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Short communication

13-valent pneumococcal conjugate vaccine-induced B cells produce serotype 6B but not serotype 3 capsule-specific IgG antibodies in young Malawian adults

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ABSTRACT

Pneumococcal conjugate vaccine (PCV13) introduction has reduced vaccine-type carriage and disease; however pneumococcal carriage persists at high rates particularly in high-transmission settings. Serotype 3 remains a particular problem in Malawi and globally, with high carriage rates, as well as strain resistance to antibiotics and antibody-mediated killing. We studied antibody and B cell responses to PCV13 in 65 healthy Malawian adults (18–40 years) taking part in a randomized controlled trial. Serum, nasal fluid, and PBMC samples were collected before and after vaccination. Anti-capsular IgG for serotypes 3 and 6B were measured by ELISA, and capsule-specific B cells were assessed by spectral flow cytometry. PCV13 increased both serum and mucosal IgG levels, and IgG^+ B cells in blood for serotype 6B but not serotype 3. The poor immunogenicity of serotype 3 capsular polysaccharide in Malawian young adults highlights the need for alternative vaccines to address persistent serotype 3 carriage and disease.

1. Introduction

Introduction of the 13-valent pneumococcal conjugate vaccine (PCV-13) substantially reduced the global burden of pneumonia and sepsis caused by vaccine-type (VT) *Streptococcus pneumoniae* (Spn) [1]. However, despite the reduction of vaccine type carriage in many countries, carriage rates of both (VT) and non-vaccine-type (NVT) pneumococcal strains remain high in high-transmission settings such as Malawi [2].

Among the PCV13-included serotypes, serotype 3 (Spn3) presents a significant global challenge accounting for over 10% of invasive pneumococcal disease [3], yet PCV13 has provided only partial or no protection against this serotype [4]. In Malawi, Spn3 is now the dominant cause of pneumococcal carriage and disease [2] with genetically distinct strains from common global strains, increased resistance to antibiotics and antibody-mediated killing [5], and poor vaccine-response in children [6].

Though several studies have reported reduced immunogenicity of the Spn3 capsule [6–8], the mechanisms are not fully understood. Additionally, while IgG secreting B cells predicted protection against experimental carriage of serotype (Spn6B) in unvaccinated UK adults [9], few studies have investigated Spn3-specific B cell responses to PCV-13 vaccination in settings with high residual pneumococcal carriage. Here we report pneumococcal polysaccharide (PS)-specific antibody and B cell responses to PCV-13 vaccination in Malawian adults to provide insights into the immunological mechanisms underlying Spn3 persistence.

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2. Methods

We compared Spn3 and Spn6B anti-capsular polysaccharide (CPS) IgG antibodies and B cells in healthy adults aged 18 to 40 years taking part in a double-blinded, parallel-arm, randomized controlled trial of PCV13 efficacy against experimental pneumococcal carriage of serotype 6B [10].

We collected peripheral blood mononuclear cells (PBMC), serum, and nasal lining fluid (Nasosorption™ devices, Mucosal Diagnostics, UK) from volunteers who received either a saline ($n = 36$) or PCV13 ($n = 30$) intramuscular injection. Samples were collected before vaccination (baseline) and at 1-month post-vaccination (1Mth_P·V). We stored serum and lining fluid at -80 °C and PBMCs in liquid nitrogen.

We measured Spn6B and Spn3 anti-CPS IgG antibody concentrations of in sera and nasal lining fluid using a standardized World Health Organization enzyme-linked immunosorbent assay (ELISA) [11,12]. We calculated antibody concentrations using a four-parameter logistic curve in MyAssays. Each ELISA plate had a separate standard curve from the Human Anti-Pneumococcal Capsule Reference Serum (UK NIBSC, 007sp).

To analyse polysaccharide-specific (PS) B cell responses, we stained cryopreserved PBMCs with fluorochrome-labelled polysaccharides in combination with cell surface markers [13]. Thirteen PCV13-included CPS (serotypes 1, 3, 4, 5, 6 A, 6B, 7F, 9 V, 14, 18C, 19 A, 19F, 23F) and NVT 15B (Statens Serum Institute Diagnostica) were separately multimerized with two streptavidin-bound fluorochromes. After unmixing raw Flow Cytometry Standard (FCS) files using the Cytek Spectraflow software, we used FlowJo version 10.10 to gate for B cells, identify PS-specific B cells and gate for IgD + IgM+, IgD+, IgM+, IgG+ and IgA+ B cells (Fig.S1). The PS-gated FCS files were loaded into RStudio version 2024.04.0 to identify and remove cross-reactive cells and calculate the frequency of PS-specific B cells as a percentage of the total B cell population per sample. Detailed steps in ELISA and PBMC staining are provided in the supplementary materials.

We performed statistical analyses and graphical presentations in R version 4.4.2 using RStudio (2024.04.0). We compared antibody titers and B cell isotypes between time points using a paired Wilcoxon signed-rank test and B cell frequencies between groups using the Mann-Whitney *U* test with Bonferroni correction for multiple testing. Differences with *p*-values less than or equal to 0.05 were considered significant. Where stars are used to represent significance, * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$, **** = $p < 0.0001$.

3. Results

Participant demographics are summarized in Table 1. In brief, the median age of the study participants was 23·9 years (22.4–27.9) in the placebo group and, 26.0 years (23.0–28.5) in the PCV13 group. 72% and 80% of the participants were male in the placebo and vaccine groups respectively. Data for natural carriage of pneumococcal serotypes at baseline and 1-month post-vaccination is provided in Fig. S3.

In the PCV13 arm, Spn3 anti-CPS IgG concentrations in serum were similar between baseline, 0.601 µg/mL [95% CI 0.523 0.691 µg/mL] and 1-month post-vaccination, 0.608 µg/mL [95% CI 0.531 0.696] (Fig. 1a). By contrast, PCV13 increased serum Spn6B anti-CPS IgG concentrations from 2.55 µg/mL [95% CI 2.19–2.98 µg/mL] at baseline to 6.15 µg/mL [95% CI 4.28–8.84 µg/mL] (Fig. 1a). In the saline group, serum antibody concentrations remained stable between baseline and 1-month post-vaccination for both Spn3 ($p = 0.39$) and Spn6B ($p = 0.97$) (Fig. 1a).

In nasal samples Spn3 anti-CPS concentrations in PCV13-vaccinated participants were similar between baseline, 0.417 µg/mL [95% CI 0.230–0.756 µg/mL] and 1-month post-vaccination, 0.285 µg/mL [95% CI 0.157–0.515 µg/mL] (Fig. 1b) while Spn6B anti-CPS IgG concentrations increased from 0.750 µg/mL [95% CI 0.470–1.19 µg/mL] at baseline to 1.76 µg/mL [95% CI 0.958 3.22 µg/mL] at 1-month post-vaccination (Fig. 1a-b). In the saline group, nasal antibody concentrations remained stable between baseline and 1-month post-vaccination for both Spn3 ($p = 0.5$) and Spn6B ($p = 0.92$) (Fig. 1b). In PCV13-vaccinated participants, Spn3 anti-CPS antibody concentrations did not significantly increase irrespective of whether participants had low, medium or high baseline antibody concentrations (Fig.S4). The results show that PCV-13 vaccination boosts Spn6B but not Spn3 anti-CPS IgG concentrations in both serum and nasal lining fluid.

The baseline frequency of PS-specific B cells recognizing vaccine included serotypes and the NVT 15B was not different between saline and PCV-13-vaccinated groups (Fig. 2a). Pre-vaccination Spn3-specific B cells in both study groups were highest among all serotypes (Fig. 2a). At 1-month post-vaccination, PS-specific B cells were higher in the PCV13 group compared to the saline group for all vaccine-included serotypes but not for NVT 15B (Fig. 2a). The frequency of both Spn3 and Spn6B-specific B cells increased significantly from baseline to 1-month post-vaccination in the PCV13 arm but not the saline arm (Fig. 2b). The results show that PCV13 robustly amplifies systemic PS-specific B cell responses in adults living in a high pneumococcal carriage setting.

At baseline IgD + IgM+ isotypes were more abundant relative to other isotypes in both study groups for most serotypes while at 1-month post-vaccination IgM+ isotypes were more abundant (Fig. S3). Notably the proportions of Spn3, Spn5 and Spn14 IgG+ cells did not increase at 1-month after PCV13 vaccination Fig. S3). Spn6B IgG+ B cells in the PCV13 arm increased significantly from baseline to 1-month post-vaccination and Spn6B IgD + IgM+ B cells decreased significantly while Spn3 showed significant increase in IgM+ and IgA+ B cells (Fig. 3a-b) during the same period. The results indicate a limited class-switching to IgG for Spn3-specific B cells relative to other serotypes despite robust expansion following PCV13 vaccination.

Table 1
Participant demographics.

	Vaccine	
	Saline	PCV-13
Characteristic	$N = 36$[1]	$N = 30$[1]
Sex[1]		
Female	10 (28%)	6 (20%)
Male	26 (72%)	24 (80%)
Age[2]	23.9 (22.4, 27.9)	26.0 (23.0, 28.5)

[1] n (%); [2]Median (Q1, Q3)

4. Discussion

The study investigated polysaccharide-specific antibody and B cell responses to PCV-13 in adults living in a setting with high residual VT carriage. We showed that while PCV-13 increased the overall frequency of B cells recognizing PCV13-included serotypes, the anti-capsular IgG+ B cell and IgG antibody response was variable, with Spn3 displaying poor induction of capsule-specific IgG+ B cells, and anti-capsular IgG antibodies in serum and nasal lining fluid.

We evaluated whether PCV-13 vaccination induces systemic and mucosal IgG antibodies targeting the Spn3 capsule in Malawian young adults. In contrast to Spn6B, Spn3 anti-CPS IgG antibodies in nasal lining fluid and in serum did not increase significantly following PCV-13 vaccination. These results are consistent with PCV immunogenicity studies [7] and an experimental human pneumococcal challenge study in UK adults [8], which also reported no significant Spn3 antibody response to PCV-13. Additionally, nasal anti-Spn3 CPS IgG antibodies did not increase significantly following PCV13 vaccination in UK adults despite a significant increase in serum Spn3 anti-CPS IgG [14]. However, population differences between the two studies could account for the differing serum Spn3 anti-CPS IgG responses. The reduced Spn3 anti-Spn3 CPS IgG antibody response in serum and nasal lining fluid may contribute to the persistence of carriage and disease considering that

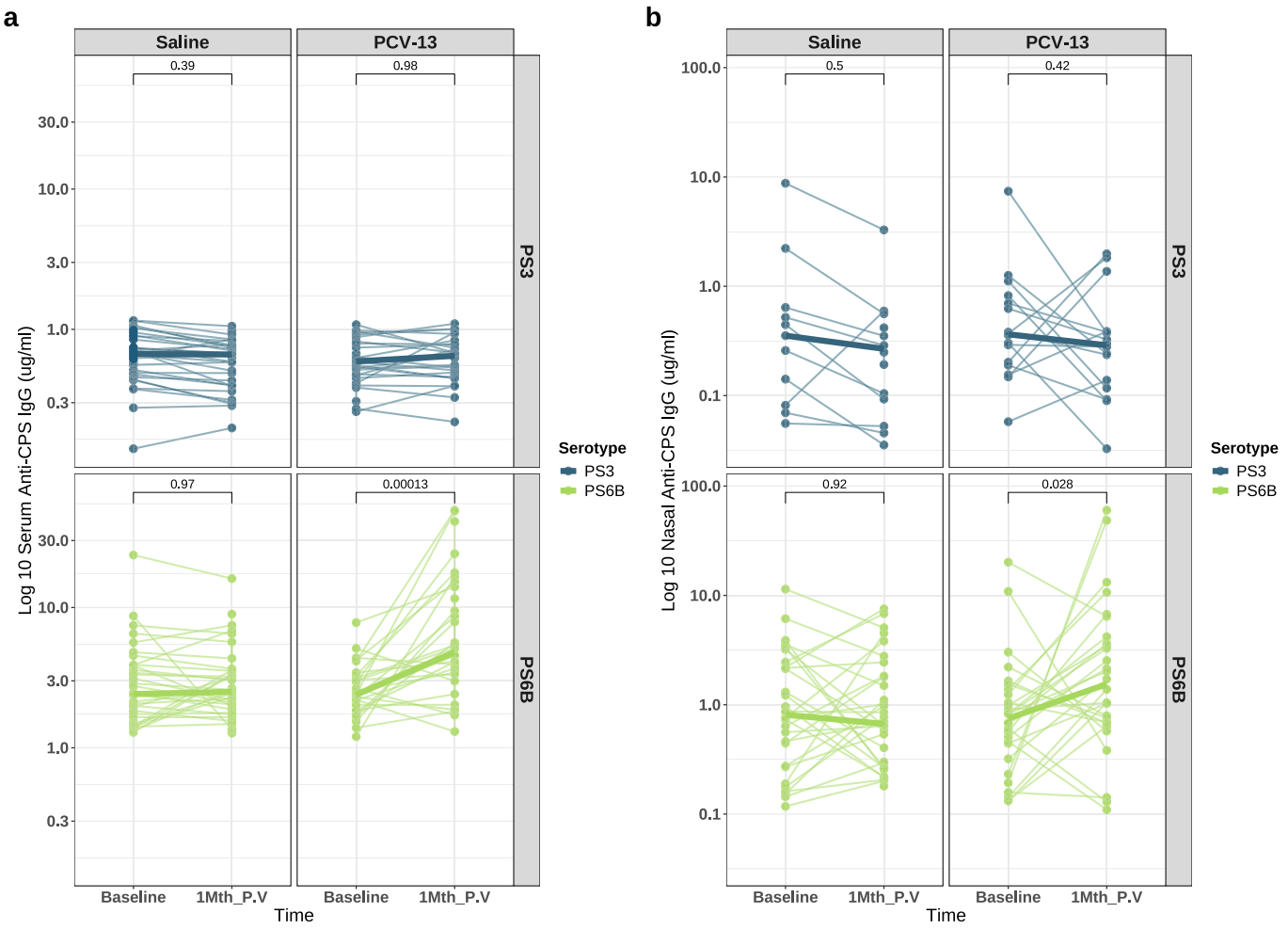

Fig. 1. Binding anti-Spn6B and anti-Spn3 CPS antibodies in serum and nasal lining fluid before and following PCV13 vaccination. Concentrations of binding anti-Spn6B CPS antibodies in serum and nasal lining fluid were measured using an enzyme-linked immunosorbent assay (ELISA). The serum and nasal samples were obtained from volunteers vaccinated with PCV13 and those given a saline placebo as a control. The samples were obtained before (Baseline) and 1-month post-vaccination (1Mth_P·V). a) Serum and b) nasal Spn6B and Spn3 anti-CPS IgG antibody titers before and after vaccination (Saline $n = 36$ vs. PCV13 $n = 30$). Paired pre- and post-vaccination data were visualized using a line plot. Dots corresponding to the same participant were connected by a line to illustrate within-subject change in concentrations of anti-Spn6B (dark blue) and anti-Spn3 (light green) CPS IgG antibodies. The thick line between baseline and 1Mth_P·V represents the median antibody concentration. Data were analysed using a paired Wilcoxon signed-rank test, comparing before (Baseline) and after vaccination (1Mth_P·V). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Spn3 strains circulating in Malawi exhibit increased resistance opsonophagocytic killing [5].

To further investigate the low Spn3 anti-CPS IgG antibody response to PCV-13, we evaluated the B cell response in a subset of participants and found that PS-specific B cells across all vaccine-included types increased following vaccination. This is in line with a previous study which reported significant increases in serotype-specific B cell populations in peripheral blood following a single dose of PCV-7 in older UK adults [15]. However, the increase in Spn3-specific B cell frequency was paradoxical as we did not observe a corresponding increase in Spn3 anti-CPS IgG antibodies following PCV13 vaccination. Moreover, the baseline frequencies of PS3-specific B cells were highest among all serotypes, reflective of the high carriage prevalence [2] but again in contrast with the low antibody titres.

Further analysis of serotype-specific B cell isotypes showed significant increase in Spn6B CPS IgG+ B cells and Spn3-specific IgM+ and IgA+ B cells. However, consistent with our observation of no significant increase in Spn3 anti-capsular IgG antibodies Spn3-specific IgG+ B cells did not increase following PCV-13 vaccination. Additionally, a study of Dutch and UK individuals also showed a reduced IgG+ switching among B cells recognizing Spn3 in contrast with other serotypes, [13], however, the small sample size limits generalizability of the findings. The reduced anti-Spn3 CPS IgG response at the antibody and B cell level highlights the poor immunogenicity of the Spn3 capsule in PCV-13 and has implications for vaccine evaluation and for protection against Spn3 disease and carriage in high transmission settings. Although serotype 5- and serotype 14-specific IgG^+ B cells did not increase following PCV13 vaccination, these cell populations were detected at very low frequencies. Therefore, interpretation of vaccine-induced changes for these serotypes is limited and would require additional analyses of serum or nasal IgG antibodies, which were not possible due to limited sample volume.

The comparison of vaccine responses to T-cell dependent (TD) and T-cell independent (TI) antigens led to the breakthrough discovery of conjugate vaccines for important respiratory pathogens including *Haemophilus influenzae* type B and *S. pneumoniae* [1,16]. Conjugate vaccines induce antigen specific memory responses in the follicular marginal zones of the spleen [15] and have been an outstanding success for most pneumococcal serotypes [17]. The paradoxical reduced anti-Spn3 CPS IgG antibody response following PCV13 vaccination in our study population is partially explained by our data which suggests a failure of B cell activation and maturation to allow class switching from IgD + IgM+

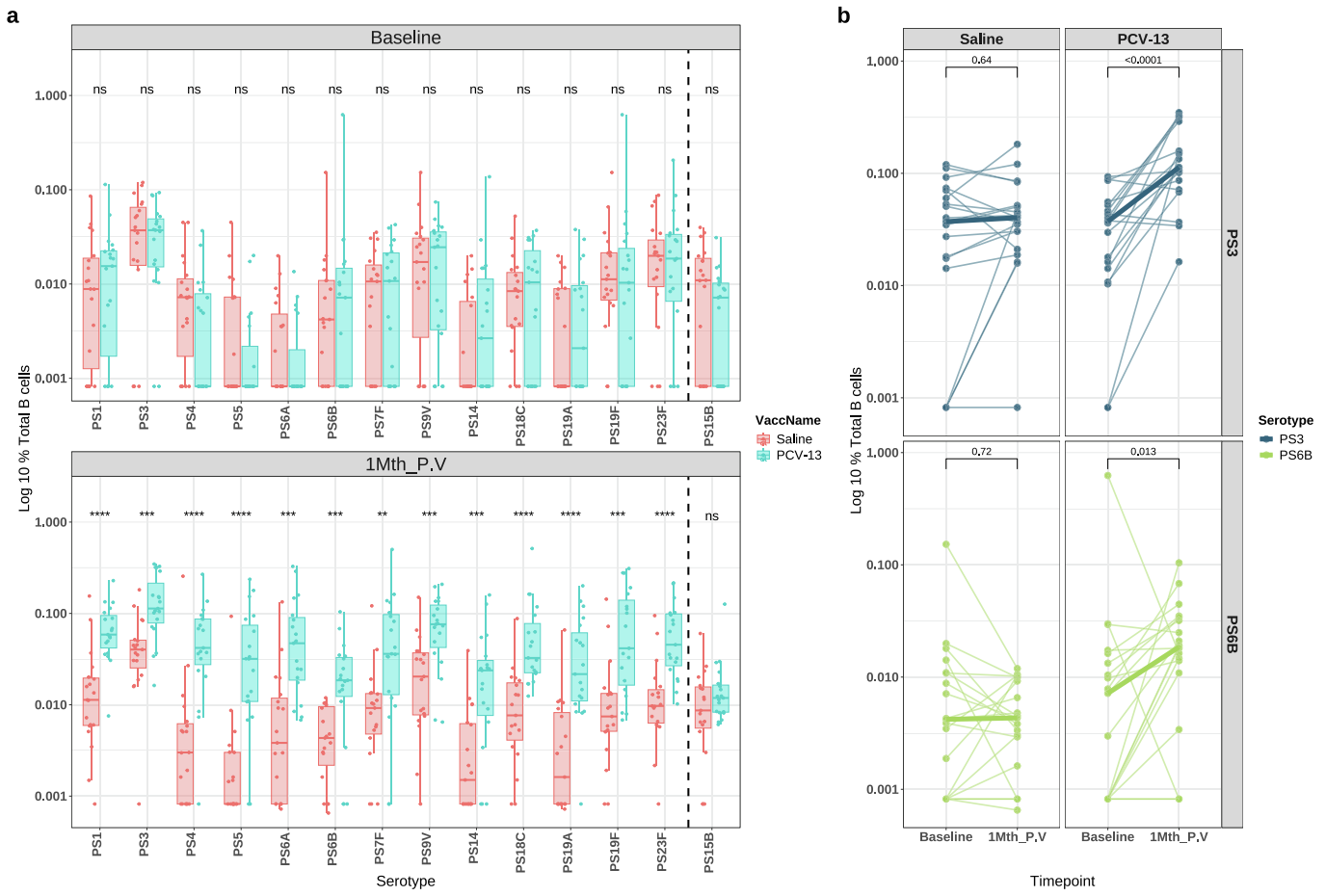

Fig. 2. Pneumococcal polysaccharide-specific B cell frequencies before and following saline or PCV-13 vaccination. Capsular polysaccharide-specific B cell frequencies in peripheral blood were measured using a flow cytometry assay. Peripheral blood mononuclear cells were isolated from blood obtained from volunteers vaccinated with PCV13 and those given a placebo as a control. The samples were obtained before (Baseline) and 1-month post-vaccination (1Mth_P·V). a) Pneumococcal polysaccharide-specific B cell frequencies as a percentage of total B cells before and after vaccination in Malawian adults (Saline $n = 19$ vs. PCV-13 n = 19). Non-vaccine serotype 15B is separated from PCV13 serotypes by a dashed line The horizontal bars represent the median and interquartile range (IQR). Statistical comparison was performed using Mann-Whitney *U* test with Bonferroni correction for multiple testing comparing saline (red) and PCV-13 (blue) for each serotype. $*p < 0.05$, $**p < 0.01$, $***p < 0.001$, $****p < 0.0001$. b) Paired pre- and post-vaccination data were visualized using a line plot. Dots corresponding to the same participant were connected by a line to illustrate within-subject change in the frequency of B cells recognizing serotype 6B capsular (dark blue) and serotype 3 capsular polysaccharides (light green). The thick line between baseline and 1Mth_P·V represents the median cell frequency. Data were analysed using a paired Wilcoxon signed-rank test, comparing before (Baseline) and after vaccination (1Mth_P·V). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

to IgG+ memory B cells or plasma cells. To reduce the persistent Spn3 burden in populations with high colonization rates, alternative vaccines such as those including different conjugation strategies and pneumococcal antigens are required and are the subject of current studies [3,18].

This study presents the first investigation of polysaccharide-specific B cell responses to PCV13 in Malawian volunteers and provides valuable insights into immunological mechanisms contributing to the persistence of Spn3. However, the study was limited by low PBMC viability and low cell numbers which constrained phenotypic analysis. Another limitation is that the study did not explore long-term immune responses beyond 1-month post-vaccination. Additionally, OPA and IgM antibody responses were not measured due to limited sample volume. Nevertheless, the study establishes a valuable methodological foundation for assessing vaccine-induced B cell responses in high-carriage settings.

CRediT authorship contribution statement

G. Tembo: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **D. Hoving:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **A.C. de Kroon:** Writing – review & editing, Methodology. **L. Chimgoneko:** Writing – review & editing, Methodology. **T. Nthandira:** Writing – review & editing, Methodology. **B. Galafa:** Writing – review & editing, Methodology. **F. Thole:** Writing – review & editing, Methodology. **E. Nsomba:** Writing – review & editing, Methodology. **D. Dula:** Writing – review & editing, Methodology. **C. Ngoliwa:** Writing – review & editing, Methodology. **N. Toto:** Writing – review & editing, Project administration. **L. Makhaza:** Writing – review & editing, Methodology, Data curation. **A. Muyaya:** Writing – review & editing, Methodology, Data curation. **E. Kudowa:** Writing – review & editing, Methodology. **A. E. Chirwa:** Writing – review & editing, Methodology, Investigation. **M. Y.R. Henrion:** Writing – review & editing, Supervision, Methodology. **T. Chikaonda:** Writing – review & editing, Supervision, Methodology. **B.C. Urban:** Writing – review & editing, Validation, Supervision, Methodology. **D.M. Ferreira:** Writing – review & editing, Validation, Supervision, Methodology. **K.C. Jambo:** Writing – review & editing, Writing – original draft, Validation, Supervision, Software, Resources, Methodology, Investigation, Funding acquisition, Formal analysis, Data

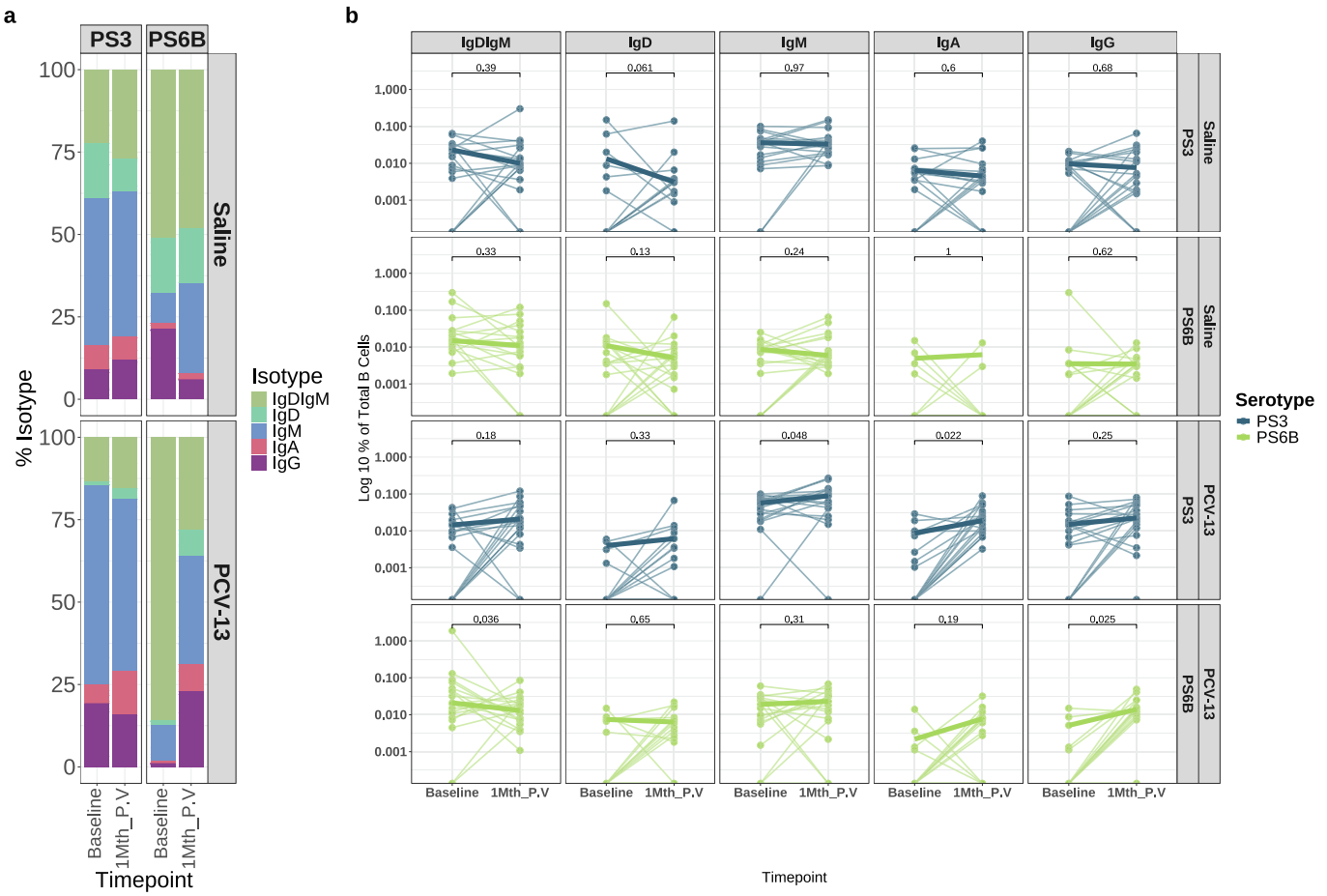

Fig. 3. Pneumococcal polysaccharide-specific B cell isotypes before and following saline or PCV-13 vaccination. Capsular polysaccharide-specific B cell isotypes in peripheral blood were measured using a flow cytometry assay. Peripheral blood mononuclear cells were isolated from blood obtained from volunteers vaccinated with PCV13 and those given a placebo as a control. The samples were obtained before (Baseline) and 1-month post-vaccination (1Mth_P·V). a) Pneumococcal polysaccharide-specific B cell isotypes before and after vaccination in Malawian adults (Saline n = 19 vs. PCV-13 n = 19). The stacked bar represents the mean proportion of B cell isotypes per time point, IgD + IgM+ (green), IgD+ (cyan), IgM+ (blue), IgA+ (red) and IgG+ (purple). b) Pneumococcal polysaccharide-specific B cell isotypes before and after vaccination in Malawian adults. Paired pre- and post-vaccination data were visualized using a line plot with the thick line between timepoints representing the median cell frequency. Dots corresponding to the same participant were connected by a line to illustrate within-subject change in the frequency of B cell isotypes serotype 6B capsular (dark blue) and serotype 3 capsular polysaccharides (light green). Data were analysed using a paired Wilcoxon signed-rank test, comparing before (Baseline) and after vaccination (1Mth_P·V). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

curation, Conceptualization. **S.P. Jochems:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **S.B. Gordon:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2026.128269.

Data availability

Data will be made available on request.

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