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Pneumococcal Conjugate Vaccine Given Shortly After Birth Stimulates Effective Antibody Concentrations and Primes Immunological Memory for Sustained Infant Protection

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Background. In developing countries, newborn immunization with pneumococcal conjugate vaccines (PCVs) could protect young infants who are at high risk of invasive pneumococcal disease (IPD) but might lead to immune tolerance.

Methods. In a randomized trial, young infants received 7-valent PCV at 6, 10, and 14 weeks (Expanded Programme on Immunization [EPI] group) or 0, 10, and 14 weeks (newborn group). Safety was monitored actively at 2–7 days and then passively. Serum samples obtained at birth and 6, 10, 14, 18, 36, and 37 weeks were assayed by enzyme-linked immunosorbent assay for anticapsular immunoglobulin G concentration and avidity. Infants were boosted with either 7-valent PCV or one-fifth dose of pneumococcal polysaccharide vaccine at 36 weeks. Nasopharyngeal swab samples were obtained at 18 and 36 weeks.

Results. Three-hundred neonates and young infants were enrolled. Newborn vaccination was well tolerated. Adverse events occurred equally in each group; none was related to immunization. One infant, immunized at birth, died of unrelated neonatal sepsis. At 18 weeks, protective concentrations (≥ 0.35 $\mu\text{g/mL}$) were achieved against each serotype by $\geq 87\%$ of infants with no significant differences between groups. Geometric mean concentrations were higher in the EPI group for serotypes 4, 9V, 18C, and 19F at 18 weeks and for serotype 4 at 36 weeks. Avidity was greater in the newborn group for serotypes 4, 6B, and 19F at 18 weeks and for serotype 19F at 36 weeks. Booster responses and vaccine-type/nonvaccine-type carriage prevalence did not differ between groups.

Conclusions. PCV was safe, immunogenic, and primed for memory when given at birth. There was no evidence of immune tolerance. Vaccination beginning at birth offers an alternative to control IPD in vulnerable young infants.

The pneumococcus causes 14.5 million episodes of serious illness in children aged <5 years worldwide and 826 000 deaths annually [1]. More than half of these deaths occur in African children. Trials in South Africa and The Gambia have shown pneumococcal conjugate

vaccine (PCV) to be highly efficacious against invasive pneumococcal disease (IPD) in human immunodeficiency virus (HIV)–positive and HIV-negative children [2] and against radiologically confirmed pneumonia and all-cause mortality [3]. The World Health Organization (WHO) has recommended that developing countries with high childhood mortality should introduce PCV into their routine immunization schedules [4].

In the industrialized world, IPD is uncommon in neonates but peaks in the second year of life [5]. In The Gambia, incidence peaks at age 6–11 months [6], but the burden of disease in young infants (aged <60 days) is notable. In a study of sepsis in young infants in 4 developing countries, the pneumococcus accounted for 17% of cases [7]. In Kenya, the IPD incidence is highest in young infants [8] and, among infants and young

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children (<2 years) targeted for vaccine, 15% of IPD episodes occurs during the first 2 months of life. The WHO recommends immunization with PCV at either 6, 10, and 14 weeks and 2, 3, and 4 months [4], but these schedules cannot protect young infants. In addition, the timing of first vaccination is often delayed [9], which further widens the gap of vulnerability.

To protect young infants, there are 2 alternative approaches: maternal immunization or newborn immunization. Newborn immunization with protein-conjugated *Haemophilus influenzae* type b (Hib) vaccine has raised a concern that vaccine given at birth could induce tolerance to subsequent doses of the same vaccine [10]. In this study, we report a prospective randomized schedule trial examining the safety and immunogenicity of 7-valent PCV (7vPCV) when the first dose was delivered within 72 hours of birth. The primary endpoint was immunogenicity at 18 weeks of age. We also assessed antibody function by assaying avidity and by monitoring the effect of vaccine on nasopharyngeal carriage. We investigated immune memory using a booster dose administered at 9 months of age.

METHODS

Study Setting and Design

This open-label randomized schedule trial took place at Kilifi District Hospital among residents of the Kilifi Health and Demographic Surveillance System (KHDSS) area, a rural population of 240 000 on the coast of Kenya [11]. Women attending antenatal clinic in their last trimester who had negative results on an HIV test were encouraged to enroll their children at birth. Neonates delivered at Kilifi District Hospital were enrolled within 24 hours of birth; those born at home were included up to 72 hours following delivery. Exclusion criteria were as follows: temporary residence in the KHDSS area; participation in another trial; suspected immune deficiency; congenital abnormality; sickness requiring hospitalization; birth weight <2500 g; heart rate >150 or <100/minute; respiratory rate >60 or <35/minute; axilla temperature of >37.5° or <35.5°C. The birth weight threshold excluded 20% of all newborns and was therefore reduced to 2000 g after 199 babies had been recruited.

Participants were divided evenly into 8 groups on 3 criteria in a factorial design: Expanded Programme on Immunization (EPI) vaccine schedule, compared with newborn schedule; additional blood sampling at 10 weeks, compared with 14 weeks; and pneumococcal polysaccharide vaccine (PPV), compared with PCV booster. Three hundred allocations were designated at the outset, and each participant was assigned a group at enrolment by automatic computer application of a random number to all residual allocations.

The EPI group received 7vPCV at 6, 10, and 14 weeks of age. The newborn group received 7vPCV at 0, 10, and 14 weeks of age. All neonates were given BCG and oral polio vaccine at birth

and pentavalent vaccine (diphtheria-tetanus-pertussis/hepatitis B/Hib) and oral polio vaccine at 6, 10, and 14 weeks according to the EPI schedule. At 36 weeks of age, each infant received a booster of either 7vPCV or a 20% fractional dose (0.1 mL) of 23-valent PPV concomitantly with measles vaccine. Cord blood samples were obtained, and venous samples were collected at 18, 36, and 37 weeks and at either 10 or 14 weeks of age. Blood samples were obtained from EPI group infants at 6 weeks. Nasopharyngeal swab samples were obtained at 18 and 36 weeks of age. Written informed consent was obtained from each mother, and the study was approved by the Kenya Medical Research Institute and WHO (Sub-Committee for Research Involving Human Subjects) Ethical Review Committees.

The 7vPCV vaccine was Prevnar (Wyeth Vaccines), containing 2 µg of capsular polysaccharides of serotypes 4, 9V, 14, 18C, 19F, and 23F and 4 µg of serotype 6B conjugated to 0.5 mg of the carrier protein CRM₁₉₇ adsorbed on aluminum phosphate. The PPV was a 23-valent unconjugated pneumococcal polysaccharide vaccine (Pneumovax; Sanofi Pasteur) containing 25 µg of each polysaccharide. Vaccines were donated by Wyeth Vaccines.

Infants were monitored clinically for 30 minutes after the first dose of 7vPCV and were reassessed by the study doctor after 7 days (after 2 days for the first 54 infants). Standard vaccine-related symptoms and signs were elicited and recorded. Parents were given 24-hour access to the pediatric research clinic and advised to return at any time during the first 37 weeks of life with any potential adverse reaction. At each illness visit, the attending physician completed an adverse event form and designated the illness as an illness unrelated to immunization, a minor adverse event, or a severe adverse event—an illness severe enough to require hospital admission. All severe adverse events were reviewed by the investigators and the Data Safety and Monitoring Board to evaluate their relationship to vaccine. The KHDSS was used to follow long-term mortality up to July 2009.

Blood samples were refrigerated and transported within 6 hours to the laboratory, where the serum was separated and stored at -80°C. Serum samples were assayed for immunoglobulin G (IgG) antibodies to 7 individual capsular polysaccharides in the WHO reference laboratory for pneumococcal serology at University College London Institute of Child Health using enzyme-linked immunosorbent assay (ELISA) following adsorption with cell wall polysaccharide and 22F polysaccharide, as described previously [12, 13]. Avidity for antibody to serotypes 4, 6B, 14, and 19F was measured by modification of an assay developed for anti-Hib avidity by incorporating an ammonium thiocyanate elution step into the pneumococcal ELISA [14].

Nasopharyngeal samples were collected using rayon-tipped flexible wire swabs and stored in skimmed milk-tryptone-glucose-glycerol medium and inoculated the same day onto gentamicin (2.5 µg/mL) blood agar [15]. The presence of

pneumococci was confirmed by means of optochin susceptibility. Up to 4 morphologically distinct colonies were serotyped, per swab, by quelling reaction [16]. All laboratory scientists were blind to the vaccine schedule and booster group allocations.

Statistical Analysis

Geometric mean concentrations (GMCs) and 95% confidence intervals were calculated for pneumococcal serotype-specific antibodies in each vaccine schedule group. Differences in means of log-transformed concentrations were analyzed by Welch test at 18 and 36 weeks. This approach was repeated with antibody avidity. For each serological analysis, results from all available serum samples (or serum pairs) were included. The proportion of samples at or above the putative protective threshold, 0.35 $\mu\text{g/mL}$ [17], in each vaccine group was tested using χ^2 . Secondary analyses were performed at the higher threshold of 1.00 $\mu\text{g/mL}$. Analysis of variance was performed for the vaccine group and booster group at 36 weeks on log-transformed ratios of the 37/36-week concentrations. The inhibitory effect of maternal antibodies, specified as quintiles of cord blood concentration, was examined by analysis of variance of the 18-week GMCs. Linear regression of the serotype-specific GMCs across quintiles was fitted using variance-weighted least squares (VWLS) to account for within-quintile variance.

To estimate the immediate protective effect of newborn vaccine, we assumed that vaccine-induced antibody in the newborn group declined at a constant rate that could be estimated from the decline of maternally derived antibody in the EPI group between 0 and 6 weeks of age. By applying this rate to the cord blood concentrations in the newborn group, we estimated the mean ratio increase attributable to a birth dose by referencing the observed concentrations at 10 weeks; to estimate 95% confidence intervals, we incorporated the sum of the standard errors of the mean concentrations at birth and 10 weeks and of the mean decay rate.

Children were classified as vaccine-serotype carriers if pneumococci of serotypes 4, 6B, 9V, 14, 18C, 19F, or 23F were isolated. Children with other serotypes were classified as nonvaccine-serotype carriers. Carriers of multiple serotypes could be included in each group. The primary endpoints were the associations between vaccine group and vaccine-serotype carriage at 18 weeks, and between vaccine group and nonvaccine-serotype carriage at 36 weeks. The study sample size was chosen to detect, with 90% power, a 12% difference in vaccine-serotype carriage at 18 weeks against a baseline of 16%. This sample size also provided >90% power to observe a difference of $\geq 30\%$ in the GMC of antibody concentrations in the 2 schedule groups.

An interim analysis of antibody concentrations was performed on 18-week serum samples for the first 30 vaccinees, to screen for immune tolerance. The International Standard Randomized Controlled Trial Number was 52829313.

RESULTS

Between 15 December 2004 and 30 August 2007, 300 neonates were recruited within 72 hours of birth and randomized in equal numbers to the EPI group and the newborn group (Figure 1). The 2 groups were similar in sex, mother's age, birth weight, and baseline vital signs (Table 1). During individual follow-up over 9 months, 26 EPI group and 32 newborn group participants were withdrawn from the study, died, or were lost to follow-up (Figure 1).

There were no significant differences in the safety observations in the 2 groups. Thirty minutes after first immunization with 7vPCV, 8 children in the EPI group (5.3%) and 10 in the newborn group (6.7%) had an axillary temperature $\geq 37.5^\circ\text{C}$. At the first follow-up visit, 1 child had swelling at the immunization site and 1 child in the EPI group (0.8%) and 5 children in the newborn group (3.4%) had a temperature $\geq 37.5^\circ\text{C}$; 1 child from each group had a temperature $\geq 38.0^\circ\text{C}$.

Between birth and 9 months of age, there were 177 adverse events and 38 serious illnesses requiring hospitalization in the EPI group and 167 adverse events and 32 serious illnesses requiring hospitalization in the newborn group, none of which was related to vaccination. One child in the newborn group died at home on day 3 of life without presenting to the research clinic. A postmortem questionnaire was conducted 40 days later. Three pediatricians who reviewed the evidence independently concluded that the cause of death was neonatal sepsis unrelated to immunization. During extended follow-up through the demographic surveillance, 1 additional death was detected, in an EPI group child aged 44 weeks.

At 18 weeks of age, the proportion of infants who had attained the protective threshold (0.35 $\mu\text{g/mL}$) was $\geq 87\%$ for antibodies to all vaccine serotypes, and there were no significant differences in these proportions by vaccine group (Table 2). However, the GMCs of anticapsular IgG were higher in the EPI group than in the newborn group for 4 of 7 serotypes (Figure 2A). By 36 weeks, these differences had disappeared, except for serotype 4, in which the GMC remained greater in the EPI group (Figure 2B). The proportion of infants with anticapsular IgG above the protective threshold at 36 weeks was significantly higher in the EPI group (91% vs 80%; $P < .05$) for serotype 4 only (Table 2). Results at 10 and 14 weeks are shown in Supplementary Table 1. A higher threshold of $\geq 1.0 \mu\text{g/mL}$ may be more appropriate for high-transmission settings in developing countries and for protection against nonbacteremia pneumonia; the proportions achieving this were indistinguishable at 36 weeks (Supplementary Table 2), but at 18 weeks they were greater among the EPI group for 3 serotypes. GMCs for serum samples collected at all time points are shown in Supplementary Table 3.

At 18 weeks of age, the geometric mean avidity index for 3 (4, 6B, 19F) of the 4 serotypes assayed was significantly

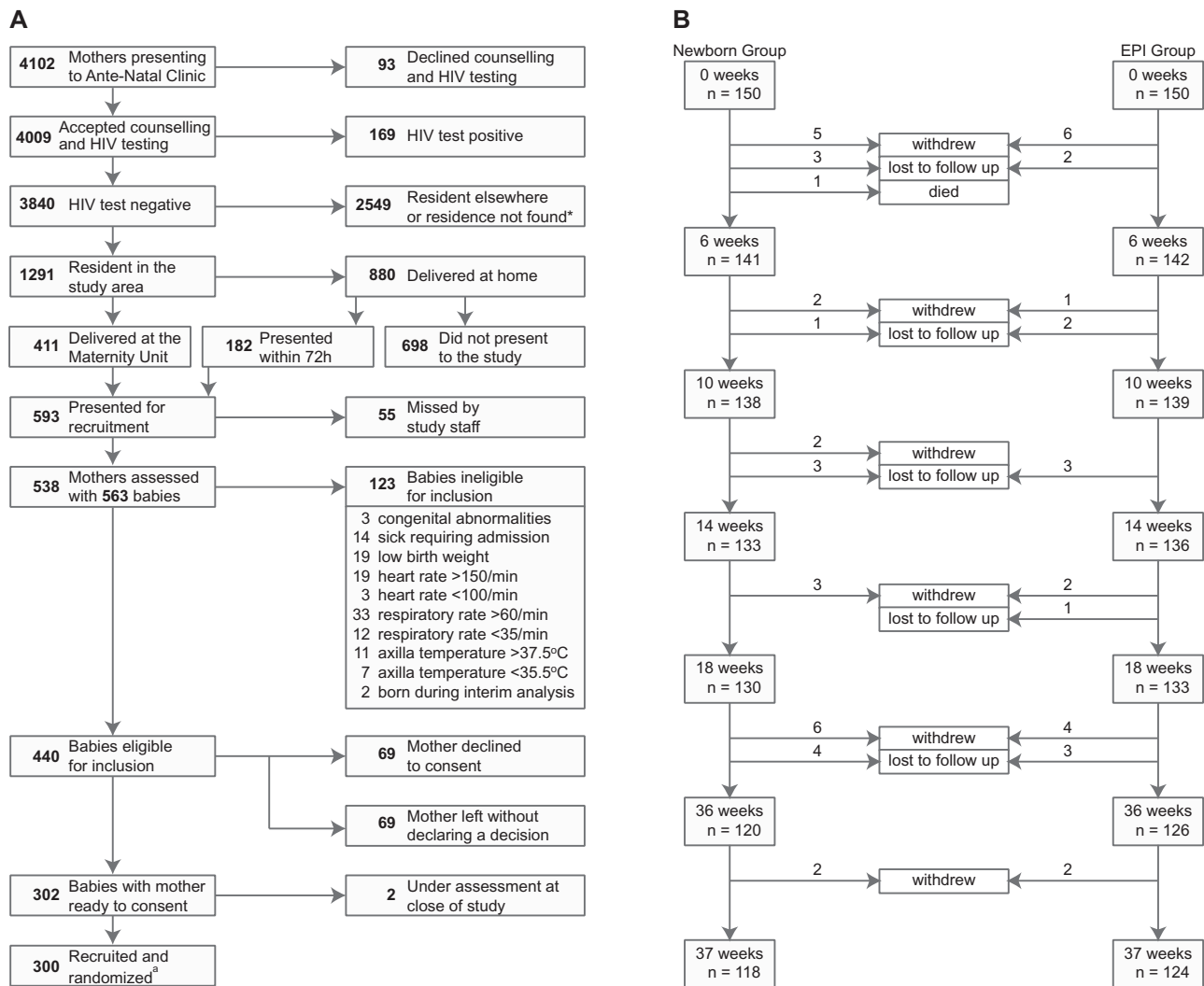


Figure 1. Flow chart of (A) mothers attending the Kilifi Ante-natal Clinic passing through study filters to recruitment and of (B) trial participants in each vaccine group illustrating losses to follow-up throughout the 37 weeks of the study. *Determining whether a mother was a resident of the Kilifi Health and Demographic Surveillance System area required a computer search that took approximately 2–10 minutes. Many mothers left at this stage without waiting to be identified. ^aThis included 2 pairs of twins.

greater in the newborn group than in the EPI group (Figure 3). At 36 weeks, the geometric mean avidity index was significantly greater in the newborn group for serotype 19F only.

The natural rate of decay of anticapsular IgG in the EPI group between birth and 6 weeks did not vary significantly by serotype, and the mean decay rate across all 7 serotypes, adjusted for correlation within individual infants, was 0.168 µg/mL/week (95% CI, 0.163–0.173). Comparing the predicted decline in anticapsular antibody concentration in the newborn group against the actual concentrations observed at 10 weeks, newborn vaccination was estimated to lead to a rise of between 1.5- and 11-fold (median, 2.4-fold), depending on serotype (Table 3).

An analysis of variance of the log ratio rise in IgG before and after booster immunization at 9 months was significantly greater following 7vPCV booster than PPV booster for all serotypes

($P < .001$) except 19F (Supplementary Figure 1). After adjusting for booster type, there were no significant differences in response ratios between the EPI group and the newborn group for any serotype. Because 7vPCV boosted more effectively, we repeated this analysis restricting to infants who received 7vPCV; there were no differences in the response ratios between the vaccine schedule groups.

To explore the effect of passively transferred maternal antibody on response to vaccine, linear regression of the 18-week serotype-specific GMCs was fitted across quintiles of homologous cord blood antibody using VWLS (Supplementary Figure 2). Quintile break points were constant for both vaccine groups. Significant downward trends were observed against quintiles for serotypes 6B, 9V, 14, and 19F ($P < .02$) in the EPI group and for serotypes 6B, 14, and 23F ($P < .001$) in the newborn group.

Table 1. Baseline Characteristics of the Randomized Schedule Groups

Variable	EPI	Newborn
Mother's age, years	28.7 (6.5)	29.8 (6.4)
Birth weight, g	3088 (341)	3137 (412)
Heart rate at evaluation, beats per minute	127.4 (12.0)	126.7 (11.0)
Respiratory rate at evaluation, per minute	51.3 (7.0)	51.0 (6.7)
Axillary temperature at evaluation, °C	36.7 (0.41)	36.7 (0.43)
Male sex, no. (%)	77 (51.3)	75 (50.0)

Data are mean (standard deviation) unless otherwise specified. Differences between groups were tested by analysis of variance, except for sex, which was analyzed by means of the χ^2 test. Abbreviations: EPI, Expanded Programme on Immunization.

The prevalence of pneumococcal carriage was 78% (205/263) at 18 weeks and 77% (188/244) at 36 weeks. Multiple strains (>1 serotype) were detected in 21 carriers at 18 weeks and in 16 carriers at 36 weeks. Although at both time points the prevalence of vaccine-serotype carriage was lower among the EPI group than among the newborn group, and the prevalence of nonvaccine-serotype carriage was higher, these differences were not statistically significant (Figure 4). The prevalence of vaccine-serotype carriage at 18 weeks was 25% in the EPI group and 31% in the newborn group ($P = .28$), and the prevalence of nonvaccine-serotype carriage was 62% in the EPI group and 51% in the newborn group ($P = .08$) at 36 weeks.

Table 2. Numbers and Percentages of Serum Samples With Anticapsular Immunoglobulin G Concentrations $\geq 0.35 \mu\text{g/mL}$ at 18 Weeks and 36 Weeks of Age by Vaccine Group

Serotype	EPI group, proportion (%)	Newborn group, proportion (%)	<i>P</i>
18 weeks			
4	133/133 (100)	127/128 (99)	.31
6B	122/133 (92)	111/128 (87)	.19
9V	130/133 (98)	125/129 (97)	.67
14	130/133 (98)	126/129 (98)	.97
18C	131/133 (98)	123/129 (95)	.14
19F	133/133 (100)	126/127 (99)	.31
23F	129/133 (97)	119/129 (92)	.09
36 weeks			
4	111/124 (90)	95/118 (81)	.049
6B	93/124 (75)	93/118 (79)	.48
9V	107/124 (86)	91/118 (77)	.06
14	118/124 (95)	109/118 (92)	.37
18C	74/124 (60)	66/118 (56)	.56
19F	113/123 (92)	102/118 (86)	.17
23F	83/124 (67)	79/118 (67)	.99

Abbreviations: EPI, Expanded Programme on Immunization.

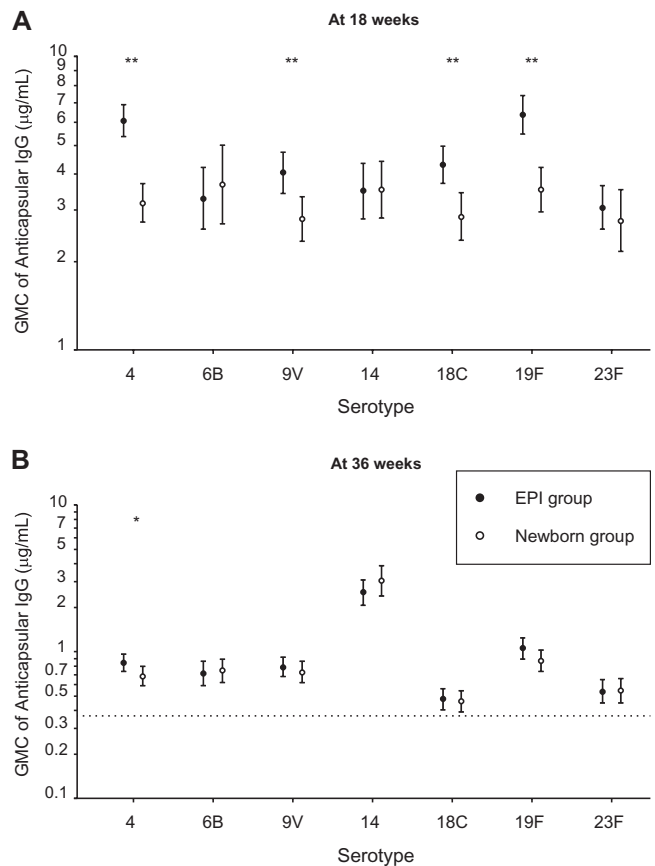


Figure 2. Geometric mean concentrations (GMCs) of anticapsular immunoglobulin G (IgG) by vaccine group for 7 serotypes. The figure shows the geometric mean and 95% confidence intervals of anticapsular IgG in 2 vaccine groups. At 18 weeks the geometric mean concentrations in the Expanded Programme on (EPI) group are significantly higher for 4 serotypes; at 36 weeks they are significantly higher for serotype 4 only. * $P < .05$; ** $P < .005$.

DISCUSSION

To our knowledge, this is the first study to report the safety and humoral immunogenicity of PCV at birth. The vaccine was safe and well tolerated. The reactogenicity and safety profiles in this study were also similar to those described for other PCV formulations elsewhere in Africa [18–21] and among newborns in Papua New Guinea [22]. The newborn schedule of 7vPCV was immunogenic at 18 weeks and induced immunological memory, as indicated by brisk booster responses at 36 weeks, with no evidence of immunological tolerance.

Tolerance following newborn immunization with conjugate vaccines has been observed in a single study of protein-polysaccharide conjugates against Hib. Infants immunized at birth and at 2 and 6 months were compared with infants immunized at 2, 4, and 6 months using a polyribosylribitol phosphate–outer membrane protein vaccine [10]. Following the second and third doses, the newborn vaccine group had

Table 3. Estimated Response to a First Dose of 7-Valent Pneumococcal Conjugate Vaccine Given at Birth

Serotype	Decay rate in $\mu\text{g/mL/week}$ (EPI group)	Observed concentration at 10 weeks versus concentration predicted from cord blood (newborn group), geometric mean ratio (95% CI)
4	0.176	10.5 (7.17–15.5)
6B	0.170	1.51 (1.06–2.15)
9V	0.157	3.11 (2.21–4.37)
14	0.142	2.09 (1.52–2.87)
18C	0.182	3.80 (2.66–5.43)
19F	0.185	2.39 (1.82–3.14)
23F	0.153	1.81 (1.22–2.69)

Natural decay rates for IgG were estimated in the cord blood and 6-week serum samples of the EPI group. The mean decay rate (0.168 $\mu\text{g/mL/week}$ [95% CI, .163–.173]) did not vary significantly by serotype. The ratio increase attributable to newborn vaccination was estimated for each infant in the newborn group as the observed concentration at 10 weeks divided by the concentration predicted by applying the common decay rate to the cord blood sample.

Abbreviations: CI, confidence interval; EPI, Expanded Programme on Immunization.

significantly lower antibody titers, implying that a birth dose may tolerize the immune system to subsequent doses of the same vaccine. Tolerance was not observed in 2 other studies of Hib conjugate vaccines in newborns [23, 24].

In the present study, anticapsular IgG concentrations at 18 weeks were lower in the newborn group than in the standard EPI group for 4 of 7 serotypes, but by 36 weeks they were indistinguishable for all except serotype 4. We observed reciprocity between antibody concentrations and function, as measured by avidity. At both 18 weeks and 36 weeks, avidity was significantly greater in the newborn group than in the EPI group to some serotypes. This intriguing finding confirms that immunization at birth primes the immune system. However, the schedule design does not allow us to differentiate whether it is age, time, or dose interval that is responsible for this avidity difference. Although the effect of maternal antibody has also been reported to interfere with early life vaccine responses, in this study several serotype-specific responses in *both* the newborn and EPI groups were adversely affected by high levels of maternal antibodies.

The responses to a booster dose did not differ between vaccine schedule groups. Similar findings have been observed in premature infants first immunized with PCV at 2 months of age [25]. These responses show that 7vPCV administered at birth does not interfere with the generation of immune memory to pneumococcal polysaccharides by subsequent 7vPCV doses and thus refute the predictions of immune

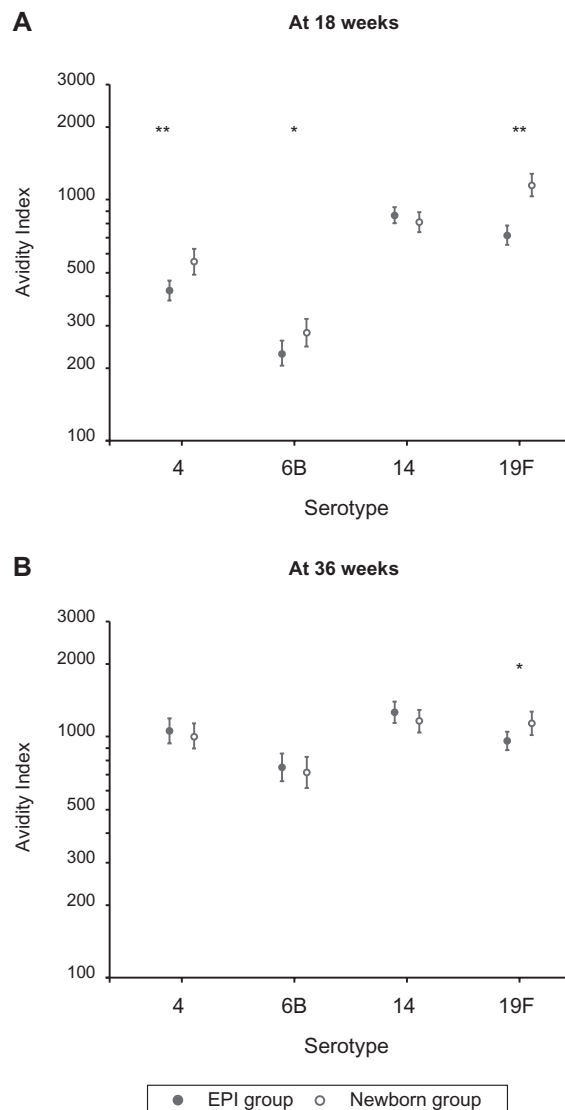


Figure 3. Geometric mean avidity indices for anticapsular immunoglobulin G (IgG) by vaccine group for 4 serotypes. The figure shows the geometric mean and 95% confidence intervals of the avidity index for anticapsular IgG in 2 vaccine groups. At 18 weeks, the geometric mean avidity index in the newborn group are significantly higher for 3 serotypes; at 36 weeks, they are significantly higher for serotype 19F only. EPI, Expanded Programme on Immunization; * $P < .05$; ** $P < .005$.

tolerance. This is important in developing countries where pneumococcal transmission is frequent. In Kilifi, half of all neonates have acquired nasopharyngeal carriage by 27 days of life [26], and nasopharyngeal exposure in an infant primed by a birth dose of PCV may lead to boosted immunity rather than early disease.

Previous studies have shown that a primary series of PCV reduces the carriage prevalence of vaccine serotypes by half but has little effect on total pneumococcal carriage [27, 28]. We did not observe any difference between vaccine schedule groups in their effect on carriage of vaccine or nonvaccine serotypes at

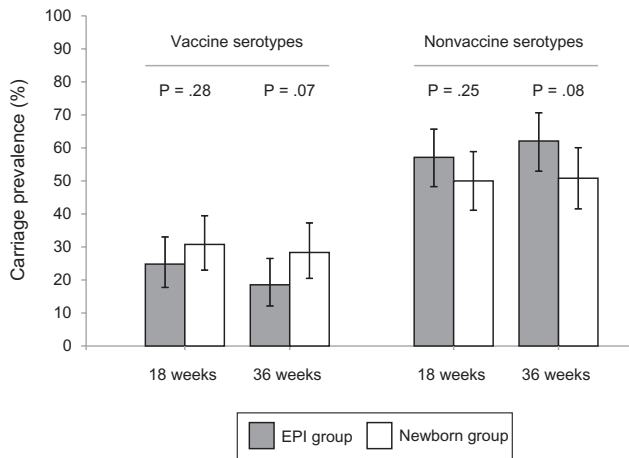


Figure 4. Nasopharyngeal carriage prevalence of pneumococcal serotypes included in the 7-valent pneumococcal conjugate vaccines (vaccine serotypes) and all other serotypes (nonvaccine serotypes) in 2 schedule groups at 18 and 36 weeks of age. *P* values reflect χ^2 analyses testing differences in the proportions of carriers in different schedule groups. Vaccine serotypes were serotype 4, 6B, 9V, 14, 18C, 19F, and 23F only. EPI, Expanded Programme on Immunization.

either 18 or 36 weeks. Compared with the newborn vaccine group, the prevalence of vaccine-type carriage in the EPI group was 6% lower at 18 weeks and 10% lower at 36 weeks. Although small changes in carriage prevalence may influence herd protection and serotype replacement disease, the size of the present study was not sufficient to determine whether newborn vaccination would shape such population effects differentially.

This study provides the empiric basis to support exploratory immunization of newborns against pneumococcal disease. The next step is to establish whether the schedule interferes with responses to other routine immunizations and to explore whether the second and third doses can also be delivered earlier. Newborn immunization could be advantageous in settings where an epidemiologically significant proportion of IPD occurs before 2 months of age, where vaccine coverage at birth is high, or where the timing of routine immunization is delayed. Although American neonates have been shown to benefit from indirect protection caused by immunization of infants [29], this may not extend to the serotypes (eg, 5 and 1) that predominate in IPD in African newborns [8]. Schedules that include a first dose of 7vPCV at birth are safe, immunogenic, and prime for immune memory and could provide protective antibodies where local epidemiological characteristics reveal a window of vulnerability in young infants.

Notes

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Potential conflicts of interest. J. A. G. S. has received research funding from GlaxoSmithKline Biologicals. D. G. has participated in advisory boards and received honoraria and consultancy fees from Pfizer (formerly Wyeth Vaccines). All other authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://www.oxfordjournals.org/our_journals/cid/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

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