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# Pneumococcal conjugate vaccine induced IgG and nasopharyngeal carriage of pneumococci: Hyporesponsiveness and immune correlates of protection for carriage

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ABSTRACT

*Background:* Prior studies have demonstrated hyporesponsiveness to pneumococcal conjugate vaccines (PCVs) when administered in the presence of homologous carriage. This may be substantially more important in Africa where carriage prevalence is high. Deriving a correlate of protection (CoP) for carriage is important in guiding the future use of extended PCVs as population control of pneumococcal disease by vaccination is now focused principally on its indirect effect. We therefore explored the complex relationship between existing carriage and vaccine responsiveness, and between serum IgG levels and risk of acquisition.

*Methods:* We undertook secondary analyses of data from two previously published clinical trials of the safety and immunogenicity of PCV in Kenya. We compared responses to vaccination between serotype-specific carriers and non-carriers at vaccination. We assessed the risk of carriage acquisition in relation to PCV-induced serum IgG levels using either a step- or continuous-risk function.

*Results:* For newborns, the immune response among carriers was 51–82% lower than that among non-carriers, depending on serotype. Among toddlers, for serotypes 6B, 14 and 19F the post-vaccination response among carriers was lower by between 29 and 70%. The estimated CoP against acquisition ranged from 0.26 to 1.93 μg/mL across serotypes, however, these thresholds could not be distinguished statistically from a model with constant probability of carriage independent of assay value.

*Conclusion:* We have confirmed hyporesponsiveness in an equatorial African setting in both infants and toddlers. Population responses to vaccination are likely to improve with time as carriage prevalence of vaccine serotypes is reduced. We have not found clear correlates of protection against carriage acquisition among toddlers in this population. Assessing the potential of new vaccines through the use of CoP against carriage is still difficult as there are no clear-cut serotype specific correlates.



## 1. Introduction

The first pneumococcal conjugate vaccine (PCV), which contained seven serotypes, reduced the incidence of pneumococcal disease and the prevalence of nasopharyngeal carriage in both vaccinated and unvaccinated children as well as adults when introduced into routine infant immunisation programme in the USA in 2000 [1]. The indirect protective effect of PCV is caused by a vaccine-induced reduction in the risk of acquiring colonisation by vaccine serotypes (VTs), which leads to a reduction in onward transmission from young children.

Recently, data have emerged that highlight the complexity of interactions between pneumococci, the human immune system and the nasopharynx. Infants carrying serotypes 6B, 19F or 23F at the time of PCV immunisation have reduced primary IgG responses to those serotypes [2,3] and this effect persists through to post-booster responses [4]. Rodenburg and colleagues showed that, at 24 months of age, children's responses to PCV against these three serotypes were reduced if they had carried them at any point in the 2 years prior to vaccination [5].

PCV responses in African children are generally thought to be higher than those seen in developed country settings [6–9]. For instance, the serotype-specific geometric mean fold-rise between

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the time of the first dose and one month after the third dose of PCV were lower in USA [7] and Finland [9] compared to South Africa [6] and The Gambia [8]. Nonetheless, in parts of Africa like The Gambia [10] and Kenya [11,12], carriage rates from very early in life are extremely high. Given high responses to PCV it is possible that hyporesponsiveness does not occur, or is immunologically irrelevant, in equatorial Africa.

The immunological mechanism that mediates vaccine-induced protection against colonisation at the mucosal level, or against disease, is not known. While circulating IgG may have a role in preventing colonisation, as demonstrated in a mouse model in which antibody blocked colonisation through agglutination [13], local B cells producing IgG and/or IgA in the nasopharynx may also be relevant and a role for T cells has also been suggested [14,15]. Nonetheless, to facilitate the licencing of new formulations of PCV, a single aggregate serological correlate of protection against invasive pneumococcal disease (IPD), has been derived based on circulating IgG [16,17]. However, a recent analysis that suggested correlates of protection (CoP) for IPD vary widely by serotype [18] has questioned the biological relevance of a single aggregate CoP common to all serotypes. It is likely that, as with IPD, the CoP against carriage also vary by serotype.

Numerous assumptions were made during the development of the common serological CoP and there is equipoise in the scientific community about the relevance of the CoP to carriage and mucosal disease [19]. For some serotypes, greater concentrations of serum IgG were likely to be required to protect at mucosal surfaces (e.g. in the nasopharynx) than in blood [20]. Subsequent analysis of vaccine-induced antibody and the prevention of carriage reinforced the notion that if circulating IgG is indeed a relevant correlate for carriage, remarkably high concentrations are required to reduce carriage acquisition [21]. Deriving CoP for carriage would guide the future use of extended PCVs, as population control of pneumococcal disease by vaccination is now focused principally on its indirect effect mediated through carriage [22].

We therefore set out to explore both the relationship between existing carriage and vaccine responsiveness and between serum IgG levels and risk of acquisition by undertaking new analyses of two existing field studies of PCV in Kenya, with the following questions: (i) Does hyporesponsiveness occur in high carriage settings like Kenya? (ii) If so, can we detect this for serotypes other than the most common (e.g. 6B, 19F and 23F)? (iii) Is it possible to derive a serological correlate of protection against carriage acquisition using vaccine-induced IgG responses detected within randomized controlled trials of PCV in Kenya?

## 2. Methods

### 2.1. Data

Data from two previously published clinical trials of the safety and immunogenicity of PCV conducted in Kenya [14,15] were further analysed in the current study. The first study (“Newborn study”) recruited 300 newborns that were randomized to receive 7-valent PCV (PCV7) in one of two vaccine schedules; at 0–10–14 weeks or at 6–10–14 weeks. The subjects received a PCV7 or 23-valent Pneumococcal Polysaccharide Vaccine (PPV23) booster dose of at 36 weeks. Serological measurements were made at 0, 6, 10, 14, 18, 36 and 37 weeks and nasopharyngeal carriage ascertained at 18 and 36 weeks. The objectives of this study were to examine the effect of a newborn vaccination schedule with PCV7 on the development of antibody and carriage prevalence. In the current analysis we used the carriage data at the time of the booster (week 36) and the serological measurements at week 36 and week 37.

The second study (“Toddler study”) recruited 600 children aged 1–4 years to examine the effect of 0, 1 or 2 doses of a 10-valent PCV (PCV10), on capsular antibody concentrations and nasopharyngeal carriage. Children were given PCV10 in three different schedules: Group A received PCV10 at day 0 and day 60; Group B received PCV10 at day 0 and day 180. Diphtheria-tetanus-pertussis (DTaP) was given as a control vaccine to group A at day 180 and to Group B at day 60. A third group, which is not considered in this analysis, received Hepatitis A virus (HAV) at day 0 and day 180 and DTaP at day 60. Antibody measurements were made at days 0, 30, 90 and 210 and nasopharyngeal carriage assessed at days 0, 30, 60, 90 and 180. Details of the study have been published elsewhere [23]. In the current analysis we used carriage data from vaccinees in Groups A and B at day 0, 60 and 180 (vaccination time points), and serological measurements 30 days post vaccination i.e. at 30, 90 and 210 days, respectively.

### 2.2. Analysis

For the newborn study, we calculated the fold-rise in serotype-specific geometric mean concentrations (GMC) between weeks 36 and 37, separately, for carriers and non-carriers for each of the seven serotypes in PCV7. The differences between the two groups (homologous carriers vs. non-carriers) were quantified as ratios of the GMC fold-rises. These ratios were derived from log-linear regression models of the booster response taking account the vaccine schedule group (6–10–14 vs 0–10–14), type of booster given (PCV7 vs PPV23) and the baseline log-concentration of IgG, at 36 weeks. Baseline IgG concentrations is adjusted for since individuals with lower concentrations have more room for greater fold-rise than individuals who already have high concentration at baseline.

For the toddler study, we pooled paired carriage data and 30-day serological responses for each of the time points of PCV10 vaccination (0, 60 and 180 days). We calculated serotype-specific fold-rises in IgG concentration 30 days later (at 30, 90 and 210 days). There were no blood samples at time 60 and 180 by design therefore we used the IgG at time 30 to adjust for responses to vaccines given at 60 and 180 days. We would expect antibody concentrations to decay from day 30 to day 60 (and from day 30 to day 180) at the same rate for subjects in both Group A and Group B; therefore, the ranks in IgG baseline between time 30 days and the time of vaccination are likely to be highly correlated, provided that natural boosting is also distributed equally in both groups. To assess the impact of carriage at the time of vaccination, GMC fold-rise ratios between homologous carriers vs. non-carriers were estimated from log-linear serotype-specific regression models of the individual level fold-rise on the carriage status, taking account of the vaccine group (Group A and B), age group (12–23, 24–35, 36–47 and 48–59 months), season (month of sample collection) and pre-vaccine (day 0 or 30) log IgG. We used Generalized Estimating Equations (GEE) to account for the correlations between the repeated measures within an individual. Data for serotypes 6B, 9V, 14, 19F and 23F were selected for the analysis since they were the most frequently carried of the 10 vaccine-type serotypes. As a supplementary analysis, we also calculated the post-vaccination GMC by pre-vaccination carriage status for both the newborn and toddler studies.

In order to derive the serotype-specific antibody threshold for vaccine efficacy against acquisition, we restricted our analysis to data from the toddler study and, in particular, to toddlers who were non-carriers at day zero. We compared carriage status at day-30 against vaccine-induced IgG concentration measured at day 30. We fitted to these two variables a model that incorporates a threshold parameter that is estimated through a profile likelihood [24], the a:b model. The model is a step-shaped function

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