

Pneumococcal Vaccine Response After Exposure to Parasites in Utero, in Infancy, or Mid-Childhood

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abstract

BACKGROUND AND OBJECTIVE: *Streptococcus pneumoniae* is a leading cause of mortality before age 5, but few studies examine details of childhood response to pneumococcal vaccine in less-developed settings. Although malnutrition, HIV, and concurrent infections can impair response, evidence suggests that chronic parasitic infections can also contribute to poor vaccination results. The objective of this study was to determine whether response to pneumococcal vaccine varied among children either exposed to parasitic infections in utero, previously infected in infancy, or infected at the time of immunization.

METHODS: Children from a 2006 to 2010 maternal–infant cohort were eligible for the current study. Children were screened for malaria, schistosomiasis, filariasis, intestinal helminths, and protozoa. Data on in utero exposure and early life infections were linked, and baseline antipneumococcal immunoglobulin G levels and nasopharyngeal carrier status were determined. Participants received decavalent pneumococcal vaccine, and 4 weeks later, serology was repeated to assess vaccine response.

RESULTS: A total of 281 children were included. Preimmunity was associated with greater postvaccination increments in anti-pneumococcal polysaccharide immunoglobulin G, especially serotypes 4, 7, 9, 18C, and 19. Present-day growth stunting was independently associated with weaker responses to 1, 4, 6B, 7, 9V, and 19. Previous exposure to *Trichuris* was associated with stronger responses to 1, 5, 6B, 7, 18C, and 23, but other parasite exposures were not consistently associated with response.

CONCLUSIONS: In our cohort, hyporesponsiveness to pneumococcal conjugate vaccine was associated with growth stunting but not parasite exposure. Parasite-related vaccine response deficits identified before age 3 do not persist into later childhood.



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Drs Nayakwadi Singer, Malhotra, C. H. King, and LaBeaud conceptualized and designed the study, supervised and coordinated data collection at the study site, performed laboratory testing for this study, analyzed the study data, and drafted the initial manuscript; Drs Heath, Vu, and C. L. King performed laboratory testing for this study and reviewed and revised the manuscript; Mr Muinde and Drs Mutuku and Mukoko performed clinical enrollment and testing of the study subjects, supervised and coordinated data collection at the study site, and reviewed and revised the manuscript; Dr Gildengorin analyzed the study data and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

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WHAT'S KNOWN ON THIS SUBJECT: *Streptococcus pneumoniae* causes vaccine-preventable invasive disease and is a leading cause of child mortality. However, children in developing countries often do not respond appropriately to life-saving vaccines. Decreased vaccine responsiveness to multiple vaccines may be associated with parasite exposure.

WHAT THIS STUDY ADDS: A pneumococcal conjugate vaccine is now available in Africa, but little is known about its effectiveness in real-world settings of polyparasitism. This study examined childhood pneumococcal vaccine response in the context of prenatal and postnatal exposure to multiple parasitic infections.

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Vaccine-preventable diseases continue to kill ~1 to 2 million children yearly despite mass vaccine campaigns that have significantly increased worldwide coverage.¹⁻⁵ Studies have demonstrated that children in developing countries do not respond appropriately to life-saving vaccines, particularly bacille Calmette–Guérin, typhoid fever, measles, rotavirus, and polio vaccines.⁶⁻¹²

Parasitic infections are endemic to low-resource communities, and young children are their most vulnerable hosts. Although poor vaccine response has been linked to nutritional and growth deficits, a growing body of evidence suggests that chronic parasitic infections also play a role in reduced responses to routine vaccination.¹³⁻¹⁶ Specifically, among the Kenyan child cohort that participated in this study, Malhotra et al¹³ observed an association between parasitic exposure in utero and reduced vaccination responses to *Haemophilus influenzae* type b (Hib) and diphtheria antigens in early infancy.

Vaccine-preventable *Streptococcus pneumoniae* invasive disease (meningitis, pneumonia, and sepsis) is one of the leading worldwide causes of mortality under age 5.¹⁷ Few studies have examined infant and child responses to pneumococcal vaccine in developing countries. Standard antipneumococcal vaccination was introduced into the Kenyan childhood vaccination schedule in 2011, yet there is a paucity of data about circulating pneumococcal serotypes and the effectiveness of immunization in the general population. This study's goal was to evaluate pneumococcal vaccine response among at-risk children known to be exposed to parasites in utero or infected with parasites in early childhood or at the time of primary antipneumococcal immunization at age 4 to 7 years.

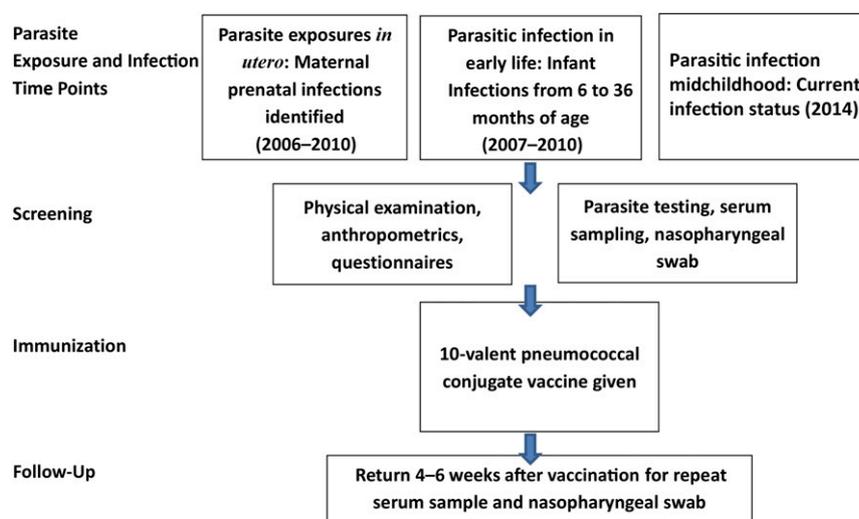


FIGURE 1 Study design: Parasitic exposures in utero and during early infancy were abstracted from 2006 to 2010 cohort study records. In 2014, reenrolled subjects, 4 to 7 years old, were retested for infection and for anti-PPS IgG and *S pneumoniae* carriage. Subjects were then retested 4 to 6 weeks after their first dose of decavalent conjugate vaccine.

METHODS

Ethics Statement

Children who had participated in a 2006 to 2010 cohort study at the Msambweni District Hospital on the southern coast of Kenya^{13,18} were eligible for the current study of antipneumococcal vaccine response. The data sharing, follow-up assessment, and vaccine outcomes reported in the present article were performed after written consent under a newly approved study protocol supervised by Kenyatta National Hospital Ethical Review Committee (protocol P85/03/2013) and the Institutional Review Board for Human Studies at University Hospitals of Cleveland Case Medical Center (protocol 01-13-13).

Study Population

We located, consented, and enrolled eligible children from a maternal–infant study cohort developed in 2006 to 2010.^{13,18} During that period, pregnant mothers were tested for parasitic infections during their second and third trimesters and upon delivery of their infants.¹³ The cohort children were followed prospectively every 6

months through age 3. Blood, urine, and stool were collected at each visit to test for parasitic infection.^{13,18}

Inclusion and Exclusion Criteria

In January 2014, all available children from the 2006 to 2010 birth cohort,¹³ now aged 4 to 7 years, were reenrolled in a follow-up study to assess their health status and test their immune response to a standard anti-pneumococcal polysaccharide (PPS) conjugate vaccine (Synflorix, GlaxoSmithKline, Brussels, Belgium). Children were excluded if they had moved from the study area, if consent was not provided, or if the child or family would be unable to return for the 4- to 6-week follow-up visit for postvaccination titers. Study design is summarized in Fig 1.

Clinical Study Procedures

For the 2014 resurvey and vaccine response testing, enrolled children were evaluated by physical examination including standardized anthropometrics and had blood, urine, and stool samples collected for diagnosis of parasitic infections. Children found to be positive for helminthic infection were treated

with mebendazole or praziquantel. At the time of initial examination and at postvaccination follow-up, calcium alginate flexible aluminum swabs (Harmony Business Supplies, Inc, Garden Grove, CA) were used to obtain a nasopharyngeal sample, which was inoculated and stored in skim milk–tryptone–glucose–glycerol storage and transport medium (Sigma-Aldrich, St Louis, MO). Multiplex polymerase chain reaction was used to determine nasopharyngeal pneumococcal colonization, by serotype.¹⁹ Caregivers were interviewed to provide interim health history and to complete socioeconomic status (SES) and nutrition questionnaires (Supplemental Information 1).

Parasitological Diagnosis

At all study time points, duplicate stool smears were examined to quantify ova of intestinal helminths and protozoa via the Ritchie Method.²⁰ Fresh urine was examined for *Schistosoma hematobium* eggs by membrane filtration of well-stirred 10-mL aliquots.²¹ Blood hemoglobin was measured by point-of-care cassette technique of finger prick blood specimens (Hemocue, Ångelholm, Sweden). To increase detection of low-intensity infections, collected serum and plasma and red blood cells were stored at -80°C and later tested by enzyme-linked immunosorbent assay for evidence of circulating filarial OG4C3 antigen (TropBioMed, Townsville, Australia) and anti-*Schistosoma* soluble worm antigen proteins immunoglobulin G4, diagnostic of current or recent infection.²² Red blood cell pellets underwent DNA extraction for polymerase chain reaction species-specific detection of malaria parasites.²³

Vaccination Procedures

The study cohort children were born before the 2011 introduction of pneumococcal conjugate vaccine

(PCV) in the Kenya/Gavi protocols for infant vaccination²⁴ and had not been previously immunized with pneumococcal vaccine. After completion of study examinations and parasitological testing, children enrolled in the current study received a 10-valent conjugated pneumococcal antigen vaccine (Synflorix)²⁵ that contained antigens from *S pneumoniae* serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F. All serotypes except for 18C and 19F were conjugated to protein D carrier protein derived from a nontypable *H influenzae*. Serotype 18C was conjugated to tetanus toxoid and 19F to a diphtheria toxoid carrier protein. The immunization was administered in accordance with the Synflorix product monograph.²⁵ Four to 6 weeks after this primary immunization, study children underwent repeat nasopharyngeal swab and serum collection.

Testing for Serum Antipneumococcal Immunoglobulin G Levels

We measured antipneumococcal immunoglobulin G (IgG) levels before and after 1 dose of the decavalent vaccine. A fluorescent bead immunoassay performed on a MagPix (Bio-Rad, Hercules, CA) system was used for specimen-sparing, multiplex serological testing. Simultaneous measurement of IgG antibody levels against the 10 vaccine pneumococcal antigens was obtained as previously described.^{26,27} Antidiphtheria CRM197 levels were also measured to provide an internal control. Briefly, dilutions of serum specimens were simultaneously tested for antigen-specific antipneumococcal IgGs by being added to a mixture of PPS carboxyl-coupled microspheres (MagPlex Beads Bio-Rad, Hercules, CA) in a 96-well plate. Standard curves for anti-PPS IgG were generated via pneumococcal standard 007sp (Supplemental Information 2).²⁸ A subject's individual levels of antigen-specific antipneumococcal IgGs were

determined from a 5-parameter logistic standard curve of the median fluorescent intensity against expected IgG concentration for 007sp²⁸ and converted to micrograms per milliliter. "Preimmunity" was defined as having a preimmunization antipneumococcal serotype specific IgG titer of $>2\ \mu\text{g}/\text{mL}$.

Testing for Pneumococcal Carriage

Nasopharyngeal carriage of pneumococcal strains was detected by *Streptococcus* Laboratory protocols of National Center for Immunization and Respiratory Diseases/Division of Bacterial Diseases/Respiratory Diseases Branch, Centers for Disease Control and Prevention (Supplemental Information 2).^{29,30}

Statistical Analysis

Primary outcomes evaluated in this study were subject's increments in antigen-specific antipneumococcal IgG directed against the pneumococcal antigens included in the 10-valent conjugated vaccine (Synflorix). Initial groupwise differences in IgG responses were compared via Mann-Whitney *U* test. After bivariate exploratory analysis for significant associations, subsequent analysis of the relative impact of subject covariates was determined by multivariable linear regression of log-transformed IgG outcomes. For this analysis, children's anthropometric measurements were converted to age-adjusted z scores in Anthro+ software (World Health Organization, Geneva, Switzerland). Growth stunting was defined as a height-for-age z score <-2 , and nutritional wasting was defined as a BMI z score of <-2 . Relative SES at birth and at the time of the 2014 examination was determined via principal component analysis of reported household inventory and monthly expenditure (ascertained on intake questionnaires), as previously described.¹³ Other environmental factors and current or past exposure

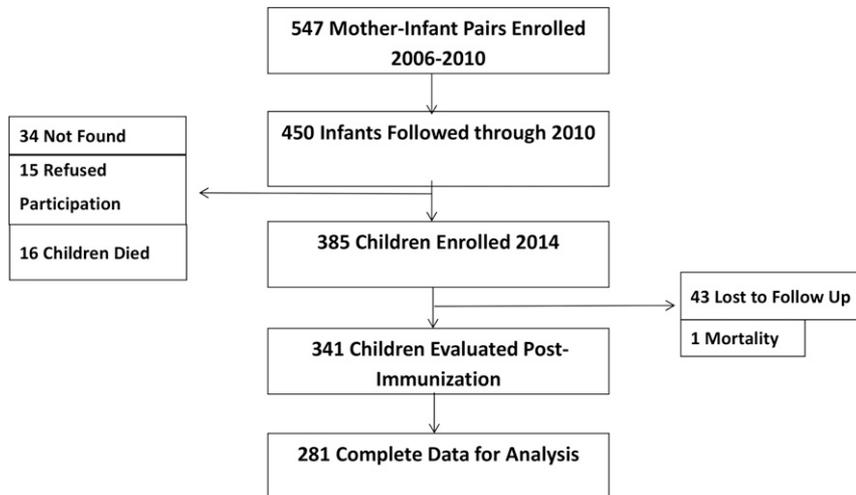


FIGURE 2

Study enrollment and follow-up: Of 547 subjects enrolled in the 2006 to 2010 cohort, 450 completed full follow-up through 2010. Fifty-six subjects could not participate for reasons indicated. In 2014, 385 of 450 subjects were reconsented and reenrolled, 44 were lost to follow-up, and 281 subjects provided complete data for final analysis.

to individual infections (eg, malaria, filaria, schistosomiasis, trichuriasis, ascariasis, hookworm infection) were entered as categorical values. For any potential explanatory variable, an association P value of $<.1$ was used to retain the variable in the model. Two-sided P values of $<.05$ were considered significant, and results are reported as multiply adjusted effect size estimated with 95% confidence intervals (CIs).

Because multiple immune response outcomes were available for each subject, to capture the aggregate effects of subject factors on vaccination outcomes, we also used a 2-step unsupervised clustering algorithm to categorize children into “high vaccine responder” and “low vaccine responder” classes, based on a combined, weighted score of their responses to all 10 pneumococcal antigens. SPSS version 22 software (IBM SPSS Statistics, IBM Corporation) was used to perform this cluster analysis and all other statistical testing.

RESULTS

Of the 547 infants initially enrolled in the 2006 to 2010 cohort, 385 children were available for the

current study and were assessed at a prevaccine visit (Fig 2). A total of 341 children returned for the postimmunization visit, with 43 children lost to follow-up and 1 interval mortality from unrelated causes. Of these, 281 children had complete laboratory testing and were included in the final analysis. Because of an unfortunate laboratory accident, 60 of 341 participants did not have paired sera for analysis.

Table 1 presents the demographics of the initial 2006 to 2010 cohort ($N = 547$) compared with the 281 children who participated fully in this study. Although there were no significant differences between these groups with respect to sex distribution, SES at birth, or maternal parasitic infections during pregnancy, the average age of nonparticipants was older (Table 1). That group also differed in that a larger percentage of their mothers had no formal education, and they had fewer parasitic infections detected during infancy (in the first 36 months of life), probably related to poor attendance with follow-up visits. For the 60 children who had complete examination and vaccination but not serological testing, prenatal infection

was significantly more common (Table 1), but there were no other significant differences between the 281 study children and this missing subgroup in terms of age, sex, household factors, or parasite exposures.

Table 2 describes characteristics of study infants at delivery and in the 2014 follow-up study. Figure 3 summarizes the study subjects’ exposures to parasite infections during gestation, during infancy (6 to 36 months of age), and at the time of the current follow-up study when the pneumococcal vaccine was provided. For the study children, maternal infections involved prenatal exposures to hookworm, *S. hematobium*, *Wuchereria bancrofti*, malaria, and *Trichuris*, in decreasing order of frequency. The most common infections during infancy were malaria, hookworm, and *Trichuris*. At the time of the follow-up study, *Trichuris* and hookworm were the most prevalent parasitic infections.

Measurable prevaccination anti-antigen IgG (“preimmunity”) was detected for ≥ 1 vaccine antigen in 128 of 281 (46%) of studied children (Fig 4). Seventy-eight of 281 (28%) had detectable preimmunity to the diphtheria CRM molecule used as one of the vaccine conjugate proteins. The greatest frequency of antigen-specific preimmunity was to pneumococcal serotypes 14, 19, 9V, 4, and 23. Forty-nine children (17%) were preimmune to ≥ 4 antigens, 24 (9%) were preimmune to 3 antigens, and 55 (20%) were preimmune to 1 or 2 antigens.

The children’s response to vaccination was assessed in 2 ways: as the absolute level of anti-PPS antigen IgG after vaccination and as the change in anti-antigen IgG levels from before to after vaccination. The mean prevaccination and postvaccination serotype-specific IgG levels and the average incremental changes from preimmunization to

TABLE 1 Characteristics of All Eligible Cohort Children and of the Participant and Nonparticipant Subgroups

	Original 2006–2010 Cohort	Current Nonparticipants From Original Cohort	Resurvey Participants Enrolled	Completed Both Study Visits and Examinations	Not Fully IgG Tested	Full Resurvey Participation and Laboratory Testing
<i>N</i>	547	162	385	341	60	281
Male:female ratio	1.2	1.5	1.1	1.1	1.2	1.0
Mean (SD) age at time of 2014 resurvey, y	6.2 (0.66)	6.3 (0.61) ^a	6.1 (0.67)	6.1 (0.66)	6.0 (0.63)	6.1 (0.67)
No formal maternal education, %	36	43 ^b	33	32	29	32
Lower SES at birth, %	59	60	59	58	53	59
Maternal parasitic infections during pregnancy, %	55	52	56	57	71 ^c	54
Parasitic infections detected during infancy (<36 mo), %	33	15 ^b	41	41	43	40
Parasitic infections detected at first 2014 resurvey visit, %	—	—	50	51	50	51

^a Significantly older than resurvey participant groups, $P < .05$ by analysis of variance and pairwise t testing.

^b Significantly different from resurvey participants, by χ^2 testing.

^c Significantly different from fully tested subjects, $P < .02$.

postimmunization can be seen in Fig 5. The strongest responses were to PPS 4, 7, 14, 18C, and 19.

In our exploration of the associations between individual subject factors and the magnitude of postvaccination IgG responses, as expected, preimmunity to any specific antigen was associated with greater response to that antigen. Nasal carriage of *S pneumoniae* was not associated with differences in postvaccination antibody levels, nor did sex, younger age, anemia, severe anemia, or clinical wasting (BMI z score < -2) at the time of vaccination have significant associations with vaccine response outcomes. A prominent feature of reduced vaccine response was its association with growth stunting at the time of PCV. After vaccination, stunted children had significantly reduced geometric mean levels of anti-PPS IgG against strains 1, 4, 6B, 7, 9V, 14, 18C, 19, and 23 (Fig 6 and Supplemental Information 3). Of note, children's growth stunting was not associated with any concurrent parasitic infections (Supplemental Information 4). By contrast, *Trichuris* infection during infancy was associated with preimmunity to PPS

TABLE 2 Study Participant Characteristics: Maternal Data From 2006–2010 Cohort Participation, Infant Data at Delivery, and Participant Data From Current Study

Maternal characteristics ($N = 545$)	
Maternal age at delivery, y	
14–22	153 (28%)
23–30	210 (39%)
>30	87 (16%)
Unknown	95 (17%)
Education	
None	100 (18%)
Lower primary	94 (17%)
Upper primary	263 (48%)
Secondary or more	86 (16%)
Unknown	2 (1%)
Household income (KSh ^a per month)	
<3000	322 (59%)
>3000	221 (40%)
Unknown	2 (1%)
Infant at delivery in 2007 ($N = 545$)	
Male	288 (55%)
Female	236 (45%)
Average head circumference, cm	34.2 \pm 1.4 (range 27.5–38)
Average length, cm	48.6 \pm 2.5 (range 40–59.5)
Average weight, g	2949 \pm 492 (range 1100–4350)
Children follow-up study in 2014 ($N = 281$ complete with data)	
Average age, y	6.1 (range 4.8–7.9)
Female	138/281 (49%)
Mean hemoglobin, g/dL	9.7 (range 5.0–17.7)
Stunted (height-for-age z score < -2 SD below median)	45/281 (16%)
Wasted (BMI < -2 SD below median)	14/281 (5%)
Current parasitic infections	144/281 (51%)

^a 74 Kenya shillings = 1 US dollar in mid-2006; 82 Kenya shillings = 1 US dollar in mid-2010.

antigens 1, 5, 6B, 7, 9V, 14, 19, and 23 (Supplemental Information 5), and *Trichuris* infection at any point during infancy was associated with

significantly higher postvaccine IgG levels against antigens 1, 4, 5, 6B, 14, 18C, 19, and 23. Any previous maternal education was associated

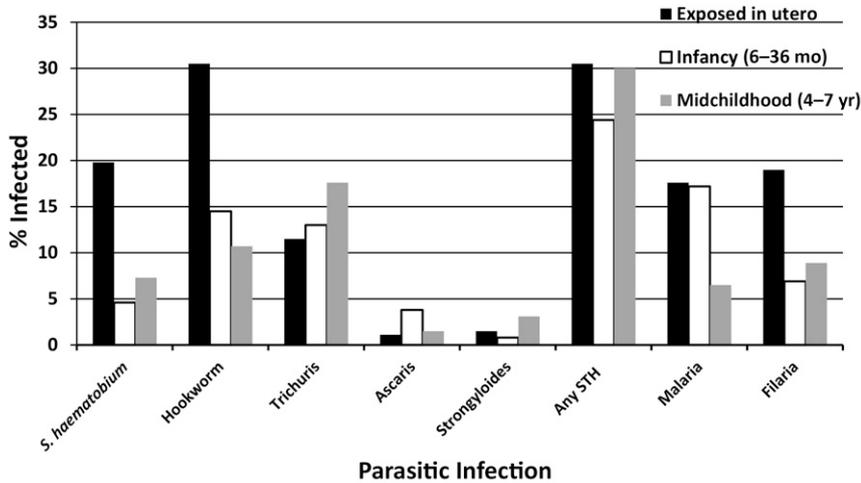


FIGURE 3

Prevalence of parasite exposures at 3 time points: in utero, during early infancy, and at midchildhood. Bars represent the percentage of participating children having *S. haematobium*, hookworm, *Trichuris trichiura*, *Ascaris lumbricoides*, *Strongyloides stercoralis*, any STH, malaria, or filaria (*Wuchereria bancrofti*). STH, soil-transmitted helminths (hookworm, *Trichuris*, *Ascaris*, or *Strongyloides* infection).

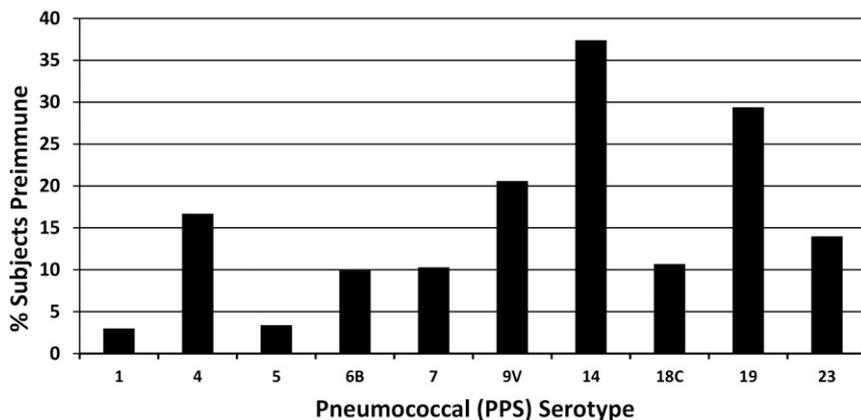


FIGURE 4

Prevalence of significant preimmunization anti-*S. pneumoniae* IgG levels by vaccine serotype. The greatest frequency of vaccine-specific preimmunity in the Msambweni, Kenya cohort children was to pneumococcal serotypes 14, 19, 9V, 4, and 23.

with improved responses to antigens 1, 4, 5, 9V, 18, and 19, although current SES and household monthly expenditure at the time of birth were not significant. Similarly, prenatal exposure to maternal parasitic infections and exposure to infection at the time of vaccination did not show a consistent association with IgG responses to PCV (Supplemental Information 6). As reported earlier,¹³ hyporesponsiveness to Hib and diphtheria vaccines was noted in a subset of this cohort who had in utero exposure to malaria, hookworm, and filarial parasites.

However, there was no correlation between a child's earlier responses to Hib during infancy and his or her ability to respond to pneumococcal antigens in the current study (Pearson R^2 values for anti-Hib IgG antibody levels versus post-PCV anti-PPS IgG levels ranged from 0.00 to 0.011, not significant) (Supplemental Information 7).

In multivariable analysis, previous immunity to a serotype was consistently associated with a strong positive effect on serotype-specific postvaccination IgG levels

(Table 3). After adjustment for other potential modifying factors, the presence of growth stunting was independently associated with significantly decreased response to PPS serotypes 1, 4, 6B, 7, 9V, and 19. After adjustment, maternal education was associated with increased postvaccination IgG levels to PPS 4, 5, 7, and 19. Male sex was associated with an increased response to PPS 14, whereas younger age was associated with lowered response to the same antigen. With multiple adjustment for these factors, *Trichuris* infection during infancy remained independently associated with higher levels of postvaccination IgG against serotypes 1, 5, 6B, 7, 18C, and 23 (Table 3). Not shown, additional multivariable analysis of the impact of infection exposure in utero or at the time of vaccination confirmed the significant associations of preimmunity, stunting, and maternal education with observed postvaccination IgG levels against multiple PPS antigens. However, there were no clear effects of parasite exposures at either of those time points on the children's present-day pneumococcal vaccine responses.

In a global assessment of responsiveness to the PCV vaccination, by using an unsupervised, computer-based clustering analysis we identified a subgroup of 67 of 281 (24%) children who had consistently greater levels of IgG increments to multiple vaccine antigens (Fig 7). Strongest weighting in this classification was based on responses to antigens 4, 18C, 7, 19, and 9V (in order of importance). Multivariable logistic regression for membership in the high responder category identified stunted status (adjusted odds ratio [aOR] 0.28; 95% CI, 0.10–0.83), *Trichuris* infection during infancy (aOR 2.0; 95% CI, 1.1–3.7), and maternal

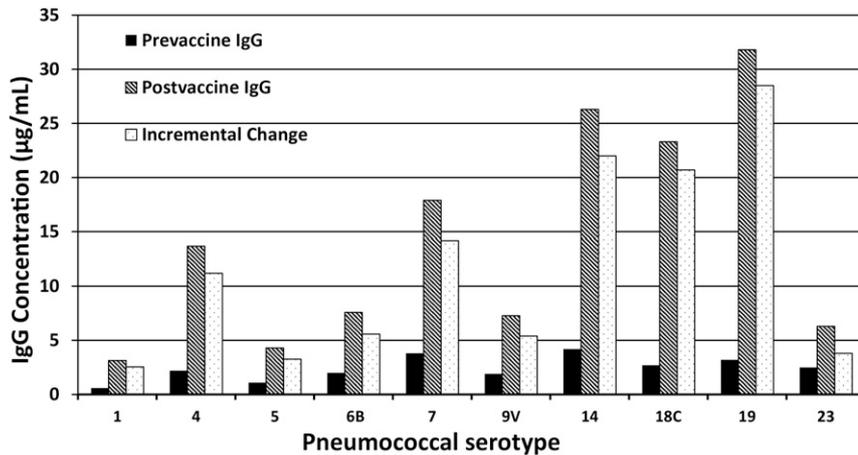


FIGURE 5 Mean anti-antigen IgG levels before and after delivery of PCV, and the amount of change in IgG, according to *S pneumoniae* serotype. Black bars represent mean preimmunization IgG levels, shaded bars represent mean postimmunization IgG levels, and stippled bars represent the difference between preimmunization and postimmunization IgG levels.

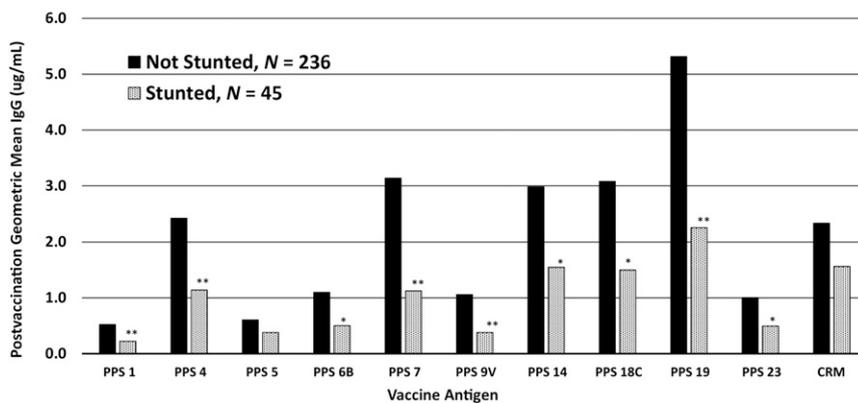


FIGURE 6 Impact of growth stunting (age-adjusted height z score <-2) on postvaccination antipneumococcal IgG levels. Subgroup analysis indicated significantly lower anti-PPS IgG against vaccine serotypes 1, 4, 6B, 7, 9V, 14, 18C, 19, and 23 among stunted children. **P* < .05, ***P* < .01.

education (aOR 2.2; 95% CI, 0.84–5.6) as independent correlates of membership in the better overall response group.

DISCUSSION

Results of this study indicate a range of responses to primary immunization with multivalent PCV among children who have been frequently exposed to chronic parasitic infections, whether in utero or during infancy or childhood. Among this study cohort, whereas in utero exposures were associated with lower vaccine responses to

conjugate Hib vaccine in infancy, our data indicate that current or previous parasitic exposures did not impair a 4- to 7-year-old child's ability to respond to PCV, and in fact, previous exposure to *Trichuris* was associated with higher levels of postvaccination antipneumococcal IgG, perhaps because of cross-species presensitization. Growth stunting, a marker of long-term malnutrition, was the most consistent significant negative correlate of anti-PPS vaccination response, whereas maternal education, an established marker of improved infant care, was associated

with better responses to some but not all antigens.

Though complex, the interrelated host factors of malnutrition and exposure to parasitic infections have been shown to affect vaccine response in other settings.^{14,15} The impact of parasitic infections on growth and development is posited to occur via direct effects on nutrient absorption, through associated chronic inflammatory status, and through reduced appetite.^{18,31} Our previous studies of this infant cohort from coastal Kenya showed a decrease in Hib vaccine response in infants when mothers were infected with malaria, hookworm, or filaria during pregnancy.¹³ However, in the current study this effect did not appear to persist into midchildhood, because these children were able to appropriately respond to conjugated pneumococcal antigens, suggesting that children may outgrow the harmful effects of antenatal parasite exposure. Others have evaluated infant B cell memory responses to decavalent pneumococcal vaccine in Kenya, finding that response to 19F was the most robust of all the serotypes, but it was the most common nasopharyngeal colonizing serotype in that community.³² In our study, preimmunity was the strongest predictor of a strong vaccine response to any given pneumococcal antigen, but we did not find an association with concurrent nasopharyngeal colonization.

A strength of this study was the longitudinal follow-up of children from gestation through midchildhood, providing detailed information on many potential factors that might influence vaccine responses. However, loss to follow-up over time may limit our ability to link current findings to different infectious histories and exposures. The 60 children missing from the serological analysis were similar to the 281 children who did

appear to have a detrimental effect on IgG response to pneumococcal vaccine antigens in midchildhood. However, where such exposures create growth stunting, there are likely to be deficiencies in response to multiple pneumococcal serotypes. To be fully effective, immunization campaigns must consider effective parasite control and nutritional supplementation to ensure adequate responses in vulnerable populations. In office practice, primary providers may consider assessing and addressing nutritional deficits before administration of “catch-up”

vaccinations to children born in such high-risk settings.

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ABBREVIATIONS

aOR: adjusted odds ratio
 CI: confidence interval
 Hib: *Haemophilus influenzae* type b
 IgG: immunoglobulin G
 PCV: pneumococcal conjugate vaccine
 PPS: pneumococcal polysaccharide
 SES: socioeconomic status

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