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Safety and Immunogenicity of Pneumococcal Conjugate Vaccines in a High-risk Population: A Randomized Controlled Trial of 10-Valent and 13-Valent Pneumococcal Conjugate Vaccine in Papua New Guinean Infants

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Background. There are little data on the immunogenicity of PCV10 and PCV13 in the same high-risk population.

Methods. PCV10 and PCV13 were studied head-to-head in a randomized controlled trial in Papua New Guinea in which 262 infants received 3 doses of PCV10 or PCV13 at 1, 2, and 3 months of age. Serotype-specific immunoglobulin G (IgG) concentrations, and pneumococcal and nontypeable *Haemophilus influenzae* (NTHi) carriage were assessed prevaccination and at 4 and 9 months of age. Infants were followed up for safety until 9 months of age.

Results. One month after the third dose of PCV10 or PCV13, >80% of infants had IgG concentrations ≥0.35μg/mL for vaccine serotypes, and 6 months postvaccination IgG concentrations ≥0.35 μg/mL were maintained for 8/10 shared PCV serotypes in > 75% of children vaccinated with either PCV10 or PCV13. Children carried a total of 65 different pneumococcal serotypes (plus nonserotypeable). At 4 months of age, 92% (95% confidence interval [CI] 85–96) of children vaccinated with PCV10 and 81% (95% CI 72–88) vaccinated with PCV13 were pneumococcal carriers ($P = .023$), whereas no differences were seen at 9 months of age, or for NTHi carriage. Both vaccines were well tolerated and not associated with serious adverse events.

Conclusions. Infant vaccination with 3 doses of PCV10 or PCV13 is safe and immunogenic in a highly endemic setting; however, to significantly reduce pneumococcal disease in these settings, PCVs with broader serotype coverage and potency to reduce pneumococcal carriage are needed.

Clinical Trials Registration. NCT01619462.

Keywords. pneumococcal conjugate vaccine; *S. pneumonia*; antibodies; carriage; Papua New Guinea.

The global implementation of pneumococcal conjugate vaccine (PCV) in childhood immunization programs has been faster than for any other vaccine in the past, reaching an estimated global coverage of 42% in 2016 [1] and has prevented an estimated 230 000 to 290 000 pneumococcal deaths in children under 5 years of age in low-income countries between 2009 and 2015 [2]. Still, many infants are not being vaccinated against pneumococcal infections. Although supply shortages have delayed PCV introduction in many countries [2], other countries are yet to decide on implementing PCV and which vaccine to choose.

Currently, 10-valent (PCV10) and 13-valent (PCV13) vaccines are licensed for immunization of infants. These vaccines differ in composition: PCV13 covers 3 additional serotypes compared to PCV10, whereas PCV10 contains a nontypeable *Haemophilus influenzae* (NTHi) Protein D carrier [3–5]. Both vaccines are effective in preventing invasive pneumococcal disease (IPD) caused by vaccine serotypes in low- and high-risk populations [6, 7]. Of the 135 countries that introduced PCV by 2016, 69% implemented PCV13, 22% PCV10, and 8% are offering both [8]. In low-income countries this pattern is similar (76% use PCV13 and 23% PCV10), but the actual number of supplied doses of PCV10 and PCV13 is comparable due to different population sizes [2].

Because countries with the highest burden of childhood pneumococcal disease in general also have the lowest national

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budgets, the decisive factor on PCV implementation and which vaccine to introduce may often be based on costs. Where available, epidemiological data including the prevalence of serotypes causing severe disease should also be considered. Compared to countries of low endemicity, the spectrum of pneumococcal serotypes causing severe disease is broader in highly endemic settings, and the proportion of disease that can be prevented by the 2 PCVs is therefore lower [9].

Empirical data on the comparative safety, short-term and longer-term immunogenicity, and impact on bacterial carriage (and hence potential herd protection) of the 2 vaccines are missing for highly endemic settings. As it is important to understand the performance of these vaccines in such settings to inform PCV selection, we conducted a randomized controlled trial, studying head-to-head the impact of 3 doses of PCV10 and PCV13 administered at 1, 2, and 3 months of age to infants in Papua New Guinea (PNG), who, given an estimated IPD incidence rate of 4762/100 000 in the first year of life (2005–2008), have one of the highest risks for severe pneumococcal disease in the world [10]. With support from GAVI (Global Alliance for Vaccines and Immunization), PNG introduced PCV13 in 2014, but vaccine was not available in the study area until 2015 and has been introduced slowly since, with coverage for 1 dose around 25% and 3 doses around 5% in late 2015 [11].

MATERIALS AND METHODS

Study Design

The trial consisted of 2 parts. The primary objectives of the first part (reported here) included assessing safety, immunogenicity and antibody persistence after PCV10 or PCV13 vaccination at 1, 2, and 3 months of age during the first 9 months of life in PNG infants. A secondary objective was to assess carriage of pneumococcal vaccine and nonvaccine serotypes, and NTHi. The second part of this study aims to assess in PCV10- and PCV13-primed PNG infants the safety and immunogenicity of 1 dose of pneumococcal polysaccharide vaccine (PPV) administered at 9 months of age (not reported here).

A detailed protocol has been published, describing the trial aims, objectives, design, study population, and methods including consenting procedures [12].

The study was conducted according to Declaration of Helsinki International Conference on Harmonisation Good Clinical Practice (ICH-GCP) and local ethical guidelines. Ethical approval was obtained from the PNG Medical Research Advisory Committee (11.03) and PNG Institute of Medical Research (PNGIMR) Institutional Review Board (1028). The study is registered with ClinicalTrials.gov (CTN NCT01619462).

Study Population

To be eligible for enrolment, children had to be between 28 and 35 days old, reside within 1 hour's drive from Goroka town, and the family had to intend remaining in the study area for 2 years. Exclusion criteria were birth weight <2000 grams; severe congenital abnormality; mother or child positive for human immunodeficiency virus; or did not provide consent. A total of 262 infants were enrolled between November 2011 and April 2014.

Randomization and Masking

Infants were randomised 1:1 to receive 3 doses of PCV10 or PCV13 using a computer-generated random number list [12]. Throughout the study, laboratory staff was blinded to the vaccine allocation.

Study Vaccines

PCV10 (Synflorix®, GSK, Belgium, batches ASPNA0099AB, ASPNA267DD) contains pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14 and 23F polysaccharide conjugated to NTHi Protein D, and serotypes 18C and 19F polysaccharide conjugated to tetanus and diphtheria toxoids, respectively. PCV13 (Prevenar13®, Pfizer, USA, batch numbers F36226, G71540) contains pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F conjugated to nontoxic diphtheria CRM_{197} protein.

Study Procedures and Specimen Collection

Prior to any vaccination, the child's medical history was assessed, and a physical examination was performed to exclude contraindications for vaccination. PCV10 and PCV13 were administered together with routine childhood vaccine [12].

Venous blood samples (3–5 mL) and nasopharyngeal swabs (NPS) were collected at 1, 4 and 9 months of age.

Immunogenicity Assessment

Serum Immunoglobulin G (IgG) antibodies against PCV13 serotypes, and non-PCV serotype 2 were measured using a WHO standardized pneumococcal enzyme-linked immunosorbent assay (ELISA) [13, 14] established earlier at PNGIMR [10], using the human pneumococcal standard reference serum 007sp [15] and 10 μg/mL cell wall polysaccharide (CPS) and 5 μg/mL of purified of serotype 22F polysaccharide for preabsorbance of samples to remove nonspecific antibodies and increase the specificity of the assay [13]. IgG-serotype-specific geometric mean concentrations (GMCs) and the proportion of children with concentrations ≥0.35μg/mL (considered the serological correlate of protection against IPD) were calculated for each time point [16].

Reactogenicity and Safety Assessment

Children were observed for 1 hour and visited at home 24–48 hours post-vaccination to assess local or systemic side effects. Children were followed for illness through passive surveillance throughout the study [12].

A serious adverse event (SAE) was defined as any event requiring hospitalisation or resulting in death. As there were disruptions of hospital services in Goroka in 2015, illnesses

deemed serious enough to require hospitalisation but managed as outpatients were documented as SAEs in this period.

Bacteriology

Pneumococcal and NTHi carriage were assessed using standard bacteriological culture, isolation, and identification methods [17]. The Quellung reaction (antisera from Statens Serum Institut, Denmark) was used to serotype 2 distinct colonies of pneumococci picked from the primary plate. Presumptive colonies of *H. influenzae* were subcultured and confirmed to be *H. influenzae* based on their X- and V- factor dependence for growth. NTHi were confirmed based on their smooth colony phenotype, whereas typeable *H. influenzae* colonies were mucoid and were serotyped using *H. influenzae* agglutinating antisera a-f (Remel, Thermo Fisher Scientific, Australia).

Statistical Methods

A sample size calculation is provided in the published methods paper [12].

Data were analyzed based on an intention-to-treat analysis using SPSS 15.0. Antibody concentrations were log-transformed. For continuous variables, differences between groups were tested using the 2 sample *t*-test, and differences within individuals over time using paired *t*-tests. For categorical variables, differences between groups were tested using Pearson χ^2 test. For all analyses, test outcomes were considered to be significantly different if the *P*-value was ≤.05.

RESULTS

Study Population

Population characteristics were similar for infants randomized to the PCV10 or PCV13 group, as reported previously [12]. In sum, 90% (118/131) of children in the PCV10 group and 83% (109/131) in the PCV13 group completed vaccination according to protocol. Follow-up until 9 months of age was completed by 108 (82%) children in the PCV10 group and 100 (76%) children in the PCV13 group (Figure 1).

Rates of Seroprotection

At 4 months of age, at least 77% of infants had IgG concentrations ≥0.35 μg/mL against any serotype for which they had been vaccinated (Table 1). For 8/10 shared PCV10/13 serotypes IgG concentrations ≥0.35 μg/mL persisted in more than 77% of children at 9 months of age. For serotype 1 seroprotection rates were significantly higher (*P* = .006), and for serotype 18C significantly lower (*P* = .041) in the PCV13 than PCV10 group at 9 months. Unexpectedly, only 33% of children in the PCV13 group had IgG concentrations ≥0.35 μg/mL for PCV13 serotype 3 at 9 months of age, compared to 51% of children in the PCV10 group (*P* = .010).

For a higher cutoff value of ≥1.0 μg/mL, predicting longer-term protection, rates are presented in Supplementary Table 1. At 9 months, the highest positive rates were found for serotypes 14 and 19F (more than 74% positive in either group) and the lowest rates for serotypes 4, 9V, and 23F (between 13% and 21% positive in either group), and serotype 3 in the PCV13 group (7%).

Serotype-specific IgG GMCs in PCV10- and PCV13-vaccinated Children

IgG GMCs against a number of shared PCV10/13 serotypes differed between PCV10 and PCV13 vaccinated children, albeit not in a consistent pattern, including higher serotype 7F, 19F, and 23F IgG GMCs at 4 months, and higher serotype 1, 5, and 7F IgG GMCs and lower serotypes 6B, 18C, and 19F IgG GMCs at 9 months in the PCV13 than in the PCV10 group (*P* < .05) (Table 1 and Figure 2).

IgG responses waned between 4 and 9 months of age by 50% to 80% for most vaccine serotypes in both groups, except for serotype 14 (15% waning) in the PCV13 group, and serotypes 19F (20% waning) and 6B (no decline) in the PCV10 group (Figure 3 and Supplementary Table 2).

Reactogenicity, Safety, and Morbidity

Reactogenicity was moderate, with no differences other than more redness at the injection site after the first dose of PCV10 (12%) compared to PCV13 (5%) (*P* = .040) (Supplementary Table 3).

A total of 438 illness episodes were documented during the 8 month follow-up period. No vaccine-related SAEs occurred. Incidence rates of all-cause morbidity and moderate/severe pneumonia tended to be higher between 1 and 4 months of age than between 4 and 9 months of age (Table 2). Three infants developed IPD, including 1 infant developing severe pneumonia at 8 weeks of age after 1 dose of PCV13 (serotype 7F cultured from blood); 1 infant developing pneumococcal meningitis at 10 weeks of age after 2 doses of PCV10 (serotype 8 cultured from CSF); and 1 infant developing pneumococcal sepsis at 12 weeks of age after 3 doses PCV10 (serotype 46 cultured from blood). There were no significant differences in incidence rates of any illness, hospitalization, ALRI, or moderate/severe ALRI between the PCV10 and PCV13 groups.

Pneumococcal and NTHi Carriage

At 1 month of age, 65% (95% confidence interval [CI] 58.4%–70.3%) of infants were pneumococcal carriers (Table 3): 34.4% (95% CI 28.6–40.4) carried nonvaccine serotypes, 14.9% (95% CI 10.8–19.8) nonserotypeable pneumococci, 14.9% (95% CI 10.8–19.8) any of the shared PCV10/13 serotype, and 3.1% (95% CI 1.3–5.9) any of the 3 additional PCV13 serotypes. At 4 months, 92% of children in the PCV10 group and 81% in the PCV13 group were pneumococcal carriers (*P* = .023), and at 9 months carriage rates were 88% and 90% in the PCV10 and PCV13 group, respectively (*P* > .05). Carriage of any shared PCV10/13 serotypes was comparable between the groups at 4 or at 9 months of age.

A total of 65 different colonizing pneumococcal serotypes were identified during the study period, already 49 at 1 month of age (Supplementary Table 4). Serotype 23F was the most

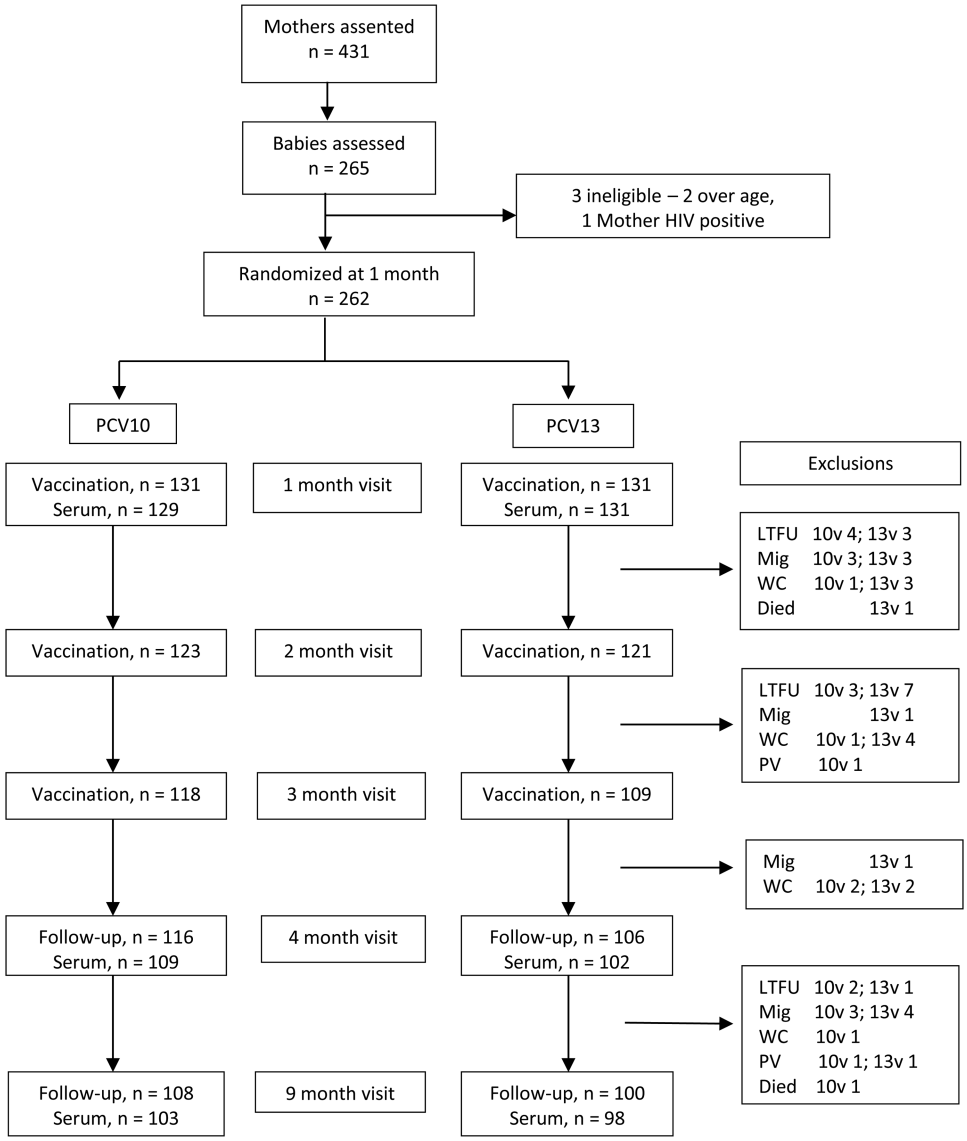

Figure 1. Flowchart. HIV, human immunodeficiency virus; LTFU, lost to follow-up; Mig, Migration; PCV10, 10-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; PV, protocol violation; WC, withdrawn consent.

frequently carried serotype at 1 and 4 months of age and serotype 19A at 9 months. Carriage of nonserotypeable pneumococci was common: (21.7%, 14.6%, and 9.5% of pneumococcal isolates at 1, 4, and 9 of age, respectively) (Table 3).

NTHi was carried by 41.3% (95% CI 35.1–47.6) of infants at 1 month of age. At 4 and 9 months carriage rates were 69.4% and 53.3% in the PCV10 group, respectively, and 58.8% and 57.1% in the PCV13 group, respectively (Table 3).

DISCUSSION

Because the epidemiology of pneumococcal infections differs with the level of endemicity, studies in highly endemic settings are important to understand the impact and possible limitations of PCVs in these environments. In this head-to-head study in a highly endemic setting in PNG, both PCV10 and PCV13 were found to be immunogenic and well tolerated when given at the accelerated national schedule of 1, 2, and 3 months of age. More than 90% of infants had seroprotective antibody levels against most vaccine serotypes at 4 months of age, which is important considering the high incidence of IPD in young infants in highly endemic settings like PNG.

Overall, antibody levels waned rapidly between 4 and 9 months of age. A booster dose of PCV in later infancy may help to sustain protective levels but may be too expensive to implement in low-income countries. Whether a 2 + 1 schedule, as implemented in several low-risk countries, is effective in high-risk settings where there is early onset of dense carriage and the incidence of IPD in young infants is high, has yet to be determined [18]. An alternative is to complement priming with 3 doses of PCV with 1 dose of 23-valent polysaccharide vaccine

Table 1. Pneumococcal Serotype-specific Immunoglobulin G (IgG) Geometric Mean Concentrations (GMCs) and Proportion of Children With Levels ≥0.35 µg/mL Before and After Vaccination With 3 Doses of PCV10 or PCV13

Serotypes		Age 1 Month (Prevaccination)			Age 4 Months (1 Month Postvaccination)			Age 9 Months (6 Months Postvaccination)		
		PCV10 (n = 129)	PCV13 (n = 131)	*P*-Value	PCV10 (n = 109)	PCV13 (n = 102)	*P*-Value	PCV10 (n = 103)	PCV13 (n = 98)	*P*-Value
Shared PCV10/PCV13										
1	GMC	0.80 (0.69–0.91)	0.81 (0.70–0.94)	.871	2.25 (1.96–2.59)	2.59 (2.21–3.03)	.195	0.62 (0.54–0.74)	0.89 (0.77–1.03)	.002
	≥0.35 µg/mL	83.7% (77.4–90.0)	84.0% (77.7–90.3)	.956	98.2% (95.6–99.5)	99.0% (97.1–99.5)	.604	79.6% (71.6–87.6)	93.0% (71.6–98.0)	.006
4	GMC	0.44 (0.38–0.51)	0.38 (0.34–0.44)	.155	1.67 (1.44–1.94)	1.90 (1.60–2.26)	.270	0.45 (0.39–0.52)	0.41 (0.35–0.47)	.325
	≥0.35 µg/mL	63.6% (55.3–71.8)	56.5% (48.0–65.0)	.241	96.3% (92.7–99.5)	93.1% (88.2–98.0)	.306	62.1% (52.5–71.7)	53.1% (43.2–62.9)	.197
5	GMC	1.03 (0.90–1.17)	0.91 (0.80–1.04)	.190	1.80 (1.61–2.02)	1.82 (1.60–2.06)	.909	0.65 (0.57–0.75)	0.82 (0.71–0.94)	.025
	≥0.35 µg/mL	90.7% (85.7–95.7)	87.8% (82.2–93.4)	.447	99.1% (97.2–99.5)	99.0% (97.1–99.5)	.963	79.6% (71.6–87.6)	85.7% (78.8–92.6)	.258
6B	GMC	1.20 (1.05–1.38)	1.09 (0.96–1.24)	.321	1.06 (0.91–1.25)	1.27 (1.05–1.53)	.166	1.09 (0.92–1.29)	0.85 (0.72–1.00)	.034
	≥0.35 µg/mL	93.0% (88.7–97.4)	93.1% (83.7–97.5)	.973	92.2% (86.9–97.4)	92.2% (86.9–97.4)	.914	91.3% (85.7–96.9)	83.7% (76.4–91.0)	.106
7F	GMC	1.24 (1.09–1.40)	1.06 (0.92–1.21)	.092	2.27 (2.02–2.55)	2.94 (2.58–3.37)	.004	0.78 (0.68–0.90)	1.05 (0.91–1.21)	.003
	≥0.35 µg/mL	94.6% (90.7–98.5)	92.4% (87.8–96.9)	.469	99.1% (97.2–99.5)	100% (100–100)	…	86.4% (79.6–93.2)	92.9% (87.8–98.0)	.136
9V	GMC	0.88 (0.77–1.00)	0.78 (0.68–0.90)	.247	1.61 (1.39–1.86)	1.92 (1.63–2.27)	.115	0.58 (0.51–0.66)	0.56 (0.49–0.65)	.785
	≥0.35 µg/mL	85.3% (79.2–91.3)	83.2% (76.8–89.6)	.646	95.4% (91.4–99.5)	95.1% (90.9–99.3)	.916	76.7% (68.3–85.1)	77.6% (69.3–85.8)	.887
14	GMC	3.65 (3.20–4.16)	3.47 (3.00–4.01)	.608	6.05 (4.9–7.5)	4.45 (3.65–5.41)	.036	2.99 (2.48–3.61)	3.74 (3.04–4.59)	.119
	≥0.35 µg/mL	98.5% (96.3–99.5)	98.5% (96.4–99.5)	.988	100% (100–100)	99.0% (97.1–99.5)	…	97.1% (93.8–99.5)	99.0% (97.0–99.5)	.339
18C	GMC	0.87 (0.76–1.01)	0.76 (0.67–0.87)	.172	2.54 (2.13–3.04)	2.25 (1.85–2.74)	.373	0.96 (0.82–1.12)	0.65 (0.56–0.74)	<.001
	≥0.35 µg/mL	86.1% (80.1–92.0)	87.8% (82.2–93.4)	.676	97.3% (94.1–99.5)	94.1% (89.6–98.7)	.270	92.2% (86.9–97.5)	82.7% (75.2–90.2)	.041
19F	GMC	2.36 (2.09–2.67)	2.20 (1.94–2.48)	.410	2.96 (2.50–3.50)	3.68 (3.21–4.22)	.048	2.33 (2.00–2.73)	1.75 (1.47–2.08)	.015
	≥0.35 µg/mL	99.2% (97.7–99.5)	98.5% (96.4–99.5)	.568	99.1% (97.2–99.5)	100% (100–100)	…	99.0% (97.1–99.5)	98.0% (95.2–99.5)	.538
23F	GMC	0.84 (0.74–0.97)	0.80 (0.70–0.91)	.538	0.88 (0.74–1.05)	1.41 (1.14–1.74)	<.001	0.43 (0.36–0.51)	0.43 (0.35–0.52)	.991
	≥0.35 µg/mL	88.4% (82.9–93.9)	86.3% (80.4–92.2)	.607	83.5% (76.3–90.7)	91.2% (85.7–96.7)	.097	54.4% (44.5–64.2)	56.1% (46.3–66.0)	.805

Table 1. Continued

Serotypes		Age 1 Month (Prevaccination)			Age 4 Months (1 Month Postvaccination)			Age 9 Months (6 Months Postvaccination)		
		PCV10 (n = 129)	PCV13 (n = 131)	*P*-Value	PCV10 (n = 109)	PCV13 (n = 102)	*P*-Value	PCV10 (n = 103)	PCV13 (n = 98)	*P*-Value
PCV13 only										
3	GMC	0.16 (0.14–0.18)	0.15 (0.13–0.18)	.773	0.32 (0.27–0.39)	0.70 (0.60–0.81)	<.001	0.34 (0.28–0.42)	0.29 (0.24–0.36)	.279
	≥0.35 μg/mL	16.3% (10.0–22.6)	15.3% (9.1–21.4)	.822	45.0% (35.3–54.6)	81.4% (73.8–88.9)	<.001	50.5% (40.6–60.4)	32.7% (23.4–41.9)	.010
6A	GMC	0.72 (0.63–0.83)	0.66 (0.58–0.75)	.318	0.24 (0.21–0.29)	0.85 (0.69–1.04)	<.001	0.26 (0.22–0.30)	0.49 (0.41–0.60)	<.001
	≥0.35 μg/mL	82.2% (37.9–88.7)	77.9% (70.8–85.0)	.384	35.8% (26.5–45.1)	77.5% (69.3–85.6)	<.001	37.9% (28.3–47.5)	64.3% (54.8–73.8)	<.001
19A	GMC	2.08 (1.86–2.33)	1.78 (1.58–2.01)	.067	0.76 (0.66–0.87)	3.63 (3.00–4.39)	<.001	0.85 (0.73–1.00)	1.21 (0.99–1.47)	.009
	≥0.35 μg/mL	100% (100–100)	100% (100–100)	…	89.0% (82.9–95.1)	98.0% (95.4–99.5)	.008	85.4% (78.5–92.4)	92.9% (87.8–98.0)	.093
Nonvaccine type										
2	GMC	0.71 (0.62–0.81)	0.73 (0.63–0.84)	.802	0.23 (0.19–0.27)	0.36 (0.31–0.43)	<.001	0.32 (0.28–0.38)	0.34 (0.29–0.39)	.717
	≥0.35 μg/mL	80.6% (73.9–87.4)	80.9% (74.2–87.7)	.952	24.8% (16.4–33.2)	58.8% (49.3–68.4)	<.001	48.5% (38.7–58.4)	49.0% (39.1–58.9)	.951

The table shows GMCs and 95% confidence intervals of serotype-specific IgG concentrations, and the proportions and 95% confidence intervals of children in each vaccine group with serotype-specific IgG concentrations equal to or above the seroprotective cutoff of 0.35 μg/mL.

Abbreviations: IgG, immunoglobulin G; PCV, pneumococcal conjugate vaccine.

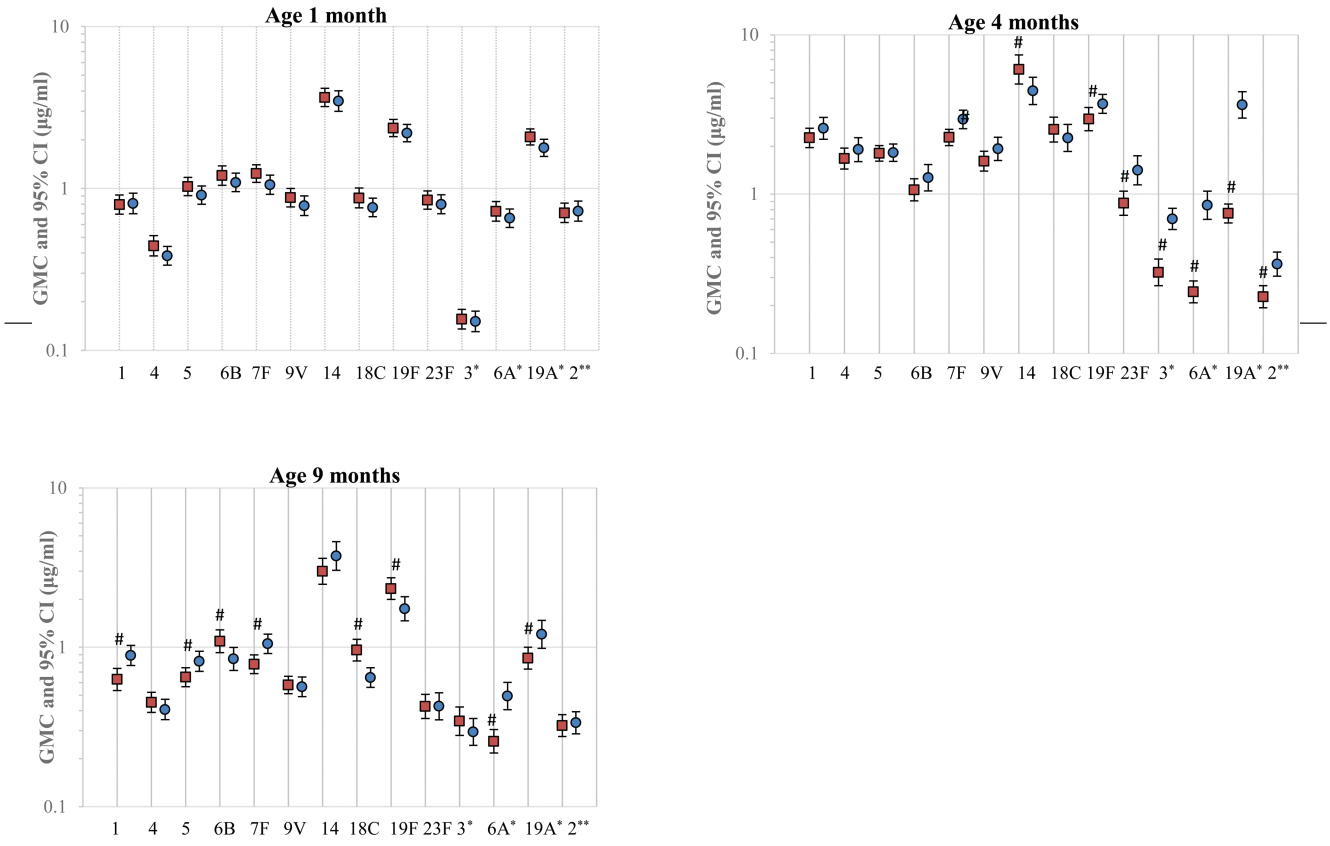

Figure 2. GMCs of serotype-specific IgG antibodies. GMCs and 95% CIs for IgG antibodies against shared PCV10/13 serotypes, (*) PCV13-only serotypes, and (**) non-PCV serotype 2 measured before vaccination, at 4 months of age, and at 9 months of age were compared between children vaccinated with either three doses of PCV10 (orange square) or PCV13 (blue circle) using a 2-sample t-test and indicated with (#) when significantly different ($P < .05$). Abbreviations: CI, confidence interval; GMC, geometric mean concentration; IgG, immunoglobulin G; PCV, pneumococcal conjugate vaccine.

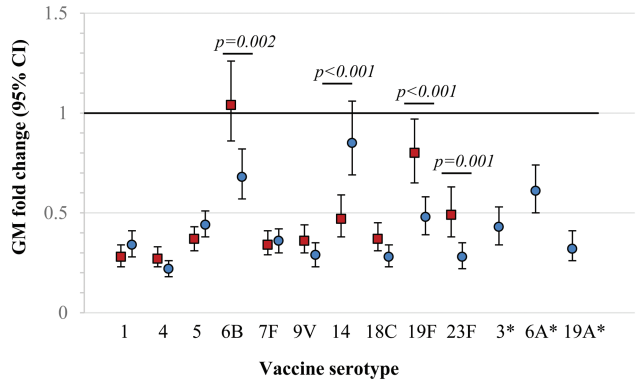

Figure 3. GM fold change in PCV-induced IgG responses between 4 and 9 months of age. GM fold changes and 95% CIs in vaccine-induced IgG antibody titers between 4 and 9 months of age were calculated for shared PCV10/13 serotypes for both PCV10- (orange square) and PCV13- (blue circle) vaccinated children, as well as for PCV13-only serotypes (*) for the PCV13-vaccinated group. GMs and 95% CIs < 1 correspond to a significant ($P < .05$) decline in antibody responses. GM fold changes were compared between the groups for each shared vaccine serotype using a 2-sample *t*-test and when a significant difference was found *P*-values were included. Abbreviations: CI, confidence interval; GM, geometric mean; IgG, immunoglobulin G; PCV, pneumococcal conjugate vaccine.

(PPV). This approach was used in Australia to increase serotype coverage in high-risk Aboriginal children but was halted after suggestions that PPV may deplete serotype-specific memory B-cells [19]. In an earlier study where PNG infants received PPV after priming with PCV7, there was no evidence of hyporesponsiveness [20], and this strategy will be further studied in the follow-up of this study.

In addition to preventing IPD, PCV immunization can prevent colonization, which can lead to herd protection in the nonvaccinated population due to reduced circulation of vaccine serotypes. In contrast to low and moderately endemic settings, there is evidence that in high-risk settings the impact of PCVs on preventing carriage is limited [21, 22]. Possible explanations are that in high-risk populations the density of colonization is too high to allow complete clearance, or that antibodies are of a low avidity and lack opsonophagocytic activity. The latter may also explain why naturally acquired maternal antibodies despite high titers do not protect infants in high-risk settings from pneumococcal colonization [23]. To optimize the effectiveness and full potential of PCVs in high-risk settings, more studies in

Table 2. Incidence Rates of Any Morbidity, Hospitalization, and Any or Moderate/Severe Acute Lower Respiratory Tract Infections (ALRI) According to Age

		PCV10		PCV13		
Age		Events	Incidence per Person-Year (95% CI)	Events	Incidence per Person-Year (95% CI)	*P*-Value
1–3 months	Any morbidity	94	3.14 (2.56–3.84)	97	3.37 (2.77–4.12)	.616
	Any hospitalization	12	0.40 (0.23–0.71)	9	0.31 (0.16–0.60)	.576
	Moderate/Severe ALRI	19	0.63 (0.40–0.99)	13	0.45 (0.26–0.78)	.347
	Any ALRI	35	1.17 (0.84–1.63)	34	1.18 (0.85–1.66)	.960
4–9 months	Any morbidity	129	2.42 (2.04–2.88)	118	2.27 (1.90–2.72)	.617
	Any hospitalisation	17	0.32 (0.20–0.51)	13	0.25 (0.15–0.43)	.510
	Moderate/Severe ALRI	27	0.51 (0.35–0.74)	19	0.37 (0.23–0.57)	.276
	Any ALRI	63	1.18 (0.92–1.51)	51	0.98 (0.75–1.29)	.324

The table shows the number of events and incidence rates (with 95% confidence intervals) of any illness, hospitalization, and acute lower respiratory tract infections (ALRI) between 1 and 3 months of age, and between 4 and 9 months of age in infants vaccinated with 3 doses of PCV10 or PCV13. Differences between groups were tested using Pearson χ^2 test.

Abbreviations: ALRI, acute lower respiratory tract infections; CI, confidence interval; PCV, pneumococcal conjugate vaccine.

these settings are required to understand the impaired impact on pneumococcal colonization, how this may be achieved (eg, PCV booster doses), what a possible impact on carriage load could mean in terms of inducing herd protection, and what the effect is on serotype-specific versus non-serotype-specific carriage load, considering findings of increased overall pneumococcal carriage load in PCV-vaccinated compared to unvaccinated children in settings of dense and diverse carriage [24, 25].

Children in high-risk settings experience pneumococcal colonization from a very young age. For example, in the highlands of PNG infants are colonized with pneumococcus at a median age of 17–18 days [26]. This increases their risk of developing pneumococcal disease and may negatively affect PCV responses [27, 28]. In settings where colonization occurs so early, starting immunization as early as possible may therefore improve PCV's immunogenicity and protection against IPD in early life. Studies in PNG and Kenya have demonstrated that neonatal vaccination with PCV7 is safe and does not compromise immunogenicity [10, 22]. Neonatal vaccination also has the potential of increasing vaccine uptake, particularly in settings where most women give birth in clinics or health centres.

Given the diversity of serotypes with the potential of causing disease carried by infants in high-risk settings (65 serotypes in this study), the coverage afforded by current PCVs is limited (<50% of IPD serotypes for PCV13 in PNG). However, because the overall incidence of pneumococcal disease in high-endemic settings is high, routine immunization with PCV10 or PCV13 can still be expected to prevent significant morbidity and mortality due to vaccine serotypes and be cost-effective [29].

A limitation of conducting a field trial as intensive as this one under challenging logistical conditions and with limited funding is that the size of the cohort that can be studied is restricted. As carriage rates of vaccine serotypes in the population were lower than predicted, a larger

Table 3. Proportion of Children Colonized With *Streptococcus pneumoniae* (Pnc) and/or Nontypeable *Haemophilus influenzae* (NTHi) Before and After Vaccination With 3 Doses of 10-valent Pneumococcal Conjugate Vaccine (PCV10) or 10-valent Pneumococcal Conjugate Vaccine (PCV13)

	Age 1 Month (Before Vaccination)			Age 4 Months (1 Month Postvaccination)			Age 9 Months (6 Months Postvaccination)		
	PCV10 (n = 131)	PCV13 (n = 131)	*P*-Value	PCV10 (n = 111)	PCV13 (n = 102)	*P*-Value	PCV10 (n = 98)	PCV13 (n = 105)	*P*-Value
Any Pnc	63.4% (54.5–71.6)	65.6% (56.9–73.7)	.699	91.9% (85.2–96.2)	81.4% (72.4–88.4)	.023	87.6% (79.8–93.2)	89.8% (82.0–95.0)	.625
PCV10/13 serotypes	13.0% (7.7–20.0)	16.8% (10.8–24.3)	.386	25.5% (17.6–34.6)	18.6% (11.6–27.6)	.232	19.0% (12.0–27.9)	13.4% (7.3–21.8)	.278
PCV13 only serotypes	1.5% (0.2–5.4)	4.6% (1.7–9.7)	.281	9.1% (4.4–16.1)	5.9% (2.2–12.4)	.377	14.3% (8.2–22.5)	8.2% (3.6–15.6)	.177
Nonvaccine serotypes	38.9% (30.5–47.8)	29.8% (22.1–38.4)	.119	52.7% (43.0–62.3)	45.1% (35.2–55.3)	.267	56.2% (46.2–65.9)	59.8% (49.3–69.6)	.604
Nonserotypeable Pnc	10.7% (6.0–17.3)	19.1% (12.7–26.9)	.056	15.5% (9.3–23.6)	22.5% (14.9–31.9)	.187	6.7% (2.7–13.3)	12.4% (6.6–20.6)	.165
NTHi	44.0% (35.1–53.2)	38.6% (30.1–47.6)	.383	69.4% (59.9–77.8)	58.8% (48.6–68.5)	.109	53.3% (43.3–63.1)	57.1% (46.7–67.1)	.586

Proportion and 95% confidence intervals of children carrying any pneumococcus; shared PCV10/13 serotypes; PCV13-only serotypes; nonserotypeable pneumococci; and NTHi at different time points before and after vaccination with three doses of PCV10 or PCV13. Differences between groups were tested using Pearson χ^2 test.

Abbreviations: NTHi, *Haemophilus influenzae*; PCV, pneumococcal conjugate vaccine; Pnc, *Streptococcus pneumoniae*.

sample size would have been needed to show an impact, if any, on vaccine serotype carriage. However, the study had sufficient power to study the safety, immunogenicity, and suitability to immunize infants with the available PCVs in this high-risk setting. Despite the high mobility of this population, almost 80% of children were followed up to 9 months of age, with nasopharyngeal and serum samples collected from nearly all children (>97%, involving more than 1100 visits). The success of this study is a reflection of the long-established relationship and trust between the community and PNGIMR staff, and the perseverance of field staff in locating participants.

PCV13 was introduced in PNG in a 3 + 0 schedule in 2014. Uptake has been slow, and it will take time before its impact can be assessed. Establishing a surveillance program in PNG to monitor the impact of PCV13 implementation on IPD and possible change in serotypes causing disease is important. The impact of PCV13 implementation on herd protection is currently being investigated in the highlands of PNG as part of a multicentre study (PneuCAPTIVE study [30]).

In summary, this head-to-head study shows that PCV10 and PCV13 are comparably safe and immunogenic and are suitable to immunize infants in a high-risk setting. Considerations by high-risk countries on which PCV to introduce will therefore depend on the local IPD epidemiology, pricing differences, and vaccine availability. The impact of either PCV on IPD may be less in a high endemicity setting than low endemicity setting due to (i) limited coverage of serotypes causing disease; (ii) less effect on vaccine serotype carriage, which constrains herd protection; and (iii) faster waning of antibody responses. Further studies are needed to better understand and optimize the potential of PCVs in these settings, including the use of booster vaccinations and accelerated schedules. Next generation PCVs are in development with different serotype compositions for use in low-income settings; these will need to be evaluated in high incidence settings to understand and maximize their impact.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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