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Supplementary appendix 1

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Supplementary materials for:

Long-term impact of pneumococcal conjugate vaccines on invasive pneumococcal disease incidence among all ages from national, active, laboratory-based surveillance, South Africa, 2005-2019: a cohort observational study

Prof Anne von Gottberg^{1,2} (PhD), Jackie Kleynhans^{1,3} (PhD), Linda de Gouveia^{1,2} (MT), Stefano Tempia^{3,4} (PhD), Susan Meiring⁵ (PhD), Vanessa Quan⁵(MBBCh, MPH), Mignon du Plessis^{1,2} (PhD), Claire von Mollendorf^{1,3}(PhD), Penny Crowther-Gibson⁵ (MSc), Prof Theunis Avenant⁶ (FC Paed [SA]), Nicolette du Plessis⁶ (PhD), Ranmini Kularatne^{2,7} (FCPath [SA] Micro), Vindana Chibabhai⁸(FCPath [SA] Micro), Prof Shabir A Madhi^{9,10}(PhD), Prof Keith P Klugman¹¹ (PhD), Cynthia G Whitney¹² (MD, MPH), and Prof Cheryl Cohen^{1,3} (PhD), for GERMS-SA

¹Centre for Respiratory Diseases and Meningitis, National Institute for Communicable Diseases, a division of the National Health Laboratory Service, Johannesburg, South Africa

²School of Pathology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

³School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

⁴Global Influenza Program, World Health Organization, Geneva, Switzerland

⁵Division of Public Health Surveillance and Response, National Institute for Communicable Diseases, a division of the National Health Laboratory Service, Johannesburg, South Africa

⁶Department of Paediatrics, Kalafong Provincial Tertiary Hospital, Faculty of Health Sciences, University of Pretoria, Pretoria, South Africa

⁷Rahima Moosa Mother and Child Hospital, and School of Pathology, Faculty of Health Sciences, University of the Witwatersrand and National Health Laboratory Service, Johannesburg, South Africa

⁸Charlotte Maxeke Johannesburg Academic Hospital, and School of Pathology, Faculty of Health Sciences, University of the Witwatersrand and National Health Laboratory Service, Johannesburg, South Africa

⁹South African Medical Research Council Vaccines and Infectious Diseases Analytics Research Unit, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

¹⁰Wits Infectious Diseases and Oncology Research Institute, University of the Witwatersrand, Faculty of Health Sciences, Johannesburg, Gauteng, South Africa

¹¹Pneumonia and Pandemic Prevention, Surveillance and Epidemic Control, Bill & Melinda Gates Foundation, Seattle, Washington, USA

¹²Global Health Institute and Rollins School of Public Health, Emory University, Atlanta, GA, USA

GERMS-SA members in 2019:

John Black, Vanessa Pearce (EC); Masego Moncho, Motlatji Maloba (FS); Caroline Maluleka, Charl Verwey, Charles Feldman, Colin Menezes, David Moore, Gary Reubenson, Jeannette Wadula, Merika Tsitsi, Maphoshane Nchabeleng, Nicolette du Plessis, Nontombi Mbelle, Nontuthuko Maningi, Prudence Ive, Theunis Avenant, Trusha Nana, Vindana Chibabhai (GA); Adhil Maharj, Fathima Naby, Halima Dawood, Khine Swe Swe Han, Koleka Mlisana, Lisha Sookan, Nomonde Dlamini, Praksha Ramjathan, Prasha Mahabeer, Romola Naidoo, Sumayya Haffejee, Surendra Sirkar (KZN); Ken Hamese, Ngoaka Sibiyi, Ruth Lekalakala (LP); Greta Hoyland, Sindi Ntuli (MP); Mirriam Selekisho, Pieter Jooste (NC); Ebrahim Variava, Ignatius Khantsi (NW); Adrian Brink, Elizabeth Prentice, Kessendri Reddy, Andrew Whitelaw (WC); Ebrahim Hoosien, Inge Zietsman, Terry Marshall, Xoliswa Poswa (AMPATH); Chetna Govind, Juanita Smit, Keshree Pillay, Sharona Seetharam, Victoria Howell (LANCET Laboratories); Catherine Samuel, Marthinus Senekal, Colleen Bamford (PathCare); Andries Dreyer, Khatija Ahmed, Louis Marcus, Warren Lowman (Vermaak and Vennote); Anne von Gottberg, Anthony Smith, Azwifarwi Mathunjwa, Cecilia Miller, Charlotte Sriruttan, Cheryl Cohen, Desiree du Plessis, Erika van Schalkwyk, Farzana Ismail, Frans Radebe, Gillian Hunt, Husna Ismail, Jacqueline Weyer, Jackie Kleynhans, Jenny Rossouw, John Freat, Joy Ebonwu, Judith Mwansa-Kambafwile, Juno Thomas, Kerrigan McCarthy, Liliwe Shuping, Linda de Gouveia, Linda Erasmus, Lynn Morris, Lucille Blumberg, Marshagne Smith, Martha Makgoba, Mignon du Plessis, Mimmy Ngomane, Myra Moremi, Nazir Ismail, Nelesh Govender, Neo Legare, Nicola Page, Nombulelo Hoho, Ntsieni Ramalwa, Olga Perovic, Portia Mutevedzi, Ranmini Kularatne, Rudzani Mathebula, Ruth Mpembe, Sibongile Walaza, Sunnieboy Njikho, Susan Meiring, Tiisetso Lebaka, Vanessa Quan, Wendy Ngubane (NICD).

Statistical Methods:

The model was adjusted for the year and to account for a transition period after PCV7 was introduced (2009 through 2011) and after PCV13 was introduced (2012 through 2019). To account for the influence of population size, we incorporated the logarithm of the population denominator in the model. The general form of the model was:

modelled cases

$$= \beta_0 + \beta_1 time_1 + \beta_2 period_{pcv7} + \beta_3 period_{pcv13} + \beta_4 time_{period_{pcv7}} + \beta_5 time_{period_{pcv13}} + 1.0 \times \log(denominator)$$

Where β_0 represents the number of imputed IPD cases for the respective age, serotype, or antibiotic susceptibility category, *period* is a binary variable to indicate the PCV7 (2009-2011) and PCV13 (2012-2019) periods, *time* is a value between 0 to 1 to indicate the progression of time in the overall study period ($time_1$) and each vaccine period and denominator is the population size for the respective category used as offset.

We investigated the use of quarterly and annual case counts, and tested both a Poisson and Negative Binomial distribution for the model. For quarterly-aggregated models, we tested both models with and without a cosine seasonality term. We compared the AIC and overdispersion parameters for all models, and based on the authors assessment, the annual case counts using a Negative Binomial distribution fared the best over most models, and are presented in the main text. The results for the other models can be found in the online repository [https://github.com/crdm-nicd/vongottberg_ipd_sa_2005_2019.git]. We used the `mvrnorm` function from the MASS R package to generate 1000 predictions of case counts for each year during the period. The function generates a random sample from a multivariate normal distribution with a specified mean vector (coefficients of linear regression model) and the variance-covariance matrix from the model. The mean of the generated case counts for each year was used as the modelled (actual) number of cases at each time point, and the 2.5th and 97.5th percentiles were used as 95% credible intervals. To assess the impact of PCV introduction on IPD, vaccine effects were set to zero in the model to generate expected case counts (counterfactual). Annual case counts (modeled (actual) and expected (no intervention)) resulting from the model were divided by the mid-year annual population (from the TEMBISA v4.6 model)³² of the respective age group and multiplied by 100,000 to calculate the incidence of IPD per 100,000 population. The corresponding 95% confidence intervals (CI) were calculated using the `epi.conf` function with the exact method from the `epiR` package in R. The 2019 actual modelled and expected annual case counts (counterfactual, if there were no intervention) were compared to calculate the risk ratio (RR) and absolute risk difference with corresponding 95% Wald CI using the `epi.2by2` function in the `epiR` package. The percentage risk difference was calculated as $(1 - RR) \times 100$. The 95% CI were calculated by substituting the RR with the respective 95% confidence intervals of the RR.

To assess the effect of the imputation of cases on the modelled reductions, we performed a sensitivity analysis using the raw case numbers instead of the imputed numbers.

Supplementary Figure 1a: Number of viable isolates serotyped, causing invasive pneumococcal disease in children 5–14 years of age, South Africa, 2005-2019, by serotype and year (graded colour scale: maximum value is red, midpoint value is yellow and minimum value is green)*

Year	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
4	12	25	14	19	23	18	8	2	6	4	0	3	0	1	0
6B	29	27	30	14	20	13	7	6	4	0	4	4	0	0	1
9V	18	18	10	13	10	11	7	4	3	1	0	0	0	1	0
14	33	28	40	29	30	21	7	6	4	1	4	0	3	0	2
18C	8	7	8	15	12	13	7	4	1	4	1	3	1	1	0
19F	12	25	22	10	10	10	5	9	3	6	4	8	4	4	5
23F	35	22	21	18	27	20	12	9	3	8	4	2	0	1	1
1	101	80	65	80	99	68	56	58	24	18	8	7	2	3	0
3	1	3	7	3	7	2	6	4	3	3	1	3	2	1	3
5	8	1	0	4	4	5	6	2	2	0	1	0	0	0	0
6A	28	22	23	25	17	17	15	9	2	6	2	2	1	1	4
7F	2	4	2	1	1	3	3	2	0	0	0	0	0	0	0
19A	17	22	12	14	16	11	9	12	9	1	4	4	4	4	2
8	4	6	7	5	4	8	1	8	7	2	5	6	6	2	9
9N	1	0	2	3	1	2	2	1	1	1	1	2	1	2	3
10A	2	1	1	2	1	2	1	1	4	1	2	2	1	4	4
11A	4	1	1	0	1	1	2	0	1	0	1	0	1	2	1
12F	10	7	8	7	9	6	7	13	6	10	10	4	4	3	9
15B/C	8	10	7	5	2	5	5	3	2	3	2	5	2	1	4
17F	4	0	1	1	2	2	3	0	1	1	0	4	2	1	0
20	1	0	1	0	0	0	1	0	0	0	0	1	0	0	1
22F	2	0	1	0	2	2	1	1	0	1	2	1	0	0	1
33F	0	2	0	1	0	0	0	1	0	0	0	0	0	0	0
16F	3	4	1	2	8	3	5	4	4	5	4	1	1	3	4
15A	2	2	2	2	0	0	2	1	4	5	1	4	0	1	1
13	0	5	1	1	3	1	2	1	0	2	1	0	3	0	0
7C	0	0	4	0	3	1	2	1	2	1	0	0	0	0	0
25A/38	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
23A	0	0	0	0	1	0	0	1	1	3	1	1	3	1	2
6C	0	1	1	0	0	1	0	1	0	1	0	0	1	3	1
23B	1	1	3	1	1	2	2	0	2	4	0	1	1	1	0
31	0	0	0	0	0	0	0	0	1	0	0	1	0	0	0
Pool G#	5	3	3	2	4	1	7	6	5	5	7	2	2	3	3
Other	6	8	11	8	5	2	1	5	1	2	2	4	2	1	5

*PCV-7 (7-valent pneumococcal conjugate vaccine) and PCV-13 were introduced in 2009 and 2011, respectively; PCV7 serotypes in blue (4, 6B, 9V, 14, 18C, 19F, 23F); additional PCV13 serotypes in green (1, 3, 5, 6A, 7F, 19A); non-PCV13 serotypes in black
 # Pool G includes serogroups 29, 34, 35, 42 and 47.

Supplementary Figure 1b: Number of viable isolates serotyped, causing invasive pneumococcal disease in individuals 15–24 years of age, South Africa, 2005-2019, by serotype and year (graded colour scale: maximum value is red, midpoint value is yellow and minimum value is green)*

Year	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
4	19	13	18	14	14	12	10	10	12	7	3	2	2	5	4
6B	8	6	10	5	16	3	2	3	0	3	4	1	1	1	1
9V	3	11	4	8	7	2	2	2	1	3	1	0	0	2	2
14	6	6	12	8	7	6	2	4	2	3	1	2	1	0	3
18C	3	5	4	0	4	3	3	6	3	0	1	1	1	1	0
19F	12	8	12	4	7	7	6	1	1	1	2	5	4	2	2
23F	6	9	11	8	9	11	5	6	2	2	0	1	0	0	0
1	35	43	35	39	47	39	40	27	13	9	4	0	0	2	0
3	8	9	5	7	9	6	2	5	3	4	3	5	3	6	4
5	2	0	1	2	2	5	4	0	0	0	0	0	0	0	0
6A	11	12	8	8	11	9	6	0	1	1	2	3	1	1	2
7F	1	4	3	5	0	2	3	2	7	2	3	3	0	0	1
19A	14	21	15	9	13	19	7	13	3	6	5	12	7	6	2
8	3	6	7	6	9	7	4	11	3	4	4	11	16	5	8
9N	3	4	0	5	5	9	5	5	4	2	5	5	2	2	2
10A	1	5	2	1	1	6	1	2	3	2	1	2	2	3	3
11A	0	4	0	1	0	2	1	0	1	0	1	3	2	3	1
12F	9	6	7	4	11	9	5	9	7	14	8	8	10	4	5
15B/C	4	3	1	2	4	2	4	5	7	3	3	2	3	4	1
17F	1	0	1	2	1	5	2	2	9	4	0	2	1	1	2
20	0	1	1	2	1	1	2	0	1	1	0	0	0	0	1
22F	1	5	0	3	1	1	1	1	2	3	3	1	0	2	2
33F	0	1	0	1	0	0	0	2	1	2	2	0	1	0	0
16F	1	9	3	0	1	2	3	5	2	2	8	3	4	1	2
15A	0	1	2	1	2	0	1	1	2	3	3	6	2	0	1
13	2	3	6	2	1	3	3	5	4	1	5	0	4	0	2
7C	0	2	4	1	2	4	1	0	0	0	1	2	4	1	1
25A/38	0	0	0	0	0	0	1	1	0	0	0	2	1	1	0
23A	2	0	1	0	1	1	0	0	4	0	3	4	1	3	1
6C	1	1	0	1	1	0	1	0	0	0	1	0	2	4	1
23B	0	2	0	0	2	0	0	0	0	1	1	1	0	3	1
31	1	1	1	2	1	0	1	0	1	2	0	0	1	0	2
Pool G#	4	5	5	4	2	4	8	4	5	2	4	7	6	5	4
Other	17	10	14	8	8	6	2	3	4	6	7	9	6	4	5

*PCV-7 (7-valent pneumococcal conjugate vaccine) and PCV-13 were introduced in 2009 and 2011, respectively; PCV7 serotypes in blue (4, 6B, 9V, 14, 18C, 19F, 23F); additional PCV13 serotypes in green (1, 3, 5, 6A, 7F, 19A); non-PCV13 serotypes in black
 # Pool G includes serogroups 29, 34, 35, 42 and 47.

Supplementary Figure 1c: Number of viable isolates serotyped, causing invasive pneumococcal disease in individuals 25–44 years of age, South Africa, 2005-2019, by serotype and year (graded colour scale: maximum value is red, midpoint value is yellow and minimum value is green)*

Year	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
4	66	59	99	100	75	78	69	59	48	49	35	38	21	49	26
6B	57	37	53	56	49	42	29	14	17	6	6	7	4	1	3
9V	38	38	35	34	31	32	21	17	8	14	4	8	5	5	7
14	69	59	59	60	57	34	24	16	12	11	11	6	5	4	9
18C	16	28	24	17	30	18	21	7	10	10	4	4	7	4	2
19F	55	34	46	41	43	33	33	30	17	13	11	17	30	23	24
23F	63	76	75	79	82	76	43	36	21	19	10	8	11	5	5
1	182	149	125	137	173	146	143	113	72	47	15	14	5	2	1
3	56	62	56	43	36	40	45	40	34	41	32	43	43	44	41
5	13	13	6	13	22	17	12	6	3	1	0	2	0	0	0
6A	87	81	75	62	79	66	76	46	27	22	14	11	15	5	9
7F	21	22	24	13	22	19	13	20	20	14	18	16	12	15	13
19A	106	122	117	112	144	137	120	88	95	65	70	51	68	54	39
8	46	66	54	50	33	38	37	41	48	54	71	77	71	69	49
9N	22	19	17	25	21	24	20	27	28	18	25	14	26	21	38
10A	20	16	13	11	9	11	13	18	23	11	24	27	12	12	19
11A	9	3	8	7	8	5	7	5	6	5	6	10	6	6	4
12F	69	56	44	51	54	77	60	81	104	97	90	58	65	54	68
15B/C	22	23	6	17	15	14	18	20	18	12	13	9	16	7	16
17F	13	8	23	16	20	10	11	16	16	21	14	8	7	11	14
20	1	0	1	3	4	1	3	1	1	3	4	1	2	2	3
22F	15	18	8	15	10	22	16	21	17	17	21	17	15	17	7
33F	5	5	7	6	3	7	5	1	5	4	3	3	4	2	2
16F	23	16	18	19	31	32	29	27	30	28	34	19	31	17	21
15A	10	8	15	10	3	9	4	20	31	37	23	17	21	23	19
13	21	15	11	12	18	15	22	22	28	10	23	18	10	19	12
7C	13	6	19	8	12	11	13	17	13	12	15	17	14	5	11
25A/38	0	0	0	0	0	0	3	3	5	4	6	4	5	5	3
23A	3	8	6	3	11	8	3	7	12	10	15	10	18	10	19
6C	9	5	6	6	4	7	7	4	2	9	6	17	15	20	31
23B	3	2	4	5	2	1	1	1	2	5	9	7	2	7	11
31	6	4	5	2	5	1	5	3	7	5	4	9	10	5	4
Pool G#	35	35	22	23	24	19	26	27	22	24	26	27	26	25	22
Other	94	77	67	74	59	47	36	25	31	19	47	37	26	26	21

*PCV-7 (7-valent pneumococcal conjugate vaccine) and PCV-13 were introduced in 2009 and 2011, respectively; PCV7 serotypes in blue (4, 6B, 9V, 14, 18C, 19F, 23F); additional PCV13 serotypes in green (1, 3, 5, 6A, 7F, 19A); non-PCV13 serotypes in black
 # Pool G includes serogroups 29, 34, 35, 42 and 47.

Supplementary Figure 1d: Number of viable isolates serotyped, causing invasive pneumococcal disease in individuals 45–64 years of age, South Africa, 2005-2019, by serotype and year (graded colour scale: maximum value is red, midpoint value is yellow and minimum value is green)*

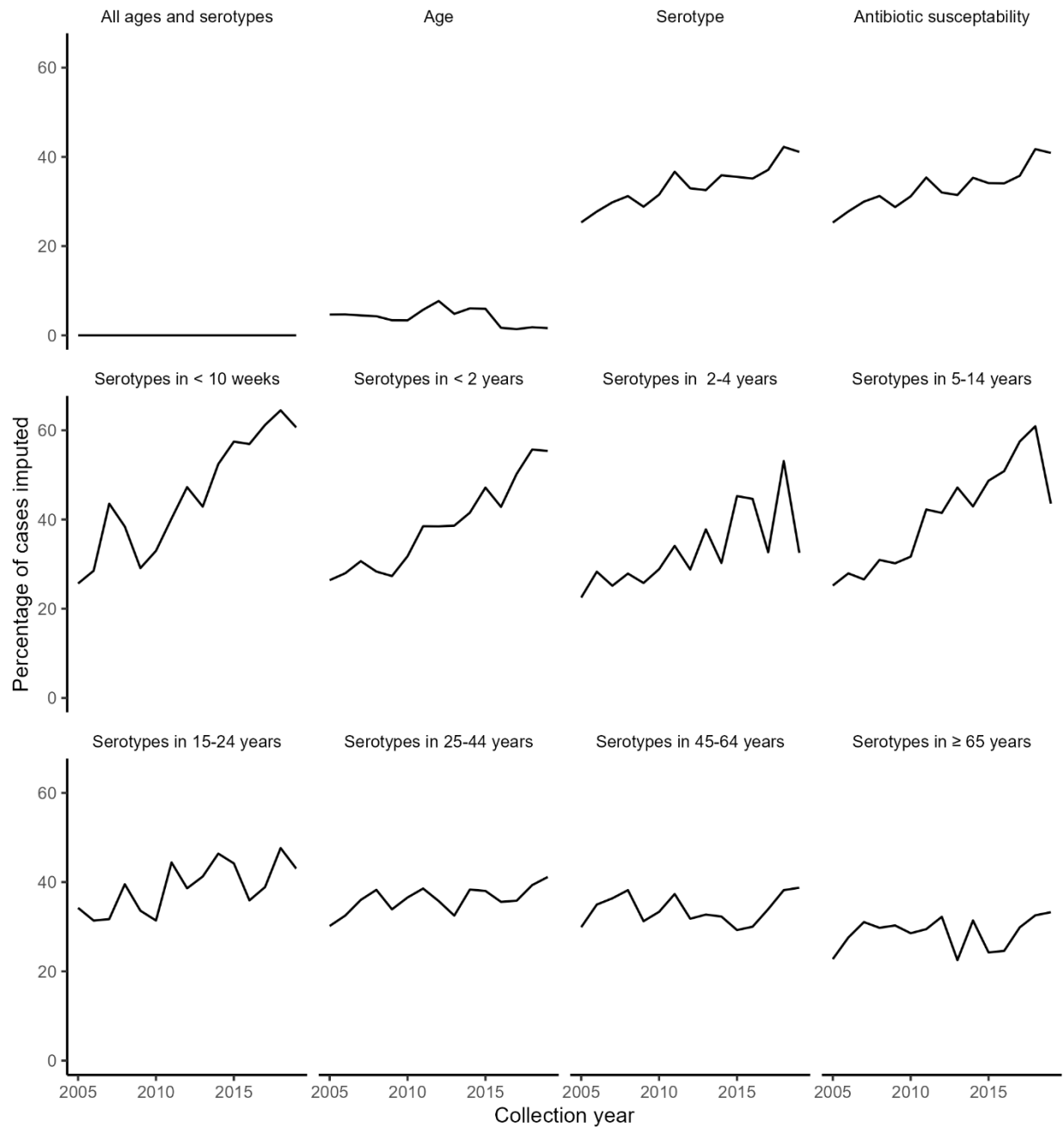
Year	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
4	28	31	32	28	33	37	22	31	23	19	19	17	16	10	11
6B	16	18	14	15	16	17	13	13	3	5	4	1	0	4	0
9V	8	13	12	10	15	16	2	6	4	2	4	2	1	2	0
14	20	20	20	26	19	18	6	11	3	7	7	1	8	4	4
18C	4	4	4	20	6	5	3	6	4	6	4	4	6	1	0
19F	25	15	19	21	19	18	18	8	12	19	10	15	15	17	16
23F	18	12	22	24	29	29	26	22	7	16	8	2	3	10	3
1	69	36	33	41	57	53	50	46	31	18	6	5	1	1	1
3	35	31	18	32	20	26	35	32	21	34	24	31	29	31	31
5	4	8	2	4	3	5	5	7	1	1	0	0	0	0	2
6A	17	21	21	28	29	47	31	29	9	9	7	9	10	4	0
7F	1	4	4	4	6	5	8	6	8	2	2	2	4	3	4
19A	32	43	38	34	42	52	72	35	35	24	45	31	25	28	23
8	22	21	20	17	27	14	17	25	30	27	49	44	62	37	64
9N	2	5	7	7	8	8	11	9	7	8	14	10	18	10	27
10A	4	7	1	6	8	8	5	4	5	10	16	10	12	8	11
11A	0	3	4	4	4	4	4	4	2	3	5	1	5	3	4
12F	14	13	13	12	27	32	38	31	39	39	52	38	37	27	31
15B/C	5	5	4	6	6	9	6	5	11	8	8	7	8	4	5
17F	3	3	6	3	5	7	6	14	5	13	9	16	13	4	8
20	3	0	1	0	0	0	2	0	1	0	1	3	0	1	3
22F	4	7	3	6	11	14	10	9	17	7	14	21	20	15	6
33F	1	0	1	2	0	0	2	0	0	2	1	1	0	1	1
16F	6	10	10	4	12	8	12	7	10	17	16	16	10	9	17
15A	4	1	5	2	8	3	13	17	15	14	18	15	16	17	15
13	5	3	10	6	7	6	5	5	10	12	7	8	20	12	9
7C	4	2	5	6	2	6	2	5	12	6	8	12	10	8	6
25A/38	0	0	0	0	0	0	0	3	6	3	4	3	1	0	1
23A	3	2	5	1	1	1	5	1	6	4	10	6	11	6	4
6C	2	6	2	1	0	1	1	2	2	5	6	10	15	16	9
23B	0	1	0	0	1	1	0	2	1	3	4	3	3	1	10
31	2	1	1	0	0	1	2	1	4	2	5	7	7	0	1
Pool G#	7	8	6	9	10	20	10	8	15	14	13	16	8	17	16
Other	32	24	20	20	18	7	12	12	17	15	22	21	14	10	10

*PCV-7 (7-valent pneumococcal conjugate vaccine) and PCV-13 were introduced in 2009 and 2011, respectively; PCV7 serotypes in blue (4, 6B, 9V, 14, 18C, 19F, 23F); additional PCV13 serotypes in green (1, 3, 5, 6A, 7F, 19A); non-PCV13 serotypes in black
 # Pool G includes serogroups 29, 34, 35, 42 and 47.

Supplementary Figure 1e: Number of viable isolates serotyped, causing invasive pneumococcal disease in individuals >64 years of age, South Africa, 2005-2019, by serotype and year (graded colour scale: maximum value is red, midpoint value is yellow and minimum value is green)*

Year	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
4	7	4	7	8	3	5	4	5	2	4	5	5	0	4	7
6B	4	2	4	5	2	5	6	2	2	2	2	3	0	0	0
9V	3	6	3	2	4	1	2	2	3	2	0	0	0	2	0
14	7	10	5	10	7	12	5	6	6	0	1	3	1	2	4
18C	0	1	0	3	1	2	0	0	1	1	2	3	2	2	0
19F	9	3	7	3	8	10	1	3	7	6	5	6	8	4	5
23F	4	4	8	3	5	4	6	4	2	1	2	0	2	0	0
1	7	8	13	10	16	13	8	12	5	2	1	0	0	0	0
3	6	8	11	7	22	11	14	15	16	11	8	22	15	18	13
5	4	3	2	2	2	4	0	2	2	0	0	0	0	0	0
6A	6	9	5	3	5	4	4	7	1	3	3	1	3	2	2
7F	1	0	0	1	2	0	2	2	4	4	4	2	3	1	1
19A	4	4	9	6	9	15	16	11	15	11	8	11	16	7	12
8	3	6	5	9	3	3	8	4	10	9	18	17	23	31	19
9N	1	3	0	3	3	4	1	5	3	4	9	5	4	5	4
10A	4	2	0	1	0	1	1	1	1	4	2	6	4	2	6
11A	1	1	0	2	1	3	3	3	0	4	4	2	3	1	2
12F	6	4	2	2	5	4	6	3	15	11	11	5	7	9	4
15B/C	2	0	0	2	0	1	2	4	1	2	2	2	6	3	5
17F	1	0	0	2	2	1	3	4	2	4	1	3	1	1	1
20	0	0	0	0	0	0	1	0	0	0	0	1	0	0	0
22F	2	5	2	7	4	2	3	5	6	4	9	9	8	5	9
33F	0	0	0	0	1	1	0	1	0	0	3	0	1	0	0
16F	1	3	2	0	3	0	1	3	4	1	3	4	2	3	3
15A	1	0	1	2	0	1	3	2	5	8	8	3	11	6	9
13	1	1	3	0	1	3	2	1	2	4	4	1	0	2	6
7C	2	1	0	0	0	2	1	3	1	3	1	1	2	1	5
25A/38	0	0	0	0	0	0	2	1	1	2	5	1	2	1	0
23A	0	2	0	2	0	2	0	0	1	3	4	2	1	2	1
6C	0	0	1	0	0	0	0	0	0	2	3	6	1	5	5
23B	0	0	0	0	0	0	0	1	2	2	1	2	0	0	1
31	0	1	0	0	0	1	0	1	1	0	6	2	3	3	2
Pool G#	2	4	4	6	0	5	1	2	3	2	3	4	5	7	3
Other	5	3	2	1	5	2	1	1	3	3	7	3	4	7	6

*PCV-7 (7-valent pneumococcal conjugate vaccine) and PCV-13 were introduced in 2009 and 2011, respectively; PCV7 serotypes in blue (4, 6B, 9V, 14, 18C, 19F, 23F); additional PCV13 serotypes in green (1, 3, 5, 6A, 7F, 19A); non-PCV13 serotypes in black
 # Pool G includes serogroups 29, 34, 35, 42 and 47.



Supplementary Figure 2: Percentage of case numbers imputed by year and analysis category, South Africa, 2005 through 2019.