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Imputing direct and indirect vaccine effectiveness of childhood pneumococcal conjugate vaccine against invasive disease by surveying temporal changes in nasopharyngeal pneumococcal colonization.

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Running Head

Inputing IPD changes using colonization data

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Abbreviations

OR, odds ratio;

CI, confidence interval;

HIV, human immunodeficiency virus;

IPD, invasive pneumococcal disease;

PCV, pneumococcal conjugate vaccine;

PCV7, serotypes included in the 7-valent pneumococcal conjugate vaccine;

PCV13, serotypes included in the 13-valent pneumococcal conjugate vaccine.

Abstract

The limited capabilities in most low-middle income countries to study the benefit of pneumococcal conjugate vaccine (PCV) 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 analysing serotype specific colonization prevalence and IPD incidence prior to and following childhood PCV immunization in South Africa. We analysed IPD incidence from 2005 to 2012 and colonization studies undertaken in HIV-uninfected and HIV-infected child-mother dyads from 2007-2009 (pre-PCV era), in 2010 (7-valent PCV era) and 2012 (13-valent PCV era). We compared the model-predicted to observed changes in IPD incidence, stratified by HIV-status in children >3months 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 and following PCV use can be used to impute PCVs' indirect effects in unvaccinated age groups, including in high HIV-prevalence settings.

Keywords: HIV, invasive pneumococcal disease, mathematical model, pneumococcal carriage, pneumococcal conjugate vaccine

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3496 main text

Introduction

Nasopharyngeal colonization by *Streptococcus pneumoniae* precedes pneumococcal disease, hence, serotypes identified in invasive pneumococcal disease (IPD) are mostly identical to that in the nasopharynx at the time of illness (1-3). Children vaccinated with pneumococcal polysaccharide-protein conjugate vaccines (PCV) have an approximately 50% reduced risk of vaccine-serotype nasopharyngeal colonization acquisition 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, reduction in prevalence of vaccine-serotype nasopharyngeal colonisation has also been described among PCV-unvaccinated individuals at the household and community level (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 2- to 10-fold greater number 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-middle income countries, mainly due to the lack of robust IPD surveillance systems to assess effectiveness of childhood PCV-immunization in protecting against IPD among PCV-unvaccinated age-groups (15, 16). Such information could inform on the public health benefit and cost-effectiveness of childhood PCV immunization. Weinberger et al. proposed that ecological studies on nasopharyngeal vaccine-serotype and non-vaccine serotype colonization prior to and following childhood PCV-immunization introduction may be useful to impute the direct and indirect effectiveness of vaccination against IPD, which was validated in high-income and low-HIV prevalence settings (17).

The aim of this study was to analyse 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, 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).

Methods

Study population

A series of pneumococcal colonization studies were undertaken in mother-child pairs in Soweto (Gauteng, South Africa), with a population of 1.8 million of whom 160,000 are under five years of age (18). 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 due to 7-valent PCV (PCV7) serotypes) than men (19). The prevalence of HIV amongst pregnant women (29%-30%) and those 15-49 years of age (20%) has remained stable in the community since 2005 (20). The mother-to-child transmission rate of HIV had, however, declined from 8% in 2008 to 1.5% by 2012 (21).

During the study period, >90% of the Sowetan population sought medical care at Chris Hani Baragwanath Academic Hospital. Although community deaths are not known, a good transport network and free healthcare mean that there are few community deaths (Shabir A Madhi, University of the Witwatersrand, unpublished data). 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 (22). This study provides temporal changes in incidence of IPD in children and women from Soweto.

Details of PCV introduction into the South African immunization program have been previously described (23) and are included in the web appendix 1. Briefly, PCV is given at 6 and 14 weeks with a booster dose at 9 months in South Africa.

Pneumococcal colonization studies in Soweto (2007 to 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) (24). Briefly, the study showed an association of vaccine serotype acquisition between young children and their mothers (25), with children transmitting PCV7-serotypes more often to their mothers than vice-versa (24). Subsequently, two cross-sectional colonization prevalence surveys in mother-child pairs with concordant HIV-status were undertaken in the same population in 2010 (PCV7-era) and 2012 (PCV13-era) as described (23). 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 (23). 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 from the mothers. The methods of sample collection, laboratory processing and serotyping have been previously described (7) and included in the web appendix 1.

Invasive pneumococcal disease surveillance (2005-2012)

Nationwide laboratory based surveillance for IPD including at Chris Hani Baragwanath Academic Hospital, has been previously described (22) and is detailed in the web appendix 1.

Statistical analysis

PCV7-serotypes were defined as any of 4, 6B, 9V, 14, 18C, 19F and 23F. The additional serotypes included in PCV13 (i.e. 1, 3, 5, 6A, 7F and 19A) were categorised as PCV13 additional serotypes. Additionally, we analysed serotype 6A separately to investigate cross protection from serotype 6B. All non-PCV13 serotypes were categorized as non-vaccine serotypes. Non-viable isolates were pro-rated based on identified serotypes, based on their similarity of distribution when analysed by PCR (26).

Incidence of IPD for children >3 months to 2 years and 2-5 years old, and adults 18-45 years of age were calculated by dividing the annual number of IPD cases identified by mid-year population estimates for Soweto (18). The average IPD incidence between 2005 and 2008 represented the pre-PCV era incidence and was compared to 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 (27), was used to evaluate the significance of the observed changes in IPD. The Chi-square 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 (22).

Colonization prevalence was compared in the different study-periods stratified by HIV-status (23). Colonization prevalence pre- and during the PCV-eras (for adults limited to women only) were used to estimate colonization prevalence ratio (i.e., carriage post-vaccine divided by carriage pre-vaccine) through 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 18-45 years age. For HIV-infected children aged >3 months to 2 years old and for children >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 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 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 both PCV7-serotype and PCV13 additional serotype colonization prevalence among HIV-uninfected children aged >3 months to 2 years in 2012 (Figure 1A and web Table 1), among whom the 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), PCV7-serotypes from 30.4% to 9.6% (OR = 0.24, 95% CI: 0.16, 0.38) and PCV13-additional serotypes from 10.4% to 4.2%

(OR = 0.38, 95% CI: 0.19, 0.73). Notably, a trend towards decline for PCV7-serotype colonization in this age-group, particularly HIV-uninfected, 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) and then 11.3% (OR = 0.51, 95% CI: 0.36, 0.73) by 2010 and 2012, respectively (Web Table 1). Stratifying by HIV-infection status, overall pneumococcal prevalence declined from 22.4% in the pre-PCV era 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 pre-PCV 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 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 in HIV-infected women 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 colonisation 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 colonisation remained unchanged

in HIV-infected women (range: 2.3% to 3.3%). There was a decline in non-vaccine serotype colonization among HIV-uninfected women between the pre-PCV era (15.2%) compared to 2012 (7.7%; OR = 0.47, 95% CI: 0.27, 0.80), and a non-significant increase in colonisation with non-vaccine serotypes among HIV-infected women (4.8% in pre-PCV era vs. 9.0% in 2012; OR = 1.99, 95% CI: 0.84, 4.73)Web.

Changes in invasive pneumococcal disease

Invasive pneumococcal disease in children

Overall trends in IPD for children aged >3 months to 2 years and >2-5years are reported in Web Table 2.

Among HIV-uninfected children >3 months to 2 years old, the annual incidence (per 100,000 persons) of PCV7-serotype IPD decreased by 84.9% in 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 >2-5years age, the incidence of PCV7-serotype IPD 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 up until 2012.

Among HIV-infected children >3 months to 2 years old, the incidence of PCV7-serotype IPD 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 >3 months to 2 years age-group of HIV-infected between the pre-PCV era and 2012. Among older (>2 to 5 years) HIV-infected children, PCV7-serotype IPD incidence (per 100,000) 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 (90%; $P=0.061$), albeit this change was not statistically significant (Figure 2D and Web Table 2). Similar to 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 in women of childbearing age

Among HIV-uninfected women, the annual incidence (per 100,000 persons) 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 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 incidence of PCV13-additional IPD ($P=0.001$), whilst non-vaccine serotype IPD incidence 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; $P=0.004$), with a further decline by 2012 (67.6% compared to 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 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 >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 (observed 91.7% vs. predicted 53.5%; Figure 3A) and similarly for both PCV7-serotype (observed 98.7% vs. predicted 72.1%, Figure 3C) and PCV13-additional serotype IPD (observed 91.9% vs. predicted 62.2%, Figure 3E), albeit with overlapping 95%CI for the latter (See also Table 1). Similar results were obtained for all PCV13 serotype IPD (Figure 4A). For the viable non-vaccine serotype IPD, the observed reduction was 64.0%, whereas the model predicted a significant 44.9% increase; Figure 4C and Table 2. Similar trends were observed when comparing the pre-PCV era to 2010.

In older HIV-uninfected children (>2-5years), who were unvaccinated with PCV at the 2010 nasopharyngeal sampling time point (PCV having been introduced into the EPI in 2009, with no catch-up campaign), the model underestimated the observed decline in PCV7-serotype IPD (observed 100% vs. predicted 36.8%, Figure 3C). The wide confidence interval for PCV13-additional and non-vaccine serotypes did permit further comparison of the observed and predicted changes in this in this age-group (Figure 3E and 4C, Table 2).

Among HIV-uninfected women, comparing the pre-PCV era and 2012, the observed reduction in all-serotype IPD (93.1%) was higher than the model-predicted estimate (79.8%) (Figure 3B and Table 1). Observed reductions were also higher for PCV7-serotype IPD (100% vs. 88.8%, Figure 3D) and PCV13-additional serotypes (96.4% vs. 69.9%, Figure 3F) compared to the model estimates; Similar results were obtained for all combined PCV13 serotype IPD (Figure 4B). However, observed and model estimates were similar for non-vaccine serotype IPD reductions (79.0% vs. 78.8%, Figure 4D).

Similarly, among HIV-infected women, when comparing the pre-PCV era to 2012, the model-predicted reductions slightly underestimated the observed estimates in IPD for all-serotypes (observed 86.2% vs. predicted 73.0%, Figure 3B) and PCV7-serotype (observed 94.5% vs. predicted 80.0%, Figure 3D), but was similar to observed reductions in IPD attributable to non-vaccine serotypes (observed 72.5% vs. predicted 72.6%, Figure 4D). The model predicted-estimate in reduction of IPD attributable to PCV13-additional serotypes from 2010 to 2012 was lower compared to observed reduction (observed 67.9% vs. predicted 31.4%) (Table 1, Figure 3F). 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 reduction of vaccine serotype IPD among HIV-infected and HIV-uninfected children less than 5 years of age and adults aged 18 to 45 years, which was also reflected by changes in pneumococcal nasopharyngeal colonization (23). In our setting, which has a high prevalence of HIV that is associated with 8.2-fold risk of IPD among adults (28), 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 HIV-uninfected, using changes in prevalence of nasopharyngeal pneumococcal colonization to estimate the contribution of PCV to decreases in vaccine-serotype IPD under-estimated its effectiveness. This is most likely due to the model 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 (29).

The observed and model-predicted reductions in IPD were similar in PCV-unvaccinated females 18-45 years of age when comparing the pre-PCV era to 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 (19, 30-33) and IPD incidence in the pre-PCV era (22). As the model estimates were similar to observed reductions in IPD incidence, this suggests that the decrease in IPD post-vaccine introduction was a result of decreases in prevalence of vaccine-serotypes colonization, likely through an interruption of transmission of these serotypes by vaccinating young children (12).

The direct and indirect associations of PCV on IPD incidence observed in our setting is similar to that initially observed in the USA, in which childhood PCV7 immunization reduced vaccine-serotype IPD among the vaccinated children as well as older PCV-unvaccinated age groups such as the high-risk elderly (11, 12, 34). In our population, the decrease in IPD among individuals 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 (22) 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 co-incidental 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 could also have contributed to the observed reduction in IPD, which may explain the trend for the observed reduction in IPD generally being higher than the model-predicted estimates as well as the reduction in colonization and IPD due to non-vaccine serotypes (22).

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 and this was attributed to lower invasiveness of these serotypes (35). In the USA, the incidence of IPD due to non-vaccine serotypes, particularly 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-PCV7 introduction period (36). This was manifest as early as three years post-PCV7 introduction (36, 37). Similarly in the UK, serotype 19A IPD increased significantly following PCV7 vaccination of infants (35). However, increases in IPD attributable to serotype 19A have also been described in unvaccinated communities (38). In our population, transitioning from PCV7 to PCV13 (which includes 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 mother-to-child transmission rate in

South Africa is now under 3% (21) and will continue to fall with improvements in HIV care and treatment, further reducing the role of HIV on the burden of IPD in children. We did not analyse the changes in IPD due to PCV on HIV-exposed uninfected children, who may still remain at high risk of IPD (39). Furthermore, our study did not have the power to detect significant IPD changes 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 a fifth of IPD in African children and are rarely identified as colonizing serotypes in otherwise healthy individuals (40, 41). 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 cause epidemics of varying proportions (42).

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 in HIV-infected populations.

Figure captions

Figure 1. Comparison of pneumococcal carriage prevalence in children and women in Soweto, South Africa in three periods January 2007 – April 2009, May 2010 – February 2011 and May 2012-April 2013. Comparisons are for all pneumococcus, PCV7, additional 6 serotypes in PCV13 and non-PCV13 serotypes between pre-PCV (periods January 2007 – April 2009) and (i) May 2010 – February 2011 (2010) and (ii) May 2012-April 2013 (2012). Age categories are: (A): HIV-uninfected children >3months to 2 years, (B): HIV-uninfected women 18-45 years, and (C): HIV-infected women 18-45 years.

Figure 2. Invasive pneumococcal disease incidence in children and adults in Soweto, South Africa, 2005 to 2012. Age categories are: (A): HIV-uninfected children >3months to 2 years, (B): HIV-infected children >3 months to 2 years, (C): HIV –uninfected children >2 to 5 years, (D): HIV-infected children >2 to 5 years, (E): HIV-uninfected w >18 to 45years and (F): HIV-infected adults >18 to 45 years

Figure 3. Comparison of observed and model-predicted IPD changes in children and women in different time periods. (A): All pneumococci IPD in children, (B): All pneumococci IPD in women, (C): PCV7 serotype IPD in children, (D): PCV7 serotype IPD in women, (E): Additional PCV13 serotype IPD in children and (F): Additional PCV13 serotype IPD in women.

Figure 4. Comparison of observed and model-predicted IPD changes in children and women in different time periods. (A): All PCV13 serotype IPD in children, (B): All PCV13 serotype IPD in women, (C): Non-PCV13 serotype IPD in children and (D): Non-PCV13 serotype IPD in women.

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Table 1: Observed and model-predicted changes in overall incidence of invasive pneumococcal disease and disease due to vaccine serotypes

HIV Status, Age, and Time Period	All Pneumococcal Disease				PCV7-Serotype Disease ¹				Additional PCV-13 Serotype Disease ²			
	Observed IPD		Predicted IPD		Observed IPD		Predicted IPD		Observed IPD		Predicted IPD	
	% Change	95% CI	% Change	95% CI	% Change	95% CI	% Change	95% CI	% Change	95% CI	% Change	95% CI
<i>Children</i>												
HIV negative												
3 months to 2 years												
Pre-PCV era ³ vs. 2010	-87.9	-93.6 to -78.8	-20.2	-32.1 to -7.64	-94.5	-98.5 to -85.4	-29.6	-43.3 to -13.5	-74.7	-91.6 to -36.0	-24.8	-10.5 to 71.2
Pre-PCV era vs. 2012	-91.7	-96.1 to -84.2	-53.5	-62.2 to -42.7	-98.7	-100 to -92.5	-72.1	-80.1 to -61.4	-91.9	-99.1 to -67.4	-62.2	-81.1 to -27.1
2010 vs. 2012	-26.2	-44.6 to -2.27	-12.9	-32.2 to 10.2	-76.2	-99.5 to 140.8	-55.3	-69.5 to -35.8	-68.2	-96.9 to 77.7	-69.3	-82.8 to -46.7
>2 years to 5 years												
2010 vs. 2012	-0.71	-81.5 to 133.1	3.39	-32.1 to 46.9	-100	-	-36.8	-60.3 to -0.37	-0.71	-92.8 to 1270	-54.2	-72.7 to -25.2
HIV positive												
>3 months to 2 years												
2010 vs. 2012	-9.11	-64.8 to 129.5	-11.4	-25.6 to 4.31	-45.5	-91.2 to 155.4	-35.1	-51.3 to -14.7	-100	-	-14.0	-53.6 to 54.6
>2 years to 5 years												
2010 vs. 2012	-60.1	-89.1 to 24.4	-28.3	-40.6 to -14.1	-12.3	-98.9 to 120.0	-56.1	-68.8 to -39.2	-43.0	-90.8 to 167	-25.4	-55.3 to 21.4
Mothers (18-45 years)												
HIV negative												
Pre-PCV era vs. 2010	-70.1	-83.3 to -43.1	-73.2	-77.8 to -68.1	-58.5	-93.1 to 81.6	-63.0	-74.2 to -47.7	-77.7	-92.5 to -44.5	-62.4	-75.1 to -44.3
Pre-PCV era vs. 2012	-93.1	-98.6 to -78.4	-79.8	-84.5 to -73.3	-100	-	-88.8	-93.6 to -81.1	-96.4	-99.9 to -77.9	-69.9	-81.6 to -52.0
2010 vs. 2012	-77.4	-95.9 to -17.9	-25.8	-49.2 to -0.16	-100	-	-74.9	-84.9 to -59.2	-83.7	-99.6 to 34.2	-35.7	-60.1 to 1.50
HIV positive												
Pre-PCV	-71.5	-76.2 to -66.0	-66.9	-72.1 to -61.0	-76.3	-83.2 to -67.2	-63.4	-73.0 to -51.0	-67.9	-75.9 to -57.8	-31.4	-56.5 to 5.7

era vs. 2010												
Pre-PCV era vs. 2012	-86.2	-89.3 to -82.6	-73.0	-78.0 to -66.4	-94.5	-97.3 to -89.9	-80.0	-85.8 to -72.3	-88.8	-92.9 to -83.0	-53.7	-70.7 to -28.6
2010 vs. 2012	-51.7	-63.6 to -36.5	-27.9	-40.5 to -23.1	-76.6	-89.1 to -54.2	-47.2	-65.1 to -21.6	-65.1	-78.8 to -44.2	-25.9	-49.0 to 5.8

n/a –there were no PCV7 serotypes detected in HIV-uninfected women during 2012

PCV7-serotypes, serotypes 4, 6B, 9V, 14, 18C, 19F, 23F

PCV13-additional serotypes, serotypes 1, 3, 5, 6A, 7F, 19A

Pre-PCV era, 2005 to 2008

CI – confidence interval, IPD – invasive pneumococcal disease

Table 1: Observed and model-predicted changes in overall incidence of invasive pneumococcal disease and disease due to vaccine serotypes

HIV Status, Age, and Time Period	Non-vaccine-serotype disease				PCV-13 Serotype Disease			
	Observed IPD		Predicted IPD		Observed IPD		Predicted IPD	
	% Change	95% CI	% Change	95% CI	% Change	95% CI	% Change	95% CI
children								
HIV negative								
3 months to 2 years								
Pre-PCV era vs. 2010	-78.4	-94.7 to -34.5	-19.9	-39.5 to 4.5	-89.7	-95.2 to -80.1	-17.2	-31.5 to -0.75
Pre-PCV era vs. 2012	-64.0	-87.3 to -9.6	44.9	7.7 to 92.0	-97.0	-99.4 to -91.1	-70.7	-77.1 to -62.9
2010 vs. 2012	66.8	-57.6 to 677	36.4	9.4 to 68.3	-71.4	-94.9 to 11.1	-60.1	-68.9 to -49.5
>2 years to 5 years								
2010 vs. 2012	98.6	-89.7 to 11616	56.3	25.7 to 91.8	-33.8	-94.5 to 117.8	-44.8	-59.0 to -26.9
HIV positive								
>3 months to 2 years								
2010 vs. 2012	90.9	-51.5 to 789	26.2	0.4 to 56.8	-59.1	-93.0 to 70.4	-30.9	-46.3 to -12.3
>2 years to 5 years								
2010 vs. 2012	-71.5	-99.4 to 188.1	44.4	15.8 to 77.9	-49.9	-89.2 to 97.1	-45.7	-57.9 to -30.8
Mothers (18-45 years)								
HIV negative								
Pre-PCV era vs. 2010	-57.0	-90.3 to 54.1	-78.2	-82.4 to -73.4	-73.6	-88.9 to -43.6	-62.7	-71.1 to -52.5
Pre-PCV era vs. 2012	-79.0	-97.8 to 1.50	-78.8	-83.6 to -72.9	-97.1	-99.9 to -82.5	-80.3	-86.6 to -71.6
2010 vs. 2012	-51.1	-95.6 to 240	1.7	-22.2 to 31.4	-89.1	-99.8 to -21.6	-55.0	-67.7 to -38.3
HIV positive								
Pre-PCV era vs. 2010	-70.5	-79.3 to -58.8	-73.8	-78.9 to -67.9	-71.9	-77.3 to -65.3	-56.3	-65.8 to -44.8
Pre-PCV era vs. 2012	-72.5	-80.7 to -61.2	-72.6	-78.2 to -66.0	-90.8	-93.5 to -87.1	-73.1	-79.7 to -64.8
2010 vs. 2012	-6.5	-39.6 to 44.5	-10.2	-27.1 to 9.6	-69.7	-79.7 to -55.6	-35.9	-51.3 to -16.8

Pre-PCV era, 2005 to 2008, 2010 as PCV-7 era, 2012 as PCV-13 era

PCV13-serotypes, serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F

Non- PCV13-serotypes, excluding serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F

CI: confidence interval; HIV: human immunodeficiency virus, IPD-invasive pneumococcal disease