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 ≥0.35 µg/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. pneumoniae; antibodies; carriage; Papua New Guinea.
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 in PNG infants. A secondary objective was to assess carriage of pneumococcal vaccine and nonvaccine serotypes, and NTHi.

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 CRM197 protein.

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 pre-absorbance 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 after 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 χ² test. For all analyses, test outcomes were considered to be significantly different if the *P*-value was ≤0.05.

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 pneumococcal meningitis at 10 weeks of age after 2 doses of PCV10 (serotype 7F cultured from blood); 1 infant developing pneumococcal meningitis at 19F (20% waning) and 6B (no decline) in the PCV10 group (Figure 3 and Supplementary Table 2).

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 serotypes 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 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
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.

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**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.
### 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 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)             | 0.81 (1.96–2.59) | 2.59 (2.21–3.03) | 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)            | 98.2% (95.6–99.5) | 99.0% (97.1–99.5) | 604 (71.6–67.6) | 79.6% (71.6–86.8) | .006 |
| 4 GMC     | 0.44 (0.38–0.51)             | 0.38 (0.34–0.44)             | 1.67 (1.44–1.94) | 1.90 (1.60–2.26) | 270 (0.39–0.52) | 0.45 (0.35–0.47) | .325 |
| ≥0.35 µg/mL | 63.6% (55.3–71.8)            | 56.5% (48.0–65.0)            | 96.3% (92.7–99.5) | 93.1% (88.2–98.0) | 306 (52.5–71.7) | 62.1% (43.2–62.9) | .197 |
| 5 GMC     | 1.03 (0.90–1.17)             | 0.91 (0.80–1.04)             | 1.80 (1.61–2.02) | 1.82 (1.60–2.06) | 909 (0.71–0.94) | 0.65 (0.52–0.75) | .025 |
| ≥0.35 µg/mL | 90.7% (85.7–95.7)            | 87.8% (82.2–93.4)            | 99.1% (97.2–99.5) | 99.0% (97.1–99.5) | 963 (71.6–87.6) | 79.6% (78.2–92.6) | .258 |
| 6B GMC    | 1.20 (1.05–1.28)             | 1.09 (0.96–1.24)             | 1.06 (0.91–1.25) | 1.27 (1.05–1.53) | 166 (0.92–1.29) | 1.09 (0.72–1.00) | .034 |
| ≥0.35 µg/mL | 93.0% (88.7–97.4)            | 93.1% (83.7–97.5)            | 92.2% (86.9–97.4) | 92.2% (86.9–97.4) | 914 (85.7–96.9) | 91.3% (76.4–91.0) | .106 |
| 7F GMC    | 1.24 (1.09–1.40)             | 1.06 (0.92–1.21)             | 2.27 (2.02–2.55) | 2.94 (2.58–3.37) | 0.04 (0.68–0.90) | 0.78 (0.91–1.21) | .003 |
| ≥0.35 µg/mL | 94.6% (90.7–98.5)            | 92.4% (87.8–96.9)            | 99.1% (972–99.5) | 100% (100–100) | ... (79.6–93.2) | 86.4% (78.3–96.0) | .136 |
| 9V GMC    | 0.88 (0.77–1.00)             | 0.87 (0.68–0.90)             | 1.61 (1.39–1.86) | 1.92 (1.63–2.27) | 115 (0.51–0.66) | 0.58 (0.49–0.65) | .785 |
| ≥0.35 µg/mL | 85.3% (79.2–91.3)            | 83.2% (76.8–89.6)            | 95.4% (91.4–99.5) | 95.1% (90.9–99.3) | 916 (68.3–85.1) | 76.7% (69.3–85.8) | .887 |
| 14 GMC    | 3.65 (3.20–4.16)             | 3.47 (3.00–4.01)             | 6.05 (4.9–7.5) | 4.45 (3.65–5.41) | 0.03 (2.48–3.61) | 2.99 (3.04–4.59) | .119 |
| ≥0.35 µg/mL | 98.5% (96.3–99.5)            | 98.5% (96.4–99.5)            | 100% (100–100) | 99.0% (97.1–99.5) | ... (93.8–99.5) | 97.1% (970–99.5) | .339 |
| 18C GMC   | 0.87 (0.76–1.01)             | 0.76 (0.67–0.87)             | 2.54 (2.13–3.04) | 2.25 (1.85–2.74) | 373 (0.92–1.12) | 0.96 (0.56–0.74) | <0.001 |
| ≥0.35 µg/mL | 86.1% (80.1–92.0)            | 87.8% (82.2–93.4)            | 97.3% (94.1–99.5) | 94.1% (89.6–98.7) | 270 (75.2–90.2) | 92.2% (86.9–97.5) | .041 |
| 19F GMC   | 2.26 (2.09–2.67)             | 2.20 (1.94–2.48)             | 2.96 (2.50–3.50) | 3.68 (3.21–4.22) | 0.48 (2.00–2.73) | 2.33 (1.47–2.08) | .015 |
| ≥0.35 µg/mL | 99.2% (97.7–99.5)            | 98.5% (96.4–99.5)            | 99.1% (972–99.5) | 100% (100–100) | ... (97.1–99.5) | 99.0% (96.2–99.5) | .538 |
| 23F GMC   | 0.84 (0.74–0.97)             | 0.80 (0.70–0.91)             | 0.88 (0.74–1.05) | 1.41 (1.14–1.71) | <0.001 (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)            | 83.5% (76.3–90.7) | 91.2% (85.7–96.7) | 0.97 (44.5–64.2) | 54.4% (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)                         | PCV10 (n = 109)                        |
|           |                              |                                        | PCV13 (n = 102)                        |
|           |                              |                                        |                                        | PCV10 (n = 103) | PCV13 (n = 98) | P-Value |
|           |                              |                                        |                                          |                   |               |         |
| PCV13 only |                              |                                        |                                          |                   |               |         |
| 3          | GMC                          | 0.16 (0.14–0.18)                      | 0.32 (0.27–0.39)                       | 0.34 (0.28–0.42) | 0.29 (0.24–0.36) | .773    |
| ≥0.35 μg/mL|                              | 16.3% (10.0–22.6)                     | 45.0% (35.3–54.6)                      | 50.5% (40.6–60.4) | 32.7% (23.4–41.9) | <.001   |
| 6A         | GMC                          | 0.72 (0.63–0.83)                      | 0.24 (0.21–0.29)                      | 0.26 (0.22–0.30) | 0.49 (0.41–0.60) | <.001   |
| ≥0.35 μg/mL|                              | 82.2% (37.9–88.7)                     | 35.8% (26.5–45.1)                     | 3.79% (28.3–47.5) | 64.3% (54.8–73.8) | <.001   |
| 19A        | GMC                          | 2.08 (1.86–2.33)                      | 0.76 (0.66–0.87)                      | 0.85 (0.73–1.00) | 1.21 (0.99–1.47) | .09     |
| ≥0.35 μg/mL|                              | 100% (100%)                           | 89.0% (82.9–95.1)                     | 85.4% (78.5–92.4) | 92.9% (87.8–98.0) | .93     |
| Nonvaccine type |                |                                        |                                          |                   |               |         |
| 2          | GMC                          | 0.71 (0.62–0.81)                      | 0.73 (0.63–0.84)                      | 0.32 (0.28–0.38) | 0.34 (0.29–0.39) | .717    |
| ≥0.35 μg/mL|                              | 80.6% (73.9–87.4)                     | 24.8% (16.4–33.2)                     | 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.
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

**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 concentration; IgG, immunoglobulin G; 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 PCV and PCV13 in High-risk Infants • CID 2019:68 (1 May) • 1479

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

| Age      | PCV10 Events | PCV10 Incidence per Person-Year (95% CI) | PCV13 Events | PCV13 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 hospitalization | 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 χ² test.

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

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 | PCV10 (n = 131) | PCV13 (n = 131) | P-Value |
|-----|-----------------|-----------------|---------|
| 1 Month (Before Vaccination) | Any Pnc | 63.4% (54.5–71.6) | 65.6% (56.9–73.7) | .699 |
|    | PCV10/13 serotypes | 13.0% (7.2–20.0) | 16.8% (10.8–24.3) | .386 |
|    | PCV13 only serotypes | 5.5% (0.2–5.4) | 4.6% (1.7–9.7) | .281 |
|    | Nonvaccine serotypes | 38.9% (30.5–47.8) | 29.8% (22.1–38.4) | .119 |
|    | Nonserotypeable Pnc | 10.7% (6.0–17.3) | 19.1% (12.7–26.9) | .056 |
|    | NTHi | 44.0% (31.1–53.2) | 38.6% (30.1–47.6) | .383 |
| 4 Months (1 Month Postvaccination) | Any Pnc | 68.9% (59.7–77.8) | 81.4% (72.4–88.4) | .023 |
|    | PCV10/13 serotypes | 15.1% (9.4–21.7) | 18.6% (11.6–27.6) | .381 |
|    | PCV13 only serotypes | 5.9% (4.4–16.1) | 5.9% (2.2–12.4) | .377 |
|    | Nonvaccine serotypes | 41.5% (35.2–47.8) | 35.2% (28.1–44.0) | .267 |
|    | Nonserotypeable Pnc | 11.5% (7.3–15.6) | 16.1% (9.3–23.6) | .187 |
|    | NTHi | 66.3% (56.3–76.3) | 71.1% (61.3–80.9) | .165 |
| 9 Months (6 Months Postvaccination) | Any Pnc | 81.4% (79.8–93.2) | 89.8% (82.0–95.0) | .625 |
|    | PCV10/13 serotypes | 21.0% (12.0–27.9) | 19.0% (7.3–21.8) | .278 |
|    | PCV13 only serotypes | 5.9% (4.2–22.5) | 5.9% (3.6–15.6) | .177 |
|    | Nonvaccine serotypes | 56.2% (48.2–65.9) | 59.8% (49.3–70.6) | .604 |
|    | Nonserotypeable Pnc | 10.2% (9.6–22.5) | 15.4% (8.8–26.2) | .227 |
|    | NTHi | 68.6% (63.3–73.8) | 76.8% (70.0–83.6) | .165 |

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 χ² 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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Potential conflicts of interest. W. S. P. has received funding from Pfizer Australia to attend a conference. A. H. J. v. d. B. was previously an employee of Janssen Pharmaceuticals, Johnson and Johnson, and conducts part-time consultancy work for vaccine companies on projects not related to this study. A. R. G. is an investigator on an investigator-initiated research grant funded by Pfizer Australia, and has received a research grant from Vedanta Biosciences for work not related to this study. L. A. K. has received educational grants and travel support from Pfizer and GSK to attend conferences, is an investigator on an investigator-initiated research grant funded by Pfizer Australia, and is an inventor on patents for a pneumococcal protein vaccine antigen. D. L. has received support from Pfizer Australia to attend conferences, an honorarium from Merck Vaccines to give a seminar at their offices in Pennsylvania and support from Merck Vaccines to attend a conference; and is an investigator on an investigator-initiated research grant that was funded by Pfizer Australia. P. C. R. has received nonfinancial support from Pfizer, grants from GlaxoSmithKline, grants from Pfizer, and nonfinancial support from GlaxoSmithKline for work outside the submitted work. The Papua New Guinea Institute of Medical Research received sponsorship from Pfizer Australia to host a national Medical Symposium in 2014. All other authors declare no competing interests. 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.

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