Can pneumococcal meningitis surveillance be used to assess the impact of pneumococcal conjugate vaccine on total invasive pneumococcal disease? A case-study from South Africa, 2005-2016

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Abstract

Introduction: South Africa introduced seven-valent pneumococcal conjugate vaccine (PCV7) in 2009 and PCV13 in 2011. We aimed to compare the estimated impact of PCV on pneumococcal meningitis (PM) to impact of PCV on total invasive pneumococcal disease (tIPD) based on risk reduction after PCV introduction.

Methods: We conducted national, laboratory-based surveillance for tIPD during 2005-2016. We estimated and compared rates of PCV13 and non-PCV13 serotype disease among tIPD and PM in individuals aged <5 years and ≥5 years, and compared these rates between the 2005-2008 pre-PCV introduction period and two time points after PCV introduction, 2012 and 2016.

Results: We enrolled 45,853 tIPD cases; 17,251 (38%) were PM. By 2016, IPD caused by all serotypes decreased 55% (95%CI -57% to -53%) for tIPD, and 54% for PM (95%CI -58% to -51%), 0.7% difference between estimates (p=0.7). No significant differences were observed between PCV7-serotype disease reduction in tIPD and PM in both age groups or the additional 6 serotypes included in PCV13 in <5 year olds in 2012 and 2016. In 2012 there was a significant difference between increases in non-PCV13 serotype disease in those ≥5 years for tIPD and PM (32% greater increase in PM, p<0.001), but this difference was absent by 2016. There was a significant difference between the estimated decrease in additional PCV13 type disease in 2016 between tIPD and PM for those aged ≥5 years (28% greater reduction in PM, p=0.008).

Conclusion: PM showed similar reductions to tIPD seven years after PCV introduction in vaccine serotype disease in those <5 years, and increases in non-vaccine serotype disease in all ages.

Words: 263/300

Keywords: *Streptococcus pneumoniae*; invasive disease; meningitis; conjugate vaccine.

Abbreviations: IPD: invasive pneumococcal disease; PM: pneumococcal meningitis; tIPD: total IPD; nmIPD: non-meningitis IPD; PCV: pneumococcal conjugate vaccine; EPI: expanded program on immunization.

Introduction

Invasive pneumococcal disease (IPD) is the infection of a normally sterile site with *Streptococcus pneumoniae*, causing primarily meningitis or bacteraemia. The young, the elderly, and individuals with underlying illnesses, especially those infected with HIV, are at increased risk of IPD.[1, 2]

The 7-valent pneumococcal conjugate vaccine (PCV7) was introduced into the South African expanded program on immunization (EPI) in 2009, and the 13-valent PCV (PCV13) in April 2011.[2] PCV13 is administered as two doses at 6 and 14 weeks of age, and a booster at 9 months.[3] The World Health Organization (WHO) and The United Nations Children's Fund (UNICEF) vaccine coverage estimates for receiving a third dose of PCV in South Africa were 70% in 2012 and 69% in 2016.[4]

IPD surveillance has been used in several countries, including South Africa, to assess the impact of PCV on IPD after its introduction in EPI. Compared to the pre-vaccine period, the rate of total IPD (tIPD) caused by all serotypes in South Africa declined by 69% and 34% by 2012 among individuals aged <2 years and 25-44 years, respectively.[5] In this study the decrease in IPD rates was not only attributable to the success of PCV, but also better HIV detection and treatment programmes.[5, 6]

Surveillance for invasive disease varies across countries and programmes, with some countries implementing only cerebrospinal fluid (CSF) surveillance for meningitis, whereas others conduct surveillance that also includes other normally sterile sites such as blood, joint, or pleural fluid. Due to limited resources in many African countries, blood coulters are not performed routinely,[7] and WHO suggested invasive disease monitoring based on meningitis surveillance for the identification of, mainly, *Neisseria meningitidis, S. pneumoniae* and *Haemophilus influenzae* serotype b.[8, 9]

There are few data to support whether assessing the impact of PCV using pneumococcal meningitis (PM)-only surveillance provides similar estimates to tIPD. We aimed to assess whether results from PM surveillance only can be used as proxies for the impact of PCV on tIPD across different age groups in South Africa during 2005-2016.

Materials and methods

IPD surveillance

IPD surveillance was conducted under GERMS-SA, which is an active, laboratory-based surveillance programme focusing on an array of bacterial and fungal pathogens including *S. pneumoniae*.[10] As part of GERMS-SA, laboratories at the National Institute for Communicable Diseases (NICD) receive clinical isolates and specimens from both private and public laboratories across South Africa based on specified case definitions. Duplicate results from the same patient in a 21-day period were excluded through matching of patient demographics. In the 11-year period, the number of

laboratories submitting isolates increased from 94 in 2005 to 189 in 2016, with 22-29 enhanced surveillance sites providing additional clinical information on IPD patients, depending on the year. Information collected at enhanced sites included symptoms, diagnosis, outcome, admission and outcome date, antibiotic use, vaccination information, HIV status and pre-disposing conditions. Enhanced surveillance sites were chosen for convenience and were not representative of all surveillance sites in the country.[11] In addition to the specimens received at NICD, the Corporate Data Warehouse (CDW) of the National Health Laboratory Service (NHLS) was searched for any positive pneumococcal laboratory result to identify any IPD cases not reported to NICD. These cases would not have any serotyping data available. This database stores the results for all laboratory tests performed in the public sector, nationally, which services approximately 80% of the South African population.[12]

Study population and case definition

The laboratory network used for GERMS-SA serves almost the entire South African population, and includes laboratories that serve the public and private sector. The estimated population under surveillance ranged from 47.6 million in 2005 to 55.9 million in 2016. [13] All cases of IPD identified through GERMS-SA during 1 January 2005 to 31 December 2016 were included in the analysis. A case of IPD was defined as a positive test for *S. pneumoniae* on culture or polymerase chain reaction (PCR), or latex antigen test and corresponding Gram stain from a normally sterile-site specimen (e.g. CSF, blood, joint, or pleural fluid) in a hospitalized patient. For this analysis, tIPD was defined as IPD diagnosed from all specimen types, PM as IPD diagnosed from CSF only, and non-meningitis IPD (nmIPD) as diagnosed from all specimen types excluding CSF. Pneumococcal serotypes were determined from all culture-positive specimens using the Quellung reaction (Statens Serum Institute, Copenhagen, Denmark). IPD was classified into three groups based on the pneumococcal serotype causing diseases as follows: (i) serotypes included in PCV7 (4, 6B, 9V, 14, 18C, 19F and 23F); (ii) additional serotypes included in PCV13 (1, 3, 5, 6A, 7F and 19A); and (iii) non-PCV13 serotypes. This was done to specifically assess the effect of the two PCVs on PCV serotypes and potential serotype replacement by non-PCV serotypes.

Data analysis

For IPD cases with missing information on age and serotype, we assumed the same proportion of cases within groups as among those with available information each year and within each syndrome. The age-specific proportion of the above defined serotype groups was used.

To assess trends of IPD over time, we calculated the annual rates of tIPD, PM and nmIPD by dividing the total number of cases (from enhanced and non-enhanced sites) by the annual mid-year population estimates obtained from Statistics SA.[13]

To assess the impact of PCV on tIPD and PM we compared the disease rates during a pre-PCV introduction period (mean annual rate during 2005-2008) and two separate years following the introduction of PCV13 (2012 and 2016) using a log-binomial model. A log binomial model was selected because it allows to estimate rate ratios from binary data and subsequently the percentage differences in rates between two or more categories. Based on the WHO recommendation to assess PCV impact at least three years after its introduction,[14] we chose 2012, and also 2016 to further investigate the full impact of the vaccine including potential non-PCV13 serotype replacement. We expressed the vaccine impact as the percentage difference in rates during the pre- and post-PCV introduction periods, calculated as the rate ratio (RR) from the log-binomial model minus 1 multiplied by 100. A negative percentage difference indicated a rate reduction, whereas a positive percentage difference indicated a rate increase between the pre-PCV introduction period and the evaluated post-PCV introduction years.

We compared PCV impact on PM to that on tIPD. This was obtained by contrasting the RR of PM of the post- (2012 or 2016) vs. pre-PCV (2005-2008) introduction years to that of tIPD through the inclusion of an interaction term for PCV period (2012 or 2016 vs. 2005-2008) and syndrome (PM vs. tIPD) in the log-binomial model. We expressed the differential impact of PCV on PM vs. tIPD as percentage effect difference calculated as the RR of the interaction term minus 1 multiplied by 100. A negative percentage effect difference indicated a lower RR of the post- vs. pre-PCV introduction periods (i.e., higher decreases in PCV serotypes or lower increases in non-vaccine serotypes) among PM compared to tIPD, whereas a positive percentage effect difference indicated a higher RR of the post- vs. pre-PCV introduction periods (i.e., lower decreases in PCV serotypes or higher increases in non-PCV serotypes) among PM compared to tIPD.

The significance of all rate comparisons were assessed at $p<0.05$. All PCV impact analyses were implemented overall (i.e., all ages and serotypes) and among individuals aged <5 or ≥5 years and/or serotype groups (i.e., PCV7 serotypes, additional PCV13 serotypes and non-PCV13 serotypes). For the non-stratified analysis, all estimates were adjusted by age and serotype categories reported above as appropriate. We did not adjust for trends or seasonality. The statistical analyses were conducted using Stata 14.2 (StataCorp©, College Station, Texas, USA).

As a sensitivity analysis, we repeated the analysis to compare PCV impact on PM to that on nmIPD to evaluate the difference in impact when one of the comparison groups is not a subset of the other. To understand possible differences in the effects of PCV on the two syndromes, we also assessed the differences between patients with PM and nmIPD during the pre- and post-PCV periods, using unconditional logistic regression with IPD type (PM or nmIPD) as the outcome variable. The analysis was implemented for two periods; before PCV introduction (2005-2008) and after PCV introduction (2013-2016), excluding the transition period after the introduction of PCV (2009-2012). Only cases from enhanced sites were included in this analysis. For the multivariable model we

assessed all variables that were significant at p<0.2 on univariate analysis, and dropped non-significant factors (p≥0.05) with manual backward elimination.

Ethical considerations

Ethics approval for GERMS-SA surveillance was obtained from the Human Research Ethics Committee (Medical), University of Witwatersrand (clearance numbers M140159, M081117, M021042) and from relevant University and Provincial Ethics Committees for the enhanced surveillance sites. GERMS-SA surveillance was considered non-research by the US Centers for Disease Control and Prevention, CDC non-research determination NRD#CGH2014-166. Ethics approval for secondary data analysis in this study was granted by the University of Pretoria Faculty of Health Sciences Research Ethics Committee (reference number 433/2016).

Results

During 2005-2016, we identified 45,853 cases of tIPD, of which 17,251 (38%) were PM. A quarter of tIPD cases (11,119) were in children younger than five years. Of the total cases, 9,281 (20%) were identified through CDW audits. The annual percentage of missing information for PM ranged between 4-11% for age and 26-38% for serotypes and for nmIPD ranged between 1-5% for age and 21-31% for serotypes.

Time trends of tIPD, PM and nmIPD rates during 2005-2016

A downward trend of all serotype IPD rates was observed for all syndromes following PCV introduction (Figure 1-3, Supplementary Figure 1). tIPD in those aged <5 years decreased from 31.8 cases per 100,000 population in 2005 to 7.0 cases per 100,000 population in 2016, and in those aged ≥5 years from 7.7 cases per 100,000 population in 2005 to 4.0 cases per 100,000 population in 2016. This decrease was driven by marked reductions in rates of PCV7 serotype disease from 2009-2010 and, additional PCV13 serotype disease from 2011-2012 onward. This trend was observed across age groups and syndromes, but it was marked among children aged <5 years. An increase in non-PCV13 serotypes was observed across age groups and syndromes following PCV introduction.

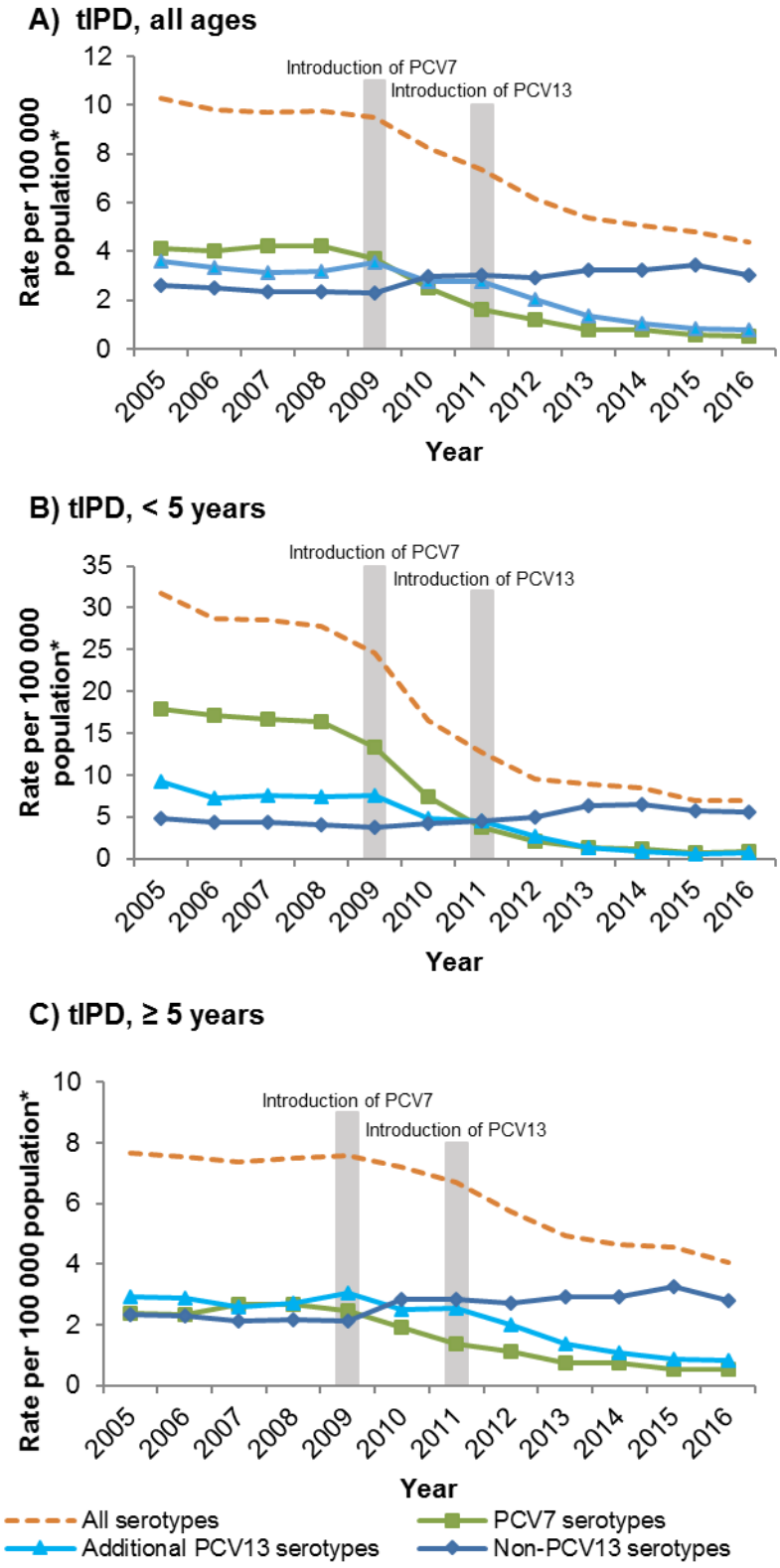

Figure 1. Trends of total invasive pneumococcal disease (IPD) incidence during 2005-2016, in all ages (A), those <5 years (B), and ≥5 years (C) by serotype group, South Africa. *Serotype groups classified by pneumococcal conjugate vaccine; PCV7 serotypes: 4, 6B, 9V, 14, 18C, 19F and 23F; Additonal PCV13 serotypes: 1, 3, 5, 6A, 7F and 19A; non-PCV13 serotypes: all serotype groups not in PCV13. *y-axis scales not uniform across figures.*

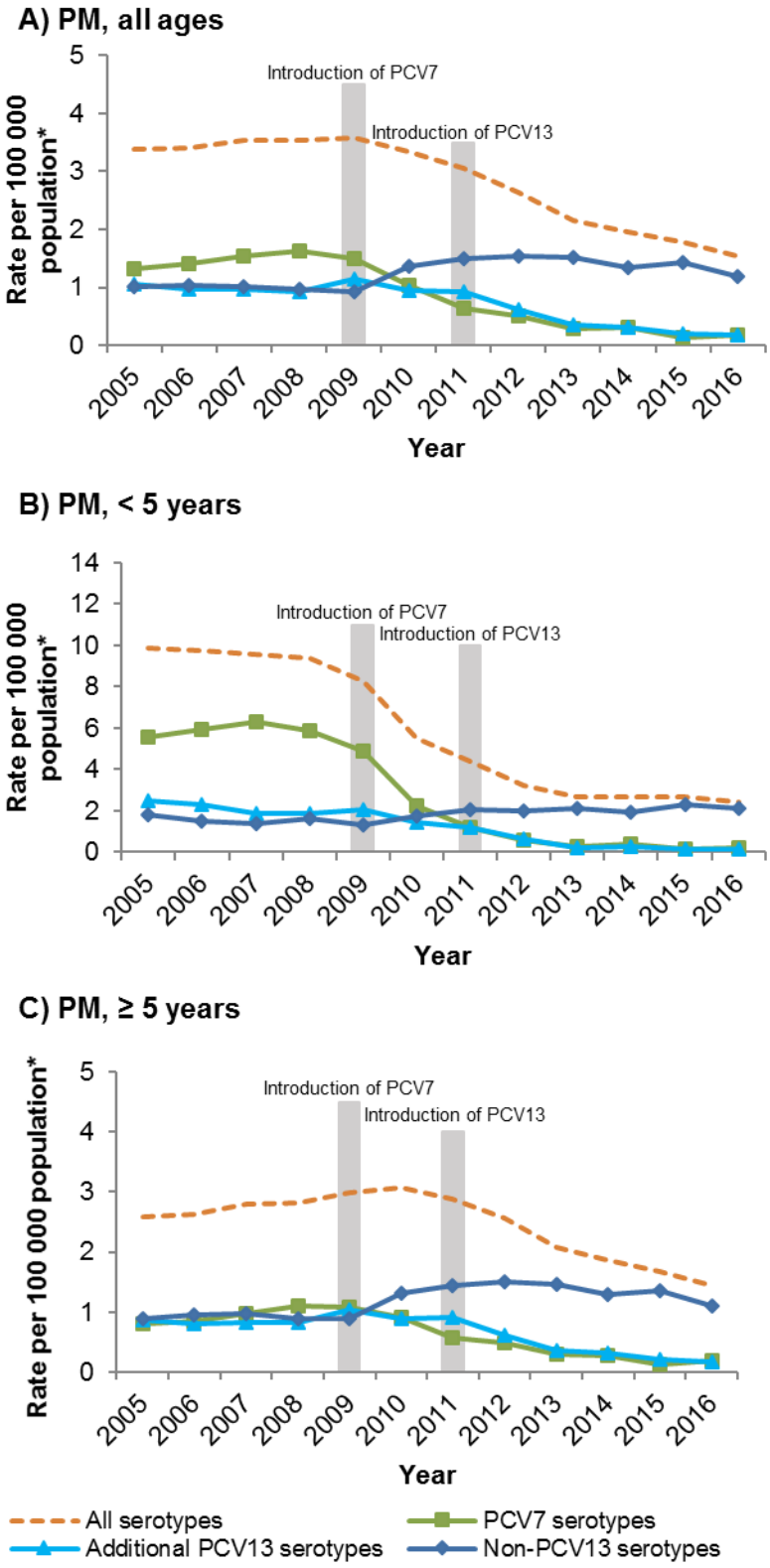

Figure 2. Trends of pneumococcal meningitis (PM) incidence during 2005-2016, in all ages (A), those <5 years (B), and ≥5 years (C) by serotype group, South Africa. *Serotype groups classified by pneumococcal conjugate vaccine; PCV7 serotypes: 4, 6B, 9V, 14, 18C, 19F and 23F; Adiditonal PCV13 serotypes: 1, 3, 5, 6A, 7F and 19A; non-PCV13 serotypes: all serotype groups not in PCV13. *y-axis scales not uniform across figures.*

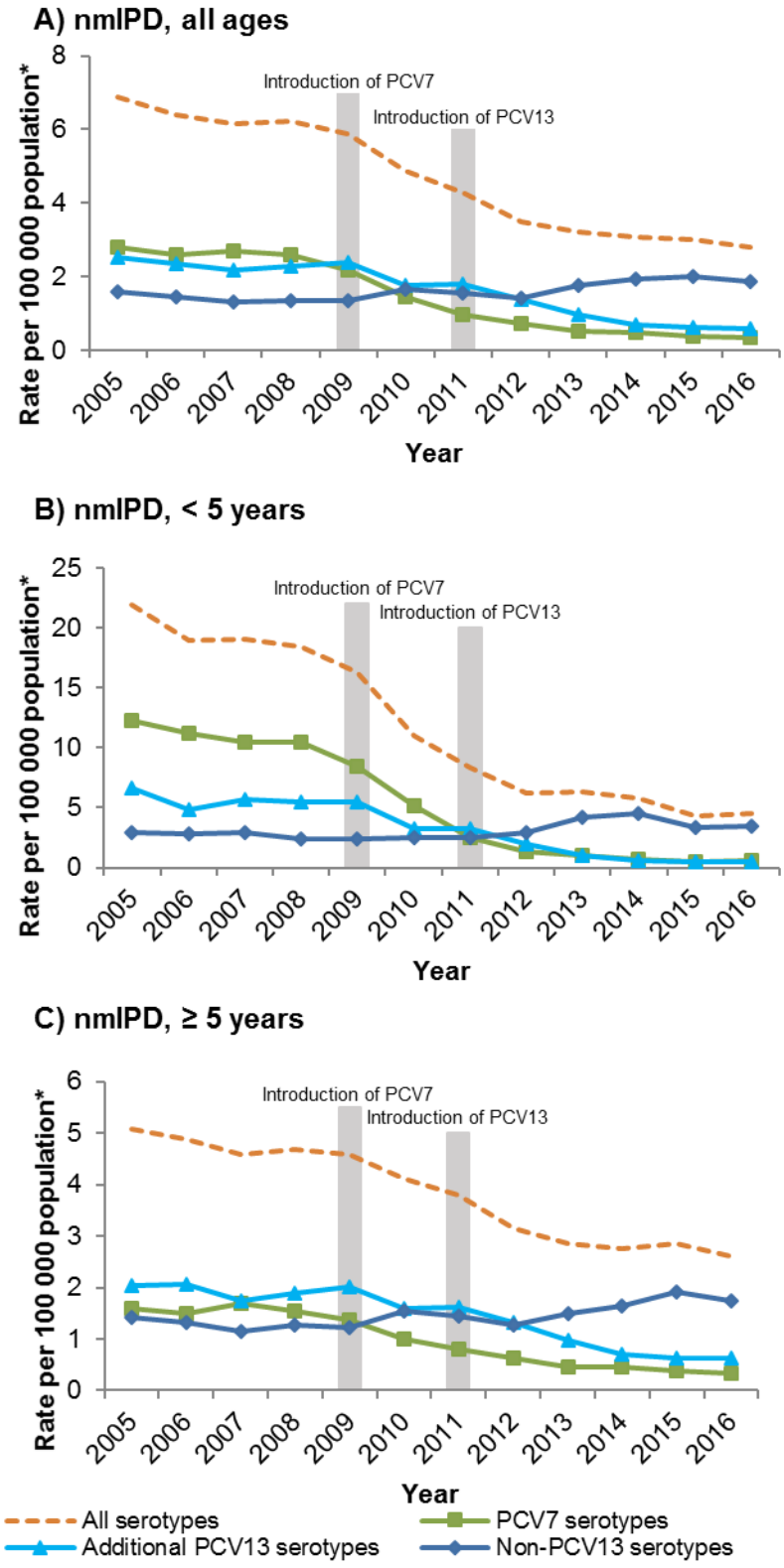

Figure 3. Trends of non-meningitis invasive pneumococcal disease (nmIPD) incidence during 2005-2016, in all ages (A), those <5 years (B), and ≥5 years (C) by serotype group, South Africa. *Serotype groups classified by pneumococcal conjugate vaccine; PCV7 serotypes: 4, 6B, 9V, 14, 18C, 19F and 23F; Additonal PCV13 serotypes: 1, 3, 5, 6A, 7F and 19A; non-PCV13 serotypes: all serotype groups not in PCV13. *y-axis scales not uniform across figures.*

Comparison of vaccine impact on tIPD and PM

PCV impact in 2012

In 2012, compared to 2005-2008 there was a statistically significant reduction in PCV7 and additional PCV13 serotype tIPD rates across age groups. The greatest decrease (-88.4%) in tIPD rates occurred in PCV7 serotypes in children younger than five years from the baseline period to 2012, and the smallest decrease (-28.3%) occurred in the additional PCV13 serotypes in individuals aged 5 years and older (Figure 4.a, Table S1). This was observed also among PM (percentage difference range: -89.9% to -26.5%). The percent effect difference in rate reduction on PCV7 and additional PCV13 serotypes for PM compared to tIPD ranged between -13% and 18%. No statistically significant differences in the percent effect reduction between PM and tIPD were observed in the above mentioned comparisons.

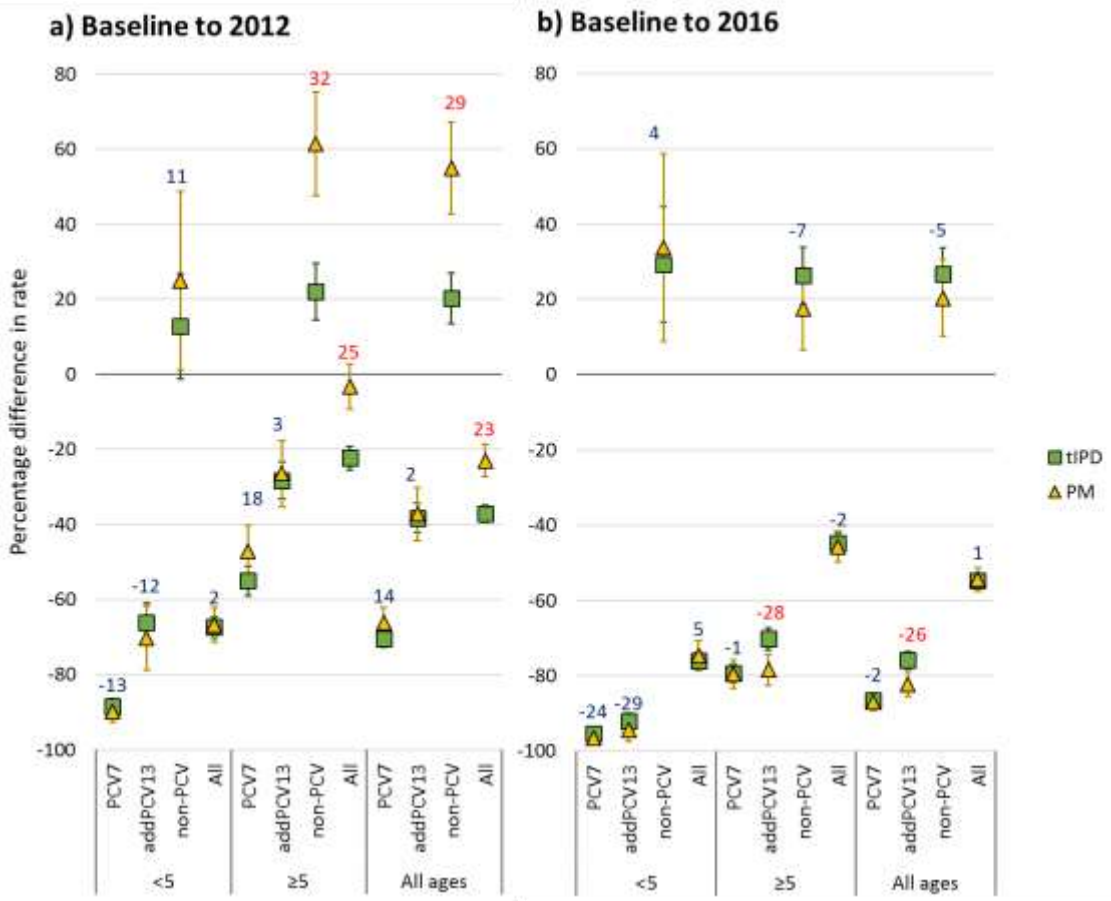

Figure 4. Percentage difference in rates of total invasive pneumococcal disease (tIPD, green squeres) and pneumococcal meningitis (PM, yellow triagles) between 2005-2008 (pre-PCV introduction) and 2012 (post-PCV introduction) (a) and percentage effect difference in rate changes between 2005-2008 and 2012 for PM (yellow triagles) compared to tIPD (green squeres) (b), South Africa, 2005-2012. *Percentages on graph indicate percentage effect difference in rate changes between (a) 2005-2008 and 2012 and (b) 2005-2008 and 2016 for PM compared to tIPD. Values >0 indicate an increase in the rate between baseline and the period under study, and values<0 indicates a decrease. Blue values show differences with p-value ≥0.05 (not statistically significant) and red values differences with p-values <0.05 (statistically significant difference between the effect of PCV on PM and tIPD. Error bars indicate 95% confidence interval of percentage difference in rate estimate.*

Across age groups the increases in non-PCV13 serotypes rates between 2005-2008 and 2012 (percentage difference) ranged between 13% and 22% for tIPD and between 25% and 61% for PM. These increases were highest among individuals aged ≥5 years. The PCV percent effect difference in rate increase on non-PCV13 serotypes PM compared to tIPD ranged between 11% to 32% with statistically significant differences observed among individuals aged ≥5 years (percent effect difference: 32%, p<0.001) and all ages (percent effect difference: 29%, p<0.001).

PCV impact in 2016

In 2016, compared to 2005-2008 there was a statistically significant reduction in PCV7 and additional PCV13 serotype tIPD rates across age groups (percentage difference range: -96 % to -70%) and this reduction was highest among children aged <5 years. This was observed also among PM (percentage difference range: -97% to -79%) (Figure 4.b, Table S2). The percent effect difference in rate reduction on PCV7 and additional PCV13 serotypes PM compared to tIPD ranged between -29% and -1% with statistically significant differences for additional PCV13 serotypes observed among individuals aged ≥5 years (percentage effect difference: -28%, p=0.008) and all ages (percentage effect difference: -27%, p=0.008).

Across age groups the increases in non-PCV13 serotypes rates between 2005-2008 and 2016 (percentage difference) ranged between 26% and 29% for tIPD and between 18% and 34% for PM. These increases were highest among individuals aged ≥5 years. The PCV percent effect difference in rate increase on non-PCV13 serotypes PM compared to tIPD ranged between -7% and 4%. No statistically significant differences of the percent effect increase between PM and tIPD were observed in these groups.

Similar trends were observed when comparing the impact of PCV on PM and the impact of PCV on nmIPD, for both periods under study (Table S3 and S4). There was however a significant difference between nmIPD and PM reductions from baseline to 2016 for the decrease of PCV7 serotype disease in individuals aged ≥5 years, with a 35% greater decrease in nmIPD compared to PM (p=0.001).

Comparison of patients with PM and nmIPD

At the enhanced sites there were 8,853 and 3,923 cases of tIPD during 2005-2008 and 2013-2016, of which 2,233 (25%) and 1,148 (29%) were PM, respectively. The prevalence of HIV infection amongst the nmIPD cases was 25% and 29% in 2005, and 10% and 26% in 2016 for those aged <5 years and ≥5 years, respectively. For PM cases, the HIV prevalence was 17% and 14% in 2005, and 7% and 18% in 2016 for those aged <5 years and ≥5 years, respectively. During 2005-2008, on multivariable analysis compared with nmIPD, PM patients were more likely than nmIPD patients to be aged <1 years compared to 1-14 years (adjusted odds ratio [aOR]: 1.5; 95% CI: 1.2-1.9), to be admitted for ≥6 days (aOR: 2.4; 95% CI: 1.9-3.0), to be infected with non-PCV13 serotypes (aOR: 1.4; 95% CI: 1.1-1.7), to have received antibiotics 24 hours prior to admission (aOR: 2.3, 95%CI 1.5-3.5) and to die (aOR: 5.0;

95% CI: 4.0-6.4), but were less likely to be HIV-infected (aOR: 0.7; 95% CI: 0.6-0.9) and to have pre-disposing medical conditions (aOR: 0.4; 95% CI: 0.3-0.6). Provincial differences were also observed (Table S5).

Similar differences between PM and nmIPD were observed during 2013-2016 (Table S6), although HIV infection did not differ significantly between patients with PM and those with nmIPD. Furthermore, in the post-PCV period, patients with PM were more likely than patients with nmIPD to have received antibiotics during admission (aOR 1.7; 95% CI: 1.0-2.7), and less likely than patients with nmIPD to be smoking (aOR 0.7; 95% CI: 0.5-1.0) or to be older than 64 years (aOR 0.2; 95% CI: 0.1-0.4).

Discussion

We observed marked reductions in IPD from 2005 to 2016 in those aged <5 years and those aged ≥5 years when looking at both PM and tIPD rates. In our setting, there was a similar impact of PCV on PM and tIPD disease estimates obtained from routine surveillance. However, the changes in IPD rates between the baseline period (2005-2008) and the post-PCV introduction time point were more comparable when considering a longer period after vaccine introduction. The direct effect of PCV on PM and tIPD in children aged <5 years were similar for PCV7 serotype disease by 2012, and PCV13 serotype disease by 2016. There was greater variation in estimates for the increase of non-PCV13 serotypes disease between PM and tIPD in all ages, but this variation was only significant for the shorter period after PCV introduction (2012). By 2016, the estimates of non-PCV13 serotype disease increases were similar for PM and tIPD.

The underestimation of the impact from baseline to 2012 for any serotype PM as compared to tIPD was driven by minimal rate reduction among individuals aged ≥5 years with PM. By 2016, the PM estimate was similar to the tIPD estimate and the differences at the two time points may be due to a higher rate of serotype replacement in PM as compared to tIPD in 2012. High rates of serotype replacement specifically in PM after the introduction of PCV7 have been described in previous studies. In France, overall PM only reduced after the introduction of PCV13 and not PCV7, due to initial serotype replacement by serotypes that were then included in PCV13.[15] The reason for greater effect differences earlier after the vaccine introduction, cannot be attributed to differences between patient characteristics in the pre- and post-PCV period, as differences between patients with PM and those with nmIPD were similar between 2005-2008 and 2013-2016.

Although we observed a few statistically significant differences in effects from baseline to 2016 for the percentage difference of PM and tIPD rates, these differences were <40% in both directions. This suggests that overall PM surveillance results can reflect the impact of PCV on tIPD, although the specific setting should be considered, keeping in mind the type of surveillance and absolute number of cases identified.

Although several studies have been published assessing the impact of PCV on different syndromes, there have not been many studies directly comparing the effect of PCV on tIPD and the effect of PCV on PM. We compared the impact of PCV on PM to tIPD, of which PM is a subset of. This comparison was chosen in order to establish if the impact of PCV on PM reflects the impact of PCV on tIPD, and not whether the impact of PCV is the same on PM than on nmIPD. In our sensitivity analysis, we saw similar differences when comparing PM and nmIPD rate changes than when comparing PM and tIPD rate changes. In our setting, PM made up 38% of tIPD cases nationally, which we acknowledge may be different in other countries and surveillance systems. We did not investigate the minimum relative proportion of PM cases needed to estimate the impact of PCV on tIPD by using PM data in this study.

In a previous study that compared rates of PM and nmIPD in children <5 years, a significant decrease was only observed in nmIPD, and may be due to the small number of PM cases identified[17]. The active surveillance system only identified 424 PM cases in the 15-year period[17], whereas our study included 17,251 PM cases from a 11-year period, providing more power to show significant reductions.

Our study had some limitations. Firstly, approximately 30% of serotype information was missing and was imputed from cases with available information. Using this approach, an error could have been introduced if such information was not missing at random. Secondly, we did not compare the impact of PCV in HIV-infected and HIV-uninfected individuals since we only had HIV status information on 30% of cases. It has been shown that among HIV-infected individuals the reduction in vaccine serotype IPD rate was greater, and that serotype replacement may be less apparent than in individuals not infected with HIV[5] but it is unknown whether the effect will be different between PM and nmIPD. By not stratifying the analysis by HIV status, we were unable to investigate this effect which may be important when considering using the impact of PCV on PM as a proxy of the impact of PCV on tIPD. However, we did see that although patients with PM were less likely to be infected with HIV than patients with nmIPD prior to the introduction of PCV (2005-2008), in the post-PCV period (2013-2016) there was no difference in HIV co-infection between patients with PM and nmIPD in the multivariable model. This is most likely due to the upscaling of HIV detection and treatment programmes since 2007[6] allowing more HIV-infected individuals to access care and reducing vulnerability to opportunistic infections. We did not adjust for disease trends or seasonality. A general downward trend was observed for both PM and nmIPD and since annual rate percentage differences were used, should not influence the results.

In conclusion, the PCV impact estimate for PM was similar to that of tIPD. The vaccine direct effect on reduction in vaccine serotype disease in children aged <5 years, the indirect effect of the vaccine on vaccine serotype disease in individuals aged ≥5 years, and the increase in non-vaccine serotype disease in all ages can be shown with PM data, especially after several years of surveillance after vaccine introduction. There were greater differences between PM and tIPD estimates earlier post-vaccine

introduction, which may be influenced by the different association of serotypes with PM and nmIPD. Countries where syndromic meningitis surveillance is implemented may be able to infer the effect of the vaccine on tIPD through PM surveillance only if sufficient number of cases are identified and sufficient data from baseline years are available. PM incidence thresholds to confidently use surveillance of PM as a proxy for tIPD warrants investigation.

Funding

This work was supported by the National Institute for Communicable Diseases; the National Health Laboratory Service; the United States Agency for International Development's Antimicrobial Resistance Initiative, transferred via a cooperative agreement [U60/CCU022088] from the United States Centers for Disease Control and Prevention; and the United States Centers for Disease Control and Prevention [U62/CCU022901]. The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the funding agencies.

Author contributions

Study idea and design: JK CC MM AvG. Data collection and management: JK CC PCG VQ LdG AvG. Analyses of data: JK CC MM ST AvG. Writing and review of manuscript: JK CC MM ST PCG VQ LdG AvG.

Conflicts of interest

AvG received research funding from Pfizer unrelated to this project. JK, CC, MM, PCG, and LK report no conflicts of interest.

Acknowledgments

We would like to acknowledge all laboratory and clinical colleagues who participated in GERMS-SA surveillance. Thank you to Mr Alfred Musekiwa for review of the protocol for this study, Dr Lazarus Kuonza for review of the protocol and manuscript, Mrs Dorothy Southern for review of the manuscript and Dr Susan Meiring for her role in GERMS-SA and for review of the manuscript.

References

[1] Meiring S, Cohen C, Quan V, de Gouveia L, Feldman C, Karstaedt A, et al. HIV Infection and the Epidemiology of Invasive Pneumococcal Disease (IPD) in South African Adults and Older Children Prior to the Introduction of a Pneumococcal Conjugate Vaccine (PCV). PLoS One. 2016;11:e0149104.
[2] von Gottberg A, Cohen C, de Gouveia L, Meiring S, Quan V, Whitelaw A, et al. Epidemiology of invasive pneumococcal disease in the pre-conjugate vaccine era: South Africa, 2003-2008. Vaccine. 2013;31:4200-8.

[3] National Institute for Communicable Diseases. Vaccine Information for Parents and Caregivers. First ed. South Africa: Ideas Wise and Wonderful (IWW); 2016.
[4] World Health Organization. WHO-UNICEF estimates of PCV3 coverage. 2017.
[5] von Gottberg A, de Gouveia L, Tempia S, Quan V, Meiring S, von Mollendorf C, et al. Effects of vaccination on invasive pneumococcal disease in South Africa. N Engl J Med. 2014;371:1889-99.
[6] Wouters E, van Rensburg HCJ, Meulemans H. The National Strategic Plan of South Africa: what are the prospects of success after the repeated failure of previous AIDS policy? Health Policy Plan. 2010;25:171-85.
[7] World Health Organization. Resistant pneumococcal infections. 2001.
[8] Centers for Disease Control and Prevention. Pediatric bacterial meningitis surveillance - African region, 2002--2008. MMWR Morb Mortal Wkly Rep. 2009;58:493-7.
[9] Murray J, Agocs M, Serhan F, Singh S, Deloria-Knoll M, O'Brien K, et al. Global invasive bacterial vaccine-preventable diseases surveillance--2008-2014. MMWR Morb Mortal Wkly Rep. 2014;63:1159-62.
[10] Bamford C, Brink A, Govender N, Lewis D, Perovic O, Botha M, et al. Part V. Surveillance activities. S Afr Med J. 2011;101:579-82.
[11] GERMS-SA. 2015 Annual Report. Johannesburg: National Institute for Communicable Diseases; 2015.
[12] Econex. The South African Private Healthcare Sector: Role and Contributionto the Economy. 2013.
[13] Statistics South Africa. Statistical release P0302 - Mid-year population estimates 2016. 2016.
[14] World Health Organization. Pneumococcal vaccines WHO position paper-2012. Wkly Epidemiol Rec. 2012;87:129-44.
[15] Alari A, Chaussade H, Domenech De Celles M, Le Fouler L, Varon E, Opatowski L, et al. Impact of pneumococcal conjugate vaccines on pneumococcal meningitis cases in France between 2001 and 2014: a time series analysis. BMC Med. 2016;14:211-22.
[16] Hampton LM, Zell ER, Schrag S, Cohen AL. Sentinel versus population-based surveillance of pneumococcal conjugate vaccine effectiveness. Bull World Health Organ. 2012;90:568-77.
[17] Ben-Shimol S, Greenberg D, Givon-Lavi N, Schlesinger Y, Miron D, Aviner S, et al. Impact of PCV7/PCV13 introduction on invasive pneumococcal disease (IPD) in young children: Comparison between meningitis and non-meningitis IPD. Vaccine. 2016;34:4543-50.