Temporal Changes in Pneumococcal Colonization in HIV-infected and HIV-uninfected Mother-Child Pairs Following Transitioning From 7-valent to 13-valent Pneumococcal Conjugate Vaccine, Soweto, South Africa

Susan A. Nzenze,1,2 Anne von Gottberg,1,3 Tinevimbo Shiri,1,2 Nadia van Niekerk,1,2 Linda de Gouveia,1,3 Avy Violari,4 Marta C. Nunes,1,2 and Shabir A. Madhi1,2,3

1Medical Research Council: Respiratory and Meningeal Pathogens Research Unit, University of the Witwatersrand, 2Department of Science and Technology/National Research Foundation: Vaccine Preventable Diseases, University of the Witwatersrand, Johannesburg, 3National Institute for Communicable Diseases (NICD): a division of the National Health Laboratory Service (NHLS), Sandringham, and 4Perinatal HIV Research Unit, University of the Witwatersrand, Johannesburg, South Africa

Background. We investigated the impact of infant pneumococcal conjugate vaccine (PCV) immunization on pneumococcal colonization among human immunodeficiency virus (HIV)–infected and HIV-uninfected mother-child pairs.

Methods. Pneumococcal colonization was assessed in May 2010–February 2011 (period 1; 7-valent PCV era) and May 2012–April 2013 (period 2; 13-valent PCV era). Standard microbiological methods were used for pneumococcus isolation and serotyping.

Results. In children 0–12 years, PCV13-serotype colonization decreased from period 1 to period 2 among HIV-uninfected (adjusted odds ratio [OR], 0.32; 95% confidence interval [CI], .25–.40) and HIV-infected children (adjusted OR, 0.37; 95% CI, .28–.49), while there was an increase in nonvaccine serotype colonization. Decreases in PCV13-serotype colonization were observed in HIV-uninfected women (adjusted OR, 0.44; 95% CI, .23–.81), with a similar trend in HIV-infected women. HIV-infected compared to -uninfected women had higher prevalence of overall (20.5% vs 9.7% in period 1; 13.8% vs 9.7% in period 2) and PCV13-serotype colonization (8.7% vs 5.4% in period 1; 4.8% vs 2.0% in period 2), P < .04 for all observations.

Conclusions. Targeted PCV vaccination of African infants in a setting with high HIV prevalence was associated with PCV13-serotype colonization reduction, including among unvaccinated HIV-infected women.

Keywords. pneumococcal conjugate vaccine; HIV; mother-infant pairs; nasopharyngeal colonization; indirect effect.

Streptococcus pneumoniae is commonly associated with asymptomatic nasopharyngeal carriage, although, invasive pneumococcal disease (IPD) may develop within 2 months of acquisition of a new serotype [1]. Human immunodeficiency virus (HIV)–infected individuals have an 8–40-fold greater risk of developing IPD, including when on antiretroviral treatment [2–4]. Furthermore, HIV-infected women are more predisposed to IPD due to “pediatric serotypes” than HIV-infected men [5].
Some carriage studies have shown that pneumococcal colonization prevalence is similar between HIV-infected and HIV-uninfected children [6, 7]. Although there are limited data on the effect of HIV infection on pneumococcal colonization in adults [8–10], HIV-infected women have a higher prevalence of colonization by pneumococcal serotypes commonly associated with IPD in children, many of which are included in the 7-valent pneumococcal conjugate vaccine (PCV7) [4, 10, 11]. Consequently, the indirect effect of infant pneumococcal conjugate vaccine (PCV) immunization in the prevention of vaccine-serotype pneumococcal disease may be attenuated in settings with a high prevalence of HIV among adults, who could serve as an additional reservoir of vaccine serotype colonization.

PCV immunization directly decreases vaccine serotype colonization in the immunized children and indirectly in healthy unvaccinated children and adults; however, there are limited data on the direct and indirect effect of routine childhood PCV immunization on nasopharyngeal carriage of S. pneumoniae among HIV-infected children and adults [12, 13]. An earlier cross-sectional study in our setting reported no difference in colonization prevalence by either vaccine serotype or nonvaccine serotypes between vaccinated and unvaccinated HIV-infected children 5 years following receipt of 3 doses of an investigational 9-valent PCV during infancy; however, that study was performed prior to routine PCV immunization or management of HIV-infected children with antiretroviral therapy [13].

The aim of this study was to evaluate the effect of routine infant PCV immunization, following transitioning from PCV7 in 2011 to 13-valent PCV (PCV13) in 2013, on the prevalence of vaccine serotype and non-PCV13 serotype colonization in HIV-infected and HIV-uninfected mother-child pairs in South Africa at a community level. This evaluation included age groups that would have been eligible for PCV immunization and age groups (including adult women) who were ineligible for PCV immunization.

METHODS

Study Population

The study was undertaken in Soweto (Gauteng, South Africa), which has a population of 1.4 million and an annual birth cohort of 28 000 [14]. The prevalence of HIV among Sowetan women has remained steady since 2005, including 30% among those attending antenatal clinics and 20% in those 15–49 years of age [15]. The vertical transmission rate of HIV has declined from 5.9% in 2008 to 1.5% in 2012 due to more effective mother-to-child preventive antiretroviral treatment regimens strategies [16]. Since 2008, all pregnant HIV-infected women were offered triple antiretroviral treatment regardless of CD4+ lymphocyte count [16].

In April 2009, PCV7 was introduced into the national public immunization program as a 2-dose primary series at 6 and 14 weeks of age, followed by a third dose at 40 weeks of age, without any catch-up campaign for older children. The vaccine formulation was subsequently changed to PCV13 in May 2011; and from February to May 2012, a limited catch-up campaign was initiated, targeting children up to 3 years of age, as well as HIV-infected children and other high-risk groups up to 6 years of age. The immunization coverage for 3 doses of PCV in Gauteng was 12.3% in 2009, 86.3% in 2010, and reportedly 100% in 2011 and 2012 [17, 18]. HIV-infected adults in South Africa do not receive any pneumococcal vaccine as standard-of-care.

Study Participants

We enrolled HIV-infected and HIV-uninfected mother-child dyads between May 2010 and February 2011 (early PCV7-era, period 1) and again from May 2012 to April 2013 (PCV13-era, period 2). Children were aged between 0 and 12 years. In period 1, we targeted enrolling 700 mother-child pairs with concordant HIV status in each arm. HIV discordant pairs were excluded from the study.

Based on the PCV7-serotype colonization prevalence among mothers during period 1, we planned on enrolling 602 HIV-infected and 1234 HIV-uninfected mother-child pairs in period 2, to detect at least a 50% reduction in PCV7-serotype colonization in period 2 compared to period 1 in the women, with 80% power. The study was also sufficiently powered (90%) to detect at least a 50% decrease in PCV13-serotype colonization between period 1 and period 2 in both groups of women. Mothers with more than 1 child were evaluated as multiple mother-child pairs.

HIV-infected mother-child pairs were recruited from 2 established HIV clinics at Chris Hani Baragwanath Academic Hospital, where the majority of HIV-infected children in Soweto received their routine care during the study period; HIV-uninfected mother-child pairs were recruited from wellness-baby clinics. The HIV-infection status of women without a documented HIV seronegative test in the previous 6 months was determined, following counseling and consenting, using a rapid HIV test (Determine–Alere International Limited, Ballybrit, Galway, Ireland). Children of HIV-uninfected women were presumed to be HIV uninfected and children of HIV-infected mothers were tested per age-dependent criteria if had not been previously tested. Overall, >98% of mothers invited to take part in the study agreed to participate.

Demographic and risk factors for colonization were evaluated in participants at the time of swab collection. Child’s risk factors assessed included daycare attendance, rhinitis at time of sampling, breastfeeding history, underlying tuberculosis, hospitalization in preceding 3 months, current antibiotic treatment, and use of antiretroviral treatment for HIV-infected children; and among mothers, risk factors assessed included age, alcohol-intake history, current antibiotic therapy, cigarette smoking,
presence of rhinitis, previous tuberculosis treatment, hospitalization in preceding 3 months, and use of antiretroviral treatment for HIV-infected mothers.

**Determination of Bacterial Colonization**

Nasopharyngeal swabs were performed by trained study personnel in the children and their mothers using an aluminum-shafted, Dacron swab (MW and E, Medical Wire and Equipment Co, Ltd, Corsham, Wiltshire, England) as described [19, 20]. Additionally, an oropharyngeal swab was collected from mothers. Specimens were placed in skimmed milk, tryptose, glycerol, and glucose broth transport media, transported in a cooler box, and stored at −70°C within 6 hours of sampling. Samples were shipped intermittently to the Centre for Respiratory Diseases and Meningitis laboratory at the National Institute for Communicable Diseases in Johannesburg on dry ice and stored at −70°C until processed. More details are in the Supplementary Appendix. Serotyping was undertaken by the Quellung method using specific antisera (Statens Serum Institute, Copenhagen, Denmark). Presumptive pneumococcal isolates that were Quellung negative were categorized as nontypeable, once pneumococcal identification was confirmed with lytA polymerase chain reaction. When >1 distinct morphological colony type was present, each colony was serotyped. Serotypes 6A, 6B, 6C, and 6D were distinguished by the Quellung method.

**Definitions and Statistical Analysis Assessed the Changes of all Pneumococci, PCV7**

To determine the impact of infant PCV immunization on the prevalence of overall pneumococcus, vaccine-serotype and non-vaccine-serotype colonization, children were stratified into 4 age groups according to the probability of having been vaccinated (ie, children likely to be incompletely vaccinated [<9 months of age]), those eligible to have been fully vaccinated in both study periods [9–24 months of age], those likely to have been fully vaccinated only in period 2 [>24–48 months of age], and those unlikely to have received PCV at all [>48–144 months of age]).

We compared colonization prevalence in children and adults between the 2 study periods, including stratification by HIV infection status. Differences in the demographic and clinical characteristics between the populations in the 2 study periods were addressed by controlling for possible confounding factors on colonization. Univariate logistic regression analysis was conducted and those characteristics with a P value <.1 were included in a multivariable analysis to calculate adjusted odds ratio and corresponding 95% confidence intervals for colonization between the study periods. Similar analyses were implemented for comparison of colonization between HIV-infected and -uninfected groups. More details are in the Supplementary Appendix. Furthermore, we did not adjust the number of tests, as we undertook an a priori planned analysis. Nevertheless, we only considered a P value <.01 as significant, to offset any chance findings based on the multiple comparisons undertaken. Comparison of serotype prevalence between period 1 and period 2 was performed using χ² or Fisher exact tests where appropriate.

**Ethics**

The study protocol was reviewed and approved by the Human Research Ethics Committee (Medical) (Ethics Number M090015) at the University of the Witwatersrand. Written informed consent was obtained from the mothers, including on behalf of their children.

**RESULTS**

**Study Participants**

We enrolled 1376 (including 704 HIV-infected) and 1556 (608 HIV-infected) women in period 1 and period 2, respectively (Table 1), together with 1411 (713 HIV-infected) and 1649 (616 HIV-infected) of their children in the respective periods (Table 2). This included 35 and 93 women in period 1 and period 2, respectively, who had more than 1 child enrolled concurrently. None of the mother-child pairs were enrolled in both study periods.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Period 1 (PCV7 era), N = 1376</th>
<th>Period 2 (PCV13 era), N = 1556</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of HIV infected</td>
<td>704 (51.2)</td>
<td>608 (39.1)</td>
<td></td>
</tr>
<tr>
<td>Mean age, years±SD</td>
<td>30.4 ± 6.50</td>
<td>29.1 ± 6.6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Smoker, n/N (%)</td>
<td>80/1375 (5.8%)</td>
<td>92/1556 (5.9%)</td>
<td>.91</td>
</tr>
<tr>
<td>Takes snuff, n/N (%)</td>
<td>78/1372 (5.7%)</td>
<td>89/1553 (5.7%)</td>
<td>.98</td>
</tr>
<tr>
<td>Drinks alcohol, n/N (%)</td>
<td>240/1375 (17.4%)</td>
<td>418/1547 (27.0%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Suffers from a chronic illness, n/N (%)</td>
<td>115/1369 (8.4%)</td>
<td>124/1421 (8.0%)</td>
<td>.76</td>
</tr>
<tr>
<td>HIV infected and on ART, n/N (%)</td>
<td>299/697 (42.9%)</td>
<td>330/608 (54.3%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Currently on tuberculosis treatment, n/N (%)</td>
<td>20/1371 (1.5%)</td>
<td>16/1538 (1.0%)</td>
<td>.31</td>
</tr>
<tr>
<td>Treated for tuberculosis in past year, n/N (%)</td>
<td>80/1357 (5.9%)</td>
<td>83/1532 (5.4%)</td>
<td>.58</td>
</tr>
<tr>
<td>Currently on antibiotic treatment, n/N (%)</td>
<td>79/1368 (5.8%)</td>
<td>20/1540 (1.3%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hospitalized in the last 3 mo, n/N (%)</td>
<td>25/1369 (1.8%)</td>
<td>19/1527 (1.2%)</td>
<td>.21</td>
</tr>
</tbody>
</table>

Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus; PCV, pneumococcal conjugate vaccine.

a Number of individuals with the investigated outcome.
b Total number of individuals with available information on the characteristic.
Table 2. Demographic Characteristics of Children Enrolled in 2010 (period 1; PCV7 era) and 2012 (period 2; PCV13 era) in Soweto, South Africa

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Children</th>
<th>HIV Infected</th>
<th>HIV Uninfected</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Period 1 (PCV7 era)</td>
<td>Period 2 (PCV13 era)</td>
<td>Period 1 (PCV7 era)</td>
</tr>
<tr>
<td>All children enrolled; n, mean age in years ±SD</td>
<td>1411; 2.7 ± 1.98</td>
<td>1649; 2.3 ± 2.05</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>&lt;9 mo; n, mean age (SD) months</td>
<td>230; 4.8 ± 1.8</td>
<td>396; 4.8 ± 2.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>9–24 mo; n, mean age in years ±SD</td>
<td>408; 1.22 ± 0.4</td>
<td>539; 1.18 ± 0.34</td>
<td>.99</td>
</tr>
<tr>
<td>&gt;24–48 mo; n, mean age in years ±SD</td>
<td>449; 3.2 ± 0.55</td>
<td>348; 2.9 ± 0.54</td>
<td>.10</td>
</tr>
<tr>
<td>&gt;48–144 mo; n, mean age in years ±SD</td>
<td>324; 5.5 ± 1.43</td>
<td>366; 5.6 ± 1.15</td>
<td>.31</td>
</tr>
<tr>
<td>Currently breastfeeding, n/N (%)</td>
<td>319/1410 (22.6)</td>
<td>565/1645 (34.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Ever breastfeeding, n/N (%)</td>
<td>499/1060 (47.1)</td>
<td>628/1056 (59.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Attendance at daycare, n/N (%)</td>
<td>623/1410 (44.2)</td>
<td>560/1632 (34.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Currently on tuberculosis treatment/prophylaxis, n/N (%)</td>
<td>60/1396 (4.2)</td>
<td>67/1643 (4.1)</td>
<td>.76</td>
</tr>
<tr>
<td>Treated for tuberculosis in the past year, n/N (%)</td>
<td>116/1349 (8.6)</td>
<td>166/1608 (10.3)</td>
<td>.11</td>
</tr>
<tr>
<td>Currently taking antibiotics, n/N (%)</td>
<td>120/1396 (8.6)</td>
<td>90/1642 (5.7)</td>
<td>.001</td>
</tr>
<tr>
<td>Hospitalized in the last 3 mo, n/N (%)</td>
<td>63/1395 (4.5)</td>
<td>109/1634 (6.7)</td>
<td>.01</td>
</tr>
<tr>
<td>Pneumococcal vaccine receiptd</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least 1 dose</td>
<td>196/230 (85.2)</td>
<td>320/396 (80.8)</td>
<td>.31</td>
</tr>
<tr>
<td>At least 2 doses</td>
<td>172/230 (74.8)</td>
<td>306/396 (77.3)</td>
<td>.48</td>
</tr>
<tr>
<td>At least 3 doses</td>
<td>83/230 (35.7)</td>
<td>142/396 (35.8)</td>
<td>.76</td>
</tr>
<tr>
<td>&gt;24–48 mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least 1 dose</td>
<td>0/449</td>
<td>145/438 (41.7)</td>
<td>NAc</td>
</tr>
<tr>
<td>At least 2 doses</td>
<td>0/449</td>
<td>143/438 (41.1)</td>
<td>NA</td>
</tr>
<tr>
<td>At least 3 doses</td>
<td>8/449 (1.8)</td>
<td>135/438 (38.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>&gt;48–144 mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least 1 dose</td>
<td>0/224</td>
<td>9/366 (2.5)</td>
<td>NA</td>
</tr>
<tr>
<td>At least 2 doses</td>
<td>0/224</td>
<td>7/366 (1.9)</td>
<td>NA</td>
</tr>
<tr>
<td>At least 3 doses</td>
<td>15/224 (11.7)</td>
<td>6/366 (1.6)</td>
<td>.022</td>
</tr>
</tbody>
</table>

Abbreviations: HIV, human immunodeficiency virus; NA, not applicable; PCV, pneumococcal conjugate vaccine; SD, standard deviation.

a Number of individuals with investigated outcome.

b Total number of individuals with available information on the characteristic.

c Not done due to limited number of observations in 1 group.

d Only for individuals with available vaccination records at time of interview.
Generally, there was no difference in the prevalence of PCV13-serotype or nonvaccine-serotype colonization in HIV-infected individuals on antiretroviral therapy compared to those not on antiretroviral therapy among women or children in either study period (Supplementary Table 1). As such, no further stratifications were undertaken for antiretroviral therapy usage.

The proportion of mother-child pairs who were concurrently colonized on the day of sampling by any pneumococcus declined from 11.0% (155 of 1411 pairs) in period 1 to 6.8% (112 of 1649 pairs) in period 2 \( (P < .001; \) Figure 1 and Supplementary Table 2). This was evident among HIV-uninfected pairs (declined from 6.7% [47 of 698] in period 1 to 4.6% [47 of 1033] in period 2; \( P = .049); as well as among HIV-infected pairs (declined from 15.2% [108 of 713] to 10.6% [65 of 616]; \( P = .013). Similar significant decreases were observed when serotypes were grouped as PCV13 serotypes.

**Temporal Changes in Pneumococcal Colonization Prevalence in Children**

Overall among children, the prevalence of any pneumococcal serotype, PCV7 serotypes, 6 additional serotypes specifically in PCV13 (PCV13-additional serotypes), and any of the PCV13 serotypes were higher in period 1 compared to period 2 (Figure 2 and Supplementary Table 3). In contrast, the prevalence of nonvaccine-serotype colonization increased in period 2 (30.8% vs 42.7%; \( P < .0001). Reduction in the prevalence of PCV13-serotype colonization was evident in all age groups, while a concomitant increase in the prevalence of nonvaccine-serotype colonization was also observed in all age groups, albeit not significant in infants <9 months of age.

Among HIV-uninfected children, reductions in PCV7-serotype colonization from period 1 to period 2 was evident among all age groups except those >48 months of age. A similar trend in the lower prevalence of PCV13-additional serotypes colonization was observed in these age groups (Figure 2). On the other hand, the prevalence of nonvaccine-serotype colonization was greater in period 2 (44.0%) than in period 1 (29.5%; \( P < .0001). This was evident in children aged 9–24 months and >24–48 months, with a similar trend also observed among infants <9 months of age, whereas it remained unchanged among those >48 months of age.

Among HIV-infected children, the prevalence of overall pneumococcal colonization tended to being higher in period 1 compared to period 2 (68.2% vs 59.9%, respectively; \( P = .012), including for PCV7 serotypes (25.8% vs 12.0%; \( P < .0001) and any PCV13 serotype (38.3% vs 19.8%; \( P < .0001). Conversely,

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**Figure 1.** The proportion of mother-child pairs sampled in 2010 (period 1; PCV7 era) and 2012 (period 2; PCV13 era) from Soweto, South Africa, who were concurrently colonized by any pneumococcus, same serotype, PCV13 serotype, and non-PCV13 serotype. Abbreviations: HIV, human immunodeficiency virus; PCV, pneumococcal conjugate vaccine.
there was a higher prevalence of nonvaccine-serotype colonization in period 2 (40.6%) compared to period 1 (32.1%; \( P = .001 \)). The decline in prevalence of PCV13-serotype colonization was detected among all HIV-infected age groups >9 months old, while there was a limited number of evaluable children <9 months old (Supplementary Table 3). An increase in prevalence of nonvaccine-serotype colonization between period 1 to period 2 among HIV-infected children was only apparent in the age group >24–48 months (29.4% vs 48.4%; \( P = .0001 \)).

The prevalence of individual serotype colonization in period 1 and period 2 among all the children and when stratified by age group is reported in Figure 3 and Supplementary Table 4, respectively. Overall, declines in colonization were observed for serotypes 3 (3.3% to 0.8%; \( P = .03 \)), 6A (6.0% vs 1.9%; \( P < .001 \)), 6B (5.2% vs 1.7%; \( P < .001 \)), 14 (3.1% vs 0.9%; \( P < .001 \)), 19A (5.0% vs 2.7%; \( P = .001 \)), 19F (8.0% vs 4.5%; \( P < .001 \)), and 23F (6.2% vs 2.2%; \( P < .001 \)) (Figure 3A). Decline in prevalence of colonization by all these serotypes were evident in both HIV-infected and HIV-uninfected children, albeit not significant for serotype 3 in both groups and for 19A among the HIV-infected children (Figure 3B and 3C). Serotypes 1, 4, 5, 7F, 9V, and 18C were uncommon (≤2%) in both periods.

Overall, the most common nonvaccine serotypes in period 2 included 11A (3.5%, \( n = 58 \)), 15A (3.0%, \( n = 49 \)), 15B (4.2%, \( n = 69 \)), 16F (3.6%, \( n = 59 \)), 34 (2.6%, \( n = 43 \)), and 35B (2.1%, \( n = 34 \)) (Figure 3). The prevalence of colonization by each of the above serotypes increased between period 1 to period 2, except for 16F and 34. Among HIV-uninfected children, an increase in nonvaccine-serotype colonization was observed specifically for serotypes 11A (2.0% vs 3.9%; \( P = .04 \)), 15A (1.0% vs 3.4%; \( P = .002 \)), 15B (2.4% vs 3.8%; \( P < .0001 \)), and 34 (1.4% vs 3.0%; \( P = .04 \)). Although similar trends were evident in HIV-infected children, this was only significant for serotype 35B (0.3% to 2.3%; \( P = .01 \)).

**Temporal Changes in Pneumococcal Colonization Prevalence in Women**

Among women, there was a decline in overall pneumococcal colonization prevalence from period 1 (15.2%) to period 2 (11.3%; \( P = .0025 \)), including PCV7-serotype (3.8% vs 1.2%);
and PCV13-serotype colonization (7.1% vs 3.1%; \( P = .0014 \)) colonization (Figure 2 and Supplementary Table 3). The decline in PCV13-serotype colonization between period 1 and period 2 was significant among HIV-uninfected women, with a similar trend observed in HIV-infected women. Similar findings were observed when analyses were limited to the PCV-7 serotypes. The overall prevalence of pneumococcal colonization remained unchanged among HIV-uninfected women, with a nonsignificant increase in nonvaccine-serotype colonization in period 2 compared to period 1 (4.5% vs 7.7%; \( P = .05 \)). In contrast, there was a reduction in colonization by any serotype among HIV-infected women between period 1 (20.5%) and period 2 (13.8%; \( P = .001 \)), due to the lower PCV13-serotype colonization (Supplementary Table 3).

Among women, the most frequently colonizing vaccine serotypes in period 1 were 19F (1.3%, \( n = 18 \)), 23F (0.9%, \( n = 13 \)), 6A (0.8%, \( n = 11 \)), and 6B (0.5%, \( n = 7 \)), the prevalence of which declined to 0.4% (\( P = .006 \)), 0.2% (\( P = .005 \)), 0.3% (\( P = .04 \)), and 0.1% (\( P = .05 \)) in period 2, respectively (Figure 4A). Serotype 3 colonization was more prevalent in HIV-infected (2.0%)

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**Figure 3.** Prevalence of common serotypes in all children (A), HIV-uninfected children (B), and HIV-infected children (C) observed in 2010 (period 1; PCV7 era) and 2012 (period 2; PCV13 era) in Soweto, South Africa. At the top of the bars are the \( P \) values for those serotypes that were significant or had a clear downward or upward trend. Abbreviations: HIV, human immunodeficiency virus; PCV, pneumococcal conjugate vaccine.
than HIV-uninfected women (0.6%; \( P = .02 \)) in period 1, with a nonsignificant decrease observed between period 1 and period 2 in HIV-infected women (2.0% vs 1.2%; \( P = .23 \)) (Figure 4B and 4C).

**Figure 4.** Prevalence of common serotypes in all women (A), HIV-uninfected women (B), and HIV-infected women (C) observed in 2010 (period 1; PCV7 era) and 2012 (period 2; PCV13 era) in Soweto, South Africa. At the top of the bars are the \( P \) values for those serotypes that were significant or had a clear downward or upward trend. Abbreviations: HIV, human immunodeficiency virus; PCV, pneumococcal conjugate vaccine.

**Differences in Carriage Between HIV-infected and HIV-uninfected Groups**

The demographic characteristics differed significantly between HIV-infected and HIV-uninfected children in both study periods (Supplementary Table 5). After adjusting for these differences, no differences in carriage of overall pneumococcus and PCV13 serotypes were observed in either study period between HIV-uninfected and HIV-infected children (Figure 5 and Supplementary Table 6).

There were more HIV-infected women who had suffered a chronic illness, were currently on tuberculosis treatment, who had been treated for tuberculosis in the previous year, or were currently on antibiotics than the HIV-uninfected women in both study periods (Supplementary Table 7). HIV-infected women compared to HIV-uninfected individuals had higher prevalence of any serotype colonization in period 1 (20.5% vs 9.7%; \( P < .0001 \)) as well as PCV13-serotype colonization (4.8% vs 2.0% in period 2; \( P = .003 \)) (Supplementary Table 6).
DISCUSSION

The targeted immunization of young South African infants with 3 doses of PCV at 6, 4, and 40 weeks of life has been temporally associated with decline in vaccine-serotype colonization among HIV-infected and HIV-uninfected individuals, including among individuals such as HIV-infected women who were not targeted for immunization. This was observed during a period when the immunization program transitioned from use of PCV7 since April 2009 to PCV13 in May 2010, and in the absence of any substantive catch-up campaign of older children.

Similar to previous reports, HIV-infected adults in our study, even in the presence of infant PCV immunization, had a higher prevalence of overall and PCV13-serotype colonization than HIV-uninfected adults [5, 10, 12, 21, 22], implying that HIV-infected adults are still at increased risk of IPD. Recently, it has been shown that the indirect effects of childhood PCV immunization in South Africa on adult IPD were similar in HIV-infected and in HIV-uninfected adults; nonetheless, incidence of IPD remained 36-fold higher in HIV-infected adults in the PCV era [23]. Specifically, post-PCV introduction, HIV-infected adults aged 25–44 years had a higher incidence of overall, PCV7-serotype, 6A, PCV13-serotype, and nonvaccine serotype IPD compared to HIV-uninfected adults [23]. Despite the heightened IPD risk, currently there is no national recommendation to vaccinate HIV-infected adults with PCV, although the PCV has been shown to be 75% efficacious against vaccine-serotype IPD in HIV-infected adults for a limited period of time [24]. As such, the indirect effect realized from vaccinating infants in South Africa is likely to have contributed to the indirect effect of protection against vaccine-serotype IPD even in HIV-infected individuals [23]. This likely culminated through reduced community transmission of these vaccine serotypes from young children to older, unvaccinated individuals, including HIV infected.

In partially vaccinated HIV-infected children (ie, age group 0–9 months), no change was observed from period 1 to period 2 in vaccine-serotype or nonvaccine-serotype colonization. This may be attributable to the small numbers of children in this age group.
group or may suggest that 2 doses of PCV given at 6 and 14 weeks are inadequate to protect against vaccine-serotype colonization [25], especially among HIV-infected children at this early stages of the PCV immunization program. We expect a reduced risk of exposure to vaccine serotypes over time, which will likely result in reduction of vaccine-serotype colonization among this age group [26]. An indirect effect against vaccine-serotype colonization has also been reported among young children not yet eligible for PCV vaccination in The Gambia, following vaccination of individuals across all age groups in selected villages [27]. The decrease in PCV7 serotypes, but not in the PCV13-additional serotypes in HIV-uninfected children <9 months of age is encouraging evidence that younger children are also benefiting from indirect protection as the immunization program continues. This is also corroborated by decreases in PCV7-serotype IPD of 78% among children younger than 10 weeks of age in South Africa [23].

The reduction in vaccine-serotype colonization from period 1 to period 2 in fully vaccinated children was, however, partially offset by the increase in nonvaccine-serotype colonization that resulted in the overall pneumococcal colonization remaining unchanged among this group. On the other hand, nonvaccine-serotype colonization among HIV-infected women did not differ significantly between the 2 study periods, which was also corroborated by no increase in nonvaccine-serotype IPD among HIV-infected adults since the introduction of PCV into the South African immunization program [23]. Among children >48 months of age, the overall prevalence of pneumococcal colonization remained unchanged in HIV-uninfected children in period 2 compared to period 1, although a decline in vaccine-serotype colonization was detected among HIV-infected children. Similarly, in a rural South African community with high HIV prevalence, there was no change in colonization among children aged >3 to 12 years, 2 years post-PCV7 introduction [25]. Although unlikely, the decrease in vaccine-serotype colonization in older HIV-infected children might have been due to the catch-up immunization campaign targeted at this age group at the time of PCV13 introduction. In The Gambia, decreases in colonization among older children were observed in villages that had additional catch-up vaccination 12 months after catch-up was initiated [28]. The high colonization prevalence among older children in settings such as ours and other low-middle-income countries suggest that catch-up campaigns aimed at older children could possibly accelerate and improve the indirect effects of PCV immunization compared to only targeting young infants for immunization [29]. Nevertheless, even with no initial catch-up campaign in our setting, an indirect effect was detected within 3 years of PCV introduction into our public immunization program, indicating young children likely to have been the most important source of transmission of these vaccine serotypes prior to the PCV immunization program. The reduction in vaccine-serotype colonization among HIV-infected children in the era of PCV immunization is in contrast to our earlier randomized, controlled trial of an investigational 9-valent PCV, in which no difference was observed in prevalence of vaccine-serotype colonization between PCV-vaccinated and –unvaccinated HIV-infected children at 5 years postvaccination [13]. This earlier study only measured direct protection at the individual level, whereas the current study is evaluating the community-wide effect of the infant PCV immunization program, and measures the composite of the direct and indirect effects among vaccinated and indirect effect among unvaccinated age groups.

Our study was not powered to detect changes in individual serotypes, especially when stratifying by HIV status or age groups; nevertheless, decreases in individual vaccine serotypes were observed among fully vaccinated children for serotypes 6A, 6B, 19F, and 23F. Furthermore, largely due to the success of the prevention of mother-to-child transmission program in South Africa, we were unable to recruit similar numbers of young HIV-infected and HIV-uninfected children; however, statistical power was achieved to demonstrate changes in older age groups. Another limitation of our study is that it is cross-sectional, and we cannot exclude the fact that the observed changes can be purely temporally driven.

In conclusion, our study suggests that PCV immunization of infants, vaccinated at 6, 10, and 40 weeks of age, was associated with a reduction in vaccine-serotype colonization among HIV-infected and HIV-uninfected individuals, including among age groups not targeted for vaccination. Although HIV-infected women are disproportionately affected by disease caused by predominantly "pediatric serotypes" included in PCV13, whom the burden remains 40-fold greater than the general adult population, even in the presence of antiretroviral therapy [30], the indirect effect against PCV13-serotype colonization in HIV-infected women is likely to reduce the burden of vaccine-serotype IPD in this group.

### Supplementary Data

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

### Notes

**Financial support.** This work was supported in part by the South African Research Chairs Initiative of the Department of Science and Technology (DST) and National Research Foundation (NRF) in Vaccine Preventable Diseases, and the Medical Research Council (MRC): Respiratory and Meningeal Pathogens Research Unit. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. Any opinion, findings, and conclusions or recommendations expressed in this material are those of the author(s) and therefore the NRF, DST, and MRC do not accept any liability with regard thereto. No funding...
bodies had any role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

**Potential conflicts of interest.** S. A. M. received research funding and honoraria from Pfizer and GlaxoSmithKline. A. V. G. received research funding from Pfizer. All other authors report no potential conflicts.

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

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