Estimated severe pneumococcal disease cases and deaths before and after pneumococcal conjugate vaccine introduction in children younger than 5 years of age in South Africa

Claire von Mollendorf, National Institute for Communicable Diseases
Stefano Tempia, Centers for Disease Control and Prevention
Anne von Gottberg, National Institute for Communicable Diseases
Susan Meiring, Natl Health Laboratory Service
Vanessa Quan, Natl Health Laboratory Service
Charles Feldman, Charlotte Maxeke Johannesburg Academic Hospital
Jeane Cloete, University of Pretoria
Shabir A. Madhi, National Institute for Communicable Diseases
Katherine L. O’Brien, Johns Hopkins Bloomberg School of Public Health
Keith Klugman, Emory University

Only first 10 authors above; see publication for full author list.

Journal Title: PLoS ONE
Volume: Volume 12, Number 7
Publisher: Public Library of Science | 2017-07-03, Pages e0179905-e0179905
Type of Work: Article | Final Publisher PDF
Publisher DOI: 10.1371/journal.pone.0179905
Permanent URL: https://pid.emory.edu/ark:/25593/s469x

Final published version: http://dx.doi.org/10.1371/journal.pone.0179905

Copyright information:
© 2017, Public Library of Science. All rights reserved. This is an Open Access work distributed under the terms of the Creative Commons Universal : Public Domain Dedication License (http://creativecommons.org/publicdomain/zero/1.0/).

Accessed January 15, 2018 10:08 AM EST
RESEARCH ARTICLE

Estimated severe pneumococcal disease cases and deaths before and after pneumococcal conjugate vaccine introduction in children younger than 5 years of age in South Africa

Claire von Mollendorf 1,2*, Stefano Tempia 3,4, Anne von Gottberg 1,5, Susan Meiring 6, Vanessa Quan 6, Charles Feldman 7,8, Jeanne Cloete 9, Shabir A. Madhi 1,10, Katherine L. O’Brien 11, Keith P. Klugman 12, Cynthia G. Whitney 3, Cheryl Cohen 1,2

1 Centre for Respiratory Diseases and Meningitis, National Institute for Communicable Diseases, a division of the National Health Laboratory Service, Johannesburg, South Africa, 2 School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa, 3 Influenza Division, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia, United States of America, 4 Influenza Program, Centers for Disease Control and Prevention, Pretoria, South Africa, 5 School of Pathology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa, 6 Division of Public Health Surveillance and Response, National Institute for Communicable Diseases of the National Health Laboratory Service, Johannesburg, South Africa, 7 Department of Internal Medicine, Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg, South Africa, 8 Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa, 9 Department of Paediatrics and Child Health, University of Pretoria, Steve Biko Academic Hospital, Pretoria, South Africa, 10 Medical Research Council: Respiratory and Meningeal Pathogens Research Unit, University of the Witwatersrand, Johannesburg, South Africa, 11 Johns Hopkins Bloomberg School of Public Health, International Vaccine Access Center, Department of International Health, Baltimore, Maryland, United States of America, 12 Hubert School of Public Health, Emory University, Atlanta, Georgia, United States of America

* Current address: Bill & Melinda Gates Foundation, Seattle, Washington, United States of America
clairevonmollendorf@yahoo.com.au

Abstract

Introduction

Streptococcus pneumoniae is a leading cause of severe bacterial infections globally. A full understanding of the impact of pneumococcal conjugate vaccine (PCV) on pneumococcal disease burden, following its introduction in 2009 in South Africa, can support national policy on PCV use and assist with policy decisions elsewhere.

Methods

We developed a model to estimate the national burden of severe pneumococcal disease, i.e. disease requiring hospitalisation, pre- (2005±2008) and post-PCV introduction (2012±2013) in children aged 0±59 months in South Africa. We estimated case numbers for invasive pneumococcal disease using data from the national laboratory-based surveillance, adjusted for specimen-taking practices. We estimated non-bacteraemic pneumococcal pneumonia case numbers using vaccine probe study data. To estimate pneumococcal deaths, we applied observed case fatality ratios to estimated case numbers. Estimates were stratified by HIV status to account for the impact of PCV and HIV-related interventions.
We assessed how different assumptions affected estimates using a sensitivity analysis. Bootstrapping created confidence intervals.

**Results**
In the pre-vaccine era, a total of approximately 107,600 (95% confidence interval [CI] 83,000±140,000) cases of severe hospitalised pneumococcal disease were estimated to have occurred annually. Following PCV introduction and the improvement in HIV interventions, 41,800 (95% CI 28,000±50,000) severe pneumococcal disease cases were estimated in 2012±2013, a rate reduction of 1,277 cases per 100,000 child-years. Approximately 5000 (95% CI 3000±6000) pneumococcal-related annual deaths were estimated in the pre-vaccine period and 1,900 (95% CI 1000±2500) in 2012±2013, a mortality rate difference of 61 per 100,000 child-years.

**Conclusions**
While a large number of hospitalisations and deaths due to pneumococcal disease still occur among children 0±59 months in South Africa, we found a large reduction in this estimate that is temporally associated with PCV introduction. In HIV-infected individuals the scale-up of other interventions, such as improvements in HIV care, may have also contributed to the declines in pneumococcal burden.

**Introduction**
*Streptococcus pneumoniae* is a leading cause of bacterial pneumonia, meningitis, and sepsis, and is estimated to have caused approximately 335,000 (240,000±460,000) deaths in children aged <5 years in 2015 globally [1]. In 2008, before pneumococcal conjugate vaccines (PCVs) were available in low-income countries, the global estimated number of pneumococcal deaths was 541,000 (95% confidence interval [CI] 376,000±594,000) [2]. The method of estimation differed between the pre- and post-PCV global death estimates. With regards to risk groups in South Africa HIV-infected and HIV-exposed-uninfected children were shown to have a higher incidence of invasive pneumococcal disease (IPD) [3] and acute lower respiratory tract infections (LRTIs) compared to HIV-unexposed-uninfected children.[4]. Prevention of pneumococcal disease by PCVs has been documented through effectiveness and impact data from more than 50 countries [5]. In South Africa, the 7-valent pneumococcal conjugate vaccine (PCV7) was introduced nationally in April 2009 and replaced by PCV13 in June 2011. National surveillance data for invasive pneumococcal disease (IPD) from South Africa showed a 69% reduction in the incidence of all-serotype IPD among children aged <2 years by 2012, with contributions by PCV and HIV-associated interventions [6].

The burden of pneumococcal disease has been described in young children in the African region [7] with epidemiological studies in a number of countries including The Gambia [8, 9], Kenya [10] and South Africa [11]. World Health Organization (WHO) country specific estimates of disease burden [1, 7, 12] generate summed regional and global estimates using country-specific inputs for syndromic mortality (pneumonia and meningitis) along with other country-specific parameters (e.g. pathogen specific case fatality ratios, HIV prevalence, population size and vaccine coverage). South Africa has robust surveillance to measure IPD incidence and thus allows for an alternative model to estimate national cases and deaths from
pneumococcal disease, anchoring on the observed value of IPD cases. The model can be updated over time to track improvements in health and be compared to other estimates.

We aimed to estimate the national burden of severe hospitalised pneumococcal disease and deaths (meningitis, bacteraemic and non-bacteraemic pneumonia, and non-pneumonia non-meningitis invasive disease) among HIV-infected and HIV-uninfected children aged 0–59 months in South Africa in two periods: 2005±2008, before PCV was introduced, and in 2012±2013, after PCV was introduced. Estimates were based on the observed IPD incidence measures from the national GERMS-SA surveillance system, as an alternative approach to that used by the WHO.

**Methods**

**Data sources**

**GERMS-SA IPD surveillance programme.** GERMS-SA is an active, national, laboratory-based surveillance programme for IPD and other invasive organisms. All public health sector microbiology laboratories (>200) are encouraged to submit isolates to the National Institute for Communicable Diseases (NICD) in Johannesburg. The public sector serves 84% of the South African population without private medical aid coverage [13]. Some private sector laboratories also submit isolates. Of the public sector facilities, 24 sites have dedicated surveillance officers who collect clinical information on identified patients thereby defining them as enhanced sites. Laboratory-based surveillance for IPD in South Africa began in 1999 [14]; the quality and strength of the surveillance programme was improved between 2003 and 2005. From 2005 the quality of the surveillance system was maintained with regular checks and audits [15]. Cases of IPD were defined as illnesses in patients with *S. pneumoniae* cultured from normally sterile-body sites (e.g. cerebrospinal fluid (CSF) or blood). Information on specimen type and age of cases is available from all sites; clinical diagnosis is reported only from cases that occurred at enhanced sites. Severe pneumococcal disease was considered as disease resulting in hospitalisation.

**National Health Laboratory Service (NHLS) Corporate Data Warehouse (CDW).** The CDW is managed by the NHLS, the sole laboratory service provider for all public health facilities in South Africa. The CDW is a repository which contains archived data on all laboratory tests requested and results from public laboratories from 2003.

**Additional input parameters for model.** Values for input parameters of the model were derived from a number of sources. For estimates of non-bacteraemic pneumococcal pneumonia cases and adjustments for expected burden in presence of systematic blood culturing practices we used published data from a South African PCV9 vaccine clinical trial [16, 17]. Published data was also used to derive the CFR for non-bacteraemic pneumococcal pneumonia [18, 19].

**Population denominators.** Annual age-specific population denominators used to calculate incidence and mortality rates were obtained from Statistics South Africa [20]. The mid-year Statistics South Africa population estimates use the cohort-component method which is based on knowledge of population structure, birth rates, death rates and migration as well as assumptions of how they change. These estimates are derived from a census conducted in 2011 and are updated on an annual basis [20]. The Thembisa model, a demographic model designed to specifically address the population impact of changing HIV interventions [21], was used to estimate population denominators by HIV status; these denominators accounted for the changes in mother-to-child HIV transmission rates and improvements in paediatric antiretroviral (ARV) treatment. In this model the probability of mother-to-child transmission was assumed to depend on the mother’s HIV disease stage, the timing of ARV therapy initiation in pregnancy, the type of ARV prophylaxis received and for postnatal transmission the
type of feeding. PCR testing in HIV-exposed infants was assumed to occur at birth and ARV
treatment eligibility was expanded from all children aged <1 year to all children aged 1±4
years from mid-2012 based on updated South African ARV treatment guidelines [21].

Model overview

We developed a conceptual model to estimate the national burden of pneumococcal cases, and
deaths as well as associated rates, in children aged 0±59 months in South Africa for the baseline
pre-vaccine era (an average estimate for the 2005±2008 period which had a stable disease inci-
dence [11]) and a two-year period in the post-vaccine era (2012±2013) (Fig 1; S1 and S2 Figs).
We used the observed cases of IPD hospitalisations from the GERMS-SA surveillance pro-
gramme at both time points, stratified by disease syndrome (meningitis, pneumonia and non-
pneumonia non-menningitis) and by age (<1 and 1±4 years of age) as the base rate and adjusted
for incomplete specimen collection based on Corporate Data Warehouse (CDW) data by prov-
ince among hospitalised children. Gauteng province was used as the reference province for
this adjustment because of its systematic testing practices. We stratified all estimates by HIV
status which has previously been documented to affect burden of disease [11]. Model param-
eters are given in Table 1 and calculations are explained further below as well as shown in Fig 1
(and S1 and S2 Figs). All reported case numbers were rounded to the closest 100, except when
counts were less than 100, to reflect that case numbers were estimates and not exact numbers.
Incidence rates were calculated from the estimated cases using population denominators from
Statistics South Africa [20]; incidence rates were reported per 100,000 population without
rounding off case numbers.

Estimated number of cases and incidence rates by clinical syndrome. IPD case numbers
were estimated from national laboratory-based surveillance (described below) and divided
into fractions attributable to meningitis, bacteraemic pneumonia and non-pneumonia non-
menningitis cases on the basis of GERMS-SA clinical data. IPD case numbers were adjusted for
incomplete specimen-taking practices. A direct adjustment was not made for sensitivity of
blood culture among truly bacteraemic cases and CSF culture among those with pneumococ-
cal meningitis. We assumed that the Gauteng Province had the most complete blood culturing
practices and multiplied up the case numbers in the other provinces to calculate what the case
numbers would have been if they had had the same complete blood culturing practices as that
in Gauteng. The relevant provincial rate ratio was calculated by dividing the blood or CSF cul-
ture rate in the Gauteng Province by the rate in each individual province. To estimate the
number of cases of non-bacteraemic pneumococcal pneumonia, we extrapolated data from
PCV probe studies in South Africa [16] by using the PCV9 vaccine attributable reduction
(VAR) ratio of clinical pneumonia to bacteraemic pneumococcal pneumonia (11:1), i.e. 11
clinical cases to 1 bacteraemic case (see S1 Text for detailed methods).

Estimated number of deaths and mortality rates. Pneumococcal death estimates for
each syndrome were calculated by multiplying case estimates (as calculated above) by observed
syndrome-specific case fatality ratios (CFRs) (from GERMS-SA enhanced sites) for IPD cases
by age group and HIV status. For non-bacteraemic pneumonia parameters were taken from
two South African studies. For the 2005±2008 model period we used data from a clinical trial
conducted from 1998±2001. The CFR for clinical LRTI in HIV-uninfected children was 1.9%
(40/2139) and in HIV-infected children was 31.3% (281/899) [16]. A later case-control study
(2010±2012) for presumed bacterial pneumonia in HIV-uninfected cases showed a CFR of 1%
(13/1326) overall for cases with hospital controls (range 0.2% to 6.3% in different sites) and
<1% (2/889) for cases with community controls [22]. These CFRs were used for the 2012±
2013 model period.
Fig 1. Flow diagram of the steps used to estimate the burden of invasive and non-invasive pneumococcal cases in children <5 years of age in South Africa in 2005±2008 and 2012±2013. Detailed figures are included in S1 Text. ^For all syndromes total case numbers as well as numbers stratified by HIV status were determined. *Additional adjustment (1.89) for difference in VE estimated with use of urinary antigen.

https://doi.org/10.1371/journal.pone.0179905.g001
Statistical analysis

We calculated the percent reduction in incidence and death rates between the two periods (2005±2008 and 2012±2013) using the following formulas:

\[
\% \text{ reduction in incidence rates } (IR) = \frac{IR_{2005-2008} - IR_{2012-2013}}{IR_{2005-2008}}
\]

\[
\% \text{ reduction in mortality rates } (MR) = \frac{MR_{2005-2008} - MR_{2012-2013}}{MR_{2005-2008}}
\]

Bootstrapping to create confidence intervals was used for all endpoints, to account for variability and uncertainty in detection rates, incidence rates and case-fatality rates from the surveillance data. For each model input/adjustment factors used in the calculations we obtained 1000 bootstrapped datasets and associated estimate providing and estimated variability of each model input/adjustment factor. This was done for either directly available data or those obtained from the published literature. The model calculation were then repeated using each of the 1000 bootstrapped datasets to propagate the level of variability associated with each model input/adjustment factor. We obtained the distribution for each parameter used in the model through resampling of the estimated parameter using the binomial distribution for proportions and the Poisson distribution for count data. We used reported measures for each of our estimates and defined the variance from 1000 resampled datasets obtained as described above. The lower and upper limits of the 95% CI were the 2.5th and 97.5th percentile of the 1000 model values obtained from the 1000 bootstrapped datasets.

Human subjects review

Ethics approval was obtained for GERMS-SA surveillance (M081117) from the Human Research Ethics Committee (Medical), University of the Witwatersrand, Johannesburg, South Africa and other local hospital or provincial ethics committees, as required. Clearance for the surveillance programme was also obtained from the U.S. Centers for Disease Control and Prevention (IRB 00001223). The national surveillance programme included routine submission of laboratory isolates to NICD with basic demographic data; this did not require patient consent as it was part of the NICD’s national public health surveillance responsibility. At enhanced sites, additional data from patient interviews, was collected from participants who provide written informed consent. For children <18 years of age, written informed consent was obtained from parents or legal guardians. All patient identifiers were removed prior to data analysis.

Sensitivity analysis

A one-way sensitivity analysis was performed by changing one variable at a time to see the effect on the total number of cases and deaths (parameters in Table 2). A Tornado diagram was fitted around the base case estimates for cases (S3 Fig) and deaths (S4 Fig) to evaluate the sensitivity of the model to changes in the assumed values of key parameters (See S1 Text).

Results

Burden of invasive pneumococcal disease in the pre-vaccine era

In the pre-vaccine era (2005±2008), an estimated national average of 107,600 (83,000±140,000) annual cases of hospitalised pneumococcal disease, corresponding to an incidence of 2,074 (1,603±2,730) per 100,000 person-years (py), occurred in children aged 0±59 months in South
Table 1. Parameters used in base case model to estimate total number of cases, incidence and mortality rates for severe pneumococcal disease among children aged <5 years in South Africa.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value used in base case model</th>
<th>Source of data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases of invasive pneumococcal disease for 3 clinical syndromes (meningitis, BPP, NPNM)</td>
<td>IPD cases detected from enhanced and non-enhanced surveillance sites</td>
<td>GERMS-SA surveillance programme</td>
</tr>
<tr>
<td>Adjustment factor for systematic blood culturing from South African clinical trial: for Gauteng Province only</td>
<td>Ratio of BPP incidence (per 100,000 population) from Soweto clinical trial (1998±1999) over the average BPP incidence (per 100,000 population) from GERMS-SA surveillance in the same age group from 2005±2008 (&lt;2 years of age) = 22 overall, 13 in HIV-uninfected and 23 in HIV-infected children.</td>
<td>Madhi 2005: VE clinical trial conducted in Soweto located in the Gauteng Province</td>
</tr>
<tr>
<td>Adjustment for specimen-taking practices in provinces other than Gauteng Province</td>
<td>Provincial incidence rates were adjusted by the relative rate of blood cultures or CSF specimens collected in each province relative to Gauteng Province (baseline = 1). Rate ratios differed by province and specimen type. CSF specimen province specific rates: in 2005±2008 GA = 1.00, WC = 1.27, KZN = 2.00, NC = 1.86, EC = 2.81, NWP = 2.48, MP = 2.53, FS = 2.04, LP = 5.60 and in 2012±2013 GA = 1.00, WC = 0.23, KZN = 2.30, NC = 1.84, EC = 0.85, NWP = 1.66, MP = 2.71, FS = 0.39, LP = 5.70. Blood culture province specific rates: in 2005±2008 GA = 1.00, WC = 1.26, KZN = 6.00, NC = 4.32, EC = 4.58, NWP = 10.51, MP = 18.06, FS = 2.43, LP = 80.13 and in 2012±2013 GA = 1.00, WC = 0.35, KZN = 35.35, NC = 11.82, EC = 1.61, NWP = 15.08, MP = 40.06, FS = 10.71, LP = 82.37.</td>
<td>NHLCS Corporate Data Warehouse (CDW): Collates data on CSF and blood specimens taken nationally &amp; submitted to NHLS laboratories</td>
</tr>
<tr>
<td>Number of cases of NBP (NBP = BPP*11)</td>
<td>Ratio of PCV9 clinical pneumonia VAR (410 cases/100,000) to all BPP VAR (37 cases/100,000) = 11:1 ± used to calculate number of NBP cases by multiplying ratio by BPP cases</td>
<td>Madhi 2005</td>
</tr>
<tr>
<td>HIV prevalence among IPD cases; used to calculate proportion of HIV-infected and HIV-uninfected cases.</td>
<td>Number of HIV-infected and HIV-uninfected cases calculated by syndrome and year</td>
<td>GERMS-SA surveillance programme DHIV data available for enhanced sites</td>
</tr>
<tr>
<td>Case fatality ratio CFR for bacteraemic syndromes</td>
<td>CFR for pneumococcal bacteraemic (meningitis, BPP, NPNM) syndromes = unadjusted pneumococcal deaths from enhanced sites/ unadjusted pneumococcal cases from enhanced sites; CFR determined by age, HIV status and syndrome.</td>
<td>GERMS-SA surveillance data</td>
</tr>
<tr>
<td>CFR for non-bacteraemic pneumonia (2005±2008 period)</td>
<td>CFR for clinical LRTI in HIV-uninfected children = 1.9% (40/2139) and in HIV-infected children = 31% (281/899).</td>
<td>Madhi 2005</td>
</tr>
<tr>
<td>CFR for non-bacteraemic pneumonia (2012±2013 period)</td>
<td>CFR for presumed bacterial pneumonia in HIV-uninfected cases = 1% (13/1326) overall for cases with hospital controls (range 0.2% to 6.3% in different sites) and &lt;1% (2/889) for cases with community controls.</td>
<td>Madhi 2015</td>
</tr>
<tr>
<td>Adjusted number of deaths</td>
<td>Adjusted number of pneumococcal deaths = CFR* Adjusted pneumococcal case numbers</td>
<td>GERMS-SA surveillance data</td>
</tr>
<tr>
<td>Incidence and death rates using mid-year population denominators</td>
<td>Incidence rates = Adjusted case numbers/population denominator Death rates = Adjusted death numbers/population denominator</td>
<td>Statistics South Africa data</td>
</tr>
<tr>
<td>HIV-specific denominators for incidence and death rates</td>
<td>Incidence and death rates by HIV status</td>
<td>Thembisa model (Johnson 2016)</td>
</tr>
</tbody>
</table>

BPP = Bacteraemic pneumococcal pneumonia; NPNM = Non-pneumonia non-menigitis; IPD = invasive pneumococcal disease; PCV9 = 9-valent pneumococcal conjugate vaccine; VAR = Vaccine-attributable reduction; VE = vaccine efficacy; CSF = cerebrospinal fluid; NHLS = National Health Laboratory Service; PCV13 = 13-valent PCV; CFR = case fatality ratio; NBP = Non-bacteraemic pneumococcal pneumonia

Provinces: GA = Gauteng, WC = Western Cape, KZN = KwaZulu-Natal, NC = Northern Cape, EC = Eastern Cape, NW = North West Province, MP = Mpumalanga, FS = Free State, LP = Limpopo Province

https://doi.org/10.1371/journal.pone.0179905.t001
Africa (Tables 3 and 4). An average of 1,100 (1,000±1,200) cases of pneumococcal meningitis (21 per 100,000 py); 8,600 (6700±11,200) bacteraemic pneumococcal pneumonia cases (163 per 100,000 py), 93,000 (71,700±123,000) non-bacteraemic pneumococcal pneumonia cases (1,797 per 100,000 py) and 4,900 (3,600±6,100) non-pneumonia non-meningitis invasive pneumococcal disease cases (93 per 100,000 py) were estimated to occur annually in children aged 0±59 months. Based on model inputs, the overall incidence for hospitalised pneumococcal disease was higher amongst infants <1 year of age (4,952 per 100,000 py) than children aged 1±4 years (1,343 per 100,000 py), a relative risk of 3.69 (95% CI 3.64±3.71); incidence was also higher among HIV-infected children (29,159 per 100,000 py) than among HIV-uninfected children aged 0±59 months (891 per 100,000 py), a relative risk of 33 (95% CI 30±34). Similar trends were observed in all syndromes (Table 4).

### Table 2. Parameters for sensitivity analysis for severe pneumococcal disease among children aged <5 years in South Africa.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value used in sensitivity model</th>
<th>Source of data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases of invasive pneumococcal disease for 3 clinical syndromes (meningitis, BPP, NPNM)</td>
<td>As for base calculations</td>
<td>GERMS-SA surveillance programme</td>
</tr>
<tr>
<td>Adjustment factor for systematic blood culturing from South African clinical trial: for Gauteng Province only</td>
<td>Ratio of IPD incidence from Soweto clinical trial (1998±1999) to the average IPD incidence from GERMS-SA surveillance in same age group from 2005±2008 (≤2 years of age) = 8.</td>
<td>Klugman 2003: VE clinical trial conducted in Soweto located in the Gauteng Province</td>
</tr>
<tr>
<td>Adjustment for specimen-taking practices in provinces other than Gauteng Province</td>
<td>As for base calculations</td>
<td>NHLS CDW</td>
</tr>
<tr>
<td>Number of cases of NBP (NBP = BPP<em>11</em>1.89)</td>
<td>PCV9 Clinical pneumonia VAR = 410 cases/100,000 and all BPP VAR = 37 cases/100,000 = ratio 11:1</td>
<td>Madhi 2005</td>
</tr>
<tr>
<td></td>
<td>Additional adjustment for vaccine probe underestimate*DVE against VT non-bacteraemic pneumonia is closer to 45% than 86% = 1.89</td>
<td>Bonten 2014</td>
</tr>
<tr>
<td>Number of cases of NBP (NBP = BPP<em>4</em>1.89)</td>
<td>PCV9 WHO CXR confirm VAR = 155 cases/100,000 and all BPP VAR = 37 cases/100,000 = ratio 4.1 with adjustment factor (1.89) = ratio 7.6:1</td>
<td>Madhi 2005</td>
</tr>
<tr>
<td>Case fatality ratio of BPP to NBP</td>
<td>Adjusted risk ratio for death of end-point pneumonia (1.98) to the adjusted risk ratio for ‘other infiltrates/abnormalities’ pneumonia (0.66) = 3:1</td>
<td>Enwere 2007</td>
</tr>
<tr>
<td></td>
<td>CFR for non-bacteraemic pneumococcal pneumonia based on published data on difference in CFR (28.2%) between hospitalised all-cause bacteraemic cases and non-bacteraemic acute medical cases (5.7%) in Kenya = 5:1.</td>
<td>Berkley 2005</td>
</tr>
<tr>
<td>Adjusted number of deaths</td>
<td>Adjusted number of pneumococcal deaths = CFR*Adjusted pneumococcal case numbersDus ed different CFR</td>
<td>GERMS-SA surveillance programme</td>
</tr>
<tr>
<td>Deaths in the community</td>
<td>(Deaths by syndrome outside hospital/Deaths by syndrome in-hospital)*(Deaths from GERMS-SA enhanced sites) by age, syndrome and year</td>
<td>Vital statistics data from Statistics South Africa</td>
</tr>
<tr>
<td>Mid-year population denominators for incidence and death rates</td>
<td>As for base case model</td>
<td>Statistics South Africa data</td>
</tr>
<tr>
<td>HIV-specifc denominators for incidence and death rates</td>
<td>As for base case model</td>
<td>Thembisa model (Johnson 2016)</td>
</tr>
</tbody>
</table>

BPP = Bacteraemic pneumococcal pneumonia; NPNM = Non-pneumonia non-meningitis; IPD = invasive pneumococcal disease; PCV9 = 9-valent pneumococcal conjugate vaccine; VAR = Vaccine-attributable reduction; VE = vaccine efficacy; CSF = cerebrospinal fluid; NHLS = National Health Laboratory Service; PCV13 = 13-valent PCV; CFR = case fatality ratio; NBP = Non-bacteraemic pneumococcal pneumonia

Provinces: GA = Gauteng, WC = Western Cape, KZN = KwaZulu-Natal, NC = Northern Cape, EC = Eastern Cape, NW = North West Province, MP = Mpumalanga, FS = Free State, LP = Limpopo Province

https://doi.org/10.1371/journal.pone.0179905.t002
### Table 3. Number of pneumococcal cases, by syndrome, in South Africa, by age and HIV status, 2005±2008 and 2012±2013.

<table>
<thead>
<tr>
<th>Syndrome/age group</th>
<th>Total</th>
<th>HIV-infected</th>
<th>HIV-uninfected</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(95% CI)</td>
<td>(95% CI)</td>
<td>(95% CI)</td>
</tr>
<tr>
<td>Pneumococcal meningitis cases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 year</td>
<td>700 (680±740)</td>
<td>190 (180±240)</td>
<td>510 (490±540)</td>
</tr>
<tr>
<td>1±4 years</td>
<td>70 (50±70)</td>
<td>230 (20±40)</td>
<td>200 (190±220)</td>
</tr>
<tr>
<td>&lt;5 years</td>
<td>1100 (1000±1200)</td>
<td>250 (230±280)</td>
<td>60 (50±80)</td>
</tr>
<tr>
<td>Bacteraemic pneumococcal pneumonia cases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 year</td>
<td>4100 (3000±5000)</td>
<td>1700 (1100±2300)</td>
<td>2400 (1900±2800)</td>
</tr>
<tr>
<td>1±4 years</td>
<td>4500 (3500±5900)</td>
<td>1800 (1200±2100)</td>
<td>2700 (2200±3000)</td>
</tr>
<tr>
<td>&lt;5 years</td>
<td>8600 (7000±12000)</td>
<td>3500 (2000±4000)</td>
<td>5100 (4700±5700)</td>
</tr>
<tr>
<td>Non-bacteraemic pneumococcal pneumonia cases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 year</td>
<td>44000 (34000±58000)</td>
<td>18000 (12000±23000)</td>
<td>26000 (21000±33000)</td>
</tr>
<tr>
<td>1±4 years</td>
<td>49000 (37300±64400)</td>
<td>19000 (12500±22400)</td>
<td>30000 (25000±38000)</td>
</tr>
<tr>
<td>&lt;5 years</td>
<td>93000 (71700±123000)</td>
<td>37000 (23000±50000)</td>
<td>56000 (48000±72000)</td>
</tr>
<tr>
<td>Non-pneumonia non-meningitis invasive pneumococcal cases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 year</td>
<td>2800 (2100±3600)</td>
<td>500 (400±800)</td>
<td>2300 (1700±3200)</td>
</tr>
<tr>
<td>1±4 years</td>
<td>2100 (1500±2600)</td>
<td>500 (400±800)</td>
<td>1600 (1100±2100)</td>
</tr>
<tr>
<td>&lt;5 years</td>
<td>4900 (3500±6200)</td>
<td>1900 (1300±2700)</td>
<td>3900 (2900±4900)</td>
</tr>
<tr>
<td>Total pneumococcal cases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 year</td>
<td>51600 (40000±68000)</td>
<td>20400 (15000±26000)</td>
<td>31200 (24000±41000)</td>
</tr>
<tr>
<td>1±4 years</td>
<td>56000 (43000±73000)</td>
<td>21400 (14000±25000)</td>
<td>34600 (26000±46000)</td>
</tr>
<tr>
<td>&lt;5 years</td>
<td>107600 (83000±140000)</td>
<td>41800 (28000±58000)</td>
<td>65800 (50000±83000)</td>
</tr>
</tbody>
</table>

CI = confidence interval; BPP = Bacteraemic pneumococcal pneumonia; NBP = Non-bacteraemic pneumococcal pneumonia; NPNM = Non-pneumonia non-meningitis invasion

Average number of cases per year;
Reduction in cases = difference in case numbers between 2005±2008 and 2012±2013

[https://doi.org/10.1371/journal.pone.0179905.t003](https://doi.org/10.1371/journal.pone.0179905.t003)

<table>
<thead>
<tr>
<th>Syndrome and age group</th>
<th>Total</th>
<th>HIV-infected (HI)</th>
<th>HIV-uninfected (HU)</th>
<th>IRR^*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Incidence rate* 2005±2008 (95% CI)</td>
<td>Incidence rate* 2012±2013 (95% CI)</td>
<td>% reduction</td>
<td>Incidence rate* 2005±2008 (95% CI)</td>
</tr>
<tr>
<td>Pneumococcal meningitis rates</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 year</td>
<td>68 (66±71)</td>
<td>18 (16±20)</td>
<td>72 (74±81)</td>
<td>1155 (965±1165)</td>
</tr>
<tr>
<td>1±4 years</td>
<td>9 (8±10)</td>
<td>1.5 (1.3±1.8)</td>
<td>88 (82±90)</td>
<td>129 (127±131)</td>
</tr>
<tr>
<td>&lt;5 years</td>
<td>21 (20±22)</td>
<td>5 (4±8)</td>
<td>77 (74±81)</td>
<td>288 (262±299)</td>
</tr>
<tr>
<td>Bacteraemic pneumococcal pneumonia rates</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 year</td>
<td>338 (300±368)</td>
<td>152 (122±200)</td>
<td>62 (60±66)</td>
<td>6511 (5530±7739)</td>
</tr>
<tr>
<td>1±4 years</td>
<td>123 (62±166)</td>
<td>42 (27±51)</td>
<td>69 (67±71)</td>
<td>762 (578±994)</td>
</tr>
<tr>
<td>&lt;5 years</td>
<td>156 (129±203)</td>
<td>64 (42±80)</td>
<td>65 (64±67)</td>
<td>1230 (1068±1396)</td>
</tr>
<tr>
<td>Non-bacteraemic pneumococcal pneumonia rates</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 year</td>
<td>4242 (3274±5574)</td>
<td>1677 (1452±2078)</td>
<td>61 (58±64)</td>
<td>71075 (6264±11908)</td>
</tr>
<tr>
<td>1±4 years</td>
<td>724 (609±871)</td>
<td>266 (194±402)</td>
<td>62 (60±65)</td>
<td>1686 (1387±1984)</td>
</tr>
<tr>
<td>&lt;5 years</td>
<td>1797 (1388±2779)</td>
<td>708 (473±843)</td>
<td>61 (58±64)</td>
<td>2821 (2187±3321)</td>
</tr>
<tr>
<td>Non-pneumonia non-meningitis invasive pneumococcal rates</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 year</td>
<td>236 (196±341)</td>
<td>49 (36±73)</td>
<td>81 (79±82)</td>
<td>4333 (2987±6467)</td>
</tr>
<tr>
<td>1±4 years</td>
<td>51 (35±68)</td>
<td>13 (9±16)</td>
<td>75 (72±76)</td>
<td>733 (489±905)</td>
</tr>
<tr>
<td>&lt;5 years</td>
<td>93 (71±123)</td>
<td>20 (15±26)</td>
<td>78 (74±80)</td>
<td>1292 (900±1690)</td>
</tr>
<tr>
<td>Total pneumonia rates</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 year</td>
<td>4652 (3363±6383)</td>
<td>1883 (1306±2353)</td>
<td>62 (59±64)</td>
<td>8376 (5197±12045)</td>
</tr>
<tr>
<td>1±4 years</td>
<td>1343 (935±1762)</td>
<td>513 (338±699)</td>
<td>62 (59±63)</td>
<td>19142 (14378±2538)</td>
</tr>
<tr>
<td>&lt;5 years</td>
<td>2074 (1603±2730)</td>
<td>797 (537±951)</td>
<td>62 (61±65)</td>
<td>2059 (1527±3692)</td>
</tr>
</tbody>
</table>
| *Per 100,000 population; CI = confidence interval; ^IRR = incidence rate ratio; IPD = invasive pneumococcal disease; BPP = Bacteraemic pneumococcal pneumonia; NBP = Non-bacteraemic pneumococcal pneumonia; NPNM = Non-pneumonia non-meningitis

https://doi.org/10.1371/journal.pone.0179905.t004
Pneumococcal related deaths and mortality rates in the pre-vaccine era

In the pre-vaccine period, an average of 5,000 (3,000±6,000) annual pneumococcal-related deaths, translating into a mortality rate of 97 per 100,000 py, was estimated to have occurred in children aged 0±59 months (Tables 5 and 6). An average of 370 (300±400) pneumococcal meningitis deaths (7 per 100,000 py), 1,300 (900±2,000) bacteraemic pneumococcal pneumonia deaths (26 per 100,000 py), 2,300 (1,500±2,500) non-bacteraemic pneumococcal pneumonia deaths (45 per 100,000 py) and 1,000 (200±2,000) non-pneumonia non-meningitis IPD deaths (19 per 100,000 py) were estimated per year. The overall pneumococcal mortality rate, based on CFRs, was higher amongst infants (303 per 100,000 py) than children aged 1±4 years (45 per 100,000 py), a relative risk of 6.73 (95% CI 6.23±7.03), and also higher amongst HIV-infected children (1,339 per 100,000 py) than amongst HIV-uninfected children aged 0±59 months (43 per 100,000 py), a relative risk of 31 (95% CI 29±32) (Table 6).

Impact of the pneumococcal conjugate vaccine and other interventions on the burden of disease in 2012±2013

Based on inputted model parameters we estimated that in 2012±2013 there was an average of 41,800 (28,000±50,000) pneumococcal cases in children aged 0±59 months, 65,800 fewer cases than would have been expected based on the incidence of disease observed in 2005±2008 among this age group (Table 3). The overall national annual incidence of pneumococcal disease in 2012±2013 was estimated as 797 per 100,000 py in children 0±59 months of age, a total rate difference of 1,277 per 100,000 (62% reduction) compared with the pre-PCV period (Table 4). The annual incidence of pneumococcal meningitis in 2012±2013 was 5 per 100,000 py in children aged 0±59 months (rate difference of 16 per 100,000, 77% reduction), 64 per 100,000 py for bacteraemic pneumococcal pneumonia (rate difference of 99 per 100,000, 65% reduction) and 708 per 100,000 py for non-bacteraemic pneumococcal pneumonia (rate difference of 1,089 per 100,000, 61% reduction). For all syndromes incidence was highest amongst infants and HIV-infected children as is expected based on the rates observed in the IPD GERMS data.

Pneumococcal related deaths and mortality rates in 2012±2013

In 2012±2013 we estimated 1,900 (1,000±2,500) annual pneumococcal deaths in children aged 0±59 months, 3,100 fewer than would have been expected based on modelled pneumococcal deaths in 2005±2008 (Table 5). The overall South African annual mortality rate for pneumococcal disease in 2012±2013 was estimated at 36 per 100,000 py in children aged 0±59 months, a rate difference of 61 per 100,000 py (63% reduction) compared with the pre-PCV years (Table 6). The mortality rate was 6.94 (6.35±7.70) times greater in infants (111 per 100,000 py) than in children aged 1±4 years (16 per 100,000 py). The average pneumococcal meningitis mortality rate in 2012±2013 was 2 per 100,000 py in children aged 0±59 months, a rate difference of 5 per 100,000 (78% reduction) compared with the 2005±2008 rate; 12 per 100,000 py for bacteraemic pneumococcal pneumonia (rate difference of 14 per 100,000, 53% reduction) and 18 per 100,000 py for non-bacteraemic pneumococcal pneumonia (rate difference of 27 per 100,000, 60% reduction).

Sensitivity analysis

The total numbers of pneumococcal cases and deaths estimated by the model changed depending on the values of key parameters used in the model (Table 2); variations resulted in both higher and lower estimates of cases and deaths, showing the importance of using the best
<table>
<thead>
<tr>
<th>Syndrome/age group</th>
<th>Total</th>
<th>HIV-infected</th>
<th>HIV-uninfected</th>
<th>Pneumococcal meningitis deaths</th>
<th>Bacteraemic pneumococcal pneumonia deaths</th>
<th>Non-bacteraemic pneumococcal pneumonia deaths</th>
<th>Non-pneumococcal non-meningitis invasive pneumococcal deaths</th>
<th>Total pneumococcal deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean number of deaths 2005±2008 (95% CI)</td>
<td>Mean number of deaths 2012±2013 (95% CI)</td>
<td>Reduction in deaths (2005/6-2012/3)</td>
<td>Mean number of deaths 2005±2008 (95% CI)</td>
<td>Mean number of deaths 2012±2013 (95% CI)</td>
<td>Reduction in deaths (2005/6-2012/3)</td>
<td>Mean number of deaths 2005±2008 (95% CI)</td>
<td>Mean number of deaths 2012±2013 (95% CI)</td>
</tr>
<tr>
<td>&lt;1 year</td>
<td>300 (200±400)</td>
<td>60 (30±90)</td>
<td>240 (170±310)</td>
<td>160 (100±240)</td>
<td>15 (4±25)</td>
<td>145 (86±165)</td>
<td>110 (90±180)</td>
<td>50 (20±90)</td>
</tr>
<tr>
<td>1±4 years</td>
<td>90 (50±130)</td>
<td>20 (10±40)</td>
<td>70 (40±90)</td>
<td>60 (10±110)</td>
<td>10 (4±20)</td>
<td>50 (10±90)</td>
<td>30 (10±60)</td>
<td>10 (5±20)</td>
</tr>
<tr>
<td>&lt;5 years</td>
<td>370 (300±400)</td>
<td>80 (50±100)</td>
<td>290 (250±330)</td>
<td>200 (100±330)</td>
<td>20 (10±40)</td>
<td>180 (90±260)</td>
<td>150 (100±200)</td>
<td>60 (40±100)</td>
</tr>
<tr>
<td>Pneumococcaldiseaseburdeninchildren</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CI=confidence interval</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><a href="https://doi.org/10.1371/journal.pone.0179905.t005">https://doi.org/10.1371/journal.pone.0179905.t005</a></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Syndrome/age group</th>
<th>Total (95% CI)</th>
<th>HIV-infected (HI) (95% CI)</th>
<th>% reduction</th>
<th>HIV-uninfected (HU) (95% CI)</th>
<th>% reduction</th>
<th>% reduction</th>
<th>MRR HI/HU 2005±2008 (95% CI)</th>
<th>MRR HI/HU 2012±2013 (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumococcal meningitis rates</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 year</td>
<td>26 (21±31)</td>
<td>6 (2±10)</td>
<td>79 (70±83)</td>
<td>490 (261±548)</td>
<td>140 (36±231)</td>
<td>71 (42±83)</td>
<td>11 (8±19)</td>
<td>4 (2±8)</td>
</tr>
<tr>
<td>1±4 years</td>
<td>2 (1±3)</td>
<td>0.6 (0.2±1)</td>
<td>77 (60±85)</td>
<td>32 (7±59)</td>
<td>12 (5±26)</td>
<td>64 (15±79)</td>
<td>1 (0.2±2)</td>
<td>0.3 (0.1±0.5)</td>
</tr>
<tr>
<td>&gt;5 years</td>
<td>7 (6±8)</td>
<td>2 (1±3)</td>
<td>78 (70±81)</td>
<td>103 (62±126)</td>
<td>25 (13±45)</td>
<td>76 (55±82)</td>
<td>3 (2±5)</td>
<td>1 (0.7±2)</td>
</tr>
<tr>
<td>Bacteraemic pneumococcal pneumonia rates</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 year</td>
<td>127 (98±167)</td>
<td>38 (19±50)</td>
<td>55 (49±59)</td>
<td>1457 (480±2454)</td>
<td>973 (22±248)</td>
<td>33 (18±49)</td>
<td>41 (15±78)</td>
<td>30 (7±66)</td>
</tr>
<tr>
<td>1±4 years</td>
<td>24 (18±31)</td>
<td>5 (0±16)</td>
<td>50 (54±68)</td>
<td>153 (0±24)</td>
<td>121 (0±44)</td>
<td>21 (12±47)</td>
<td>4 (0±12)</td>
<td>3 (0±10)</td>
</tr>
<tr>
<td>&gt;5 years</td>
<td>26 (17±40)</td>
<td>12 (2±24)</td>
<td>53 (53±61)</td>
<td>355 (137±655)</td>
<td>209 (47±84)</td>
<td>41 (30±55)</td>
<td>12 (4±22)</td>
<td>9 (2±17)</td>
</tr>
<tr>
<td>Non-bacteraemic pneumococcal pneumonia rates</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 year</td>
<td>127 (98±167)</td>
<td>50 (38±67)</td>
<td>61 (59±67)</td>
<td>2150 (1474±2607)</td>
<td>1272 (966±1872)</td>
<td>41 (30±60)</td>
<td>60 (50±88)</td>
<td>39 (26±51)</td>
</tr>
<tr>
<td>1±4 years</td>
<td>24 (18±31)</td>
<td>9 (5±15)</td>
<td>61 (50±75)</td>
<td>335 (251±445)</td>
<td>205 (118±251)</td>
<td>39 (37±53)</td>
<td>9 (7±13)</td>
<td>5 (3±6)</td>
</tr>
<tr>
<td>&gt;5 years</td>
<td>45 (28±48)</td>
<td>18 (10±26)</td>
<td>60 (50±64)</td>
<td>617 (373±642)</td>
<td>315 (154±333)</td>
<td>49 (47±61)</td>
<td>20 (12±22)</td>
<td>12 (6±16)</td>
</tr>
<tr>
<td>Non-pneumonia non-menengitis invasive pneumococcal rates</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 year</td>
<td>63 (44±141)</td>
<td>16 (5±42)</td>
<td>74 (62±72)</td>
<td>1069 (223±2172)</td>
<td>415 (0±1000)</td>
<td>61 (38±68)</td>
<td>30 (7±68)</td>
<td>13 (0±30)</td>
</tr>
<tr>
<td>1±4 years</td>
<td>8 (0±23)</td>
<td>1 (0±8)</td>
<td>85 (80±89)</td>
<td>115 (0±320)</td>
<td>26 (0±184)</td>
<td>77 (60±83)</td>
<td>3 (0±9)</td>
<td>1 (0±5)</td>
</tr>
<tr>
<td>&gt;5 years</td>
<td>19 (4±35)</td>
<td>4 (0±12)</td>
<td>78 (70±77)</td>
<td>263 (50±472)</td>
<td>66 (0±232)</td>
<td>75 (62±78)</td>
<td>9 (2±16)</td>
<td>3 (0±9)</td>
</tr>
<tr>
<td>Total pneumococcal rates</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 year</td>
<td>303 (204±424)</td>
<td>111 (77±216)</td>
<td>64 (51±62)</td>
<td>566 (317±733)</td>
<td>2800 (1556±5411)</td>
<td>46 (33±51)</td>
<td>142 (105±221)</td>
<td>87 (62±174)</td>
</tr>
<tr>
<td>1±4 years</td>
<td>45 (29±68)</td>
<td>16 (10±34)</td>
<td>64 (50±66)</td>
<td>636 (364±1048)</td>
<td>364 (132±614)</td>
<td>43 (41±64)</td>
<td>17 (10±30)</td>
<td>9 (4±17)</td>
</tr>
<tr>
<td>&gt;5 years</td>
<td>97 (63±117)</td>
<td>36 (19±58)</td>
<td>63 (51±69)</td>
<td>1339 (829±1651)</td>
<td>615 (247±977)</td>
<td>54 (51±67)</td>
<td>43 (28±56)</td>
<td>25 (13±33)</td>
</tr>
</tbody>
</table>

* Mortality rate (MR) per 100,000; MRR = Mortality rate ratio; CI = confidence interval

https://doi.org/10.1371/journal.pone.0179905.t006
estimates (S2 and S3 Tables; Tornado diagrams, S3 and S4 Figs). For the pre-vaccine estimates, the inclusion of death estimates in the community did not change the number of cases (109,500) and deaths (3700) significantly from our base model (107,600 cases and 5000 deaths), while variations in the CFR resulted in an increase in the estimated number of pneumococcal deaths and separate HIV estimates doubled the death rates likely fully accounting for HIV-infected rates. In the sensitivity analysis when we changed other parameters, including the VAR NBP/BPP ratio of 7.6:1 and the adjustment factor for systematic blood culturing the case numbers were reduced by 25% and 9% respectively. When the same parameters were altered in estimating pneumococcal deaths, numbers were reduced by 8% and 32%. Adding an additional adjustment to account for the lack of sensitivity of determining the VE in pneumonia increased the case estimates by 83% and the death estimates by 23% as a higher proportion of pneumonia was assumed to have been caused by the pneumococcus.

Discussion

Our South African pneumococcal disease burden model has estimated that in the pre-vaccine era (2005±2008) an average of 107,600 (83,000±140,000) cases of severe pneumococcal disease were experienced per year in children aged 0±59 months. In 2012±2013, 41,800 cases were estimated, a 1,277 per 100,000 py rate difference. This 62% reduction in all serotype IPD compared with a non-PCV period was likely due to PCV introduction as well as improvements in HIV care and prevention. Despite the elevated relative risk of IPD in HIV-infected children, the low HIV prevalence in children may mean that HIV prevention has a limited effect on the reduction of pneumococcal disease at a population level. Other studies in the PCV13 era, which compared reductions with the PCV7 period, showed a 64% (95% CI 59±68%) reduction in all IPD in the USA in children aged <5 years [23] and in the Gambia a 55% (95% CI 30±71%) reduction in children aged 2±23 months and 56% (95% CI 25±75%) reduction in children aged 2±4 years [24]. In the UK in 2014/2015 in all age groups the overall incidence of IPD, compared to the pre-PCV7 period, declined by 47%, but an increase was noted in non-PCV13 serotypes in this period [25].

The model estimated 5,000 (3,000±6,000) annual pneumococcal deaths in children aged 0±59 months in the pre-vaccine era; this translated into a mortality rate of 97 per 100,000 py. In children aged 0±59 months in South Africa there was an average of 61,749 annual all cause deaths, 19,072 annual all respiratory deaths and 14,927 annual pneumonia and influenza deaths over the 2005±2008 period based on Statistics South Africa data [26]; the estimated pneumococcal deaths would have made up 8%, 26% and 33% of these deaths respectively. A meta-analysis, including studies from the US, South Africa, Gambia and the Philippines, which assessed PCV efficacy on pneumonia, concluded that approximately 21.2% of severe clinical pneumonia and 35.8% of chest radiograph (CXR) confirmed pneumonia was attributable to pneumococcal disease [7]; the clinical trial estimates included lower-valency vaccines and the Philippines study included a lower efficacy vaccine. In 2012±2013 we estimated that an average of 1,900 (1,000±2,500) annual pneumococcal-related deaths occurred in children aged 0±59 months, a mortality rate reduction of 61 per 100,000 py. In 2012±2013, in children <5 years there were an estimated 35,989 overall deaths, 8,720 all respiratory and 3,946 annual pneumonia and influenza deaths per annum in South Africa, based on Statistics South Africa data [26]; the estimated pneumococcal deaths would have contributed to 5%, 22% and 48% of these deaths respectively. A review by Izadnegahdar, et. al. in 2013 [27] proposed that even in the post-PCV13 period, S. pneumoniae pneumonia may still make up 44% of pneumonia deaths due to non-PCV13 serotypes. This estimate is higher than that reported in a Child Health Epidemiology Reference Group (CHERG) systematic review which estimated that in
2011 *S. pneumoniae* made up 32.7% of pneumonia deaths in the African region and globally [28].

An updated global burden model that includes a time series from 2000±2015 [1] with annual rates, calculated a total pneumococcal death rate of 203 (164±241) per 100,000 py, 19 (16±23) per 100,000 py for pneumococcal meningitis and 166 (133±198) per 100,000 py for pneumococcal pneumonia in children aged 1±59 months in 2008 for South Africa. When compared with our model from the pre-PCV era which included children 0±59 months, the point estimates for the global model were higher than all our rates; our overall rates, 97 (63±117) per 100,000 py; pneumonia rates, 71 (45±88) per 100,000 py, and calculated meningitis rates, 7 (6±8) per 100,000 py. In 2012±2013, our overall rates, 36 (19±58) per 100,000 py and pneumonia rates, 30 (12±50) per 100,000 py, were still slightly lower than the South African estimates from the global model, 70 (57±83) and 56 (45±66) per 100,000 py respectively. The two models differed in their conceptual approach, their approach to neonatal deaths, and the inclusion of different input parameters, including case fatality rates which likely accounts for the difference in death rate estimates. The global disease burden model is centred on a proportional mortality approach, taking as a given the all-pathogen deaths for meningitis and for pneumonia provided by the Maternal and Child Epidemiology Estimation (MCEE) Group. These deaths are apportioned out to pneumococcus using country specific empirical data for meningitis and PCV clinical trial data (for pneumonia). In contrast, the South Africa specific model used a ‘bottom-up’ approach using IPD cases from surveillance data as the anchor for the estimates, but it used the same PCV clinical trial data for pneumonia estimates. Lastly our model used HIV prevalence rates differently to other models; our model used HIV prevalence rates for children identified with pneumococcal disease from our surveillance programme, while other models usually apply community HIV prevalence rates.

Stratifying data by HIV status revealed a 47% reduction in the incidence of all serotype pneumococcal disease in HIV-uninfected children, and a 48% reduction in HIV-infected children aged 0±59 months based on data inputted into the model. Based on observations from IPD trends in South Africa, and assuming that these IPD trends reflect all pneumococcal trends, it is likely that all of the reductions in HIV-uninfected children and approximately half of the reductions in HIV-infected children may be attributable to the vaccine [6]. In HIV-infected children antiretroviral therapy and improvements in the prevention of mother-to-child transmission of HIV programme, contribute to reductions in all serotypes.

Since the IPD syndromic distribution observed in 2005±2008 and in 2012±2013 drives the case and death estimates for these two periods, any reductions by syndrome are inherently a result of the differences observed by syndrome in the IPD cases. As a result of those differences, the model output had reductions in all syndromes between the pre- and the post-PCV periods. Similarly reductions were greatest in infants and HIV-infected children, the latter driven by the relative risk inputted into the model. Similarly the overall pneumococcal mortality rate, which was driven by CFRs inputted into the model, was higher amongst infants.

This study is subject to a number of limitations. First, the model is anchored on the GERMS-SA IPD surveillance data which is primarily drawn from public sector laboratories, so may not be representative of all sectors in South Africa; however, 84% of the population access public health care in South Africa [13]. The surveillance programme aims to include all cases including those detected in private laboratories however not all private sector cases may be captured. Second, a number of assumptions were made to adjust for the lack of sensitivity of detecting cases. Although all the assumptions were based on published literature, it is possible that some of these assumptions were not accurate. We could also not find data on all possible model parameters, for example the relative risk of pneumococcal disease in HIV-infected children pre- and post-ART introduction. To simplify the model some estimates, for example
VARs, were used for all patients even though in reality there may be some differences by age
and HIV status. Some estimates were only available for the pre-vaccine period and were
assumed to be relevant to the post-PCV period, which may have underestimated the reduction
in disease in the post-PCV period. The variation in our estimates was shown in our sensitivity
analysis which demonstrated the wide range of results possible by varying key parameters. This
shows the importance of using best estimates for key values. Third, we only calculated the bur-
den of severe pneumococcal disease and did not include pneumococcal disease that was cared
for only in the outpatient setting. We were unable to include otitis media burden calculations
in this model due to a lack of reliable African data. A US study showed that in children <5
years of age, acute otitis media made up 74% of pneumococcal cases [29], so this burden model
is an underestimate of true pneumococcal burden. Fourth, as we used adjustment factors from
a PCV-probe study in children [16] which based the diagnosis of pneumonia on clinical and
CXR findings only, both of which have limitations in detection, we may have underestimated
the burden of non-bacteraemic pneumonia in our calculations. Fifth, we assumed similar PCV
impact across all age strata among children less than 5 years and did not account for direct or
indirect vaccine effects separately; we assumed that by using actual reported cases this would
account for different impact rates. Sixth, there was a reduction in all-cause pneumonia deaths
in South Africa over the 2005 to 2008 period [26]; for the pre-PCV death rate calculations we
assumed that rates were similar over this period and we may have therefore overestimated the
change in pneumococcal death rates when we compared the average and not the end of the
pre-vaccine period (2008) with 2012±2013. Seventh, we included neonates as part of the <1
year old age group and did not separate them out due to small case numbers and lack of spe-
cific adjustment parameters for this group only. Although the epidemiology of disease in neo-
ates differs somewhat from older children, leaving this group out may have underestimated
the total burden of disease. Eighth, rates of disease are not entirely independent of pneumococ-
al disease and it is possible that provinces with higher rates of culture also have higher rates of
pneumococcal disease [30]. Lastly, we used bootstrapping to generate confidence intervals to
try and account for some of the uncertainty around our estimates; however some external
parameters derived from different settings and the full scope of variability may not be fully rep-
resented by our assumptions. We attempted to reduce this by including as many factors as pos-
sible in our bootstrap resampling and running 1,000 replications. It is however likely that the
confidence intervals around case count and impact estimates are narrower than in reality.

GERMS-SA IPD surveillance data demonstrated a reduction in vaccine-type IPD of around
50% among adults aged 25 to 44 years by 2012 [6]. The indirect vaccination effects were similar
in HIV-infected (40%) and HIV-uninfected (52%) adults. It would be useful to calculate simi-
lar burden estimates, as in this paper, for individuals ≥5 years of age.

In summary, pneumococcal disease represents a major public health burden in children
aged 0±59 months in South Africa. Pneumococcal conjugate vaccination, in conjunction with
other interventions, has resulted in a significant reduction in severe pneumococcal disease
with approximately 130,000 cases and 5,000 deaths averted over a 5-year period. Although
other interventions likely contribute to reductions in pneumococcal disease it is possible that
PCV use was the major contributor to the reduction in invasive disease.

Supporting information

S1 Text. Supplementary material: Estimated severe pneumococcal disease cases and deaths
before and after pneumococcal conjugate vaccine introduction in children younger than 5
years of age in South Africa.

(DOCX)

S2 Table. Sensitivity analysis for case numbers showing key variables altered in analysis, 2005±2008 and 2012±2013.

S3 Table. Sensitivity analysis for numbers of deaths showing key variables altered in analysis, 2005±2008 and 2012±2013.

S1 Fig. Initial step in estimating the burden of invasive and non-invasive pneumococcal cases in children aged <5 years in South Africa, 2005±2008 and 2012±2013.

S2 Fig. Second step in estimating the burden of invasive and non-invasive pneumococcal cases in children <5 years in South Africa, 2005±2008 and 2012±2013.

S3 Fig. Tornado sensitivity diagram representing change in pneumococcal case estimates in children <5 years of age in the pre-vaccine era, when values of key variables are modified.

S4 Fig. Tornado sensitivity diagram representing change in pneumococcal death estimates in children <5 years of age in the pre-vaccine era, when values of key variables are modified.

Acknowledgments

We acknowledge all GERMS-SA clinical and laboratory staff members who contribute towards this surveillance programme; the staff at the NICD laboratory, Centre for Respiratory Diseases and Meningitis, who process and characterise isolates submitted from all the GERMS-SA sites; and the NHLS Corporate Data Warehouse for assistance with data extraction.

Author Contributions

Conceptualization: Claire von Mollendorf, Stefano Tempia, Anne von Gottberg, Cheryl Cohen.

Data curation: Claire von Mollendorf.

Formal analysis: Claire von Mollendorf, Stefano Tempia.


Supervision: Anne von Gottberg.

Validation: Claire von Mollendorf.

Visualization: Claire von Mollendorf.

Writing ± original draft: Claire von Mollendorf.
Writing ± review & editing: Claire von Mollendorf, Stefano Tempia, Anne von Gottberg, Susan Meiring, Vanessa Quan, Charles Feldman, Jeane Cloete, Shabir A. Madhi, Katherine L. O’Brien, Keith P. Klugman, Cynthia G. Whitney, Cheryl Cohen.

References


