule for both PCV10 and PCV13. The superior GMC results obtained in the present study for the 1+1 schedule of PCV10 and PCV13 at post-booster timepoint (10 months of age) are very similar to that obtained by Madhi et al (15) and Goldblatt et al (14) using 1+1 schedule. Similarly, the OPA GMTs were higher with a 1+1 schedule as compared to 2+1 of PCV10 for 8 out of 10 serotypes at 10 months and 7 out of 10 serotypes at 18 months. For PCV13, OPA GMTs were higher for 1+1 as compared to 2+1 for 9 out of 13 serotypes at 10 months and 5 out of 13 serotypes at 18 months of age. The serotype-specific IgG GMCs and OPA GMT elicited by the 1+1 schedule were higher than those elicited by the 3+0 schedule for almost all serotypes at 18 months of age. For serotypes 6B, 9V and 23F, the serotype-specific IgG GMC were lower for 1+1 as compared to 2+1, especially at 10 months timepoint. However, the percentage of OPA sero-responders was similar across the groups. These findings indicate that the 1+1 schedule can elicit an immune response that is non-inferior to 2+1 and superior to 3+0 after booster vaccination.

The primary dosing for the 1+1 schedule was done at 14 weeks which was similar to one of the 1+1 schedules used in the South African study (15). This schedule was chosen as primary dosing at 14 weeks is associated with better immunogenicity as compared to primary dosing at 6 weeks due to better maturity of the immune system of the infant, reduced interference by maternal antibodies, and possible priming by vaccination with the diphtheria-containing vaccine (15,40). On one hand, this is likely to improve the immune response post-primary vaccination for the 1+1 schedule and on the other hand, it increases the period of enhanced disease risk in very early infancy. For mature programs in developed countries, where the burden of IPD has substantially reduced after the rollout of PCV using 3-dose schedules (41,42), the transition to a 1+1 schedule may not be associated with an enhanced risk of IPD (14). In view that pneumococcal colonisation occurs early in India (24,30) and the first year of life is associated with the major burden of IPD (43), the 1+1 schedule should be considered for maintenance after adequate initial control with the WHO recommended regimens and will need to be supported with strong surveillance data.

The study indicates immunological equivalence of 3+0, 2+1, and 1+1 schedules of PCV10 and PCV13 in Indian children, which supports the booster dose requirement and introduction of the 2+1 schedule in the national immunisation program of India as it is associated with optimal immune response during the first year and significant carriage reduction the second year of life as well. Despite the use of a 2+1 schedule in the current program, in the long run, as a 1+1 schedule of PCV can effectively provide direct as well as indirect (herd) protection against IPD and pneumococcal colonisation and is easy to implement, this may be a cost-effective and feasible option for a large country like India. High-quality population-based surveillance studies are needed to assess the change in pneumococcal colonisation and the burden of IPD in regions with the rollout of PCV. These data are also important for policymakers to estimate the potential impact of the newly approved 10-valent pneumococcal polysaccharide conjugate vaccine (PNEUMOSIL^{TM}). PNEUMOSIL, despite being a low-cost alternative for

pneumococcal vaccination, considering the magnitude of Indian birth cohort, the 1+1 strategy is likely to be beneficial for future implementation of PNEUMOSIL and would also help in reducing the cluttering of paediatric vaccination schedule in India.

To our knowledge, this is the first study to demonstrate the benefit of reduced-dose schedules of PCV10 and PCV13 using VT-carriage reduction and the first study in Indian children to demonstrate the impact of the 1+1 schedule on the carriage and immunological outcomes. The strengths of this study include the incorporation of two licensed PCVs products (Prevenar13^{TM} and Synflorix^{TM}) using both their WHO-recommended schedules (3+0 and 2+1) in the study design, PCV-naïve control group, and bio-sampling at multiple timepoints allowing uniform comparisons across study groups with reliable estimates.

The present study has a few limitations. The study findings are limited to a single geographical site with a high baseline NPC, however, are in agreement with 1+1 studies done in UK and Africa. The study is not powered to assess differences between the two PCV products and the serotype-specific differences between various schedules were very small to draw any conclusion about the superiority of one schedule over the other. The immunological outcomes are secondary and do not involve any sample size calculation. Nonetheless, the study provides reasonable evidence of benefits offered by the 1+1 schedule of PCV10 and PCV13 after booster doses in Indian children, which in the future could help in sustaining reductions in pneumococcal disease and maintaining herd protection once PCV programs mature. In future, long-term studies are needed to assess whether the protection is sustained beyond the second year of life. Also, detailed studies are needed to discuss the serotype-specific issues or exact differences between regimes and vaccines.

Conclusion

The reduced dose schedule (1+1) of PCV10 and PCV13 resulted in significant VT-carriage reduction and immune protection in Indian children during the second year of life which is comparable to WHO-recommended 3-dose schedules. This is despite lower immunogenicity and VT-carriage reduction in the first year of life. The 1+1 schedule could be a cost-effective alternative for the sustainability of the PCV program in India in the future.

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Conflict of interest

None

Data sharing policy

Data described in the manuscript, code book, and analytic code will be made available upon request pending application and approval.

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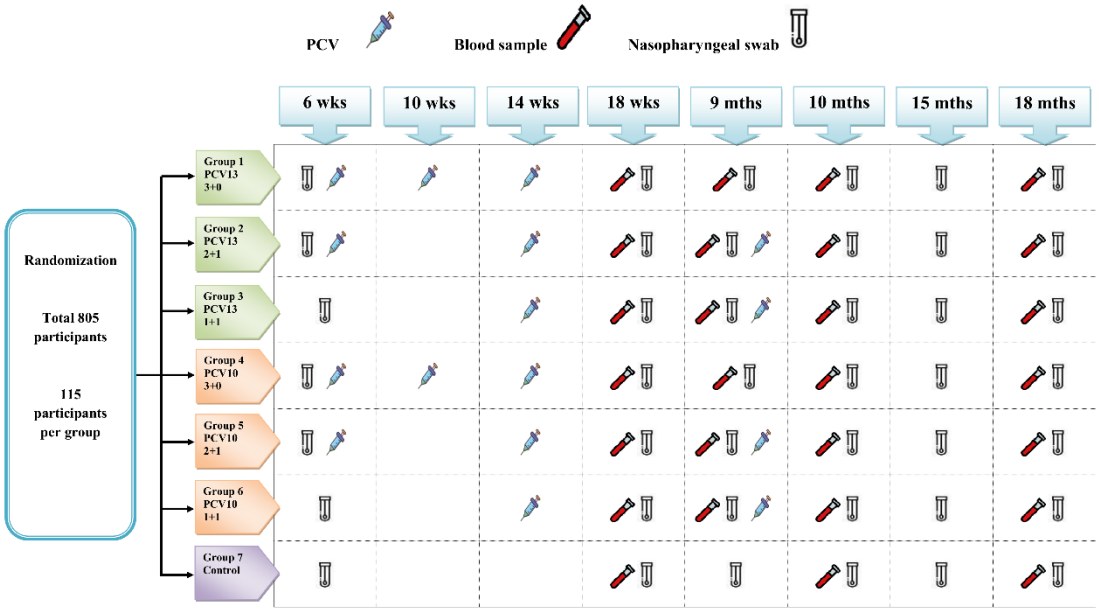

Figure 1: Study design

W=Week; M=Month; PCV=Pneumococcal Conjugate Vaccine; NPS=Nasopharyngeal Swab

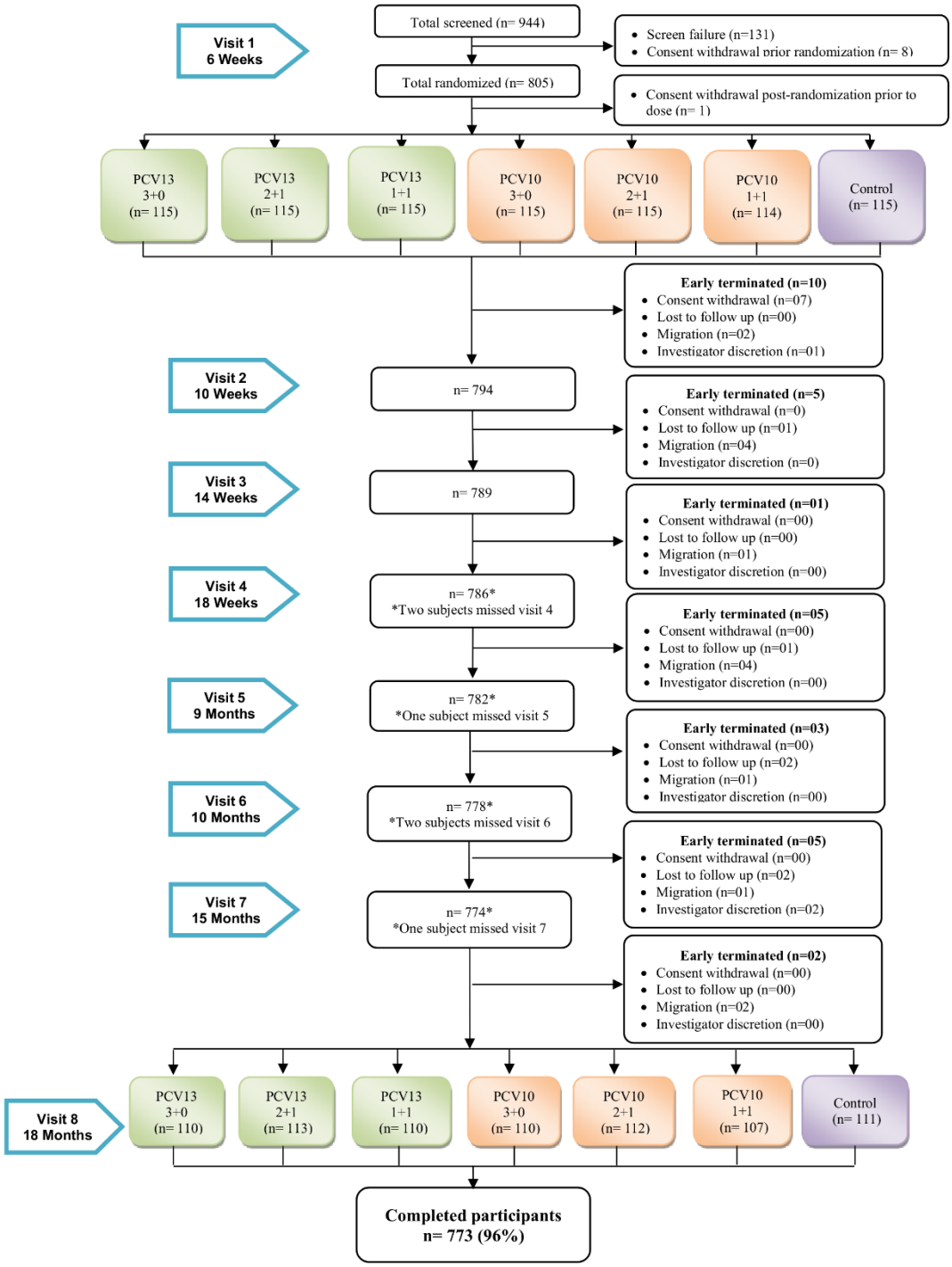

Figure 2: Participant disposition chart

Figure 3: VT-Carriage Reduction in the first two years of life with 3+0, 2+1, and 1+1 schedules of PCV13 and PCV10

a)VT-carriage reduction for PCV13 is for 13VT serotypes present in PCV13 (Prevnar13™)
b) VT-carriage reduction for PCV10 is for 10VT serotypes present in PCV10 (Synflorix™),
c) VT-carriage reduction for PCV10 is for 10VT+6A+19A serotypes

PCV=Pneumococcal Conjugate Vaccine; VT=Vaccine Type

Table 1: Baseline demographic characteristics

Characteristics	Total (n=805)	PCV 13 (3+0) (n=115)	PCV 13 (2+1) (n=115)	PCV 13 (1+1) (n=115)	PCV 10 (3+0) (n=115)	PCV 10 (2+1) (n=115)	PCV 10 (1+1) (n=115)	Control (n=115)	*#p-Value*
Age in Days [Mean (SD)]	47.65 (4.63)	47.37 (4.84)	47.62 (4.49)	47.18 (4.58)	48.19 (4.42)	47.50 (4.47)	47.74 (4.81)	47.92 (4.82)	*0.714*
Number of females [n (%)]	399 (50)	59 (51)	62 (54)	54 (47)	55 (48)	54 (47)	59 (51)	56 (49)	*0.924*
Height in cm [Mean (SD)]	54.86 (2.11)	54.90 (2.29)	54.71(2.12)	55.00 (1.83)	54.73 (2.21)	54.87 (1.98)	54.87 (2.14)	54.97(2.2)	*0.932*
Weight in kg [Mean (SD)]	4.23 (0.54)	4.21 (0.61)	4.14 (0.57)	4.25 (0.47)	4.26 (0.53)	4.23 (0.53)	4.26 (0.54)	4.25(0.50)	*0.628*
History of Antibiotic Therapy [n, (%)]	126 (15.65)	15 (13.04)	22 (19.13)	17 (14.78)	18 (15.65)	15 (13.04)	19 (16.52)	20 (17.39)	*0.849*
Pneumococcal Carriage [n, (%)]	170 (21.14)	22 (19.13)	25 (21.74)	31 (26.96)	25(21.74)	20 (17.39)	19 (16.67)	28 (24.35)	*0.457*
13 VT serotype [n, (%)]	48 (10.43)	12 (10.43)	10 (8.70)	12 (10.43)	-	-	-	14 (12.17)	0.523
10 VT serotypes [n, (%)]	26 (5.65)	-	-	-	7 (6.09)	9 (7.83)	2 (1.75) *	8 (6.96)	0.388
10 VT +6A+19A serotypes [n, (%)]	37 (8.04)	-	-	-	9 (7.83)	11 (9.57)	5 (4.39)	12 (10.43)	0.695

*PCV= Pneumococcal Conjugate Vaccine; SD= Standard Deviation; VT=Vaccine Type, #p-value for multiple comparisons using Chi-square Test; * p=0.053 vs. control group using Chi-square test.*

Table 2: Effect of PCV13 on the nasopharyngeal pneumococcal carriage during first two years of life

Vaccine and target state	**PCV13**			
Schedule	**3+0**	**2+1**	**1+1**	**Control**
	18 Weeks			
Total NP Swabs	110	113	112	114
Overall Carriage n (%)	60 (54.55)	63 (55.75)	63 (56.25)	74 (64.91)
VT Carriage n (%)	28 (25.45)	33 (29.2)	33 (29.46)	44 (38.60)
OR[a] (95% CI)	0.51 (0.28-0.95)	0.67(0.37-1.22)	0.64 (0.35-1.16)	Reference
P-value	0.034	0.192	0.139	--
	9 Months			
Total NP Swabs	110	113	111	112
Overall Carriage n (%)	68 (61.82)	71 (62.83)	66 (59.46)	76 (67.86)
VT Carriage n (%)	27 (24.55)	37 (32.74)	39 (35.14)	41 (36.61)
OR[a] (95% CI)	0.55 (0.30-0.99)	0.84 (0.48-1.48)	0.93 (0.53-1.62)	Reference
P-value	0.045	0.553	0.792	--
	10 Months			
Total NP Swabs	110	113	110	111
Overall Carriage n (%)	63 (57.27)	68 (60.18)	63 (57.27)	65 (58.56)
VT Carriage n (%)	29 (26.36)	35 (30.97)	31 (28.18)	41 (36.94)
OR[a] (95% CI)	0.61 (0.34-1.08)	0.78 (0.44-1.36)	0.67 (0.38-1.19)	Reference
P-value	0.091	0.376	0.173	--
	15 Months			
Total NP Swabs	111	113	110	110
Overall Carriage n (%)	65 (58.56)	63 (55.75)	64 (58.18)	68 (61.82)
VT Carriage n (%)	27 (24.32)	27 (23.89)	30 (27.27)	45 (40.91)
OR[a] (95% CI)	0.46 (0.26-0.82)	0.45 (0.25-0.81)	0.55 (0.31-0.97)	Reference

P-value	0.008	0.007	0.038	--
	18 Months			
Total NP Swabs	109	113	110	111
Overall Carriage n (%)	54 (49.54)	56 (49.56)	72 (65.45)	68 (61.26)
VT Carriage n (%)	15 (13.76)	24 (21.24)	26 (23.64)	40 (36.04)
OR[a] (95% CI)	0.28 (0.14-0.55)	0.48 (0.26-0.87)	0.55 (0.30-0.98)	Reference
P-value	0.000	0.016	0.043	--

PCV=Pneumococcal Conjugate Vaccine; VT=Vaccine Type; SP=Streptococcus pneumoniae; ORa= Odds Ratio adjusted for sex, history of antibiotic usage and baseline VT carriage; CI=Confidence Interval

Table 3: Effect of PCV10 on the nasopharyngeal pneumococcal carriage during first two years of life

Vaccine and target state	**PCV10**				**PCV10+6A+19A**			
Schedule	**3+0**	**2+1**	**1+1**	**Control**	**3+0**	**2+1**	**1+1**	**Control**
	18 Weeks							
Total NP Swabs	114	114	109	114	114	114	109	114
Overall Carriage n (%)	60 (52.63)	64 (56.14)	58 (53.21)	74 (64.91)	60 (52.63)	64 (56.14)	58 (53.21)	74 (64.91)
VT Carriage n (%)	18 (15.79)	24 (21.05)	17 (15.60)	29 (25.44)	26 (22.81)	31 (27.19)	25 (22.94)	41 (35.96)
OR[a] (95% CI)	0.51(0.25-1.01)	0.72(0.37-1.38)	0.60(0.30-1.20)	Reference	0.50(0.27-0.93)	0.63(0.35-1.15)	0.59 (0.32-1.09)	Reference
P-value	0.054	0.323	0.147		0.029	0.136	0.093	--
	9 Months							
Total NP Swabs	113	114	109	112	113	114	109	112
Overall Carriage n (%)	59 (52.21)	72 (63.16)	64 (58.72)	76 (67.86)	59 (52.21)	72 (63.16)	64 (58.72)	76 (67.86)

VT Carriage n (%)	21 (18.58)	28 (24.56)	20 (18.35)	32 (28.57)	28 (24.78)	40 (35.09)	30 (27.52)	40 (35.71)
OR[a] (95% CI)	0.55 (0.29-1.04)	0.79 (0.43-1.44)	0.60 (0.31-1.13)	Reference	0.59 (0.33-1.05)	0.97 (0.56-1.68)	0.74 (0.41-1.31)	Reference
P-value	0.066	0.439	0.113	--	0.072	0.908	0.301	--
	10 Months							
Total NP Swabs	112	114	108	111	112	114	108	111
Overall Carriage n (%)	58 (51.79)	68 (59.65)	61 (58.56)	65 (58.56)	58 (51.79)	68 (59.65)	61 (58.56)	65 (58.56)
VT Carriage n (%)	23 (20.54)	26 (22.81)	17 (15.74)	29 (26.13)	32 (28.57)	35 (30.71)	26 (24.07)	40 (36.04)
OR[a] (95% CI)	0.73 (0.39-1.37)	0.83 (0.45-1.52)	0.54 (0.28-1.07)	Reference	0.72 (0.41-1.27)	0.78 (0.45-1.37)	0.59 (0.33-1.07)	Reference
P-value	0.325	0.538	0.076	--	0.252	0.396	0.082	--
	15 Months							
Total NP Swabs	110	113	107	110	109	113	107	110
Overall Carriage n (%)	60 (54.55)	57 (50.44)	60 (56.07)	68 (61.82)	60 (54.55)	57 (50.44)	60 (56.07)	68 (61.82)
VT Carriage n (%)	22 (20.00)	24 (21.24)	19 (17.76)	29 (26.36)	27 (24.55)	31 (27.43)	32 (29.90)	45 (40.91)
OR[a] (95% CI)	0.69 (0.37-1.31)	0.75 (0.40-1.39)	0.62 (0.32-1.19)	Reference	0.47 (0.26-0.84)	0.55 (0.31-0.96)	0.63 (0.36-1.12)	Reference
P-value	0.259	0.359	0.15	--	0.011	0.036	0.114	--
	18 Months							
Total NP Swabs	110	112	107	111	110	112	107	111
Overall Carriage n (%)	51 (46.36)	60 (53.57)	60 (56.07)	68 (61.26)	51 (46.36)	60 (53.57)	60 (56.07)	68 (61.26)
VT Carriage n (%)	17 (15.45)	17 (15.18)	14 (13.08)	24 (21.62)	25 (22.73)	24 (21.43)	25 (23.36)	40 (36.03)
OR[a] (95% CI)	0.66 (0.33-1.31)	0.64 (0.32-1.27)	0.56 (0.27-1.15)	Reference	0.52 (0.29-0.94)	0.48 (0.26-0.87)	0.55 (0.30-0.99)	Reference
P-value	0.236	0.201	0.113	--	0.030	0.015	0.046	--

PCV=Pneumococcal Conjugate Vaccine; VT=Vaccine Type; SP=Streptococcus pneumoniae; ORa= Odds Ratio adjusted for sex, history of antibiotic usage and baseline VT carriage; CI=Confidence Interval

Table 4: Percentage of children with serotype specific pneumococcal antibody concentrations (SSIgG) >=0.35 mcg/ml from PCV-10 and PCV-13 study groups

Sero type	Timepoint	PCV10 (3+0)		PCV10(2+1)		PCV10(1+1)			PCV13 (3+0)		PCV13(2+1)		PCV13(1+1)
		N	%(95%CI)	N	%(95%CI)	N	%(95%CI)	N	%(95%CI)	N	%(95%CI)	N	%(95%CI)
1	18 W	113	95.6(90-98.5)	114	93(93.9-99.8)	108	81.5(72.9-88.3)	110	93.6(87.3-97.4)	113	95.6 (90.4-98.6)	112	78.6(69.8-85.8)
	9 M	112	61.6(51.9-70.6)	113	45.1(35.8-54.8)	107	47.7(37.9-57.5)	109	62.4(52.6-71.5)	113	61.1(51.4-70.1)	110	56.4(46.6-69.8)
	10 M	101	67.3(57.3-76.3)	103	99(94.7-100)	95	99(94.3-100)	107	64.5(54.6-73.5)	95	99(94.3-1.00)	102	100(96.4-100)
	18 M	108	8.3(3.9-15.2)	112	32.1(23.6-41.6)	107	33.6(24.8-43.4)	109	10.9(5.1-17.3)	113	43.4(34.1-53.0)	109	79.82(71.1-86.9)
4	18 W	113	95.6(90-98.6)	114	96.5(91.3-99)	108	81.5(72.9-88.3)	110	98.2(93.6-99.8)	113	94.7(88.8-98)	112	88.4(81-93.7)
	9 M	113	78.8(70.1-85.9)	113	54(44.4-63.4)	108	53.7(43.8-63.3)	109	45.9(36.3-55.7)	113	38.1(29.1-47.7)	111	43.2(33.9-53)
	10 M	111	66.7(57.1-75.3)	114	99.1(95.2-100)	108	98.2(93.5-99.8)	109	33(24.3-42.7)	113	99.1(95.2-100)	110	100(96.7-100)
	18 M	109	24.8(17-34)	112	33(24.4-42.6)	107	42.1(32.6-52)	109	17.4(10.8-25.9)	113	27.4(19.5-36.6)	109	49.5(39.8-59.3)
5	18 W	113	94.7(88.9-98)	114	86(78.2-91.8)	108	70.4(60.8-78.8)	110	93.6(87.3-97.4)	113	85(77-91)	112	61.6(52-70.6)
	9 M	112	60.2(51-69.8)	113	53.1(43.5-62.5)	108	55.6(45.7-65.1)	109	64.2(54.5-73.2)	113	63.7(54.1-72.6)	111	69.4(60-77.8)
	10 M	111	59.5(49.7-68.7)	114	94.7(88.9-98)	108	97.2(92.1-99.4)	108	65.7(56-74.6)	113	99.1(95.2-100)	110	100(96.7-100)
	18 M	108	69.4(59.8-78)	112	74.1(65-82)	106	76.4(67.2-84.1)	109	74.3(65.1-82.2)	113	85.8(78-91.7)	109	82.6(74.1-89.2)
6B	18 W	113	77(68.1-84.4)	113	62(52.3-70.9)	108	5.6(2.2-12.4)	110	77.3(68.3-84.7)	111	44.1(34.7-53.9)	112	4.5(1.5-10.6)
	9 M	113	85(77-91)	113	76.1(67.2-83.6)	108	53.7(43.8-63.3)	109	64.2(54.5-73.2)	113	44.3(34.9-53.9)	110	9.1(4.44-16.1)
	10 M	111	84.7(76.6-90.8)	113	95.6(90-98.5)	107	94.4(88.2-97.9)	108	63.9(54.1-73)	110	97.3(92.2-99.4)	109	93.6(87.2-97.4)
	18 M	109	80.7(72.1-87.7)	112	88.4(80.1-93.7)	106	77.4(68.2-84.9)	109	63.3(53.5-72.3)	113	88.5(81.1-93.7)	108	84.3(76-90.6)
7F	18 W	113	100	114	98.3(93.8-99.8)	108	50.9(41.1-60.7)	110	98.2(93.6-99.8)	113	98.2(93.8-99.8)	112	82.1(73.8-88.7)
	9 M	113	91.2(84.3-95.7)	113	77(68.1-84.4)	108	75(65.7-82.8)	109	94.5(88.4-98)	112	91.2(84.2-95.6)	111	88.3(80.8-93.6)
	10 M	111	91(84.1-95.6)	111	99.1(95.2-100)	108	99.1(95-100)	109	96.3(90.9-99)	113	100(96.8-100)	110	100(96.7-100)
	18 M	108	67.6(58-76.3)	112	83.1(74.8-89.5)	107	79.4(70.5-86.6)	109	76.2(67-83.8)	113	89.4(82.2-94.4)	109	88.1(80.5-93.5)
9V	18 W	113	96.5(91.2-99)	114	91.2(84.5-95.7)	108	41.7(32.2-51.5)	110	94.6(88.5-98)	113	84.1(76-90.3)	112	50(40.4-59.6)
	9 M	113	68.1(58.7-76.6)	113	43.36(34.1-53)	107	31.78(23.2-41.5)	109	60.6(50.7-69.8)	113	45.1(35.8-54.8)	110	25.5(17.6-34.6)
	10 M	111	64(54.3-72.9)	114	97.7(92.5-99.5)	108	97.2(92.1-99.8)	108	44.4(34.9-54.3)	113	96.5(91.2-99)	110	98.2(93.6-99.8)
	18 M	107	48.6(38.8-58.5)	112	68.8(59.3-77.2)	107	56.1(46.1-65.7)	109	44(34.5-53.9)	113	59.3(49.6-68.4)	109	61.5(51.7-70.6)
14	18 W	113	98.2(93.8-99.8)	113	98.2(93.8-99.8)	108	53.7(43.8-63.3)	109	99.1(95-100)	109	93.6(87.2-97.4)	112	69.6(60.2-78)
	9 M	113	89.4(82.2-94.4)	113	88.5(81.1-93.7)	108	74.1(64.8-82)	109	86.2(78.3-92.1)	113	82.3(74-88.4)	111	80.2(71.5-87.1)
	10 M	111	90.1(83-95)	114	93.9(87.8-97.5)	107	94.4(88.2-98)	109	85.3(77.3-91.4)	113	96.5(91.2-99)	110	98.2(93.6-99.8)
	18 M	108	75(65.7-82.8)	111	90.1(83-95)	106	85.9(77.7-91.9)	108	84.3(76-90.6)	113	95.6(90-98.5)	109	95.4(89.6-98.5)
18C	18 W	113	97.4(92.4-99.4)	114	94.7(88.9-98)	108	29.6(21.2-39.2)	110	93.6(87.3-97.4)	113	83.2(75-89.6)	112	61.6(51.9-70.6)
	9 M	113	85(77-91)	113	65.2(56-74.2)	108	42.6(33.1-52.5)	109	33(24.3-42.7)	113	27.4(19.5-36.6)	111	15.3(9.2-23.4)

	10 M	111	73.9(64.7-81.8)	114	97.4(92.5-99.5)	108	99.1(94.9-100)	109	22(14.6-31)	113	98.2(93.8-100)	110	98.2(93.6-99.8)
	18 M	109	23.8(16.2-33)	112	84.8(76.8-90.9)	107	73.8(64.4-81.9)	109	11.9(6.5-19.5)	111	27(19-36.3)	109	26.6(18.6-35.9)
19F	18 W	112	98.2(93.7-99.8)	113	99.1(95.2-100)	108	81.5(72.9-88.3)	110	98.2(93.6-99.8)	112	98.2(93.7-99.8)	110	84.6(76.4-90.7)
	9 M	111	97.3(92.3-99.4)	111	99.1(95.1-100)	106	92.5(85.7-96.7)	109	96.3(90.9-99)	111	91(84.1-95.6)	110	90 (82.8-94.9)
	10 M	111	97.3(92.3-99.4)	112	100	106	100	108	96.3(90.8-99)	112	100(96.8-100)	108	100(96.6-100)
	18 M	108	94.4(88.3-97.9)	112	99.1(95.1-100)	105	100	105	89.5(82-94.7)	111	96.4(91-99)	108	99.1(94.9-100)
23F	18 W	113	74.3(65.3-82.1)	114	53.5(43.9-62.9)	108	5.6(2.1-11.7)	110	83.6(75.4-90)	113	60.2(50.5-65.3)	112	5.4(2-11.3)
	9 M	113	48.7(39.2-58.3)	113	36.3(27.4-45.9)	108	10.2(5.2-17.5)	109	23.9(16.2-33)	113	13.3(7.62-20.9)	111	7.2(3.2-13.7)
	10 M	111	41.4(32.2-51.2)	114	90.4(83.4-95.1)	108	90.7(83.6-95.5)	109	16.5(10.1-24.1)	113	93.8(87.6-97.5)	110	94.6(88.5-98)
	18 M	109	26.6(18.6-35.9)	111	36.9(28-46.6)	106	28.3(20-37.9)	109	17.4(10.8-25.9)	112	42(32.7-51.7)	109	34.9(26-44.6)
3	18 W		--		---			98	88.8(80.8-94.2)	93	64.5(53.9-74.2)	84	85.7(76.4-92.3)
	9 M		--		--			107	68.2(58.5-76.9)	110	70.9(61.5-79.2)	108	68.5(58.9-77.1)
	10 M		--					109	66.1(56.4-74.9)	110	93.6(87.3-97.4)	107	95.3(89.4-98.5)
	18 M		--					104	46.2(36.3-56.2)	110	52.7(43-62.3)	106	52.8(42.9-62.6)
6A	18 W	113	15.9(9.7-24)	114	17.5(11.1-25.8)	108	9.3(4.5-16.4)	110	85.5(77.5-91.4)	113	75.2(66.2-82.9)	112	17(10.5-25.2)
	9 M	112	46.4(40-56.1)	111	39.6(30.5-49.4)	107	22.4(14.9-31.5)	109	79.8(71.1-86.9)	113	77(68.1-84.4)	111	44.1(34.7-53.9)
	10 M	111	52.3(42.6- 61.8)	112	77.7(68.8-85)	106	79.3(70.3-86.5)	109	80.7(72.1-87.7)	113	96.5(91.2-99)	109	97.3(92.2-99.4)
	18 M	109	73.4(64.1-81.4)	110	66.4(56.7-75.1)	107	78.8(64.4-81.9)	109	81.7(73.1-88.4)	112	95.5(89.9-98.5)	109	95.4(89.6-98.5)
19A	18 W	113	58.4(48.8-67.6)	113	69.9(60.6-78.2)	108	26.9(18.8-36.2)	110	99.1(95-100)	113	97.4(92.4-99.4)	112	79.5(70.8-86.5)
	9 M	113	53.1(43.5-62.5)	112	52.7(43-62.5)	108	32.4(23.7-42.1)	109	89.9(82.7-94.9)	112	74.1(65-82)	111	61.3(51.5-70.4)
	10 M	111	58.6(48.8-67.8)	114	88.6(81.3-93.8)	107	92.5(85.8-96.7)	109	86.2(78.3-92.1)	113	99.1(95.2-100)	110	100(96.7-100)
	18 M	109	82.6(74.1-89.2)	109	86.2(78.3-92.1)	105	91.4(84.4-96.0)	105	90.5(83.2-95.3)	111	92.8(86.3-96.3)	107	96.3(90.7-99)

Table 5: Percentage of children with pneumococcal serotype-specific opsonophagocytic activity titers above LLOQ and antibody geometric mean concentrations (GMC) from PCV 10 study groups

Serotype	Time Point	% of children with OPA titers above LLOQ						OPA GMC (mcg/ml)		
		PCV10 (3+0)		PCV10(2+1)		PCV10(1+1)		PCV10 (3+0)	PCV10(2+1)	PCV10(1+1)
		N	%(95%CI)	N	%(95%CI)	N	%(95%CI)	Value(95%CI)	Value(95%CI)	Value(95%CI)
1	10 M	22	13.6 (2.9-34.9)	23	95.7 (78.1-99.9)	22	95.5 (77.2-99.9)	36.49(1.3-1060.5)	219.14(128.9-372.7)	384.99(232.2-638.3)
	18 M	20	5.00 (0.1-24.9)	22	22.73 (7.8-45.4)	22	27.3 (10.7-50.2)	35	48.97(7.35-326.43)	26.68(8.09-87.95)
4	10 M	22	90.9 (70.8-8.9)	23	95.7 (78.1-100)	22	95.5 (77.2-100)	285.2(150.1-542)	1709.8 (1125-2598)	2193.5(1455-3307)
	18 M	18	72.2(46.5-0.3)	21	90.5 (69.6-98.8)	22	86.4 (65.1-97.1)	174.5(112.3-171.2)	168.2(87.1-324.5)	450.8(291.9-696.1)
5	10 M	19	79 (54.4-93.9)	23	100 (85.2-100)	22	95.5 (77.2-99.9)	34.7(17.1-70.1)	393.3(235.6-656.4)	618.3(420.7-908.7)
	18 M	18	72.2(46.5-90.3)	22	90.9(70.8-98.9)	22	90.9 (70.8-98.9)	28.5(21-38.6)	41.5(26.2-65.8)	72.7(43.5-121.6)
6A	10 M	21	47.6(25.7-70.2)	21	76.2 (52.8-91.8)	20	80(56.3-94.3)	591.4(321.3-1089)	1061.7(694.3-1621.4)	1454.5(861.7-2455.1)
	18 M	19	26.32 (9.1-51.2)	21	28.57 (11.3-52.2)	20	45.00 (23.1-68.5)	385.3(81.5-1822.5)	742.8(169.5-3254.6)	704.9(377.1-1314.7)
6B	10 M	21	76.2 (52.8-91.7)	23	95.7 (78.1-99.9)	22	86.4(65.1-97.1)	438.8(252.3-763.1)	2169.4(1448.1-3250)	1721.6(880.2-3367.3)
	18 M	22	72.7 (49.8-89.3)	22	72.7 (49.8-89.3)	21	76.2 (52.8-91.8)	284.9(180.9-449)	234(113.3-483.2)	382.6(373.5-2381.3)
6C	10 M	20	20(5.7-43.7)	19	68.4 (43.5-787.4)	22	63.6 (40.7-82.8)	938.6(279.3-3154)	1001.8(575.8-1743.2)	1563.1(828.3-2949.8)
	18 M	20	25(8.7-49.1)	20	20(5.7-43.7)	21	33.3 (14.6-57)	836.5(410.9-1703)	1359(741.8-2489.9)	943.2(373.6-2381.3)
7F	10 M	21	100 (83.9-100)	23	100 (85.2-100)	22	95.45 (77.2-99.9)	1130.1(645.5-1979)	3660.8(2737.2-4896)	2838.9(2047.1-3937)
	18 M	21	95.2 (76.2-99.9)	22	95.5(77.2-99.9)	22	100 (84.6-100)	331.8(202.2-544.6)	669.8(475.3-943.8)	861.4(593.5-1250.2)
9V	10 M	21	81 (58.1-94.6)	23	100 (85.2-100)	21	100(83.9-100)	260(137.2-492.4)	1239.2(909.3-1688.8)	1179.6(794.8-1750.5)
	18 M	18	72.2 (46.5-90.3)	18	88.9 (65.3-98.6)	21	85.71(63.7-97.0)	294.6(130.7-663.8)	485.4(207.9-1132.8)	652(356.2-1193.4)
14	10 M	22	95.5 (77.2-99.9)	23	100 (86.2-100)	22	90.9(70.8-98.9)	533(322.3-881.3)	1780.2(1023-3097.9)	2529.6(1319.4-4850)
	18 M	22	77.3 (54.6-92.2)	22	95.5(77.2-99.9)	20	95 (75.1-99.9)	428.8(248.7-739.34)	411.2(225.1-751.2)	318.1(154.9-653.2)
18C	10 M	22	86.4 (65.1-97.1)	23	100 (85.2-100)	22	95.5 (77.2-99.9)	244.1(145.3-410.3)	2539.5(1266.5-5092)	5678(3734.7-8632.7)
	18 M	22	77.3(54.6-92.2)	22	100 (84.6-100)	22	100(84.6-100)	139.7(83.3-234.5)	1222.9(852.8-1753.8)	662.1(362.3-1209.9)
19F	10 M	22	90.9(70.8-99.0)	23	95.7(78.1-99.9)	22	86.4 (65.1-97.1)	281.3(186.3-424.6)	2122.1(1402-3212.4)	3702.3(2645-5181.3)
	18 M	22	77.3(54.6-92.2)	22	95.5(77.2-99.9)	22	90.9 (70.8-98.9)	269.4(131.6-551.5)	323.6(216.6-483.5)	300(170.2-528.7)
23F	10 M	22	72.7 (49.8-89.3)	23	91.3(72.0-98.9)	22	95.5(77.2-99.9)	900.4(469-1728.7)	2972.9(1920-4604.4)	2519.1(1597.7-3972)
	18 M	22	68.2(45.1-86.1)	21	76.19 (52.8-91.8)	21	85.71 (63.7-97.0)	441.1(171.7-1133.2)	614.2(299.7-1258.5)	792.6(367.9-1707.8)
3	10 M	21	9.5(1.2-30.4)	23	13.0 (2.8-33.6)	21	14.3 (3.0-36.3)	42(0.01-153014.7)	31.9(1.9-543.1)	31.1(11.2-86.6)
	18 M	21	9.5 (1.2-30.4)	22	9.1 (1.1-29.2)	22	18.2 (5.2-40.3)	31.5(0.6-1675)	385.9(1.8-8.5)	66.1(22-199.2)
6A	10 M	21	47.6(25.7-70.2)	21	76.2 (52.8-91.8)	20	80(56.3-94.3)	591.4(321.3-1089)	1061.7(694.3-1621.4)	1454.5(861.7-2455.1)
	18 M	19	26.32 (9.1-51.2)	21	28.57 (11.3-52.2)	20	45.00 (23.1-68.5)	385.3(81.5-1822.5)	742.8(169.5-3254.6)	704.9(377.1-1314.7)

19	10 M	22	22.7 (7.8-45.4)	23	91.3 (72.0-98.9)	22	86.4 (65.1-97.1)	107.3(12.9-890.2)	754.9(493.3-1155.4)	657.1(313.5-1376.9)
A	18 M	21	42.9 (21.9-66)	21	42.9(21.9-66.0)	18	44.4(21.5-69.2)	47.3(14.3-156.3)	125.9(28.4-558)	199.3(34.6-1148.5)

LLOQ- Lower limit of quantitation

Table 6: Percentage of children with pneumococcal serotype-specific opsonophagocytic activity (OPA) titers above LLOQ and antibody geometric mean concentrations (GMC) from PCV 13 study groups

Sero type	**Time point**	**% of children with OPA titers more than LLOQ**						**OPA GMC (mcg/ml)**		
		PCV13 (3+0)		**PCV13(2+1)**		**PCV13(1+1)**		**PCV13 (3+0)**	**PCV13(2+1)**	**PCV13(1+1)**
		N	**%(95%CI)**	**N**	**%(95%CI)**	**N**	**%(95%CI)**	**Value(95%CI)**	**Value(95%CI)**	**Value(95%CI)**
1	10 M	21	28.6 (11.3-52.2)	22	95.5 (77.2-99.9)	22	100(84.6-100)	23.3(12.3-44.2)	183.5(107.3-313.7)	1430(919.8-2223.8)
	18 M	22	0.00	19	15.8 (3.4-39.6)	22	54.55 (32.2-75.6)	-	27.22(3.7-201.10)	44(23.5-82.5)
4	10 M	20	75 (51-91.3)	22	100 (84.6-100)	22	100(84.6-100)	122.9(60.7-248.6)	2545.4(1730.5-3744)	3541.9(2391.15246.5)
	18 M	22	59.1 (36.4-79.3)	21	95.2(76.2-99.9)	22	95.5(77.2-99.9)	155.2(62.3-387)	340.1(171.9-672.7)	297.4(168.7-524.4)
5	10 M	21	81 (58.1-94.6)	22	100 (84.6-100)	22	100 (84.6-100)	29.7(16.8-52.7)	383.2(257.4-570.3)	760.8(548.1-1056)
	18 M	19	68.4 (43.4-87.4)	21	100 (83.9-100)	23	91.3(72.0-98.9)	21(13.8-31.9)	35.4(24.8-50.5)	50.7(36-71.5)
6B	10 M	20	60 (36.1-80.9)	21	100(83.9-100)	22	95.5(77.2-99.9)	403.3(222.9-729.6)	26423(1175.3-1941.5)	2767.3(1582.3-4840)
	18 M	22	50(28.2-71.8)	21	90.5(69.6-98.8)	23	65.2(42.7-83.6)	401.1(138.1-1165.5)	278(164.8-468.9)	286.5(121.5-675.9)
6C	10 M	22	81.8 (59.7-94.8)	22	90.9(70.8-98.9)	20	100(83.2-100)	990.8(638.4-1537.8)	5623(3233.2-9778.8)	3936.8(2522.4-6144)
	18 M	20	50 (27.2-72.8)	20	85(62.1-96.8)	21	90.5(69.6-98.8)	650.8(183.1-2312.9)	496.2(198.5-1240.8)	611.8(359.3-1041.6)
7F	10 M	22	100 (84.6-100)	22	100 (84.6-100)	22	100 (84.6-100)	1036(697.2-1539.3)	5578.4(3870.5-8040)	3837.6(2869.7-5132.4)
	18 M	22	100 (84.6-100)	22	100 (84.6-100)	23	100 (85.2-100)	791.3(465.2-1345.9)	1301.1(863-1961.4)	636.1(349.8-1157)
9V	10 M	20	85(62.1-96.8)	22	100 (84.6-100)	22	100 (84.6-100)	176.8(92.3-338.3)	2280(1509.4-3442.6)	1791.1(1245.8-2575)
	18 M	18	61(35.7-82.7)	22	77.3 (54.6-92.2)	21	90.5 (69.6-98.9)	344.1(118.2-1001.6)	717.4(392.2-1312.4)	590.2(300.9-1157.4)
14	10 M	22	81.8(59.7-94.8)	22	100 (84.6-100)	22	100 (84.6-100)	532.1(248-1141.7)	2285(1273.9-4097.3)	2596.8(1724.5-3910.3)
	18 M	21	85.7 (63.7-97.0)	22	95.5 (77.2-99.9)	23	95.7 (78.1-99.9)	347.5(173.5-695.93	674.4(390.6-1164.3)	263.7(118.4-587.3)
18C	10 M	20	85(62.1-97.0)	22	100 (84.6-100)	22	100 (84.6-100)	67.1(27.8-162.5)	1227.9(845.9-1782.2)	1336.7(878.6-2033.7)
	18 M	21	47.6 (25.7-70.2)	20	80 (56.3-94.3)	22	90.9 (70.8-98.9)	184.8(58.4-584.6)	130.7(68.7-248.6)	77(38-156.1)
19F	10 M	22	81.8 (59.8-94.8)	22	95.5 (77.2-99.9)	22	95.5 (77.2-99.9)	36.5(20.7-64.3)	1350.9(970.6-1879.8)	1830(1091.1-3069.4)
	18 M	21	42.9 (21.8-66.0)	21	81 (58.1-95.0)	23	87 (66.4-97.2)	169.9(42.9-673.2)	175.5(78.4-392.8)	200.2(95.3-420.5)
23F	10 M	21	57.1 (34.0-78.2)	22	95.5 (77.2-99.9)	22	95.5 (77.2-99.9)	662.2(381.4-1149.7)	4403.1(2697-7187.9)	7453.4(3859.8-14393)
	18 M	20	65 (40.8-84.6)	22	95.5 (77.2-99.9)	21	95.3(76.2-99.9)	677.7(222.5-2064.4)	1886(1215.5-2926.9)	1443.2(892.2-2334.3)
3	10 M	20	45(23.1-68.5)	22	100 (84.6-100)	22	95.5(77.2-99.9)	33.3(14.5-77.9)	105.9(74.9-149.7)	170(139.6-207)
	18 M	21	23.8 (8.2-47.2)	17	52.4(27.8-77.0)	21	47.62(25.7-70.2)	20.4(14.1-29.5)	47.9(11.2-204.5)	23(14.3-36.9)

6A	10 M	21	90.5 (69.6-98.8)	22	90.9 (70.8-98.9)	21	90.5 (69.6-98.8)	510.8(267.4-975.8)	6840.6(3730.4-12544)	5618.7(3007.4-10497)
	18 M	22	68.2(45.1-86.1)	21	85.7(63.7-97.0)	22	95.5(77.2-99.9)	269.8(102.7-709.1)	399.4(229.8-694.3)	472.9(281-795.9)
19A	10 M	21	76.2 (52.8-91.8)	22	100 (84.6-100)	22	100 (84.6-100)	65.2(27.7-162.5)	2399(1749.5-3290.6)	4038.4(2698.2-6044.2)
	18 M	20	80 (56.3-94.3)	21	85.7 (63.7-97.0)	22	90.9 (70.8-98.9)	209.4(79.3-552.8)	475.8(162.8-1390.6)	432.3(242.6-770.3)

LLOQ- Lower limit of quantitation

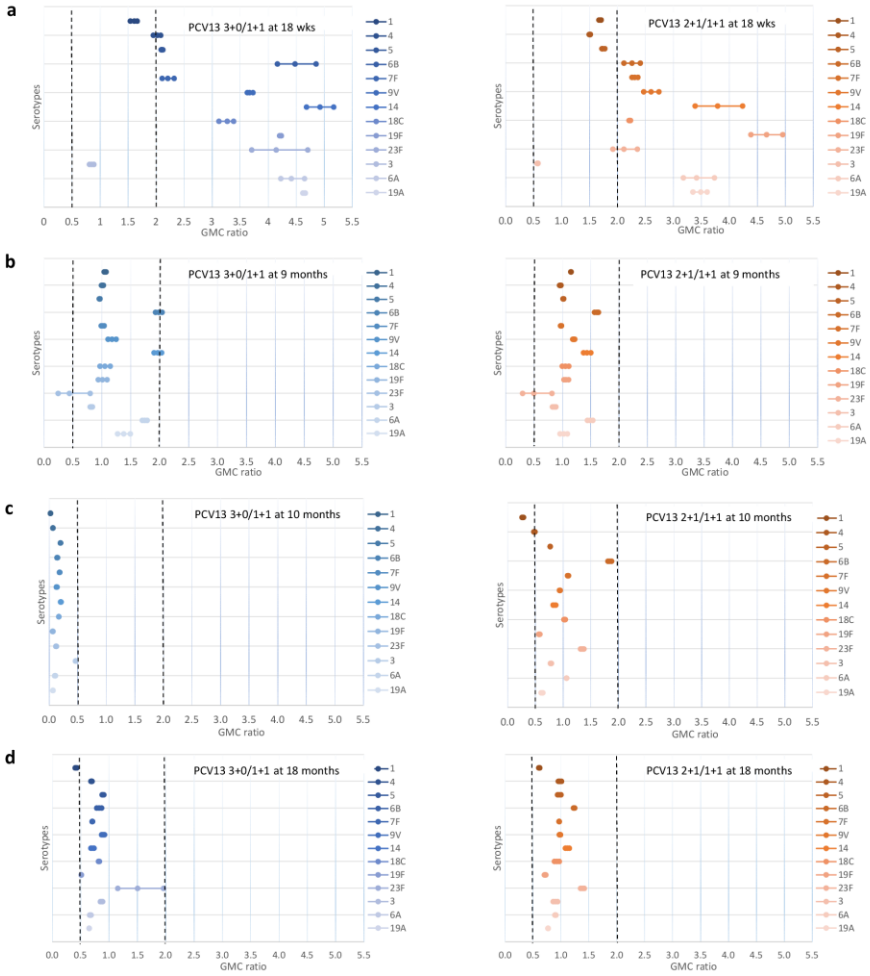

Figure 4: GMC ratios for 3+0/1+1 and 2+1/1+1 for PCV10 study groups [a: 18 weeks, post-primary vaccination; b: 9 months, pre-booster vaccination; c: 10 months, 1 month post-booster vaccination; d: 18 months, 9 months after booster vaccination]

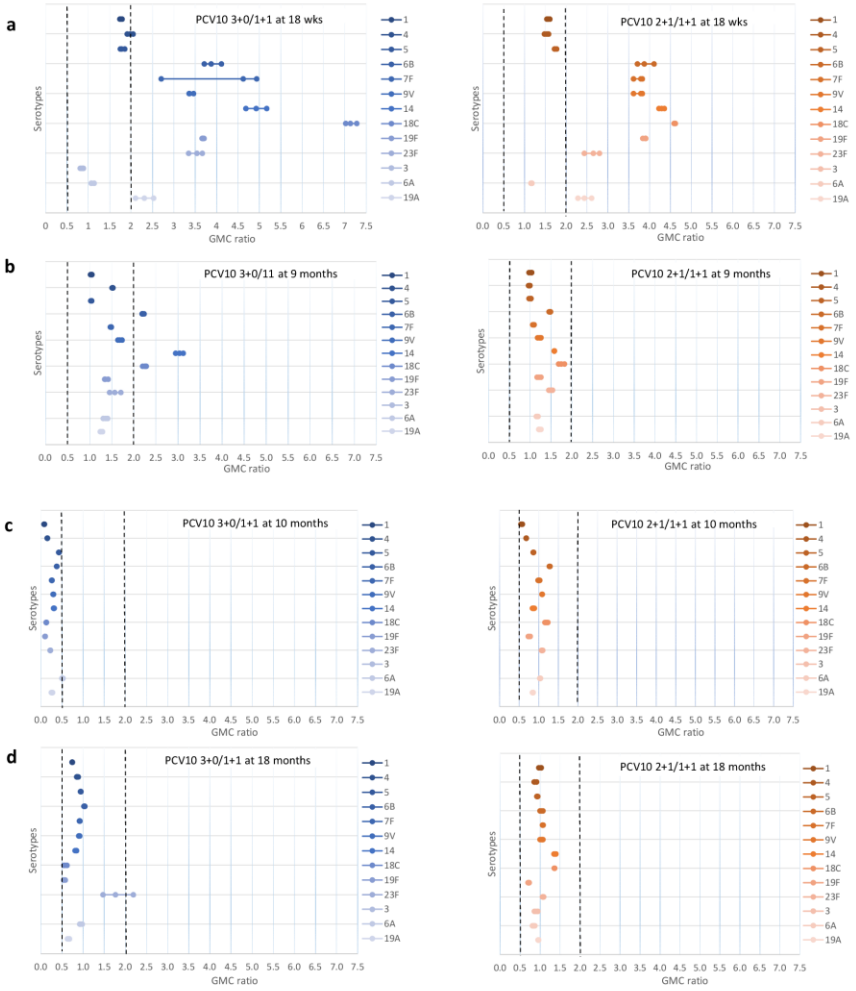

Figure 5: GMC ratios for 3+0/1+1 and 2+1/1+1 for PCV13 study groups [a: 18 weeks, post-primary vaccination; b: 9 months, pre-booster vaccination; c: 10 months, 1 month post-booster vaccination; d: 18 months, 9 months after booster vaccination]

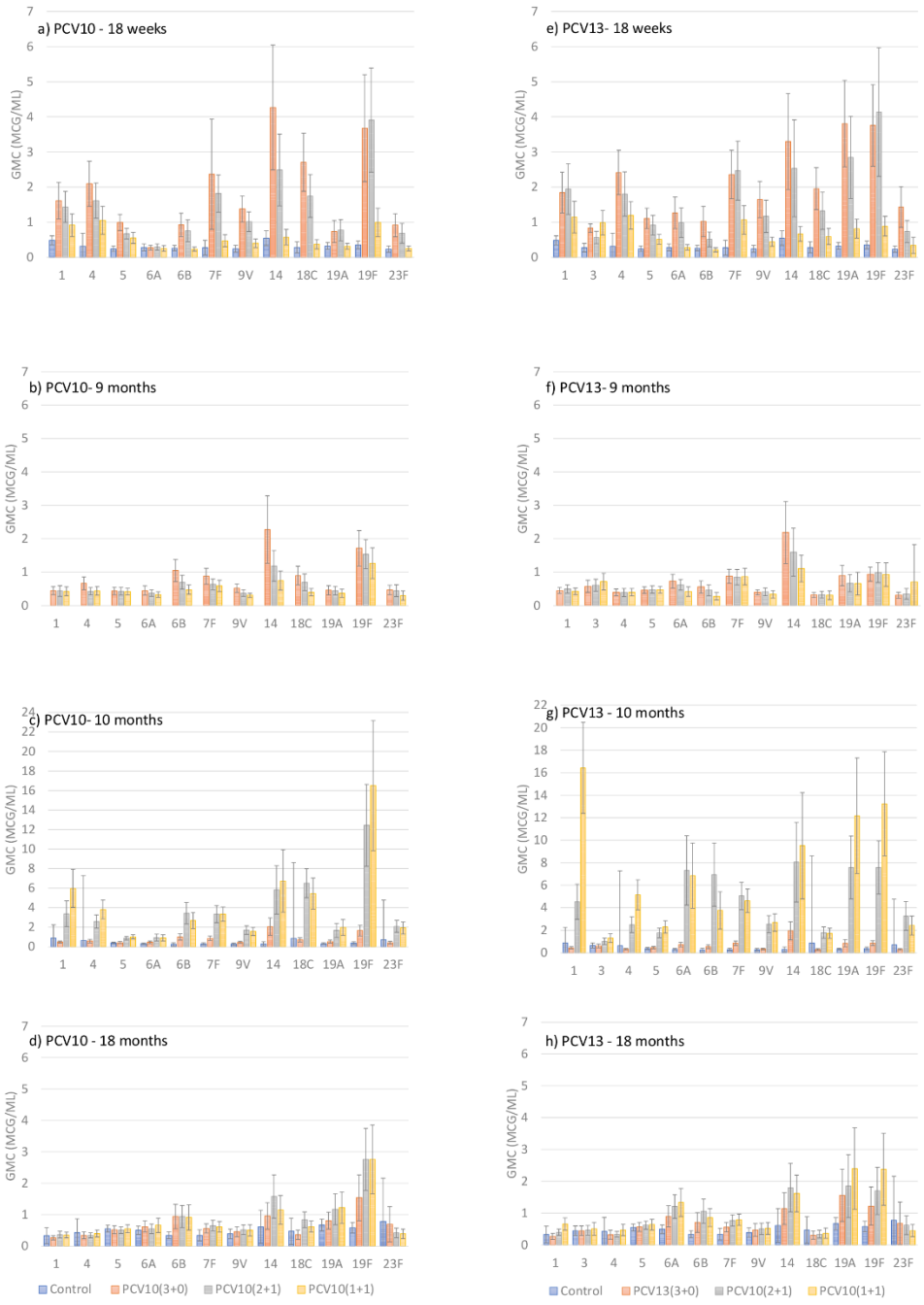

Figure 6: Geometric mean titres (95% confidence intervals) for PCV10 and PCV13 schedules at post-primary(18 weeks), pre-booster(9 months), post-booster(10 months) and second year of life (18 months) timepoints.