Imputing IPD Changes Using Colonization Data

Imputing Direct and Indirect Vaccine Effectiveness of Childhood Pneumococcal Conjugate Vaccine Against Invasive Pneumococcal Disease by Surveying Temporal Changes in Nasopharyngeal Pneumococcal Colonization

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The limited capabilities in most low- to middle-income countries to study the benefit of pneumococcal conjugate vaccine (PCV) in protecting against invasive
pneumococcal disease (IPD) calls for alternate strategies to assess this. We used a mathematical model, to predict the direct and indirect effectiveness of PCV by analyzing serotype-specific colonization prevalence and IPD incidence prior to and following childhood PCV immunization in South Africa. We analyzed IPD incidence from 2005–2012 and colonization studies undertaken in HIV-human immunodeficiency virus (HIV)-uninfected and HIV-infected child-mother dyads from 2007–2009 (pre-PCV era), in 2010 (7-valent PCV era), and in 2012 (13-valent PCV era). We compared the model-predicted changes in IPD incidence with observed changes in IPD incidence, stratified by according to HIV-status, in children ≥3 months to ≤5 years and also in women aged ≥18–45 years. We observed reductions in vaccine-serotype colonization and IPD due to vaccine serotypes among children and women after PCV introduction. Using the changes in vaccine-serotype colonization data, the model-predicted changes in vaccine-serotype IPD incidence rates were similar to the observed changes in PCV-unvaccinated children and adults, but not among children <24 months. Surveillance of colonization prior to and following PCV use can be used to impute the indirect associations protection afforded by PCV in unvaccinated age groups, including those in high-HIV-prevalence settings.

HIV; invasive pneumococcal disease; mathematical model; pneumococcal carriage; pneumococcal conjugate vaccine

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; IPD, invasive pneumococcal disease; OR, odds ratio; PCV, pneumococcal conjugate vaccine; PCV7,
serotypes included in the 7-valent pneumococcal conjugate vaccine; PCV13, serotypes included in the 13-valent pneumococcal conjugate vaccine.

Nasopharyngeal colonization by *Streptococcus pneumoniae* precedes pneumococcal disease, hence, serotypes identified in invasive pneumococcal disease (IPD) are mostly identical to those in the nasopharynx at the time of illness (1–3). Children vaccinated with pneumococcal polysaccharide-protein conjugate vaccine (PCV) have an approximately 50% reduced risk of acquisition of vaccine-serotype nasopharyngeal colonization compared to unvaccinated children (4). Since young children are the main source of transmission of the pneumococcus (1), targeted PCV-immunization of children has interrupted transmission of vaccine-serotypes within communities (5). Consequently, a reduction in the prevalence of vaccine-serotype nasopharyngeal colonization has also been described among PCV-unvaccinated individuals at the household and community levels (5–10).

Concurrently, a decline in the incidence of vaccine-serotype IPD among PCV-vaccinated and -unvaccinated individuals has been observed, along with reductions in colonization (11–13). In the USA, the indirect effect of childhood PCV-immunization has resulted in the prevention of 2- to 10-fold greater numbers of IPD cases prevented among PCV-unvaccinated adults than among the childhood age-groups targeted for vaccination (11, 14). There is a paucity of data from low- to middle-income countries, mainly due to the lack of robust IPD surveillance systems to assess the effectiveness of childhood PCV-immunization in protecting against IPD among PCV-unvaccinated age-groups (15, 16). Such information could help improve the public health benefit and cost-effectiveness of
childhood PCV immunization. Weinberger et al. (17) proposed that ecological studies on nasopharyngeal vaccine-serotype and non-vaccine-serotype colonization prior to and following the introduction of childhood PCV-immunization introduction may be useful to impute for imputing the direct and indirect effectiveness of vaccination against IPD, which was validated in high-income and low-HIV-prevalence settings (17). Human immunodeficiency virus (HIV)-prevalence settings.

Our aim in this study was to analyze the direct and indirect effects of infant PCV-immunization on nasopharyngeal colonization and IPD among HIV-infected and HIV-uninfected children and women in Soweto, Johannesburg, South Africa. Furthermore, we evaluated the fit of the model proposed by Weinberger et al. to determine whether temporal changes in vaccine-serotype colonization relative to childhood PCV-immunization were predictive of the direct and indirect effects of PCV against IPD (17). To determine whether temporal changes in vaccine-serotype colonization relative to childhood PCV immunization were predictive of the direct and indirect effects of PCV against IPD.

METHODS

Study population

A series of pneumococcal colonization studies were undertaken among mother-child pairs in Soweto (Johannesburg, Gauteng Province, South Africa), a township with a population of 1.8 million, of whom 160,000 are under five years of age (Mrs Andy Valashiya, Department of Health, Gauteng Sub-district population midyear estimates for 2005–2012). We enrolled HIV-infected and HIV-uninfected children aged >3 months to 5 years and their mothers aged >18–45 years.
We specifically targeted enrolling mothers of the children, since in our setting women have greater contact with children than men, which may contribute to their having a higher incidence of IPD (particularly IPD due to 7-valent PCV (PCV7) serotypes) than men (18). The prevalence of HIV among pregnant women (29%–30%) and those aged 15–49 years of age (20%) has remained stable in the community since 2005 (19). However, the rate of mother-to-child HIV transmission rate of HIV had, however, declined from 8% in 2008 to 1.5% by 2012 (20).

During the study period, >more than 90% of the Sowetan population sought medical care at Chris Hani Baragwanath Academic Hospital. Although numbers of community deaths are not known, the presence of a good transport network and the provision of free healthcare mean that there are few deaths in the community (Shabir A. Madhi, University of the Witwatersrand, unpublished data, 2014). The effectiveness of infant PCV immunization against IPD in this community was included in a recent national analysis on IPD trends in South Africa in relation to PCV introduction into the national immunization program (21). This study provides information on temporal changes in the incidence of IPD in children and women from Soweto.

Details of PCV introduction into the South African immunization program have been previously described (22) and are included in the Web Appendix (available at http://aje.oxfordjournals.org/https://academic.oup.com/aje). Briefly, PCV is given at ages 6 and 14 weeks in South Africa, with a booster dose at age 9 months in South Africa.
Pneumococcal colonization studies in Soweto (2007–2012)

Prior to introduction of PCV7, we undertook a longitudinal cohort study to investigate the dynamics of pneumococcal transmission in HIV-uninfected mother-child pairs between January 2007 and April 2009 (pre-PCV era) (23). Briefly, the study showed an association of vaccine serotype acquisition between young children and their mothers (24), with children transmitting PCV7-serotypes more often to their mothers more often than vice-versa (23).

Subsequently, two cross-sectional colonization prevalence surveys carried out in mother-child pairs with concordant HIV-status were undertaken in the same population in 2010 (PCV7-era) and 2012 (PCV13-era), as described elsewhere (22). We demonstrated a reduction of PCV7-serotype colonization regardless of HIV-status in mothers and their children, with a concomitant increase in non-vaccine-serotype colonization in children but not in the mothers between 2010 and 2012 (22). We transformed longitudinal data into cross-sectional data by randomly selecting a single visit for each mother-child pair that participated in the longitudinal study.

In the colonization studies, nasopharyngeal swabs were collected in children and nasopharyngeal and oropharyngeal swabs were collected from the mothers. The methods of laboratory processing and serotyping have been previously described (7) and; details are included in the Web Appendix.

Invasive pneumococcal disease (IPD) surveillance (2005–2012)

Nationwide laboratory-based surveillance for IPD, including at Chris Hani Baragwanath Academic Hospital, has been previously described (21) and is detailed. Details are provided in the Web Appendix.
Statistical analysis

PCV7- serotypes were defined as any of the following: 4, 6B, 9V, 14, 18C, 19F, and 23F. The additional serotypes included in PCV13 (i.e., serotypes 1, 3, 5, 6A, 7F, and 19A) were categorized as PCV13 additional serotypes. Additionally, we analyzed serotype 6A separately to investigate cross-protection from serotype 6B. All non-PCV13 serotypes were categorized as non-vaccine serotypes. Non-viable isolates were prorated based on identified serotypes, based on their similarity of distribution when analyzed by PCR.

Incidence of IPD for among children aged 3 months to 2 years and 2–5 years old, and adults aged 18–45 years of age were calculated by dividing the annual number of IPD cases identified by mid-year population estimates for Soweto (Mrs Andy Valashiya, Department of Health, Gauteng Sub-district population midyear estimates for 2005–2012). The average IPD incidence between 2005 and 2008 represented the pre-PCV-era incidence and was compared with that observed in 2010 and 2012; the percentage change and absolute differences were calculated. The 95% confidence interval (95% CI), constructed using a Poisson distribution and test-based methods (26), was used to evaluate the significance of the observed changes in IPD. The $\chi^2$ test was used to assess differences in proportions. Since HIV prevalence among IPD cases in years prior to 2008 may have been underestimated because of a lower proportion of cases having been tested for HIV (70% in 2005 vs. >88% in 2012), we used a previously developed method to account for this potential bias (21).

Colonization prevalence was compared in the different study-periods stratified by HIV-status (22). Colonization prevalence pre-before and during the PCV-eras (for adults,
limited to women only) were used to estimate the colonization prevalence ratio (i.e., carriage post-vaccine divided by carriage pre-vaccine; see Web Appendix) through the use of a weighted regression model proposed by Weinberg et al. (17). The estimated prevalence ratio was then used to calculate the expected IPD incidence post-PCV introduction. We predicted IPD incidence for all serotypes, PCV7- serotypes, PCV13- additional serotypes, and non-vaccine serotypes based on the changes in observed prevalence of pneumococcal colonization for these serotype groups between the pre-PCV era and 2010 and 2012. This was undertaken for HIV-uninfected children aged ≥3 months to <2 years and for HIV-infected and HIV-uninfected women aged 18–45 years age. For HIV-infected children aged ≥3 months to <2 years old and for children ≥aged 2–5 years of age, regardless of HIV status, in whom pre-PCV colonization data were unavailable, the predicted incidence of IPD using colonization prevalence in 2010 (PCV7- era) was compared to with observed incidence in 2012 (PCV13- era). Pro-rating of non-viable serotypes was not possible to implement in the model; therefore, we only predicted disease changes due to viable serotypes, and we compared these to with observed IPD changes that were due to viable serotypes only.

Ethics

The Human Research Ethics Committee at the University of the Witwatersrand approved all components of this study (Ethics Numbers: HREC 050705, M060359 and M090015). Informed written consent was obtained from participants in the colonization studies.
RESULTS

Temporal changes in pneumococcal colonization among children

Compared to the pre-PCV era, there was a reduction in the prevalence of both PCV7-serotype colonization and PCV13-additional-serotype colonization among HIV-uninfected children aged ≥3 months to 2 years in 2012 (Figure 1A and Web Table 1). Among these children, colonization prevalence between the pre-PCV era and 2012 decreased for all serotypes from 66.4% to 56.6% (odds ratio (OR) = 0.66, 95% confidence interval (CI): 0.44, 0.98) for all serotypes, from 30.4% to 9.6% (OR = 0.24, 95% CI: 0.16, 0.38) and PCV13-additional for PCV7 serotypes, and from 10.4% to 4.2% (OR = 0.38, 95% CI: 0.19, 0.73) for PCV13-additional serotypes. Notably, a trend towards a decline in PCV7-serotype colonization in this age-group, particularly HIV-uninfected children, was already evident within one year of PCV7 introduction (OR = 0.72, 95% CI: 0.46, 1.12).

In contrast, colonization prevalence due to PCV13-additional serotypes between the pre-PCV era and 2010 was similar (10.4% vs. 13.5%; OR = 1.34, 95% CI: 0.71, 2.54), decreasing to 4.2% one year post PCV13 introduction. Compared to the pre-PCV era, the prevalence of non-vaccine-serotype colonization increased from 25.6% to 42.9% by 2012 (OR = 2.18, 95% CI: 1.42, 3.34) (Figure 1A and Web Table 1).

Pneumococcal colonization in women

Overall, the prevalence of pneumococcal colonization in women was 19.9% in the pre-PCV era, which decreased to 15.2% (OR = 0.72, 95% CI: 0.51, 1.01) by 2010 and then to 11.3% (OR = 0.51, 95% CI: 0.36, 0.73) by 2012, respectively.
When stratifying results by HIV-infection status, overall pneumococcal prevalence declined from 22.4% in the pre-PCV area compared to 9.7% in 2010 and 9.7% in 2012 (OR = 0.37, 95% CI: 0.23, 0.60) among HIV-uninfected women. Among HIV-infected women, prevalence remained unchanged between the pre-PCV era and 2010 (17.5% vs. 20.5%; OR = 1.22, 95% CI: 0.74, 1.99) and 2012 (17.5% vs. 13.9%; OR = 0.76, 95% CI: 0.45, 1.27). See Figures 1B and 1C, and Web Table 1).

PCV7-serotype colonization remained unchanged between the pre-PCV era and 2010 (4.0% vs. 3.9%) but declined to 0.7% in 2012 (OR = 0.18, 95% CI: 0.06, 0.57) among HIV-uninfected women, whilst it decreased from 10.3% in the pre-PCV era to 5.3% in 2010 (OR = 0.48, 95% CI: 0.25, 0.94) and 2.5% in 2012 (OR = 0.22, 95% CI: 0.10, 0.47). There was a trend towards reduced colonization with PCV13-additional serotypes, from 3.2% in the pre-PCV era to 1.5% in 2010 (OR = 0.46, 95% CI: 0.14, 1.48) and 1.3% in 2012 (OR = 0.39, 95% CI: 0.12, 1.22), in HIV-uninfected women, but colonization remained unchanged in HIV-infected women (range, 2.3%–3.3%). There was a decline in non-vaccine-serotype colonization among HIV-uninfected women between the pre-PCV era (15.2%) and 2012 (7.7%; OR = 0.47, 95% CI: 0.27, 0.80) and a non-significant increase in colonization with non-vaccine serotypes among HIV-infected women (4.8% in the pre-PCV era vs. 9.0% in 2012; OR = 1.99, 95% CI: 0.84, 4.73) (Web Table 1). (Web Table 1).

**Changes in invasive pneumococcal disease (IPD) incidence**

**Invasive pneumococcal disease (IPD) in children**

Overall trends in IPD incidence for children aged ≥3 months to <2 years and ≥2–5 years are reported in the Web Appendix and Web Table 2.
Among HIV-uninfected children aged 3 months to 2 years old, the annual incidence (per 100,000 children of that age) of PCV7-serotype IPD had decreased by 84.9% by 2010 (from 68.6 in the pre-PCV era to 10.3; \( P < 0.001 \)) and by 96.4% in 2012 (from 68.6 in the pre-PCV era to 2.5; \( P < 0.001 \)) (Figure 2A and Web Table 2). Similarly, among HIV-uninfected children aged 2–5 years old, the incidence of PCV7-serotype IPD had declined by 83.3% in 2010 (from 8.6 in the pre-PCV era to 1.4; \( P = 0.016 \)), whilst no PCV7-serotype IPD cases were recorded in 2012 (100% reduction; \( P < 0.001 \)) (Figure 2C and Web Table 2). The incidence of IPD attributable to PCV13-additional and non-vaccine serotypes remained unchanged for both childhood age groups between the pre-PCV era until 2012.

Among HIV-infected children aged 3 months to 2 years old, the incidence of PCV7-serotype IPD had declined by 62.4% in 2010 (from 1,341 in the pre-PCV7 era to 504.7; \( P = 0.001 \)) and by 86.1% in 2012 (from 1,341 in the pre-PCV7 era to 184.4; \( P < 0.001 \)) (Figure 2B and Web Table 2). Furthermore, the incidence (per 100,000) of IPD attributable to PCV13-additional serotypes declined from 268.2 in the pre-PCV era to 63.1 in 2010 \( (P = 0.055) \), whilst no cases were observed in 2012 (100% reduction; \( P = 0.009 \)). The incidence of non-vaccine-serotype IPD remained unchanged among the HIV-infected children aged 3 months to 2 years age group of HIV-infected between the pre-PCV era and 2012. Among older (ages 2–5 years) HIV-infected children, PCV7-serotype IPD incidence (per 100,000 children of that age) declined from 389.0 in the pre-PCV era to 244.7 in 2010 (a 37.1% reduction; \( P = 0.124 \)) and 38.9 in 2012 (a 90% reduction; \( P = 0.061 \)), albeit this change was not statistically significant (Figure 2D and Web Table 2). Similar to the case with HIV-uninfected children, the incidence of PCV13-additional serotypes and non-vaccine-serotype IPD was unchanged between the pre-PCV era until 2012.
Invasive pneumococcal disease (IPD) in women of childbearing age

Among HIV-uninfected women of childbearing age (ages 18–45 years), the annual incidence (per 100,000 persons of that age) of IPD attributable to all serotypes, PCV7-.serotypes, PCV13-additional serotypes and non-vaccine serotypes were 114, 43, 48, and 21, respectively, in the pre-PCV era (Figure 2E, Web Appendix and Web Table 3). The incidence of PCV7-serotype IPD subsequently declined by 63.9% in 2010 ($P = 0.016$), whilst no PCV7 cases were observed in 2012 (a 100% reduction; $P < 0.001$). Similar declines (84.0%) were observed in the incidence of PCV13-additional IPD ($P = 0.001$), whilst incidence of non-vaccine-serotype IPD remained the same between the pre-PCV era and 2012 (1.1 vs. 0.4; $P = 0.076$).

The incidence of IPD attributable to all serotypes, PCV7-serotypes, PCV13-additional serotypes and non-vaccine serotypes in HIV-infected women were 1,216, 388, 428, and 332, respectively, in the pre-PCV era (Figure 2F and Web Table 3). The incidence of PCV7-serotype IPD had declined by 42.1% ($P < 0.001$) by 2010 and by 83.1% in 2012 ($P < 0.001$). Similarly, there was a 26.7% reduction in PCV13-additional-serotype IPD between the pre-PCV era and 2010 (109.2 vs. 80.0 per 100,000 women aged 18–45 years vs. comparison with the pre-PCV era; $P < 0.001$) (Figure 2F and Web Table 3). A more modest decline in incidence (per 100,000) of non-vaccine-serotype IPD, from 84.7 in the pre-PCV era to 59.9 in 2012 (29.2%; $P = 0.005$), was detected.

Serotype The incidence of serotype 6A IPD was unchanged for both HIV-infected and HIV-uninfected individuals during the study period.
Evaluation of a model using temporal nasopharyngeal colonization data to predict IPD incidence

Model results in children

Among HIV-uninfected children aged 3 months to 2 years old, the model underestimated the decline in all-serotype IPD (viable serotypes only) between the pre-PCV7 era and 2012 (91.7% observed vs. 53.5% predicted; Web Figure 1A), and similarly for both PCV7-serotype IPD (98.7% observed vs. 72.1% predicted; Web Figure 1C) and PCV13-additional-serotype IPD (91.9% observed vs. 62.2% predicted; Web Figure 1E), albeit with overlapping 95% CI confidence intervals for the latter (Table 1). Similar results were obtained for all-PCV13-serotype IPD (Web Figure 2A). For the viable non-vaccine-serotype IPD, the observed reduction was 64.0%, whereas the model predicted a significant 44.9% increase (Web Figure 2C and Table 2). Similar trends were observed when comparing the pre-PCV era to 2010.

In older HIV-uninfected children (ages 2–5 years), who were unvaccinated with PCV at the 2010 nasopharyngeal sampling time point (PCV having been introduced into the EPIWorld Health Organization’s Expanded Program on Immunization in 2009, with no catch-up campaign), the model underestimated the observed decline in PCV7-serotype IPD (100% observed vs. 36.8% predicted; Web Figure 1C). The wide confidence interval for PCV13-additional and non-vaccine serotypes did not permit further comparison of the observed and predicted changes in this age-group (Web Figures 1E and 2C, Table 2).
Model results in women

Among HIV-uninfected women, comparing the pre-PCV era with 2012, the observed reduction in all-serotype IPD (93.1%) was higher than the model-predicted estimate (79.8%) (Web Figure 1B and Table 1). Observed reductions were also higher for PCV7-serotype IPD (100% vs. 88.8%; Web Figure 1D) and PCV13-additional serotypes (96.4% vs. 69.9%; Web Figure 1F) compared to the model estimates. Similar results were obtained for all combined PCV13-serotype IPD (Web Figure 2B). However, observed and model estimates were similar for non-vaccine-serotype IPD reductions (79.0% vs. 78.8%; Web Figure 2D).

Similarly, among HIV-infected women, when comparing the pre-PCV era with 2012, the model-predicted reduction estimates slightly underestimated the observed estimates in IPD for all-serotypes (86.2% observed vs. 73.0% predicted; Figure 2B) and PCV7-serotype (serotypes (94.5% observed vs. 80.0%; Web Figure 1D), but the model-predicted estimates were similar to observed reductions in IPD attributable to non-vaccine-serotypes (72.5% observed vs. predicted; Web Figure 2D). The model-predicted estimate of the reduction in IPD attributable to PCV13-additional serotypes from 2010 to 2012 was lower compared to the observed reduction (67.9% observed vs. predicted 31.4%; Table 1, Web Figure 1F). Overall, the differences between model predictions and observed changes were small for children ≥2 years and adults, but very large for children below 2 years of age.
DISCUSSION

Our study suggests that the introduction of PCV into the South African immunization program resulted in a reduction in the incidence of vaccine-serotype IPD among HIV-infected and HIV-uninfected children less than 5 years of age and adults aged 18–45 years, which was also reflected by changes in pneumococcal nasopharyngeal colonization (22). In our setting, which has a high prevalence of HIV that is associated with an 8.2-fold increased risk of IPD among adults (27), we demonstrated that measuring temporal trends in nasopharyngeal colonization in relation to introduction of PCV into the public immunization program could be used as a proxy to determine the likely association of PCV against IPD among HIV-infected and HIV-uninfected women. This was evident from the magnitude of a model-predicted reduction in vaccine-serotype IPD being similar to the observed reductions in adults, as well as child age-groups too old to have been vaccinated. However, among the child age-group targeted for vaccination, especially if children were HIV-uninfected, using changes in the prevalence of nasopharyngeal pneumococcal colonization to estimate the contribution of PCV to decreases in vaccine-serotype IPD underestimated its effectiveness. This was most likely due to the model’s not accounting for the direct efficacy of PCV in preventing vaccine-serotype IPD in this age-group, which is mediated through humoral induced immunity that is more efficacious in preventing vaccine-serotype IPD than nasopharyngeal colonization (28).

The observed and model-predicted reductions in IPD were similar in PCV-unvaccinated females aged 18–45 years of age when comparing the pre-PCV era with the PCV7 and PCV13 eras. This was evident among HIV-uninfected and HIV-infected women, the latter of whom had a higher prevalence of pneumococcal (including vaccine-serotype) colonization
(18, 29–32) and IPD incidence in the pre-PCV era (21). Because the model estimates were similar to observed reductions in IPD incidence, this suggests that the decrease in IPD post-vaccine was a result of decreases in the prevalence of colonization with vaccine-serotypes, likely through an interruption of transmission of these serotypes by vaccinating young children (12).

The direct and indirect associations of PCV with IPD incidence observed in our setting are similar to those initially observed in the USA, in which childhood PCV7 immunization reduced the incidence of vaccine-serotype IPD among the vaccinated children as well as older PCV-unvaccinated age groups, such as the high-risk elderly (11, 12, 33). In our population, the decrease in IPD among persons aged 19–45 years old represents a potential significant public health benefit of infant PCV immunization, as this adult age-group has the highest prevalence of HIV in South Africa (20). Similar to elsewhere, the reductions in vaccine-serotype IPD among the HIV-uninfected adults in South Africa (21) is most likely attributable to the indirect associations of infant PCV immunization reducing transmission of the vaccine-serotypes to this population. It is, however, also possible that coincidental secular reductions in transmission of the vaccine serotypes may have contributed to this decline. Among HIV-infected individuals, in addition to the indirect associations of PCV, the increased availability of ART antiretroviral therapy could also have contributed to the observed reduction in IPD incidence, which may explain the tendency for the observed reduction in IPD to generally be higher than the model-predicted estimates, as well as the reduction in colonization and IPD due to non-vaccine serotypes (21).
In children, we observed substantial replacement in nasopharyngeal colonization by non-vaccine pneumococcal serotypes, although there was a non-significant increase in non-vaccine-serotype IPD. In the UK, despite an increase in non-vaccine-serotype colonization post-PCV, there was a net reduction in IPD incidence, and this was attributed to lower invasiveness of these serotypes (34). In the USA, the incidence of IPD due to non-vaccine serotypes, particularly serotype 19A, increased by 58% among children aged less than 2 years and by 135% in children aged 2–4 years in the post-PCV7 period compared to the pre-period before PCV7 introduction period (35). This was manifest as early as three years post-after PCV7 introduction (35, 36). Similarly, in the UK, the incidence of serotype 19A IPD increased significantly following PCV7 vaccination of infants (34). However, increases in IPD attributable to serotype 19A have also been described in unvaccinated communities (37). In our population, transitioning from PCV7 to PCV13 (which includes serotype 19A as part of its formulation) within a short period of time may have prevented additional 19A invasive disease.

Limitations of our study include the absence of carriage data for HIV-infected children prior to the introduction of PCV in the national immunization program, so some analyses were limited to HIV-uninfected children. However, the HIV transmission rate in South Africa is now under 3% (20), and it will continue to fall with improvements in HIV care and treatment, further reducing the role of HIV in the IPD burden of IPD imposed on children. We did not analyze the changes in IPD due to PCV on HIV-exposed uninfected children, who may still remain at high risk of IPD (38). Furthermore, our study did not have the statistical power to detect significant IPD changes in IPD by individual vaccine serotypes.
An inherent limitation of the model that we evaluated is that some of the additional serotypes included in PCV13, especially serotypes 1 and 5, account for up to one-fifth of IPD cases in African children and are rarely identified as colonizing serotypes in otherwise healthy individuals (39, 40). It is possible that the observed and model-predicted changes in IPD might differ more should there be an outbreak of disease from these serotypes, which are known to temporally fluctuate more than many of the other serotypes included in PCV13 and to cause epidemics of varying proportions (41).

Our data show that changes in colonization in unvaccinated individuals following vaccine introduction can approximate IPD changes in the same population and can potentially be used in resource-limited settings to predict post-PCV-introduction changes in IPD, including those in HIV-infected populations.

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**Figure 1.** Comparison of pneumococcal prevalence of *Streptococcus pneumoniae* carriage prevalence in children and women of childbearing-age (18–45 years) in Soweto, South Africa in three, during 3 time periods (January 2007–April 2009, May 2010–February 2011, and May 2012–April 2013) pertaining to the introduction of pneumococcal conjugate vaccine (PCV) in South Africa. Comparisons are for all pneumococcus, the serotypes included in the 7-valent pneumococcal conjugate vaccine (PCV7), the additional (add) 6 serotypes included in the 13-valent pneumococcal conjugate vaccine (PCV13), and non-PCV13 serotypes (NVT13) between the pre-PCV (periods 1) (January 2007–April 2009) and (i) May 2010–February 2011 (‘2010”) and (ii) May 2012–April 2013 (“2012–Age
Figure 2. Incidence of invasive pneumococcal disease incidence in *Streptococcus pneumoniae* among children and adult women of childbearing-age (18–45 years) in Soweto, South Africa, before and after the introduction of pneumococcal conjugate vaccine (PCV), 2005–2012. Age categories are: (A) Human immunodeficiency virus (HIV)-uninfected children ≥3 months to ≤2 years; (B) HIV-uninfected women aged 18–45 years; and (C) HIV-infected women aged 18–45 years. Bars, 95% confidence intervals. NVT, nonvaccine type.
### Table 1. Observed and Model-Predicted Changes in Overall Incidence of Invasive Pneumococcal Disease (*Streptococcus pneumoniae*) and Disease Due to Vaccine PCV7 and Additional PCV13 Serotypes After the Introduction of Pneumococcal Conjugate Vaccine, Soweto, South Africa, 2005–2012

<table>
<thead>
<tr>
<th>HIV Status, Age, and Time Period</th>
<th>All Pneumococcal Disease</th>
<th>PCV7-Serotype Disease</th>
<th>Additional PCV-13 Serotype Disease</th>
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<tr>
<td></td>
<td>Observed IPD</td>
<td>Predicted IPD</td>
<td>Observed IPD</td>
</tr>
<tr>
<td></td>
<td>% Change</td>
<td>95% CI</td>
<td>% Change</td>
</tr>
<tr>
<td>HIV-negative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 months to 2 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-PCV era vs. 2010</td>
<td>−87.9</td>
<td>−93.6, −78.8</td>
<td>−20.2</td>
</tr>
<tr>
<td>Pre-PCV era vs. 2012</td>
<td>−91.7</td>
<td>−96.1, −84.2</td>
<td>−53.5</td>
</tr>
<tr>
<td>2010 vs. 2012</td>
<td>−26.2</td>
<td>−44.6, −2.27</td>
<td>−12.9</td>
</tr>
<tr>
<td>2 years to 5 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2010 vs. 2012</td>
<td>−0.71</td>
<td>−81.5, 133.1</td>
<td>3.39</td>
</tr>
<tr>
<td>HIV-positive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;3 months to 2 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2010 vs. 2012</td>
<td>−9.11</td>
<td>−64.8, 129.5</td>
<td>−11.4</td>
</tr>
<tr>
<td>2 years to 5 years</td>
<td>−60.1</td>
<td>−89.1, 24.4</td>
<td>−28.3</td>
</tr>
</tbody>
</table>

*Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; IPD, invasive pneumococcal disease.*

*Children (Ages 0–5 Years) — Mothers (Ages 18–45 Years)*
n/a—the there were no; N/A, not applicable; PCV, pneumococcal conjugate vaccine; PCV7, serotypes detected in HIV-uninfected women during 2012 included in the 7-valent pneumococcal conjugate vaccine; PCV13, serotypes included in the 13-valent pneumococcal conjugate vaccine.

a PCV7-serotypes, included serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F.

b PCV13-additional serotypes, included serotypes 1, 3, 5, 6A, 7F, and 19A.

c Pre-PCV era was 2005–2008.

d No such serotypes were detected in 2012, and hence no comparison was made with 2010.
Table 2. Observed and Model-Predicted Changes in the Incidence of Invasive Pneumococcal Disease and Disease Due to Vaccine PCV13 and Non-PCV13 Serotypes After the Introduction of Pneumococcal Conjugate Vaccine, Soweto, South Africa, 2005–2012

<table>
<thead>
<tr>
<th>HIV Status, Age, and Time Period</th>
<th>Non-Vaccine PCV13 Serotype Disease</th>
<th>PCV-13 Serotype Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observed IPD</td>
<td>Predicted IPD</td>
</tr>
<tr>
<td></td>
<td>% Change</td>
<td>95% CI</td>
</tr>
<tr>
<td><strong>Children</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-negative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 months to 2 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-PCV era vs. 2010</td>
<td>-78.4</td>
<td>-94.7, -34.5</td>
</tr>
<tr>
<td>Pre-PCV era vs. 2012</td>
<td>-64.0</td>
<td>-87.3, -9.6</td>
</tr>
<tr>
<td>2010 vs. 2012</td>
<td>66.8</td>
<td>-57.6, 677</td>
</tr>
<tr>
<td>2 years to 5 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2010 vs. 2012</td>
<td>98.6</td>
<td>-89.7, 11,16</td>
</tr>
<tr>
<td>HIV-positive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 months to 2 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2010 vs. 2012</td>
<td>90.9</td>
<td>-51.5, 789</td>
</tr>
<tr>
<td>2 years to 5 years</td>
<td>-71.5</td>
<td>-99.4, 188.1</td>
</tr>
<tr>
<td>Mothers (Ages 18–45 Years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-negative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-PCV era vs. 2010</td>
<td>-57.0</td>
<td>-90.3, 54.1</td>
</tr>
</tbody>
</table>
### HIV Status, Age, and Time Period

<table>
<thead>
<tr>
<th>HIV Status, Age, and Time Period</th>
<th>Non-Vaccine PCV13 Serotype Disease</th>
<th>PCV-13 Serotype Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observed IPD</td>
<td>Predicted IPD</td>
</tr>
<tr>
<td></td>
<td>% Change</td>
<td>95% CI</td>
</tr>
<tr>
<td>Pre-PCV era vs. 2012</td>
<td>−79.0</td>
<td>−97.8, 1.50</td>
</tr>
<tr>
<td>2010 vs. 2012</td>
<td>−51.1</td>
<td>−95.6, 240</td>
</tr>
<tr>
<td>HIV-positive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-PCV era vs. 2010</td>
<td>−70.5</td>
<td>−79.3, −58.8</td>
</tr>
<tr>
<td>Pre-PCV era vs. 2012</td>
<td>−72.5</td>
<td>−80.7, −61.2</td>
</tr>
<tr>
<td>2010 vs. 2012</td>
<td>−6.5</td>
<td>−39.6, 44.5</td>
</tr>
</tbody>
</table>

**Abbreviations:**
- CI, confidence interval
- HIV, human immunodeficiency virus
- IPD, invasive pneumococcal disease
- PCV, pneumococcal conjugate vaccine
- PCV13, serotypes included in the 13-valent pneumococcal conjugate vaccine

**Notes:**
- Non-PCV13- serotypes, excluding excluded serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F.
- PCV13- serotypes, included serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F.
- Pre-PCV era was 2005–2008.