Long-term effect of pneumococcal conjugate vaccines on invasive pneumococcal disease incidence among people of all ages from national, active, laboratory-based surveillance in South Africa, 2005–19: a cohort observational study

Anne von Gottberg, Jackie Kleynhans, Linda de Gouveia, Stefano Tempia, Susan Meiring, Vanessa Quan, Mignon du Plessis, Claire von Mollendorf, Penny Crowther-Gibson, Theunis Avenant, Nicolette du Plessis, Ranmini Kularatne, Vindana Chibabhai, Shabir A Madhi, Keith P Klugman, Cynthia G Whitney, Cheryl Cohen, on behalf of GERMS-SA

Summary

Background In South Africa, 7-valent pneumococcal conjugate vaccine (PCV7) was introduced in 2009 and 13-valent PCV (PCV13) was introduced in 2011, both in a two plus one schedule. We evaluated the ongoing effects of PCV on the prevention of invasive pneumococcal disease (IPD) over 15 years of sustained surveillance in South Africa before the COVID-19 pandemic.

Methods We conducted national, active, laboratory-based surveillance for IPD among all ages in South Africa, including isolate serotyping and susceptibility testing. We fitted linear regression models with vaccine covariates to imputed IPD case counts each year by serotype and age to compare expected and actual IPD cases in 2019, which was the main outcome. Vaccine effects were set to zero to identify expected incidence after the introduction of PCV7 and PCV13.

Findings From Jan 1, 2005, to Dec 31, 2019, surveillance identified 52 957 IPD cases. Among the 50 705 individuals with age data available, 9398 (18·5%) were infants aged younger than 2 years. Compared with expected case numbers (no vaccination) predicted using all available data, overall IPD rates among children younger than 2 years declined by 76·0% (percentage risk difference; 95% CI –79·0 to –72·8%) in 2019; notably, PCV7 and additional PCV13 serotype IPD rates declined by 95·5% (–97·0 to –93·4%) and 93·8% (–96·2 to–90·5%), respectively, whereas non-vaccine serotypes (NVTs) did not change significantly. Among adults aged 25–44 years, overall IPD declined by 50·4% (–54·2 to –46·3%), and PCV7 and additional PCV13 serotype IPD rates declined by 86·1% (–88·7 to –83·1%) and 77·2% (–80·9 to –73·0%), respectively, whereas NVTs increased by 78·5% (56·8 to 103·4%). Individuals aged older than 64 years also benefited from declines in IPD (–30·2%; –41·9 to –16·2%), but NVTs increased (234·9%; 138·1 to 379·4%).

Interpretation We documented sustained direct and indirect benefits of PCV across age groups, and NVT increases in adults older than 24 years. Higher valency PCVs would have the added benefit of preventing this residual disease.

Funding National Institute for Communicable Diseases of the National Health Laboratory Service (South Africa) and US Agency for International Development Antimicrobial Resistance Initiative, US Centers for Disease Control and Prevention.

Introduction

Pneumococcal conjugate vaccine (PCV) effectiveness in preventing pneumococcal disease in children has been well documented, initially for 7-valent PCV (PCV7; Pfizer, NY, USA)[1] and then for higher valency vaccines such as 10-valent PCV (PCV10; Synflorix, GlaxoSmithKline, Rixensart, Belgium)[2] and 13-valent PCV (PCV13; Prevnar 13 and Prevenar 13, Pfizer, NY, USA).[3] The earliest effectiveness reports were from high-income countries but, more recently, similar findings have been reported from middle-income and low-income countries for PCV7, PCV10,[4] and PCV13.[5,6] The effectiveness of PCV in reducing vaccine serotype disease has also been reported from regions with a high disease burden, and countries with a high HIV prevalence that have an additional pneumococcal disease burden among younger adults.[7] Nevertheless, there are few data on the long-term effects of childhood PCV immunisation a decade after vaccination, including on the effect of childhood PCV immunisation on long-term patterns of possible serotype replacement invasive pneumococcal disease (IPD).

Childhood PCV immunisation changes the patterns of pneumococcal carriage, with non-vaccine serotype (NVT) strains filling the gap left by vaccine serotypes. However, the overall carriage prevalence has stayed the same in many settings.[8] Many high-income countries

Lancet Glob Health 2024; 12: e1470–84

See **Comment** page e1375

Centre for Respiratory Diseases and Meningitis (Prof A von Gottberg PhD, J Kleynhans PhD, L de Gouveia MT, M du Plessis PhD, C von Mollendorf PhD, Prof C Cohen PhD) **and Division of Public Health Surveillance and Response** (S Meiring PhD, V Quan MBBCh MPH, P Crowther-Gibson MSc), **National Institute for Communicable Diseases, a division of the National Health Laboratory Service, Johannesburg, South Africa; School of Pathology** (Prof A von Gottberg, L de Gouveia, M du Plessis, R Kularatne FCPath [SA] Micro), **School of Public Health** (J Kleynhans, S Tempia PhD, C von Mollendorf, Prof C Cohen), **South African Medical Research Council Vaccines and Infectious Diseases Analytics Research Unit** (Prof S A Madhi PhD), **and Wits Infectious Diseases and Oncology Research Institute** (Prof S A Madhi), **Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa; Global Influenza Program, World Health Organization, Geneva, Switzerland** (S Tempia); **Department of Paediatrics, Kalafong Provincial Tertiary Hospital, Faculty of Health Sciences, University of Pretoria, Pretoria, South Africa** (Prof T Avenant FCPaed [SA], N du Plessis PhD); **Rahima Moosa Mother and Child Hospital** (R Kularatne) **and Charlotte Maxeke Johannesburg Academic Hospital** (V Chibabhai FCPath [SA] Micro),

School of Pathology, Faculty of Health Sciences, University of the Witwatersrand and National Health Laboratory Service, Johannesburg, South Africa; Pneumonia and Pandemic Prevention, Surveillance and Epidemic Control, Bill & Melinda Gates Foundation, Seattle, WA, USA (Prof K P Klugman PhD); Global Health Institute and Rollins School of Public Health, Emory University, Atlanta, GA, USA (C G Whitney MD MPH)

Correspondence to: Prof Anne von Gottberg, Centre for Respiratory Diseases and Meningitis, National Institute for Communicable Diseases, a division of the National Health Laboratory Service, Johannesburg 2131, South Africa **annev@nicd.ac.za**

or

Prof Cheryl Cohen, Centre for Respiratory Diseases and Meningitis, National Institute for Communicable Diseases, a division of the National Health Laboratory Service, Johannesburg 2131, South Africa|**cherylc@nicd.ac.za**

Research in context

Evidence before this study

We searched PubMed between July 19, 2023, to Feb 29, 2024, for papers published only in English, using the search terms "invasive pneumococcal disease (impact)" AND "pneumococcal conjugate vaccine (PCV)" OR "PCV effectiveness" AND "Africa". We identified 112 publications, 91 of which were published after 2008 (2009 was the year in which pneumococcal conjugate vaccine [PCV] was first introduced into routine childhood immunisation programmes in Africa). Of these 91 studies, five studies from four countries discussed the effect on invasive pneumococcal disease (IPD) 5 or more years after the introduction of routine childhood PCV immunisation. One study in Malawi (N=2638) over 13 years using a three plus zero schedule (three primary doses [at ages 6, 10, and 14 weeks] with no booster dose) documented the direct effects at 7 years after 13-valent PCV introduction (with their study period ending on Dec 31, 2018), and found a 74% reduction in vaccine serotype IPD in children aged 1–4 years and a 79% reduction in children aged 5–14 years, with no non-vaccine serotype replacement. Although in the same setting and period, another study, limited to infants younger than 90 days, identified a reduction in the disease due to indirect effects. Another study from Zambia, using the same vaccine schedule as the Malawi study, was limited to meningitis among children younger than 5 years, and documented a reduction in pneumococcal meningitis and vaccine serotypes 6 years after the introduction of 10-valent PCV (PCV10; 148 episodes identified of pneumococcal meningitis over 10 years). In The Gambia, 342 cases of IPD were identified in one study with a three plus zero vaccine schedule, showing a reduction of 80% in overall IPD incidence. In Kenya, PCV10 was introduced with a catch-up campaign, and one study identified 667 cases of IPD over 17 years, documenting reductions in vaccine serotype IPD in children younger than 5 years (>90% reduction) and individuals older than 15 years (approximately 80% reduction), but without significant replacement disease.

Added value of this study

Our study adds data from a large, stable, systematic, active national surveillance programme of people with IPD (N=52 957) in South Africa, with data collected over 15 years. Participants were from all age groups. We documented sustained reductions in vaccine serotype IPD in children directly benefiting from vaccination (PCV was introduced in the routine childhood immunisation programme with a two plus one schedule). Sustained indirect benefits in those too young or too old to directly benefit from PCV were also documented, but with some vaccine serotypes (4, 19A, and 19F) still causing some residual disease. In addition, little serotype replacement was shown over the study period, with older children, adults, and those older than 64 years showing a significant increase in non-vaccine type disease, primarily serotype 8. The previously published early benefits of declines in antimicrobial resistant IPD were also shown in our study in South Africa.

Implications of all the available evidence

PCV introduction in Africa has been associated with sustained reductions in vaccine serotype disease in groups targeted for vaccination as well as individuals not targeted for vaccination through reductions in transmission. There have been low levels of serotype replacement over an extended period after vaccine introduction. Ongoing surveillance will be needed to monitor and assess the effect of the change in vaccine formulation with the more affordable Serum Institute of India PCV10 being introduced in South Africa in 2024, with potentially substantial cost saving for the immunisation programme. Disease due to vaccine serotypes 4 and 18C would need to be monitored carefully, because they are not covered by Serum Institute of India PCV10. Other countries might feel confident in introducing schedules similar to South Africa (a two plus one schedule) and consider further dose reductions (a one plus one schedule) with this evidence that indirect effects are sustained over many years in multiple settings.

have reported NVT disease increases after the introduction of PCV10–13; however, the increase in NVT disease was lower than expected after the increase in NVT carriage.[9]

To improve serotype coverage and make PCV more affordable, new vaccines are currently being assessed. A more affordable novel Serum Institute of India PCV10 (Serum Institute of India, Pneumosil, Pune, India) contains ten of the serotypes in PCV13 but excludes serotypes 3, 4, and 18C.[10] Serum Institute of India PCV10 has been proposed to replace PCV13 in South Africa in 2024. 15-valent PCV (PCV15; Vaxneuvance, Merck Sharp & Dohme, Whitehouse Station, NJ, USA) adds 22F and 33F to the 13 serotypes in PCV13 (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) and has recently been recommended for use in children in the USA.[11] 20-valent PCV (PCV20; Prevnar 20, Pfizer, NY, USA), which adds serotypes 8, 10A, 11A, 12F, and 15B/C to PCV15 to make it PCV20, is currently only recommended for use in adults.[11]

PCVs have been shown to reduce pneumococcal disease not only in vaccinated infants and children, but also in unvaccinated children and adults at risk of pneumococcal disease. These indirect effects have greatly increased the cost–benefit ratio.[12] Data from South Africa have documented that adults living with HIV and children too young to be vaccinated benefited from the initial declines in PCV7 serotype disease, suggesting early indirect effects.[5] It is unclear to what degree these benefits have been sustained over time, and for some countries the full benefits might only be apparent 5–10 years after vaccine intoduction.[13] Any changes to the vaccine schedules, such as reducing three or four dose schedules (three plus zero, two plus one, or three plus one)

to a one plus one schedule, or changes in vaccine formulations, will benefit from the documentation of whether indirect effects are sustained over time.

Another benefit of routine childhood PCV immunisation has been the decline in antibiotic non-susceptible pneumococcal disease, both in vaccinated and unvaccinated age groups.[14] In many settings this decline has reversed the trend of the steadily increasing prevalence of antimicrobial resistance that had been modelled to increase unabated in the absence of another intervention.[14] Some of these initial declines were counteracted by increases in NVT diseases that were antibiotic non-susceptible.[15] Initial data from South Africa showed promising declines in vaccine serotype disease from antibiotic non-susceptible strains.[5] Nevertheless, ongoing monitoring is required to establish if the initial findings are sustained with ongoing selective pressure from antibiotic use and within a population with a high HIV prevalence.

In South Africa, PCV7 was introduced in 2009 and PCV13 in 2011, in a two plus one infant schedule (doses at the ages of 6 weeks and 14 weeks, and at 9 months). Using data from national, active, laboratory-based surveillance for IPD in South Africa, we aimed to evaluate the ongoing effects (direct and indirect) of PCV on the prevention of PCV13 serotypes, effects on replacement disease by NVT, and effects on antimicrobial resistance over 15 years of surveillance. We restricted the analysis to up to Dec 31, 2019, to avoid confounding after the effects of the COVID-19 pandemic from 2020.

Methods

Study design and participants

The study was a cohort observational study using national, laboratory-based surveillance data in South Africa for the primary outcome of IPD. In 2019, the South African population was estimated to be 57·7 million, of which 2 225 505 (4%) were younger than 2 years, 3 348 426 (6%) were aged 2–4 years, 18 721 960 (32%) were aged 25–44 years, and 3 419 058 (6%) were older than 64 years.[16] HIV prevalence among pregnant women was stable at 30% from 2004 to 2019.[17] The indirect effects of PCV were considered in this study in age groups older than 14 years (predominantly unvaccinated). In addition, we evaluated infants younger than 10 weeks for the possible indirect effects of PCV: a low proportion (9–85%)[18] of children 1 month after the 6-week PCV dose had seroprotective titres to the majority of serotypes, and one dose at 6 weeks had poor effectiveness in a nested case–control study.[5] The population of children younger than 10 weeks was estimated from the relative proportion of infants younger than 3 months, assuming the birth rate was constant throughout the year and adjusting for neonatal and infant mortality.

Within the population of South Africa (in whom the IPD outcome was measured) PCV vaccine use was estimated from multiple sources. The coverage of the third PCV dose in 2009 was 10%. From 2011 to 2018, the estimated coverage ranged between 62% and 85%, with 2019 coverage at 86%, according to official or administrative coverage estimates.[19] Estimates of the receipt of the third PCV dose by the age of 12 months during a nationwide coverage survey in 2019 was 83·9% overall (ranging from 65% to 100% between different districts).[20] Routine vaccines are accessed through the public sector (which includes >80% of the population), with low use of PCV after registration of PCV in 2005 in the private sector before the introduction of the routine vaccination programme in 2009.[21] Although recommended, pneumococcal vaccines (both PCV13 and 23-valent pneumococcal polysaccharide vaccine [PPV23]) are underused in people aged 65 years or older, among whom exact coverage is unknown.[22]

Ethics approval was obtained for GERMS-SA surveillance (approval numbers M081117 and M1809107) from the Human Research Ethics Committee of the University of the Witwatersrand, Johannesburg, South Africa. GERMS-SA surveillance study protocols were also approved by the local hospital and provincial ethics committees, as required. Patients gave written informed consent for the enhanced surveillance data.

IPD surveillance

National laboratory-based surveillance for IPD in South Africa began in 1999, which is where all data for our study were obtained from. In addition, since 2003, enhanced surveillance (GERMS-SA) at 24 sentinel hospitals, located in all nine provinces in South Africa, collected additional information including admission date, HIV infection status, discharge diagnosis, and outcome.[5] Our primary outcome was the difference between actual and expected IPD cases throughout the country, from private and public sector laboratories. Cases of IPD were defined as illnesses where *Streptococcus pneumoniae* was cultured from normally sterile site specimens (eg, cerebrospinal fluid [CSF] or blood or joint fluid) and included all episodes identified from Jan 1, 2005, to Dec 31, 2019. Duplicate isolates within 21 days of the initial positive culture were excluded. Quarterly audits of the national laboratory information system ensured completeness of reporting from the public sector.[5]

Serotyping and susceptibility testing

Pneumococci were serotyped by the Quellung method (SSI Diagnostica, Copenhagen, Denmark) at the national reference laboratory at the National Institute for Communicable Diseases, Johannesburg, South Africa. Due to cross-reactions acknowledged by the manufacturer, we classified serotypes 29, 34, and 42, and serogroups 35 and 47 into a category called pool G. We identified antimicrobial minimum inhibitory concentrations using broth microdilution.[5] Isolates with

	Patients with IPD 2005–08 (before PCV)	Patients with IPD 2009–12 (transitional period)	Patients with IPD 2013–19 (after PCV13)	Patients with IPD total
Year				
Year data available	19 197 (36·3%)	15 986 (30·2%)	17 774 (33·6%)	52 957 (100·0%)
2005	4886 (25·5%)	..	..	..
2006	4733 (24·7%)	..	..	..
2007	4743 (24·7%)	..	..	..
2008	4835 (25·2%)	..	..	..
2009	..	4762 (29·8%)	..	..
2010	..	4197 (26·3%)	..	..
2011	..	3804 (23·8%)	..	..
2012	..	3223 (20·2%)	..	..
2013	..	..	2866 (16·1%)	..
2014	..	..	2732 (15·4%)	..
2015	..	..	2638 (14·8%)	..
2016	..	..	2433 (13·7%)	..
2017	..	..	2440 (13·7%)	..
2018	..	..	2313 (13·0%)	..
2019	..	..	2352 (13·2%)	..
Sex				
Sex data available	18 753/51 992 (36·1%)	15 669/51 992 (30·1%)	17 570/51 992 (33·8%)	51 992 (98·2%)*
Female	9563/18 753 (51·0%)	8177/15 669 (52·2%)	8835/17 570 (50·3%)	26 575/51 992 (51·1%)
Male	9190/18 753 (49·0%)	7492/15 669 (47·8%)	8735/17 570 (49·7%)	25 417/51 992 (48·9%)
Age				
Age data available	18 328/50 705 (36·1%)	15 218/50 705 (30·0%)	17 159/50 705 (33·8%)	50 705 (95·7%)*
<2 years	4568/18 328 (24·9%)	2522/15 218 (16·6%)	2308/17 159 (13·5%)	9398/50 705 (18·5%)
2–4 years	1352/18 328 (7·4%)	931/15 218 (6·1%)	571/17 159 (3·3%)	2854/50 705 (5·6%)
5–14 years	1695/18 328 (9·2%)	1393/15 218 (9·2%)	973/17 159 (5·7%)	4061/50 705 (8·0%)
15–24 years	1086/18 328 (5·9%)	990/15 218 (6·5%)	1037/17 159 (6·0%)	3113/50 705 (6·1%)
25–44 years	6849/18 328 (37·4%)	6188/15 218 (40·7%)	7161/17 159 (41·7%)	20 198/50 705 (39·8%)
45–64 years	2261/18 328 (12·3%)	2570/15 218 (16·9%)	3843/17 159 (22·4%)	8674/50 705 (17·1%)
>64 years	517/18 328 (2·8%)	624/15 218 (4·1%)	1266/17 159 (7·4%)	2407/50 705 (4·7%)
Laboratory specimen type				
Cerebrospinal fluid	6735 (35·1%)	6472 (40·5%)	6329 (35·6%)	19 536 (36·9%)
Blood	10 733 (55·9%)	7819 (48·9%)	9977 (56·1%)	28 529 (53·9%)
Other†	1729 (9·0%)	1695 (10·6%)	1468 (8·3%)	4892 (9·2%)
Serotype group‡				
Serotyping result available	13 724/35 776 (38·4%)	10 832/35 776 (30·3%)	11 220/35 776 (31·4%)	35 776 (67·6%)*
PCV13 serotypes	10 340/13 724 (75·3%)	8034/10 832 (74·2%)	4402/11 220 (39·2%)	22 776/35 776 (63·7%)
Antimicrobial susceptibility				
Antimicrobial susceptibility result available	13 722/35 766 (38·4%)	10 829/35 766 (30·3%)	11 215/35 766 (31·4%)	35 766 (67·5%)*
Penicillin non-susceptible	4970/13 722 (36·2%)	4167/10 829 (38·5%)	3169/11 215 (28·3%)	12 306/35 766 (34·4%)
Multidrug resistant	2664/13 722 (19·4%)	2264/10 829 (20·9%)	1754/11 215 (15·6%)	6682/35 766 (18·7%)
Proportion of IPD cases that presented at enhanced surveillance sites	8905 (46·4%)*	6300 (39·4%)*	6651 (37·4%)*	21 856 (41·3%)*
HIV status				
HIV status known	5513/8905 (61·9%)	4725/6300 (75·0%)	5041/6651 (75·8%)	15 279/21 856 (69·9%)
Positive for HIV	4488/5513 (81·4%)	3398/4725 (71·9%)	3266/5041 (64·8%)	11 152/15 279 (73·0%)
Clinical presentation				
Clinical presentation data available	7671/8905 (86·1%)	5929/6300 (94·1%)	6325/6651 (95·1%)	19 925/21 856 (91·2%)
Meningitis	2355/7671 (30·7%)	2108/5929 (35·6%)	2110/6325 (33·4%)	6573/19 925 (33·0%)
Pneumonia	4466/7671 (58·2%)	3276/5929 (55·3%)	3366/6325 (53·2%)	11 108/19 925 (55·7%)
Other§	850/7671 (11·1%)	545/5929 (9·2%)	849/6325 (13·4%)	2244/19 925 (11·3%)

(Table 1 continues on next page)

	Patients with IPD 2005–08 (before PCV)	Patients with IPD 2009–12 (transitional period)	Patients with IPD 2013–19 (after PCV13)	Patients with IPD total
(Continued from previous page)				
Duration of stay in hospital				
Duration data available	7354/8905 (82·6%)	5706/6300 (90·6%)	6026/6651 (90·6%)	19 086/21 856 (87·3%)
≥6 days	4256/7354 (57·9%)	3380/5706 (59·2%)	3649/6026 (60·6%)	11 285/19 086 (59·1%)
Vaccination status				
Patients at enhanced sites and younger than 5 years with vaccination history assessed	2911/8905 (32·7%)	1528/6300 (24·3%)	1244/6651 (18·7%)	5683/21 856 (26·0%)
Vaccination status known	2303/2911 (79·1%)	1390/1528 (91·0%)	1164/1244 (93·6%)	4857/5683 (85·5%)
Not vaccinated	2303/2303 (100·0%)	954/1390 (68·6%)	407/1164 (35·0%)	3664/4857 (75·4%)
Partially vaccinated for age¶	0	354/1390 (25·5%)	629/1164 (54·0%)	983/4857 (20·2%)
Completely vaccinated for age	0	82/1390 (5·9%)	128/1164 (11·0%)	210/4857 (4·3%)
Comorbidities				
Comorbidity or risk factor data available‖	5449/8905 (61·2%)	4818/6300 (76·5%)	5436/6651 (81·7%)	15 703/21 856 (71·8%)
Comorbidity or risk factor present	1908/5449 (35·0%)	1934/4818 (40·1%)	2582/5436 (47·5%)	6424/15 703 (40·9%)
Antibiotics				
Data available on whether antibiotics were received before hospitalisation	5341/8905 (60·0%)	4334/6300 (68·8%)	4928/6651 (74·1%)	14 603/21 856 (66·8%)
Did receive antibiotics before hospitalisation	180/5341 (3·4%)	218/4334 (5·0%)	197/4928 (4·0%)	595/14 603 (4·1%)
Data available on whether antibiotics were received during hospitalisation	8556/8905 (96·1%)	5661/6300 (89·9%)	5843/6651 (87·9%)	20 060/21 856 (91·8%)
Did receive antibiotics during hospitalisation	6915/8556 (80·8%)	5386/5661 (95·1%)	5380/5843 (92·1%)	17 681/20 060 (88·1%)
In-hospital outcome of IPD				
Outcome data available	7394/8905 (83·0%)	5762/6300 (91·5%)	6059/6651 (91·1%)	19 215/21 856 (87·9%)
Died	2046/7394 (27·7%)	1760/5762 (30·5%)	1916/6059 (31·6%)	5722/19 215 (29·8%)

Data are n (%) or n/N (%). A total of 52 957 IPD cases were identified (actual, not imputed), in addition to the subset with additional information collected through enhanced surveillance. PCV7 was introduced in 2009 and PCV13 was introduced in 2011. IPD=invasive pneumococcal disease. PCV=pneumococcal conjugate vaccine. PCV7=7-valent PCV. PCV13=13-valent PCV. *Of total episodes reported. †Includes joint, pleural, pericardial, peritoneal, and vitreous fluids. ‡Serotype groups classified by PCV13. PCV13–4, 6B, 9V, 14, 18C, 19F, 23F, 1, 3, 5, 7F, and 19A compared with all serotypes not in PCV13. §Includes bacteraemia without focus, bacteraemia with sites not related to pneumonia or meningitis, deep-seated abscesses, and endophthalmitis. ¶At least one dose of PCV7 or PCV13. ‖Pre-existing risk conditions were defined as any one or more of the following: alcohol dependency, burns, chronic lung disease (including asthma, chronic obstructive pulmonary disorder, or cystic fibrosis), chronic liver disease, chronic renal disease, cardiac conditions (including valvular disease and heart failure), cerebrovascular accident, stroke, neuromuscular diseases, cerebral palsy, smoking, metabolic diseases (including diabetes), head injury, cerebrospinal fluid leaks, ventricular shunts, cochlear implants, primary immunodeficiency conditions, complement deficiency, immunosuppression treatment (steroids, chemotherapy, or cancer treatment) protein energy malnutrition, functional or anatomic asplenia (including sickle cell disease), malignancy, organ transplant, chromosomal conditions (including Down syndrome), prematurity, and aplastic anaemia.

Table 1: **Comparison of the characteristics of patients with IPD in 2005–19 in South Africa, by period**

minimum inhibitory concentrations of 12 mg/L or more were interpreted as non-susceptible to penicillin, and 1 mg/L or more were interpreted as non-susceptible to ceftriaxone. Multidrug resistance was classified as non-susceptible to three or more drug classes among penicillin, ceftriaxone, erythromycin, clindamycin, chloramphenicol, tetracycline, rifampin, and trimethoprim–sulfamethoxazole. Sensitivity analyses are discussed in appendix 1 (p 3).

Statistical analysis

For analysis of trends, serotypes were categorised as PCV7 serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F), additional PCV13 serotypes (1, 3, 5, 6A, 7F, and 19A), and NVTs (serotypes not in PCV13). Where age, serotype, or antibiotic susceptibility data were not available, we imputed the total number of cases (referred to as imputed case counts), by assuming that the information was missing at random and that the distribution of age within each year was the same as for cases with known age, and that the age-specific proportion of serotype category among cases with missing pneumococcal isolates was the same as among cases with available data each year by age group.[1] IPD cases were not stratified by known HIV infection. Where antibiotic susceptibility data were not available, we assumed that the distribution of susceptibility was the same as among isolates from the same specimen type (CSF *vs* other specimens) for the specific year. The proportion of data imputed for each category and year was calculated by dividing the number of added cases by the imputed case numbers for each respective category.

See Online for appendix 1

We fitted individual linear regression models to imputed IPD case counts from 2005 to 2019 by serotype to compare expected and actual IPD cases in 2019 (all, PCV7, PCV13, and NVTs), age (<10 weeks, <2 years, 2–4 years, 5–14 years, 15–24 years, 25–44 years, 45–64 years, and >64 years), and

	Cases per 100 000 person-years (95% CI)		Absolute risk difference (95% CI)	% risk difference (95% CI)
	Modelled incidence	Expected incidence		
All ages				
All serotypes	3·9 (3·8 to 4·0)	8·1 (6·9 to 9·3)	−4·2 (−3·9 to −4·5)	−51·9 (−54·3 to −49·4)
PCV7 serotypes	0·5 (0·4 to 0·5)	3·3 (1·5 to 7·3)	−2·9 (−2·7 to −3·0)	−86·2 (−87·9 to −84·3)
Additional PCV13 serotypes	0·6 (0·5 to 0·7)	3·1 (1·5 to 6·6)	−2·5 (−2·3 to −2·6)	−80·3 (−82·5 to −77·9)
Non-vaccine serotypes	2·9 (2·7 to 3·1)	1·6 (1·1 to 2·6)	1·3 (1·5 to 1·1)	78·1 (64·4 to 93·0)
Aged <10 weeks				
All serotypes	31·1 (27·4 to 35·5)	70·5 (39·1 to 128·8)	−39·3 (−27·6 to −51·1)	−55·8 (−66·0 to −43·0)
PCV7 serotypes	2·7 (1·7 to 4·1)	27·0 (11·1 to 68·2)	−24·3 (−17·9 to −30·6)	−90·0 (−96·0 to −79·0)
Additional PCV13 serotypes	3·4 (2·3 to 5·2)	13·4 (2·2 to 81·5)	−10·0 (−5·2 to −14·8)	−74·5 (−88·8 to −47·5)
Non-vaccine serotypes	26·1 (21·6 to 30·8)	36·0 (10·5 to 132·1)	−9·9 (−0·7 to −19·1)	−27·5 (−47·0 to −1·3)
Aged <2 years				
All serotypes	13·1 (12·2 to 14·3)	54·8 (41·0 to 71·5)	−41·7 (−38·3 to −45·1)	−76·0 (−79·0 to −72·8)
PCV7 serotypes	1·3 (0·9 to 1·8)	29·1 (7·2 to 126·6)	−27·8 (−25·5 to −30·1)	−95·5 (−97·0 to −93·4)
Additional PCV13 serotypes	1·0 (0·8 to 1·3)	16·0 (8·0 to 32·0)	−15·0 (−13·3 to −16·7)	−93·8 (−96·2 to −90·5)
Non-vaccine serotypes	11·1 (10·1 to 12·4)	9·4 (5·1 to 18·6)	1·7 (3·6 to −0·2)	18·3 (−2·0 to 42·9)
Aged 2–4 years				
All serotypes	1·9 (1·6 to 2·2)	7·1 (4·9 to 10·8)	−5·2 (−4·2 to −6·2)	−73·3 (−80·1 to −64·7)
PCV7 serotypes	0·3 (0·2 to 0·4)	3·7 (2·1 to 6·6)	−3·4 (−2·7 to −4·0)	−91·3 (−95·8 to −83·8)
Additional PCV13 serotypes	0·1 (0·1 to 0·2)	3·9 (2·0 to 7·7)	−3·8 (−3·1 to −4·4)	−97·3 (−99·4 to −92·5)
Non-vaccine serotypes	1·6 (1·4 to 2·0)	0·2 (0·1 to 0·8)	1·4 (1·9 to 1·0)	678·0 (254·4 to 1914·9)
Aged 5–14 years				
All serotypes	0·9 (0·8 to 1·0)	2·6 (1·4 to 4·5)	−1·7 (−1·4 to −2·1)	−65·9 (−73·2 to −56·9)
PCV7 serotypes	0·2 (0·1 to 0·2)	1·0 (0·6 to 1·7)	−0·8 (−0·6 to −1·0)	−84·1 (−91·1 to −73·2)
Additional PCV13 serotypes	0·1 (0·1 to 0·2)	1·3 (0·5 to 3·2)	−1·2 (−0·9 to −1·4)	−91·1 (−95·5 to −84·0)
Non-vaccine serotypes	0·7 (0·6 to 0·8)	0·3 (0·1 to 0·8)	0·4 (0·6 to 0·2)	109·7 (39·5 to 220·3)
Aged 15–24 years				
All serotypes	1·3 (1·1 to 1·4)	3·8 (2·4 to 5·9)	−2·5 (−2·1 to −3·0)	−66·3 (−72·8 to −58·4)
PCV7 serotypes	0·2 (0·1 to 0·2)	1·3 (0·6 to 2·8)	−1·1 (−0·9 to −1·4)	−87·8 (−93·4 to −79)
Additional PCV13 serotypes	0·2 (0·1 to 0·2)	1·7 (0·8 to 3·3)	−1·5 (−1·3 to −1·8)	−89·7 (−94·2 to −82·9)
Non-vaccine serotypes	1·0 (0·9 to 1·1)	0·8 (0·4 to 1·9)	0·1 (0·4 to −0·1)	17·4 (−14·0 to 60·7)
Aged 25–44 years				
All serotypes	4·9 (4·7 to 5·1)	9·8 (8·2 to 11·7)	−5·0 (−4·4 to −5·5)	−50·4 (−54·2 to −46·3)
PCV7 serotypes	0·6 (0·5 to 0·7)	4·4 (2·2 to 8·8)	−3·8 (−3·5 to −4·2)	−86·1 (−88·7 to −83·1)
Additional PCV13 serotypes	0·9 (0·8 to 1·0)	3·8 (2·4 to 5·9)	−2·9 (−2·6 to −3·2)	−77·2 (−80·9 to −73·0)
Non-vaccine serotypes	3·5 (3·2 to 3·8)	2·0 (1·2 to 3·2)	1·5 (1·9 to 1·2)	78·5 (56·8 to 103·4)
Aged 45–64 years				
All serotypes	5·7 (5·4 to 6·0)	10·1 (7·6 to 13·5)	−4·4 (−3·6 to −5·2)	−43·4 (−49·1 to −37·2)
PCV7 serotypes	0·6 (0·5 to 0·7)	4·3 (2·1 to 9·0)	−3·7 (−3·2 to −4·1)	−86·2 (−89·7 to −81·8)
Additional PCV13 serotypes	0·9 (0·8 to 1·0)	2·5 (1·3 to 5·1)	−1·7 (−1·3 to −2·0)	−64·9 (−72·8 to −55·1)
Non-vaccine serotypes	4·4 (3·9 to 5·0)	3·6 (1·6 to 7·6)	0·9 (1·4 to 0·3)	24·5 (7·9 to 43·7)
Aged >64 years				
All serotypes	6 (5·5 to 6·5)	8·6 (4·5 to 16·2)	−2·6 (−1·3 to −3·9)	−30·2 (−41·9 to −16·2)
PCV7 serotypes	0·6 (0·5 to 0·8)	1·4 (0·5 to 4·3)	−0·8 (−0·3 to −1·3)	−57·8 (−76·1 to −28·0)
Additional PCV13 serotypes	1·2 (0·9 to 1·4)	9·8 (2·9 to 34·1)	−8·6 (−7·5 to −9·7)	−88·1 (−91·7 to −83·5)
Non-vaccine serotypes	4·4 (3·8 to 5·1)	1·3 (0·3 to 5·1)	3·1 (3·8 to 2·3)	234·9 (138·1 to 379·4)

PCV7 was introduced in 2009 and PCV13 was introduced in 2011. Missing serotype data were imputed from those with known serotypes by age group: PCV7 serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F) and additional PCV13 serotypes (1, 3, 5, 6A, 7F, and 19A). PCV=pneumococcal conjugate vaccine. PCV7=7-valent PCV. PCV13=13-valent PCV.

Table 2: **Risk of invasive pneumococcal disease cases among children and adults, by age group and serotype group, in South Africa in 2019 compared with expected case numbers if the vaccine had never been introduced**

antibiotic susceptibility (penicillin non-susceptible, penicillin susceptible, multidrug resistant, and multidrug susceptible). Further details are provided in appendix 1 (pp 2–3).

All analyses were performed in R studio version 23.12.0. The analytical framework was adapted from existing code for the evaluation of PCV effect.[23] All data and code used for the current study are available online.[23,24]

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

From Jan 1, 2005, to Dec 31, 2019, surveillance identified 52 957 IPD cases. Among the 50 705 individuals with age data available, 9398 (18·5%) were infants younger than 2 years and 2854 (5·6%) were children aged 2–4 years (table 1). Among those with HIV results, the proportion of people living with HIV decreased from 81·4% (4488/5513) in the pre-vaccine era (2005–08) to 64·8% (3266/5041) in 2013–19, whereas the proportion of individuals with other comorbidities increased from 35·0% (1908/5449) in 2005–08 to 47·5% (2582/5436) in 2013–19 (table 1). The proportion of cases with missing information requiring imputation (appendix p 9) increased over time for serotype and antibiotic susceptibility categories. This issue was most pronounced when considering serotypes in children younger than 14 years and was driven by small numbers of IPD cases identified (appendix p 9).

By 2019, overall IPD rates compared with expected case numbers declined among children younger than 2 years by 76·0% (percentage risk difference: 95% CI –79·0 to –72·8%; absolute risk difference: –41·7, 95% CI –38·3 to –45·1; table 2; figures 1, 2A). Of these, PCV7 and additional PCV13 serotype IPD rates declined by 95·5% (–97·0 to –93·4%) and 93·8% (–96·2 to–90·5%), respectively (table 2). Vaccine serotypes causing five or more cases of disease among children younger than 2 years in 2019 were serotypes 19F (n=10), 14 (n=5), and 3 (n=5; figure 3A), with all except serotype 3 showing reductions compared with the pre-vaccine era (before the introduction of PCV7 in 2009, serotype 14 had 128–169 cases, serotype 19F had 82–92 cases, and serotype 3 had 4–13 cases). Overall, NVT IPDs did not increase significantly in the past 15 years (18·3% increase; 95% CI –2·0 to 42·9%; table 2). NVT 8 was the most common serotype in 2019 (n=32), an increase from a range of 14–22 cases before 2009 (figure 3A). IPD due to serotypes 8, 12F, 15B/C, and pool G serotypes were seen (figure 3A).

Similar changes were seen for children aged 2–4 years and 5–14 years (figures 1, 2A), with significant reductions in vaccine serotypes (excluding serotype 3). However, significant increases in NVTs with wide CIs were noted, with some serotypes (8, 12F, and 15B/C) fluctuating over the years (table 2; figure 3B; appendix p 5). Similar changes were also seen for adolescents and young adults (aged 15–24 years) but the magnitude of change was smaller (figures 1, 2B; table 2; appendix p 6). NVTs in this age group increased (109·7%; 95%CI 39·5–220·3%). Serotype 1 was the most common serotype causing disease in older children and young adults aged 5–24 years before 2009 (appendix pp 5–6), and reductions were sustained up to 2019 with no serotype 1 cases identified in 2019.

Infants younger than 10 weeks and therefore too young to benefit from PCV13 directly showed sustained reductions in vaccine serotype disease, accompanied by a small decrease in NVT disease (predominantly serotype 8, causing a total of more than ten reported cases annually [range, 11–19] in the last 5 years; table 2; figure 2A). PCV7 and PCV13 serotype IPD rates declined by 90·0% (95% CI –96·0 to –79·0%) and 74·5% (–88·8 to –47·5), respectively.

During the whole surveillance period of the study we identified a large proportion of IPD in adults aged 25 years or older (31 279/50 705 [61·7%]), among whom 7·7% were older than 64 years (2407/31 279; table 1). Among adults aged 25–44 years, overall IPD rates declined by 50·4% (95% CI –54·2 to –46·3%; figures 1, 2B; table 2). Vaccine serotypes declined significantly in this age group: PCV7 and additional PCV13 serotype IPD rates declined by 86·1% (–88·7 to –83·1%) and 77·2% (–80·9 to –73·0%), respectively. Vaccine serotypes (excluding serotype 3) that still caused IPD in this age group included serotypes 4, 19F, and 19A (appendix p 6). In addition, increases in NVTs were noted (78·5%; 56·8 to 103·4%; table 2; figure 2B). Fluctuations in the number of cases with NVTs 8, 12F, and 9N were seen, with these three

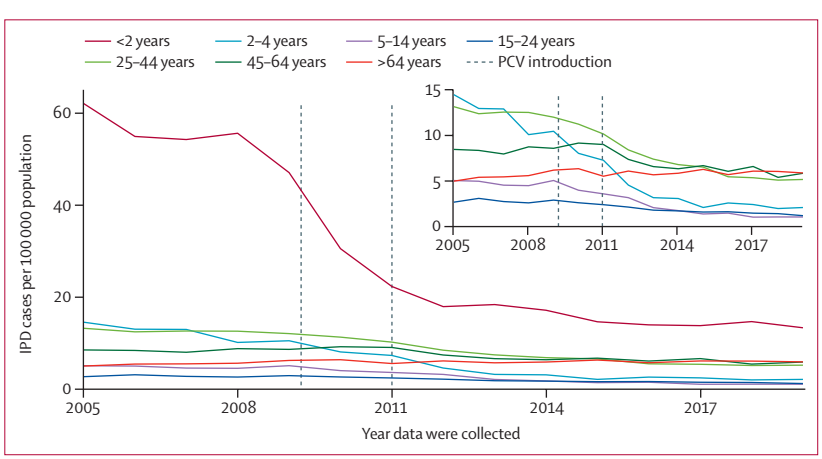
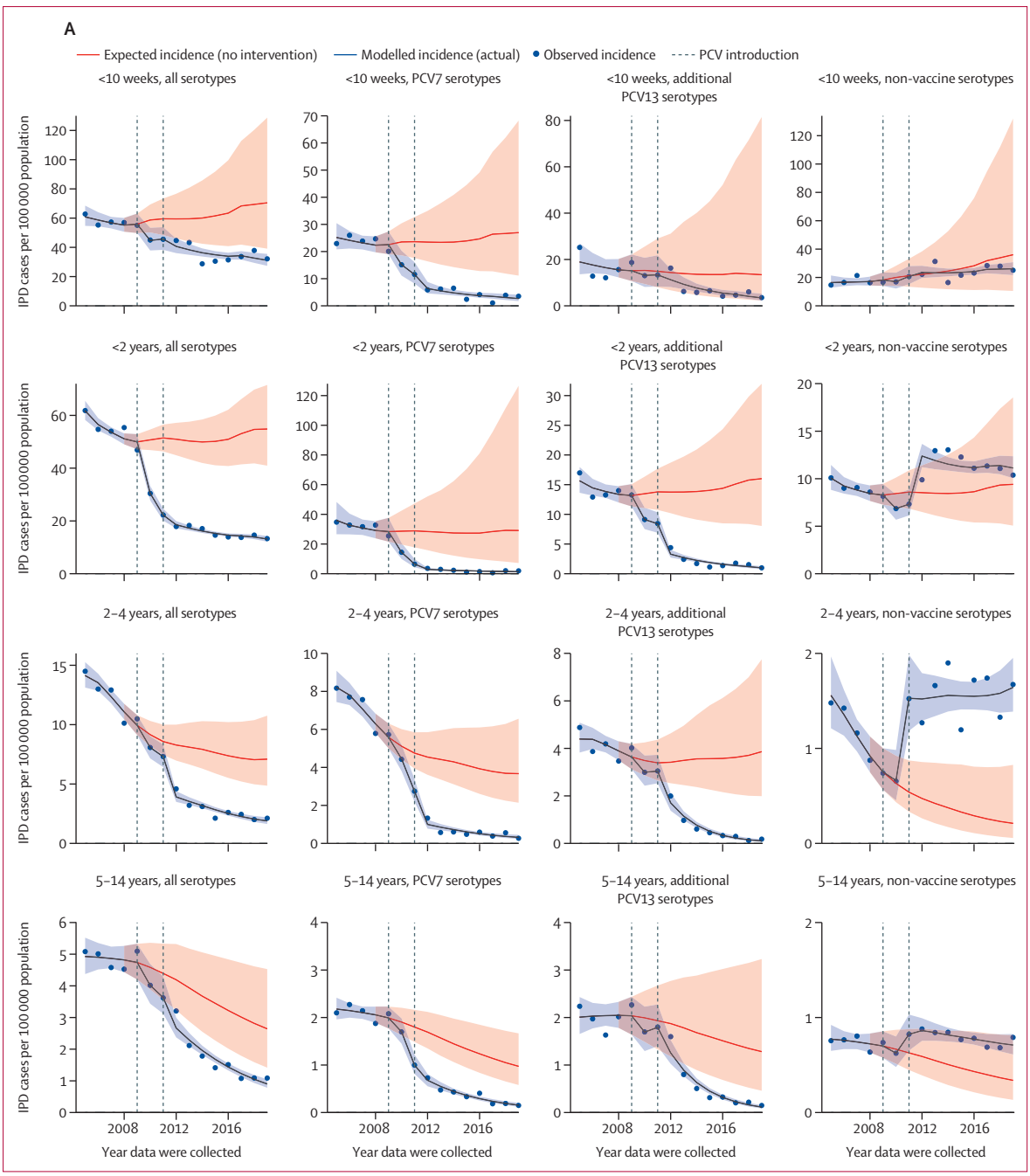


Figure 1: **Incidence of IPD reported by year and age group, and the insert graph excluding children younger than 2 years, in South Africa in 2005–19**

PCV7 was introduced in 2009 and PCV13 was introduced in 2011. Individuals with an unknown age (2283/50 606 [4·5%]) were imputed from those with known age. IPD=invasive pneumococcal disease. PCV=pneumococcal conjugate vaccine. PCV7=7-valent PCV. PCV13=13-valent PCV.



(Figure 2 continues on next page)

types becoming the most predominant NVTs in this age group by 2019. What is notable in this age group is the sudden increase in 6C between 2015 and 2019, increasing from a range of five to nine cases before 2009, to 31 cases identified in 2019. Serotype 1 was the vaccine serotype causing the most cases of disease in this age group before the vaccines were introduced (182 cases reported in 2005), declining to one to two cases in 2018–19.

In those aged 45–64 years, overall IPD declined (–43·4%; 95% CI –49·1 to –37·2%), mainly because of declines in vaccine serotypes except for serotype 3 (figure 1; table 2; appendix p 7) and a short-lived increase in 19A before PCV13 was introduced, with similar vaccine serotypes still prevalent in 2019 similar to younger adults. NVTs increased significantly (24·5%; 7·9 to 43·7%), driven by sustained increases in especially serotypes 8, 9N, and 12F. The number of cases of these NVTs stabilised during 2015–19,

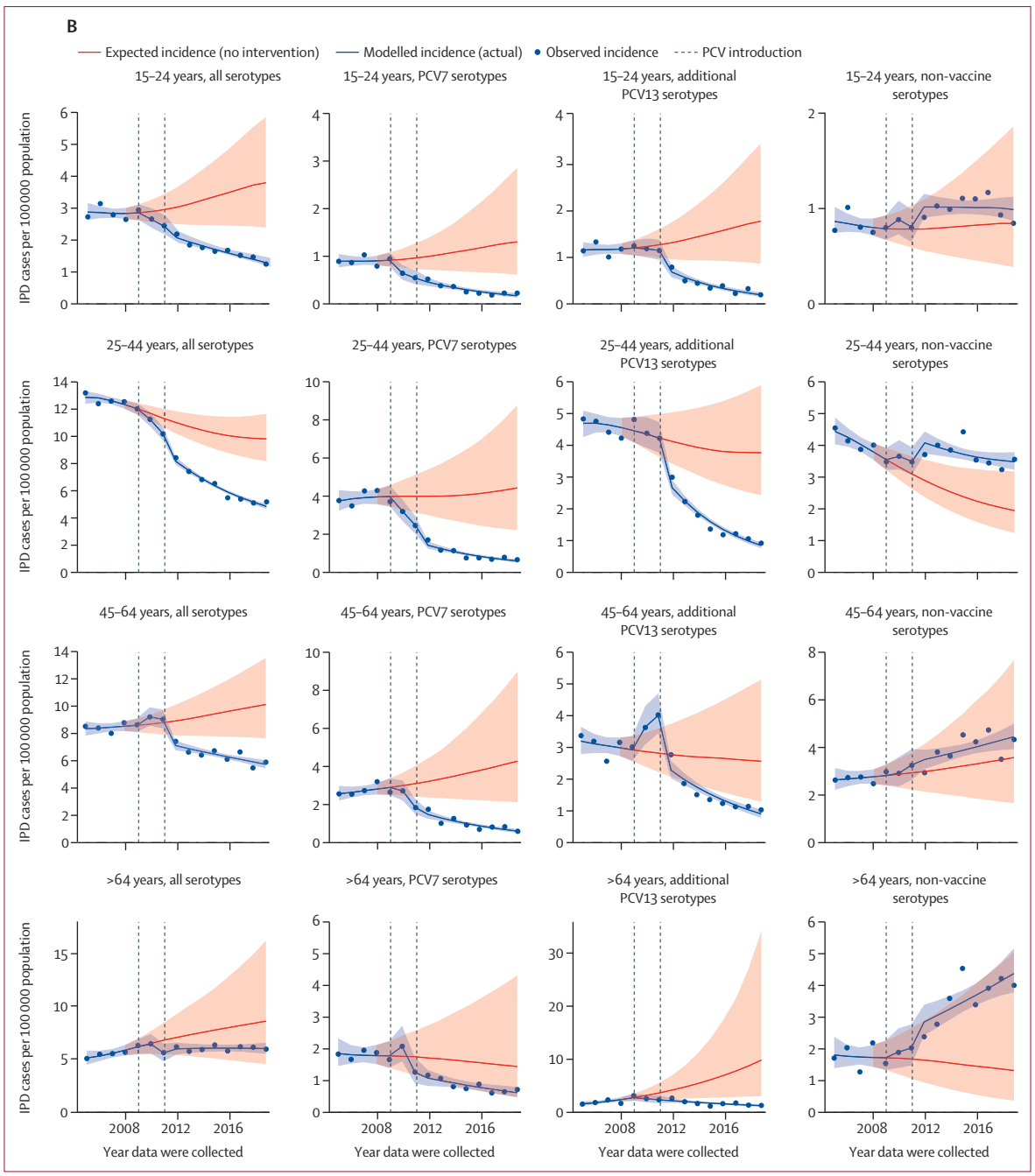


Figure 2: **Incidence of IPD modelled and expected among different age groups in South Africa in 2005–19**
(A) Incidence of IPD modelled (blue line and blue dots) and expected (red line) among different age groups in children aged up to 14 years in South Africa in 2005–19. Red and blue ribbons are 95% credible intervals (2·5th and 97·5th percentile of 1000 predictions divided by the population). Axes differ for each age group and category. (B) Incidence of IPD modelled (blue line and blue dots) and expected (red line) among different age groups in children and adults older than 15 years in South Africa in 2005–19. Red and blue ribbons are 95% credible intervals (2·5th and 97·5th percentile of 1000 predictions divided by population). Axes differ for each age group and category. PCV7 was introduced in 2009 and PCV13 was introduced in 2011. Individuals with an unknown serotype group (16 217/50 606 [32·0%]) were assigned a group by imputation within each age group. PCV7 serotypes were 4, 6B, 9V, 14, 18C, 19F, and 23F; additional PCV13 serotypes were 1, 3, 5, 6A, 7F, and 19A. IPD=invasive pneumococcal disease. PCV=pneumococcal conjugate vaccine. PCV7=7-valent PCV. PCV13=13-valent PCV.

whereas other individual NVTs fluctuated (eg, 10A, 15A, 15B/C, 16F, 17F, and 22F). Again, serotype 1 had all but disappeared in this age group, with only one case in 2019.

In 2019, the older than 64 years age group had the smallest significant declines in overall IPD (–30·2; 95% CI –41·9 to –16·2), because the reduction in vaccine

A

	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
4	19	20	10	13	18	3	4	1	1	1	2	3	0	0	1
6B	113	122	101	102	99	51	24	3	8	9	0	1	0	1	2
9V	27	25	25	24	13	15	3	1	3	1	0	0	0	1	0
14	145	128	131	169	118	47	17	7	0	2	0	3	3	2	5
18C	18	27	35	23	11	9	6	3	6	4	2	2	0	1	1
19F	88	92	82	90	71	57	10	22	11	7	5	7	4	13	10
23F	101	81	91	100	85	38	25	13	12	7	5	3	0	2	0
1	27	19	21	26	28	17	16	11	2	3	0	1	0	0	0
3	12	11	4	13	10	8	6	5	7	2	5	5	9	4	5
5	18	7	9	12	17	9	15	13	1	1	0	0	0	0	0
6A	105	88	99	101	83	60	34	13	11	3	1	2	2	2	2
7F	3	4	1	2	4	0	0	0	3	1	1	1	0	1	0
19A	83	66	64	69	75	46	45	19	10	13	7	9	9	8	3
8	22	14	20	16	20	17	22	24	28	22	39	36	30	35	32
9N	9	6	8	9	8	4	4	6	2	8	3	1	4	3	4
10A	9	8	7	4	1	6	5	5	9	6	12	7	8	4	3
11A	3	5	1	1	2	1	1	4	2	5	0	0	2	1	1
12F	12	10	4	15	11	8	13	9	18	21	12	13	5	4	11
15B/C	7	13	22	11	14	10	9	21	14	17	12	8	8	7	7
17F	4	2	6	2	4	2	2	5	6	6	4	5	2	2	1
20	2	0	1	1	2	1	1	0	2	0	4	1	2	0	1
22F	0	3	1	5	4	1	4	3	1	0	5	4	3	3	2
33F	1	1	3	2	1	1	2	1	2	2	0	2	1	0	0
16F	7	6	3	6	7	5	3	8	16	17	6	5	10	9	1
15A	3	1	2	6	5	5	5	6	16	9	7	8	9	4	3
13	11	7	3	4	6	2	5	2	6	11	4	6	7	1	2
7C	8	5	6	4	6	3	4	5	6	8	7	1	7	2	3
25A/38	0	0	0	0	0	0	2	1	1	3	0	0	2	1	1
23A	2	2	3	1	1	2	0	1	1	6	2	2	0	2	2
6C	1	4	3	3	0	1	0	0	0	0	0	5	1	1	2
23B	1	1	2	2	1	0	0	1	1	0	1	4	6	7	4
31	0	1	0	1	2	0	1	0	1	1	1	0	1	1	1
Pool G*	25	13	14	21	14	18	10	23	30	20	20	23	10	14	11
Other	25	35	28	24	27	19	8	12	19	13	10	14	9	8	11

(Figure 3 continues on next page)

type IPD was offset by a significant increase in NVTs (234·9%; 138·1 to 379·4%; figure 1; table 2; appendix p 9), especially serotype 8. The numbers of IPD cases identified in this age group were, however, small, and individual serotypes fluctuated over the surveillance period.

The percentage of penicillin non-susceptible isolates causing IPD in all ages decreased from 36·2% (4970/13 722) in the 2005–08 period to 28·3% in the 2013–19 period (3169/11 215; table 1). Penicillin non-susceptible and multidrug resistant pneumococcal disease incidence among individuals of all ages declined in the first 2 years after the introduction of PCVs, and did not increase during 2015–19 (figure 4), when there were small increases in the number of episodes without isolates available for testing (appendix p 10). In the sensitivity analysis using original (not imputed) case numbers, the overall result trends were similar to the main results.[24]

Discussion

Using a rich and long-standing dataset of IPD in South Africa in the past 15 years in all ages, which is not

B

	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
4	5	8	11	4	9	9	4	3	0	2	0	1	0	0	0
6B	43	36	46	43	25	28	12	4	2	1	3	1	1	0	0
9V	15	9	6	9	7	5	4	2	0	0	1	0	1	0	0
14	42	33	33	23	34	25	12	5	2	0	0	2	1	0	1
18C	6	7	5	4	11	4	7	2	1	0	0	0	0	1	0
19F	21	25	27	15	20	8	7	8	1	9	4	6	6	8	5
23F	39	33	33	26	26	22	13	7	6	2	1	1	0	0	0
1	42	24	24	35	37	24	27	23	8	4	2	0	0	0	0
3	2	1	4	0	2	1	4	2	2	1	2	1	3	0	2
5	5	1	2	1	0	4	2	3	2	0	0	0	0	0	0
6A	42	29	35	24	40	21	15	8	3	5	2	0	0	0	1
7F	0	0	0	0	0	1	2	0	1	0	0	0	0	0	0
19A	11	21	23	14	14	17	16	11	4	4	2	5	4	2	1
8	0	0	0	3	1	0	1	2	0	2	2	4	7	5	4
9N	2	1	2	1	3	1	0	0	0	1	0	1	1	0	0
10A	1	2	1	0	0	0	0	0	0	2	0	1	3	0	2
11A	0	0	0	1	0	1	2	1	1	0	0	1	2	0	2
12F	1	5	2	0	2	1	5	5	5	9	2	2	5	4	5
15B/C	7	2	6	2	1	0	3	9	8	4	3	3	3	3	3
17F	1	0	0	2	0	3	4	1	2	2	1	0	0	1	2
20	0	0	0	0	1	0	0	0	0	0	0	0	1	0	0
22F	0	2	0	1	1	0	2	1	2	1	1	0	0	0	0
33F	0	0	0	0	0	1	0	0	1	2	0	0	1	0	0
16F	3	4	2	1	1	2	7	2	3	3	2	3	3	1	3
15A	0	1	1	2	0	1	2	1	1	5	1	2	5	0	3
13	1	1	2	1	0	0	2	1	2	0	2	2	0	1	2
7C	1	0	0	1	1	1	0	0	0	1	0	0	1	0	1
25A/38	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0
23A	0	1	1	1	0	1	0	1	3	2	2	1	1	1	1
6C	0	0	1	0	0	1	0	3	0	1	0	2	0	1	1
23B	2	1	2	0	1	0	2	0	1	2	1	1	2	2	1
31	1	1	0	0	0	0	0	0	0	0	1	0	0	0	0
Pool G*	5	2	1	0	2	1	2	1	5	5	2	5	3	0	1
Other	6	5	5	3	3	1	1	1	0	2	2	3	2	2	7

Figure 3: **Number of viable isolates serotyped causing IPD in South Africa in 2005–19, by serotype and year**

(A) Number of viable isolates serotyped causing IPD in children younger than 2 years, in South Africa in 2005–19, by serotype and year (graded colour scale; the maximum value is red, midpoint value is yellow, and the minimum value is green; actual numbers with no imputation). (B) Number of viable isolates serotyped causing IPD in children aged 2–4 years, in South Africa in 2005–19, by serotype and year (graded colour scale; the maximum value is red, midpoint value is yellow, and the minimum value is green; actual numbers with no imputation). PCV7 was introduced in 2009 and PCV13 was introduced in 2011. PCV7 serotypes are in blue (4, 6B, 9V, 14, 18C, 19F, and 23F), additional PCV13 serotypes are in grey (1, 3, 5, 6A, 7F, and 19A), and non-PCV13 serotypes are in black. IPD=invasive pneumococcal disease. PCV=pneumococcal conjugate vaccine. PCV7=7-valent PCV. PCV13=13-valent PCV. *Pool G includes serogroups 29, 34, and 42, and serogroups 35 and 47.

commonly available for Africa, we documented sustained reductions of IPD after PCV was introduced, demonstrating the long-term effects of PCV. Maturation or stabilisation of vaccine effects are thought to occur 5–7 years after introduction, depending on whether PCV was introduced with a catch-up or after another PCV product was already in use.[13] In our setting, reductions were seen more quickly for vaccinated age groups compared with older age groups who were affected indirectly. The most important vaccine serotype still causing some residual disease in 2019 in South African children was serotype 19F, although the 19F burden was

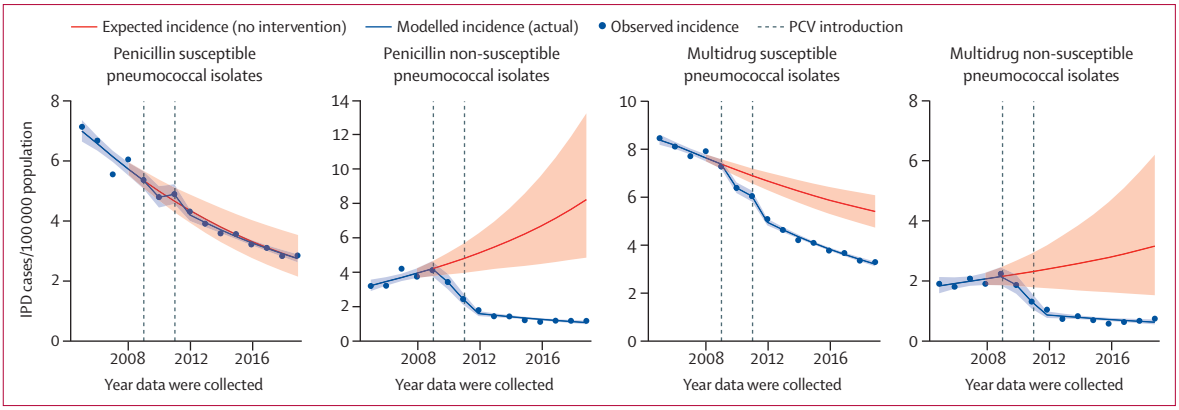


Figure 4: **Incidence of disease caused by penicillin susceptible and non-susceptible and multidrug susceptible and non-susceptible pneumococcal isolates among all ages, in South Africa in 2005–19**

Red and blue ribbons are 95% credible intervals (2·5th and 97·5th percentile of 1000 predictions divided by the population). Axes differ for each group. PCV7 was introduced in 2009 and PCV13 was introduced in 2011. IPD=invasive pneumococcal disease. PCV=pneumococcal conjugate vaccine. PCV7=7-valent PCV. PCV13=13-valent PCV.

substantially reduced compared with baseline (2005–08). Indirect benefits in those too young or too old to directly benefit from PCV were also documented, but with some vaccine serotypes (ie, serotypes 4, 19A, and 19F) still causing some residual disease. Serotype 3 showed little or no reduction in all age groups, as has been shown elsewhere, possibly because of inadequate immunogenicity of the serotype 3 capsular antigen.[25] Serotypes 4 and 18C, which are included in PCV13 but not in the Serum Institute of India PCV10 formulation, were not the serotypes most likely to cause disease in children before or after the introduction of PCV in South Africa. However, among adults, the ongoing circulation of serotype 4 and potential for a rebound in IPD burden is a concern.

In addition, we documented significant serotype replacement (ie, increases in NVT) in older children (aged 2–14 years) and adults aged 25 years and older, including those older than 64 years, led by serotype 8. All age groups showed fluctuating NVT disease, with serotypes 8, 12F, 15B/C, and 22F being notable serotypes causing residual disease that could be covered by higher valency vaccines, some of which are still in development and some of which are available in the USA and Europe, but none of which are currently available in South Africa. Antimicrobial resistant pneumococcal disease did not increase during the study period, reflecting the ongoing benefits of decreased vaccine serotypes associated with resistance and no appreciable increase in resistance in NVT strains.

The overall decline in IPD in children younger than 5 years is significant after 8 years since the introduction of PCV13 in South Africa (76% in infants younger than 2 years and 73% in children aged between 2 years and 4 years). In comparison, in the USA, PCV13 resulted in a 64% reduction in overall IPD in children younger than 5 years (3 years after PCV13 introduction) compared with the number of cases expected if only PCV7 had been continued,[26] whereas in Europe, 47% of all serotype disease decreased in this age group (4 years after PCV introduction).[27] Time after introduction and previous PCV use might explain the differences when comparing studies, with countries often needing at least 5 years for the maturation of effects.[13] Vaccination coverage differences might also contribute to measured differences; for example measured reductions were larger in Europe when low coverage countries were excluded.[27] Another reason for differences in the overall effect against IPD might be explained by the proportion of disease caused by vaccine serotypes before PCV introduction or the contribution of NVT replacement.[3] The PCV effect on vaccine serotypes is consistently high, with the UK and the USA showing an approximately 100% reduction in PCV7 serotypes[3] and 93% reduction for PCV13 serotypes,[26] whereas we documented declines ranging from 91% to 97% among children younger than 5 years. In the UK, serotype 3 disease did not decline, as in our setting, and 19A was the vaccine serotype causing the highest number of cases of IPD in the UK.[3]

We documented ongoing indirect benefits for adults, shown by vaccine serotype disease declines greater than NVT disease declines. This overall benefit might reflect the improvement in HIV care earlier in the surveillance period, especially in the 15–44 year age group.[28] In our setting, indirect effects were also confirmed in infants too young to be immunised. Indirect effects for both infants and adults have not, however, been as apparent in Malawi and other low-income and middle-income countries.[29] These sustained indirect effects are essential to inform the decision of potentially moving to a one plus one schedule.[30] Before the COVID-19 pandemic, annual PCV coverage in South Africa was approximately 85%, higher than the threshold of vaccine coverage projected to induce indirect effects: with vaccine coverage thresholds of 67–75% in Massachusetts, USA[31] and 58% among Native American children.[32] However, the

coverage needed to maintain indirect effects over time is unknown.[30] In our setting, sustained indirect effects were seen in all adult age groups, but were partly offset in those older than 45 years by increases in NVT disease, similar to the UK.[3] Data from older Canadian adults (aged 65 years and older) with low PPV23 coverage, 6 years after PCV13 implementation, also showed decreases in vaccine serotype disease, particularly PCV13 serotypes, but no decrease in the number of cases reported from NVT disease.[33] In Canada, serotype 3 disease in older adults (65 years and older) did not decrease, whereas 22F was the most prevalent serotype causing disease in 2016. The most notable increases in Canadian older adults were in serotypes 8, 7C, 24F, 31, and 34. Similarly in Ireland, vaccine serotypes declined in older adults, with the persistence of serotypes 3 and 19A.[34] A sudden increase in 6C serotype IPD in adults that has been observed might reflect natural fluctuations and less cross-protection if relying on indirect effects. In our setting, adults might benefit from vaccines that cover serotypes not currently prevented by PCV13.

In South Africa, unlike other African countries,[4] older children (aged 2–14 years) and adults (older than 25 years) had significant increases in NVT disease, but the contributing serotypes (serotypes 8, 12F, 22F, and 15A) fluctuated over the years. In our setting, we also documented NVT increases in children aged 2–4 years, but with very wide 95% CIs. In other settings, serotypes important for serotype replacement included serotype 24F, which caused meningitis in children in France,[35] and 12F, which caused meningitis in Israel.[36] Notably, authors in Germany discussed reaching maximal effects against IPD after 5 years, and then observed a rebound with NVT (serotypes 10A, 24F, 15B/C, 12F, 38, 22F, and 23B).[37] In the UK, NVT (serotypes 8, 12F, and 9N) rapidly increased, especially in older adults (aged 45 years and older).[3] Overall, NVTs with high invasiveness potential were serotypes 8, 12F, 24F, and 33F.[38] An earlier meta-analysis had highlighted specific NVTs (serotypes 22F, 12F, 33F, 24F, 15B/C, 23B, 10A, and 38) as important in causing IPD after PCV introduction.[39]

The previously documented early benefits of declines in antimicrobial resistant IPD[5] have been sustained in South Africa, 8 years after the introduction of PCV13. Similar declines have been seen elsewhere, albeit for shorter surveillance periods.[14] No change in antimicrobial resistance, including multidrug resistance, was noted in IPD among older Canadians.[33] Unlike other settings, increases in 35B in South Africa have not been associated with multidrug resistance.[40]

The limitations of our data include the fact that these are only observational data and changes probably reflect a combination of vaccine effects, HIV prevention and treatment, and secular trends. As a result, replacement disease might be underestimated, especially in adults, because HIV-driven declines in both vaccine serotype and NVT disease might be masking vaccine-driven increases.[17] HIV infection rates in infants born to women living with HIV have declined, reaching levels of 4·3% at 18 months by 2014.[41] Since the implementation of comprehensive HIV and AIDS treatment programmes in 2003, antiretroviral therapy access has steadily increased.[28] Almost 8 million South Africans were living with HIV in 2019, an estimated 60% of whom are on treatment.[28] We could not account for these changes throughout the 15-year surveillance period, as in this study we assumed trends in HIV treatment and vaccine coverage stayed the same.

In addition, as a laboratory-based surveillance system, variations in specimen-taking practices and submission of isolates for serotyping might lead to missing data. We addressed this through imputation where isolates were unavailable. We assumed information to be missing at random; however, if this was not the case, we could have introduced bias, especially considering the increase in missing information throughout the study period. However, there is no a priori reason to suspect that the distribution of serotypes within age groups would systematically differ between the observed (known) and unobserved (imputed) groups. Individuals not seeking health care would be missed, and approximately a third of individuals with pneumonia did not seek health care in South Africa in 2012.[42] This factor would underestimate the overall burden of disease. Specimen taking and health care seeking might be especially low in rural areas. We included all laboratory-confirmed cases, including those treated in the community or those who died in the community, and had postmortem specimens collected. Antibiotic resistance was also assumed to be the same between ages, and missing data were imputed on the basis of CSF compared with other specimens. The strengths of our analyses include the number of cases reported and the length of time of the surveillance, including all age groups.

In conclusion, we documented sustained reductions in vaccine serotype IPD in children directly benefiting from vaccination, in a middle-income country with a high HIV prevalence, South Africa. Indirect benefits in those too young or too old to directly benefit from PCV were also seen. Ongoing surveillance will be important as the effect of the COVID-19 pandemic and the change in vaccine formulation with Serum Institute of India PCV10 being introduced in South Africa in 2024 are monitored, with substantial cost savings for the immunisation programme. Disease from current vaccine serotypes 4 and 18C would need to be monitored carefully once no longer covered by Serum Institute of India PCV10.

Contributors

AvG, JK, LdG, ST, SM, VQ, SAM, KPK, CGW, and CC contributed to the conceptualisation, funding acquisition, supervision, validation, and formal analysis. MdP, CvM, PC-G, TA, NdP, RK, VC, and SAM contributed to the supervision, data curation, project administration, and data validation. AvG, JK, and SM wrote the original draft. All authors reviewed and edited the final manuscript. AvG, JK, and SM have directly

accessed and verified the underlying data. All authors have full access to all the data and accept the responsibility to submit for publication.

Equitable partnership declaration

See Online for appendix 2

The authors of this paper have submitted an equitable partnership declaration (appendix 2). This statement allows researchers to describe how their work engages with researchers, communities, and environments in the countries of study. This statement is part of *The Lancet Global Health*'s broader goal to decolonise global health.

Declaration of interests

SAM has received grant funds from MSD, Pfizer, GSK, and the Bill and Melinda Gates Foundation; and honoraria from GSK, related to this work. CvM declares grant funds from Pfizer. CvM and VC declare honoraria from MSD and Pfizer. CC declares grant funds from Sanofi and the Bill and Melinda Gates Foundation. All other authors declare no competing interests.

Data sharing

We welcome enquiries about possible collaborations and requests for access to the dataset. Data (including individual participant data and a data dictionary defining each field in the set) will be shared after the approval of a proposal and with a signed data access agreement. Investigators interested in more details about this study, or in accessing these resources, should contact the principle investigator and corresponding author (annev@nicd.ac.za).

Acknowledgments

We thank all laboratory and clinical staff throughout South Africa for contributing to national surveillance. This study was supported by the National Institute for Communicable Diseases of the National Health Laboratory Service, the President's Emergency Plan for AIDS Relief, the US Agency for International Development's Antimicrobial Resistance Initiative, and the Centers for Disease Control and Prevention (cooperative agreements U62/PSO022901, 5U2GPS001328, and U60/CCU022088).

References

1 Whitney CG, Farley MM, Hadler J, et al. Decline in invasive pneumococcal disease after the introduction of protein-polysaccharide conjugate vaccine. *N Engl J Med* 2003; **348:** 1737–46.

2 De Wals P, Lefebvre B, Defay F, Deceuninck G, Boulianne N. Invasive pneumococcal diseases in birth cohorts vaccinated with PCV-7 and/or PHiD-CV in the province of Quebec, Canada. *Vaccine* 2012; **30:** 6416–20.

3 Ladhani SN, Collins S, Djennad A, et al. Rapid increase in non-vaccine serotypes causing invasive pneumococcal disease in England and Wales, 2000-17: a prospective national observational cohort study. *Lancet Infect Dis* 2018; **18:** 441–51.

4 Hammitt LL, Etyang AO, Morpeth SC, et al. Effect of ten-valent pneumococcal conjugate vaccine on invasive pneumococcal disease and nasopharyngeal carriage in Kenya: a longitudinal surveillance study. *Lancet* 2019; **393:** 2146–54.

5 von Gottberg A, de Gouveia L, Tempia S, et al. Effects of vaccination on invasive pneumococcal disease in South Africa. *N Engl J Med* 2014; **371:** 1889–99.

6 Mackenzie GA, Hill PC, Jeffries DJ, et al. Impact of the introduction of pneumococcal conjugate vaccination on invasive pneumococcal disease and pneumonia in The Gambia: 10 years of population-based surveillance. *Lancet Infect Dis* 2021; **21:** 1293–302.

7 Meiring S, Cohen C, Quan V, 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.

8 Mbelle N, Huebner RE, Wasas AD, Kimura A, Chang I, Klugman KP. Immunogenicity and impact on nasopharyngeal carriage of a nonavalent pneumococcal conjugate vaccine. *J Infect Dis* 1999; **180:** 1171–76.

9 Feikin DR, Kagucia EW, Loo JD, et al. Serotype-specific changes in invasive pneumococcal disease after pneumococcal conjugate vaccine introduction: a pooled analysis of multiple surveillance sites. *PLoS Med* 2013; **10:** e1001517.

10 Clarke E, Bashorun A, Adigweme I, et al. Immunogenicity and safety of a novel ten-valent pneumococcal conjugate vaccine in healthy infants in The Gambia: a phase 3, randomised, double-blind, non-inferiority trial. *Lancet Infect Dis* 2021; **21:** 834–46.

11 Kobayashi M, Farrar JL, Gierke R, et al. Use of 15-valent pneumococcal conjugate vaccine among U.S. children: updated recommendations of the Advisory Committee on Immunization Practices - United States, 2022. *MMWR Morb Mortal Wkly Rep* 2022; **71:** 1174–81.

12 Centers for Disease Control and Prevention. Direct and indirect effects of routine vaccination of children with 7-valent pneumococcal conjugate vaccine on incidence of invasive pneumococcal disease--United States, 1998-2003. *MMWR Morb Mortal Wkly Rep* 2005; **54:** 893–97.

13 Garcia Quesada M, Yang Y, Bennett JC, et al. Serotype distribution of remaining pneumococcal meningitis in the mature PCV10/13 period: findings from the PSERENADE Project. *Microorganisms* 2021; **9:** 738.

14 Kyaw MH, Lynfield R, Schaffner W, et al. Effect of introduction of the pneumococcal conjugate vaccine on drug-resistant *Streptococcus pneumoniae*. *N Engl J Med* 2006; **354:** 1455–63.

15 Lo SW, Mellor K, Cohen R, et al. Emergence of a multidrug-resistant and virulent *Streptococcus pneumoniae* lineage mediates serotype replacement after PCV13: an international whole-genome sequencing study. *Lancet Microbe* 2022; **3:** e735–43.

16 Johnson LF, May MT, Dorrington RE, et al. Estimating the impact of antiretroviral treatment on adult mortality trends in South Africa: a mathematical modelling study. *PLoS Med* 2017; **14:** e1002468.

17 Woldesenbet SA, Lombard C, Manda S, et al. The 2019 National Antenatal Sentinel HIV Survey key findings. April 30, 2021. https://www.nicd.ac.za/wp-content/uploads/2021/11/Antenatal-survey-2019-report_FINAL_27April21.pdf (accessed Nov 29, 2022).

18 Madhi SA, Izu A, Violari A, et al. Immunogenicity following the first and second doses of 7-valent pneumococcal conjugate vaccine in HIV-infected and -uninfected infants. *Vaccine* 2013; **31:** 777–83.

19 UNICEF. Immunization coverage by antigen (country, regional, and global trends). July 17, 2023. https://data.unicef.org/wp-content/uploads/2023/07/wuenic2023rev_web-update.xlsx (accessed June 27, 2024).

20 Makamba-Mutevedzi PC, Madhi SA, Burnett R. Republic of South Africa expanded programme on immunisation (EPI) national coverage survey report 2020. https://www.health.gov.za/wp-content/uploads/2022/03/National-EPI-Coverage-Survey_Final-full-report-Dec-2020.pdf (accessed Dec 28, 2022).

21 Madhi SA, Bamford L, Ngcobo N. Effectiveness of pneumococcal conjugate vaccine and rotavirus vaccine introduction into the South African public immunisation programme. *S Afr Med J* 2014; **104** (suppl 1)**:** 228–34.

22 Feldman C, Dlamini S, Richards GA, et al. A comprehensive overview of pneumococcal vaccination recommendations for adults in South Africa, 2022. *J Thorac Dis* 2022; **14:** 4150–72.

23 Weinberger DM. isppd_workshop2022. 2022. https://github.com/DanWeinberger/isppd_workshop2022/tree/main (accessed June 19, 2022).

24 von Gottberg A, Kleynhans J, Cohen C. crdm-nicd/vongottberg_ipd_sa_2005_2019: von Gottberg Lancet Global Health 2024 https://doi.org/10.5281/zenodo.12802956 (accessed July 23, 2024).

25 Lapidot R, Shea KM, Yildirim I, Cabral HJ, Pelton SI. Characteristics of serotype 3 invasive pneumococcal disease before and after universal childhood immunization with PCV13 in Massachusetts. *Pathogens* 2020; **9:** 396.

26 Moore MR, Link-Gelles R, Schaffner W, et al. Effect of use of 13-valent pneumococcal conjugate vaccine in children on invasive pneumococcal disease in children and adults in the USA: analysis of multisite, population-based surveillance. *Lancet Infect Dis* 2015; **15:** 301–09.

27 Savulescu C, Krizova P, Lepoutre A, et al. Effect of high-valency pneumococcal conjugate vaccines on invasive pneumococcal disease in children in SpIDnet countries: an observational multicentre study. *Lancet Respir Med* 2017; **5:** 648–56.

28 Zuma K, Simbayi L, Zungu N, et al. The HIV epidemic in South Africa: key findings from 2017 National Population-Based Survey. *Int J Environ Res Public Health* 2022; **19:** 8125.

29 Swarthout TD, Fronterre C, Lourenço J, et al. High residual carriage of vaccine-serotype *Streptococcus pneumoniae* after introduction of pneumococcal conjugate vaccine in Malawi. *Nat Commun* 2020; **11:** 2222.

30 Choi YH, Andrews N, Miller E. Estimated impact of revising the 13-valent pneumococcal conjugate vaccine schedule from 2+1 to 1+1 in England and Wales: a modelling study. *PLoS Med* 2019; **16:** e1002845.

31 Loughlin AM, Hsu K, Silverio AL, Marchant CD, Pelton SI. Direct and indirect effects of PCV13 on nasopharyngeal carriage of PCV13 unique pneumococcal serotypes in Massachusetts' children. *Pediatr Infect Dis J* 2014; **33:** 504–10.

32 Grant LR, Hammitt LL, O'Brien SE, et al. Impact of the 13-valent pneumococcal conjugate vaccine on pneumococcal carriage among American Indians. *Pediatr Infect Dis J* 2016; **35:** 907–14.

33 Demczuk WHB, Martin I, Desai S, et al. Serotype distribution of invasive *Streptococcus pneumoniae* in adults 65 years of age and over after the introduction of childhood 13-valent pneumococcal conjugate vaccination programs in Canada, 2010-2016. *Vaccine* 2018; **36:** 4701–07.

34 Corcoran M, Vickers I, Mereckiene J, et al. The epidemiology of invasive pneumococcal disease in older adults in the post-PCV era. Has there been a herd effect? *Epidemiol Infect* 2017; **145:** 2390–99.

35 Ouldali N, Levy C, Varon E, et al. Incidence of paediatric pneumococcal meningitis and emergence of new serotypes: a time-series analysis of a 16-year French national survey. *Lancet Infect Dis* 2018; **18:** 983–91.

36 Ben-Shimol S, Greenberg D, Givon-Lavi N, 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.

37 Weinberger R, von Kries R, van der Linden M, Rieck T, Siedler A, Falkenhorst G. Invasive pneumococcal disease in children under 16 years of age: incomplete rebound in incidence after the maximum effect of PCV13 in 2012/13 in Germany. *Vaccine* 2018; **36:** 572–77.

38 Balsells E, Dagan R, Yildirim I, et al. The relative invasive disease potential of *Streptococcus pneumoniae* among children after PCV introduction: a systematic review and meta-analysis. *J Infect* 2018; **77:** 368–78.

39 Balsells E, Guillot L, Nair H, Kyaw MH. Serotype distribution of *Streptococcus pneumoniae* causing invasive disease in children in the post-PCV era: a systematic review and meta-analysis. *PLoS One* 2017; **12:** e0177113.

40 Ndlangisa KM, du Plessis M, Lo S, et al. A *Streptococcus pneumoniae* lineage usually associated with pneumococcal conjugate vaccine (PCV) serotypes is the most common cause of serotype 35B invasive disease in South Africa, following routine use of PCV. *Microb Genom* 2022; **8:** 000746.

41 Goga AE, Lombard C, Jackson D, et al. Impact of breastfeeding, maternal antiretroviral treatment and health service factors on 18-month vertical transmission of HIV and HIV-free survival: results from a nationally representative HIV-exposed infant cohort, South Africa. *J Epidemiol Community Health* 2020; **74:** 1069–77.

42 Wong KKL, von Mollendorf C, Martinson N, et al. Healthcare utilization for common infectious disease syndromes in Soweto and Klerksdorp, South Africa. *Pan Afr Med J* 2018; **30:** 271.