

Population genomics reveals vaccination-induced genotypic changes in carried pneumococcal population

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Introduction

Recent clinical trials globally have increasingly demonstrated the effectiveness of PCV13 *Streptococcus pneumoniae* (*Spn*) vaccine but population-wide vaccine-induced perturbations in *Spn* populations remain poorly understood¹. To assess the vaccine-driven epidemiological, genomic and ecological changes in healthy *Spn* carriers following PCV13 introduction in a previously vaccine-naïve setting in northern Malawi, we characterised the genetic population structure, strain type and lineage diversity, antibiotic resistance and accessory genome dynamics of whole genome sequenced carried *Spn* strains sampled pre- and post-PCV13 introduction. Because carriage remains largely unchanged post-PCV, ‘frequency’ means proportion among carriers.

Results

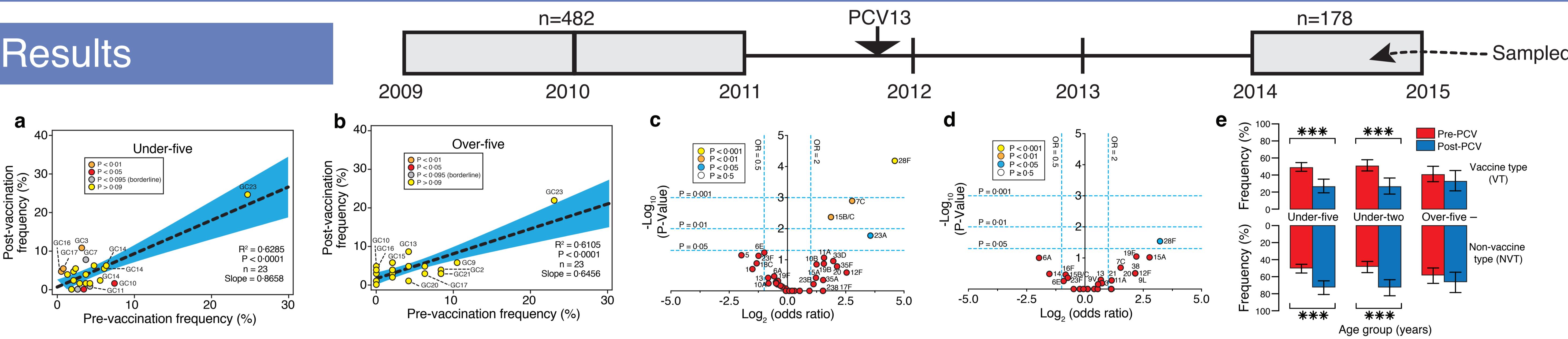


Fig. 1 | Frequency of Genomic Clusters (GC) in pneumococcal carriage population.

(a) The scatter plot showing the frequency of GCs in the under-fives and (b) in the over-fives. The dots in the scatter plots represent GCs and those whose frequency did not change significantly are shown in yellow changed significantly (or borderline significant) are shown in non-yellow colour differentiated according to their degree of statistical significance: $P < 0.05$ (red), $P < 0.01$ (orange) and borderline significance $P < 0.095$ (grey) shown in the key at the top of each plot. The overall association between the GC frequency pre- and post-vaccination is shown by the fitted linear regression line (black, dashed) bordered by the 95% CI (blue) with estimated parameters shown at the bottom right of the plots. The volcano plot for the strains among (c) under-five and (d) the over-five carriage populations showing the magnitude (\log_2 of the odds ratio) in the x-axis and statistical significance ($-\log_{10}$ P-Value) in the y-axis of the change in frequency of serotypes post-vaccination relative to pre-vaccination. Each circles in the plots represent a specific serotype frequency coloured according to the level of statistical significance: $P < 0.05$ (blue), $P < 0.01$ (yellow) and $P > 0.05$ (red). Some serotypes especially those with significant changes in frequency are labelled in the plots. (e) The bar graph showing serotype frequency in different age groups pre- and post-vaccination. The upward facing bar graph shows changes in frequency of VT strains while the bar graph facing downwards shows corresponding changes in frequency of NVT strains. The error bars in the bar graphs represent 95% CIs for the frequency. The age groups with significant changes in frequency of VT and NVT strains are marked with asterisks: $P < 0.001$ (***)

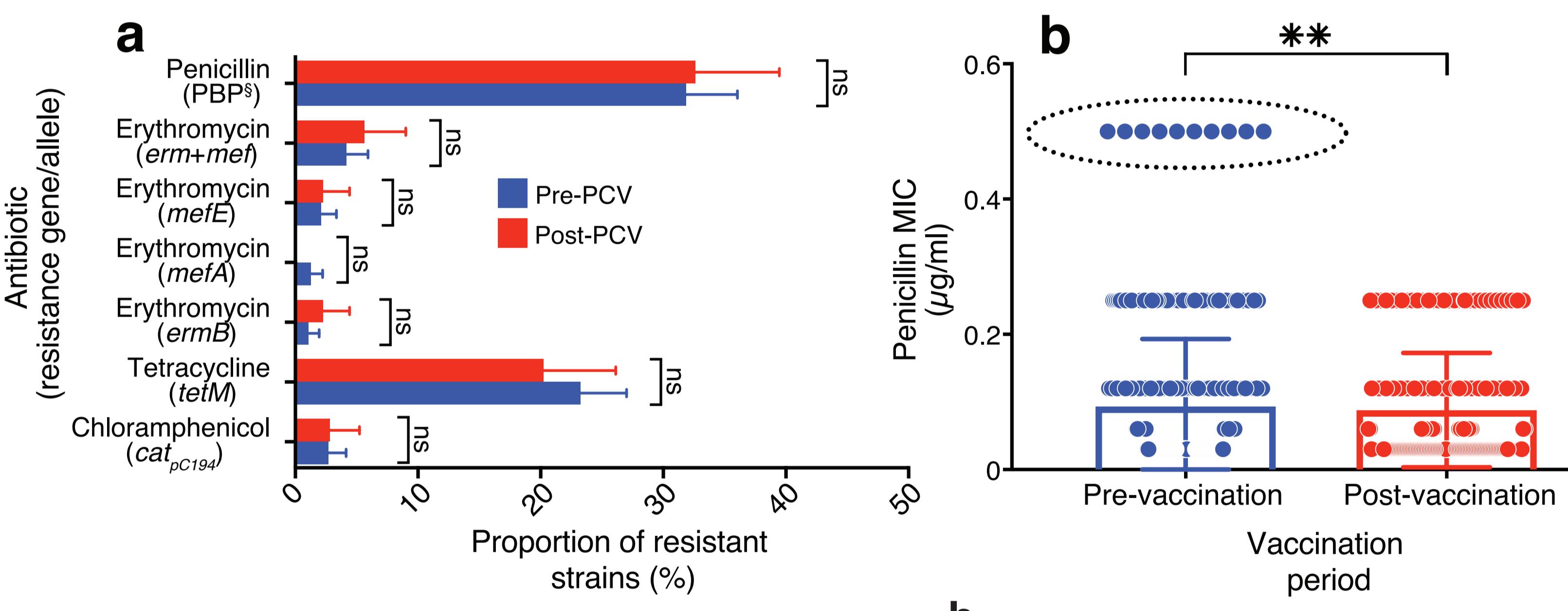


Fig. 2 | Antibiotic resistance in the pneumococcus.

(a) Prevalence of antibiotic resistance (genotypic) pre and post-vaccination. (b) Penicillin minimum inhibitory concentrations (MICs) pre- and post-vaccination. The resistance rates and penicillin resistance rates were inferred genotypically. For penicillin resistance, minimum inhibitory concentrations (MIC) were predicted using a pipeline by the Centres for Disease Control and Prevention (CDC) which predicts the MIC levels with high sensitivity and specificity based on the allelic profiles of the transpeptidase domain (TPD) sequences of penicillin binding proteins (PBP) - PBP1A, PBP-2B and PBP2X². The binary resistance phenotypes (resistant or susceptible) were inferred from the MICs using the clinical laboratory standards institute (CLSI) meningitis breakpoints. The double asterisks imply $P < 0.001$.

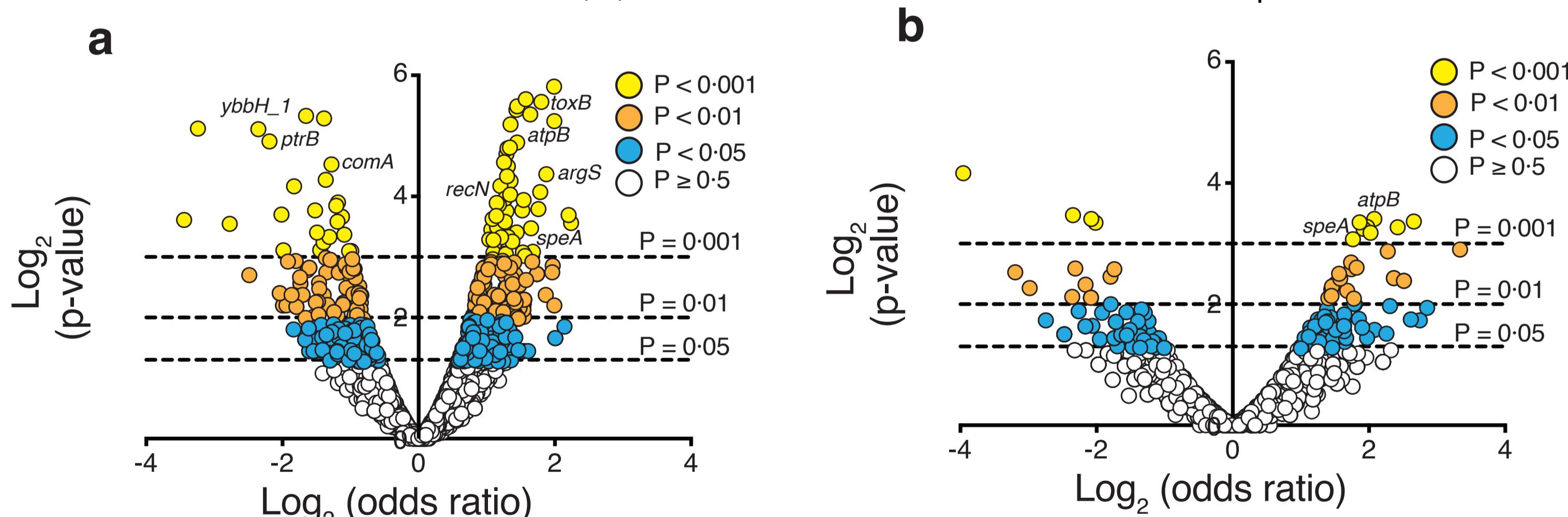


Fig. 3 | Vaccine induced accessory genome dynamics.

The distribution of the accessory genes with frequency between $\geq 5\%$ and $\leq 95\%$ (intermediate) in the entire population. The scatter plots with circles (red) representing frequency of specific genes pre- and post-vaccination among VT strains sampled from (a) under-five and (b) over-five *Spn* carriers. The volcano plots show the magnitude (\log_2 of the odds ratio) in the x-axis and statistical significance ($-\log_{10}$ P-Value) in the y-axis of the change in frequency of the genes. Fisher's exact test was used to determine the P-Values shown in the volcano plots and these were distinguished by the levels of statistical significance: $P < 0.05$ (blue), $P < 0.01$ (orange), $P < 0.001$ (yellow) and no significance $P > 0.05$ (white). The horizontal dashed lines that crosses the y-axis in volcano plots demarcates different significance levels.

Key Findings & Conclusions

- Significant fluctuation of strain types and lineages among *Spn* carriers pre- and post-vaccination (Fig. 1a-b).
- Significant reduction in frequency of VT strains in under-fives (direct effect) but not over-fives (indirect effect) (Fig 1. c-e).
- Evidence of serotype replacement by NVTs e.g. 23A, 15B/C, 7C & 28F with minor individual serotype contribution (Fig. 1c-e).
- No significant changes in resistance rates possibly because of the already low resistance rates in carriage although clearance of certain lineages was associated with a decrease in their penicillin MIC levels.
- Significant changes in frequency of accessory genes by age group (Fig. 3a-b) and vaccination status (VT or NVT, not shown) mostly in the under-fives consistent with findings in Fig1. Majority of the changes occurred in mobile genetic elements and bacteriocin associated genes consistent with recent findings in carried *Spn* in the USA³.
- These findings reveal high-resolution insights into the genotypic changes in *Spn* carriage post-vaccination but continued surveillance remain crucial to monitor population changes such as expansion of replacement NVT serotypes.

References



Global Pneumococcal Sequencing (GPS) Project

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