

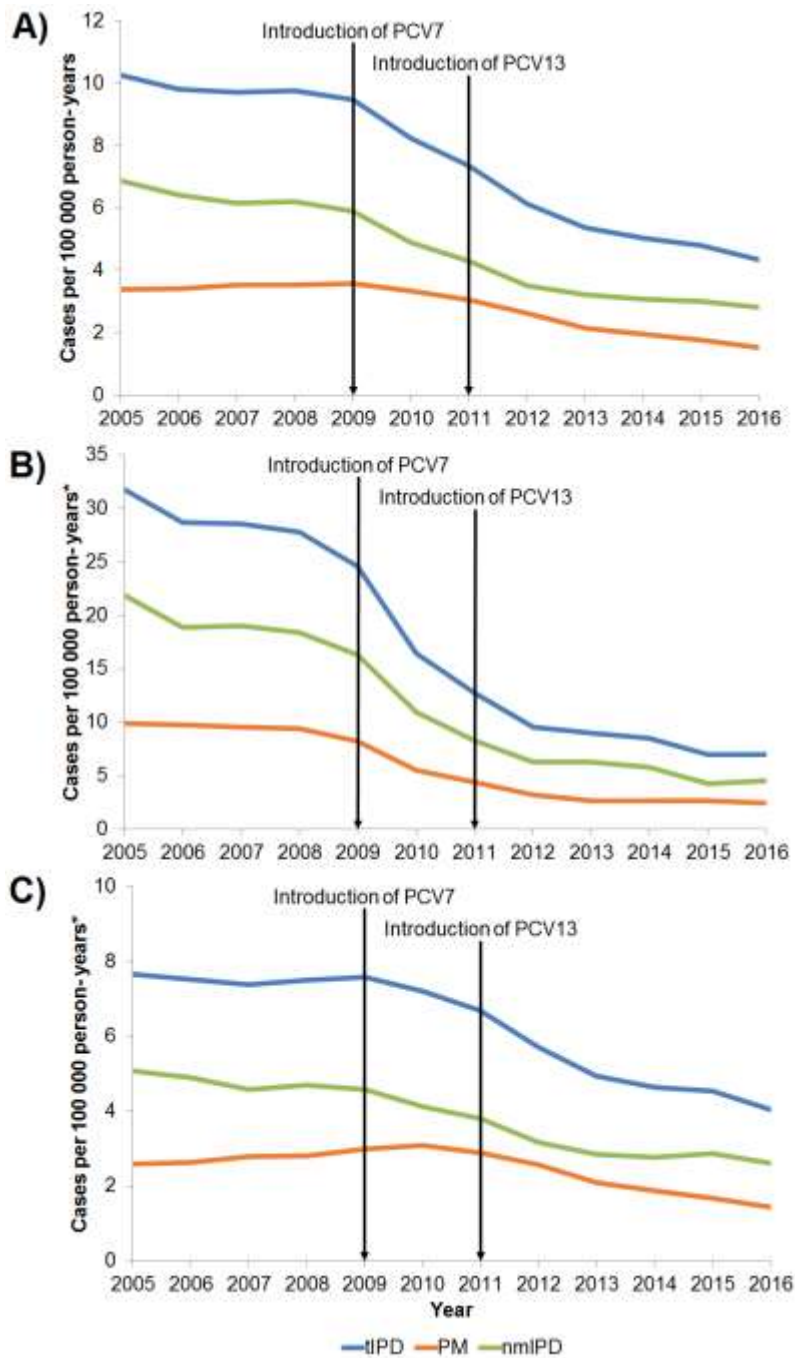
## Supplementary Material

Supplement to: Can pneumococcal meningitis surveillance be used to assess the impact of pneumococcal conjugate vaccine on total invasive pneumococcal disease?

A case-study from South Africa, 2005-2016

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**Supplementary Figure 1.** Trends of invasive pneumococcal disease (IPD) incidence from 2005 – 2016, by specimen type used for diagnosis, South Africa. A) In all ages, B) in those <5 years old, and C) in those ≥5 years old.

**Supplementary Table 1.** Percentage difference in rates of total invasive pneumococcal disease (tIPD) and pneumococcal meningitis (PM) between 2005-2008 (pre-PCV introduction) and 2012 (post-PCV introduction) and percentage effect difference in rate changes between 2005-2008 and 2012 for PM compared to tIPD, South Africa, 2005-2012

<b>Serotype groups</b>	<b>tIPD % difference (95% CI)</b>	<b>PM % difference (95% CI)</b>	<b>% effect difference PM vs. tIPD<sup>a</sup> (p value)</b>
<b>Children aged &lt;5 years</b>			
PCV7 serotypes	<b>-88.4 (-90.3 to -86.0)</b>	<b>-89.9 (-92.8 to -85.8)</b>	-12.8 (0.49)
Additional PCV13 serotypes	<b>-66.2 (-71.3 to -60.1)</b>	<b>-70.2 (-78.7 to -58.4)</b>	-12.0 (0.50)
Non-PCV13 serotypes	12.8 (-1.3 to 28.8)	<b>25.0 (1.1 to 54.5)</b>	10.8 (0.42)
All serotypes <sup>b</sup>	<b>-67.4 (-70.1 to -64.4)</b>	<b>-66.7 (-71.3 to -61.3)</b>	2.0 (0.82)
<b>Individuals aged ≥5 years</b>			
PCV7 serotypes	<b>-55.0 (-59.0 to -50.7)</b>	<b>-47.1 (-54.0 to -39.2)</b>	17.7 (0.06)
Additional PCV13 serotypes	<b>-28.3 (-33.2 to -23.0)</b>	<b>-26.5 (-35.3 to -16.5)</b>	2.5 (0.74)
Non-PCV13 serotypes	<b>22.1 (14.5 to 30.1)</b>	<b>61.4 (47.6 to 76.4)</b>	<b>32.2 (&lt;0.01)</b>
All serotypes <sup>b</sup>	<b>-22.3 (-25.5 to -19.0)</b>	-3.2 (-9.2 to 3.1)	<b>24.6 (&lt;0.01)</b>
<b>Individuals of all ages</b>			
PCV7 serotypes <sup>c</sup>	<b>-70.4 (-72.7 to -67.9)</b>	<b>-66.2 (-70.2 to -61.6)</b>	14.3 (0.08)
Additional PCV13 serotypes <sup>c</sup>	<b>-38.3 (-42.1 to -34.1)</b>	<b>-37.2 (-44.2 to -29.3)</b>	1.7 (0.80)
Non-PCV13 serotypes <sup>c</sup>	<b>20.3 (13.5 to 27.4)</b>	<b>54.9 (42.7 to 68.1)</b>	<b>28.8 (&lt;0.01)</b>
All serotypes <sup>d</sup>	<b>-37.2 (-39.5 to -34.8)</b>	<b>-23.0 (-27.3 to -18.4)</b>	<b>22.5 (&lt;0.01)</b>

Abbreviations: CI: confidence intervals; PCV: pneumococcal conjugate vaccine; PCV7 serotypes: 4, 6B, 9V, 14, 18C, 19F and 23F; Additional PCV13 serotypes: 1, 3, 5, 6A, 7F and 19A; Non-PCV13 serotypes: all serotype not in PCV13.

<sup>a</sup> Percentage effect difference calculated as the rate ratio of the interaction term for PCV period (2012 vs. 2005-2008) and syndrome (PM vs. tIPD) term minus 1 multiplied by 100

<sup>b</sup> Model adjusted by serotype groups: PCV7, additional PCV13 and non-PCV13 serotypes.

<sup>c</sup> Model adjusted by age groups: individuals <5 and ≥5 years of age.

<sup>d</sup> Model adjusted by serotype and age groups.

**Supplementary Table 2.** Percentage difference in rates of total invasive pneumococcal disease (tIPD) and pneumococcal meningitis (PM) between 2005-2008 (pre-PCV introduction) and 2016 (post-PCV introduction) and percentage effect difference in rate changes between 2005-2008 and 2016 for PM compared to tIPD, South Africa, 2005-2016

Serotype groups	tIPD % difference (95% CI)	PM % difference (95% CI)	% effect difference PM vs. tIPD <sup>a</sup> (p value)
<b>Children aged &lt;5 years</b>			
PCV7 serotypes	-95.5 (-96.6 to -93.9)	-96.5 (-98.0 to -93.9)	-23.6 (0.41)
Additional PCV13 serotypes	-92.1 (-94.4 to -89.1)	-94.4 (-97.3 to -88.2)	-28.8 (0.42)
Non-PCV13 serotypes	29.3 (14.0 to 46.6)	33.9 (8.9 to 64.5)	3.5 (0.78)
All serotypes <sup>b</sup>	-76.0 (-78.3 to -73.5)	-74.7 (-78.7 to -70.0)	5.4 (0.60)
<b>Individuals aged ≥5 years</b>			
PCV7 serotypes	-79.4 (-81.9 to -76.7)	-79.6 (-83.4 to -74.8)	-0.6 (0.96)
Additional PCV13 serotypes	-70.3 (-73.1 to -67.1)	-78.5 (-82.6 to -73.3)	-27.6 (0.01)
Non-PCV13 serotypes	26.3 (18.7 to 34.3)	17.5 (6.6 to 29.6)	-6.9 (0.23)
All serotypes <sup>b</sup>	-44.7 (-47.3 to -42.1)	-45.7 (-49.8 to -41.3)	-1.7 (0.71)
<b>Individuals of all ages</b>			
PCV7 serotypes <sup>c</sup>	-86.6 (-88.1 to -85.0)	-86.9 (-89.2 to -84.1)	-2.1 (0.85)
Additional PCV13 serotypes <sup>c</sup>	-75.8 (-78.0 to -73.4)	-82.2 (-85.5 to -78.1)	-26.5 (0.01)
Non-PCV13 serotypes <sup>c</sup>	26.8 (20.0 to 34.0)	20.3 (10.2 to 31.4)	-5.1 (0.32)
All serotypes <sup>d</sup>	-54.7 (-56.6 to -52.8)	-54.4 (-57.5 to -51.0)	0.7 (0.87)

Abbreviations: CI: confidence intervals; PCV: pneumococcal conjugate vaccine; PCV7 serotypes: 4, 6B, 9V, 14, 18C, 19F and 23F; Additional PCV13 serotypes: 1, 3, 5, 6A, 7F and 19A; Non-PCV13 serotypes: all serotype not in PCV13.

<sup>a</sup> Percentage effect difference calculated as the rate ratio of the interaction term for PCV period (2016 vs. 2005-2008) and syndrome (PM vs. tIPD) term minus 1 multiplied by 100

<sup>b</sup> Model adjusted by serotype groups: PCV7, additional PCV13 and non-PCV13 serotypes.

<sup>c</sup> Model adjusted by age groups: individuals <5 and ≥5 years of age.

<sup>d</sup> Model adjusted by serotype and age groups.

**Supplementary Table 3.** Percentage difference in rates of non-meningitis invasive pneumococcal disease (nmIPD) and pneumococcal meningitis (PM) between 2005-2008 (pre-PCV introduction) and 2012 (post-PCV introduction) and percentage effect difference in rate changes between 2005-2008 and 2012 for PM compared to nmIPD, South Africa, 2005-2012

Serotype groups	nmIPD % difference (95% CI)	PM % difference (95% CI)	% effect difference PM vs. nmIPD <sup>a</sup> (p value)
<b>Children aged &lt;5 years</b>			
PCV7 serotypes	<b>-87.6 (-90.1 to -84.5)</b>	<b>-89.7 (-92.6 to -85.7)</b>	-17.3 (0.35)
Additional PCV13 serotypes	<b>-64.6 (-70.7 to -57.2)</b>	<b>-70.3 (-78.8 to -58.5)</b>	-16.1 (0.37)
Non-PCV13 serotypes	5.9 (-10.7 to 25.6)	<b>25.0 (1.1 to 54.5)</b>	18.0 (0.23)
All serotypes <sup>b</sup>	<b>-67.7 (-70.9 to -64.0)</b>	<b>-66.7 (-71.3 to -61.3)</b>	3.1 (0.74)
<b>Individuals aged ≥5 years</b>			
PCV7 serotypes	<b>-59.7 (-64.3 to -54.6)</b>	<b>-47.1 (-54.0 to -39.2)</b>	<b>31.4 (0.01)</b>
Additional PCV13 serotypes	<b>-29.0 (-34.8 to -22.7)</b>	<b>-26.6 (-35.4 to -16.6)</b>	3.4 (0.67)
Non-PCV13 serotypes	-6.5 (-14.8 to 2.7)	<b>61.5 (47.7 to 76.5)</b>	<b>72.6 (&lt;0.01)</b>
All serotypes <sup>b</sup>	<b>-33.1 (-36.7 to -29.2)</b>	-3.3 (-9.2 to 3.1)	<b>44.5 (&lt;0.01)</b>
<b>Individuals of all ages</b>			
PCV7 serotypes <sup>c</sup>	<b>-72.8 (-75.6 to -69.8)</b>	<b>-66.2 (-70.2 to -61.6)</b>	<b>24.6 (0.01)</b>
Additional PCV13 serotypes <sup>c</sup>	<b>-38.6 (-43.2 to -33.7)</b>	<b>-37.3 (-44.3 to -29.4)</b>	2.2 (0.77)
Non-PCV13 serotypes <sup>c</sup>	-3.8 (-11.3 to 4.4)	<b>54.9 (42.7 to 68.1)</b>	<b>61.0 (&lt;0.01)</b>
All serotypes <sup>d</sup>	<b>-44.8 (-47.4 to -42.0)</b>	<b>-23.0 (-27.4 to -18.4)</b>	<b>39.4 (&lt;0.01)</b>

Abbreviations: CI: confidence intervals; PCV: pneumococcal conjugate vaccine; PCV7 serotypes: 4, 6B, 9V, 14, 18C, 19F and 23F; Additional PCV13 serotypes: 1, 3, 5, 6A, 7F and 19A; Non-PCV13 serotypes: all serotype not in PCV13.

a Percentage effect difference calculated as the rate ratio of the interaction term for PCV period (2012 vs. 2005-2008) and syndrome (PM vs. nmIPD) term minus 1 multiplied by 100

b Model adjusted by serotype groups: PCV7, additional PCV13 and non-PCV13 serotypes.

c Model adjusted by age groups: individuals <5 and ≥5 years of age.

d Model adjusted by serotype and age groups.

**Supplementary Table 4.** Percentage difference in rates of non-meningitis invasive pneumococcal disease (nmIPD) and pneumococcal meningitis (PM) between 2005-2008 (pre-PCV introduction) and 2016 (post-PCV introduction) and percentage effect difference in rate changes between 2005-2008 and 2016 for PM compared to nmIPD, South Africa, 2005-2016

Serotype groups	nmIPD % difference (95% CI)	PM % difference (95% CI)	% effect difference PM vs. nmIPD <sup>a</sup> (p value)
<b>Children aged &lt;5 years</b>			
PCV7 serotypes	<b>-94.9 (-96.4 to -92.8)</b>	<b>-96.6 (-98.1 to -93.9)</b>	-32.8 (0.24)
Additional PCV13 serotypes	<b>-91.4 (-94.1 to -87.6)</b>	<b>-94.0 (-97.1 to -87.7)</b>	-30.5 (0.38)
Non-PCV13 serotypes	<b>26.8 (8.1 to 48.6)</b>	<b>33.7 (8.8 to 64.4)</b>	5.5 (0.69)
All serotypes <sup>b</sup>	<b>-76.7 (-79.4 to -73.6)</b>	<b>-74.7 (-78.6 to -70.0)</b>	8.5 (0.44)
<b>Individuals aged ≥5 years</b>			
PCV7 serotypes	<b>-79.4 (-82.4 to -75.8)</b>	<b>-79.5 (-83.4 to -74.8)</b>	-0.8 (0.95)
Additional PCV13 serotypes	<b>-66.8 (-70.4 to -62.7)</b>	<b>-78.4 (-82.6 to -73.2)</b>	<b>-35.1 (&lt;0.01)</b>
Non-PCV13 serotypes	<b>32.5 (22.4 to 43.5)</b>	<b>17.6 (6.7 to 29.7)</b>	-11.2 (0.06)
All serotypes <sup>b</sup>	<b>-44.2 (-47.4 to -40.9)</b>	<b>-45.6 (-49.7 to -41.2)</b>	-2.5 (0.62)
<b>Individuals of all ages</b>			
PCV7 serotypes <sup>c</sup>	<b>-86.5 (-88.3 to -84.4)</b>	<b>-86.9 (-89.2 to -84.1)</b>	-3.2 (0.79)
Additional PCV13 serotypes <sup>c</sup>	<b>-73.2 (-76.0 to -70.1)</b>	<b>-82.1 (-85.4 to -78.0)</b>	<b>-33.1 (&lt;0.01)</b>
Non-PCV13 serotypes <sup>c</sup>	<b>31.3 (22.3 to 41.0)</b>	<b>20.4 (10.2 to 31.5)</b>	-8.3 (0.13)
All serotypes <sup>d</sup>	<b>-54.9 (-57.2 to -52.5)</b>	<b>-54.3 (-57.5 to -51.0)</b>	1.3 (0.78)

Abbreviations: CI: confidence intervals; PCV: pneumococcal conjugate vaccine; PCV7 serotypes: 4, 6B, 9V, 14, 18C, 19F and 23F; Additional PCV13 serotypes: 1, 3, 5, 6A, 7F and 19A; Non-PCV13 serotypes: all serotype not in PCV13.

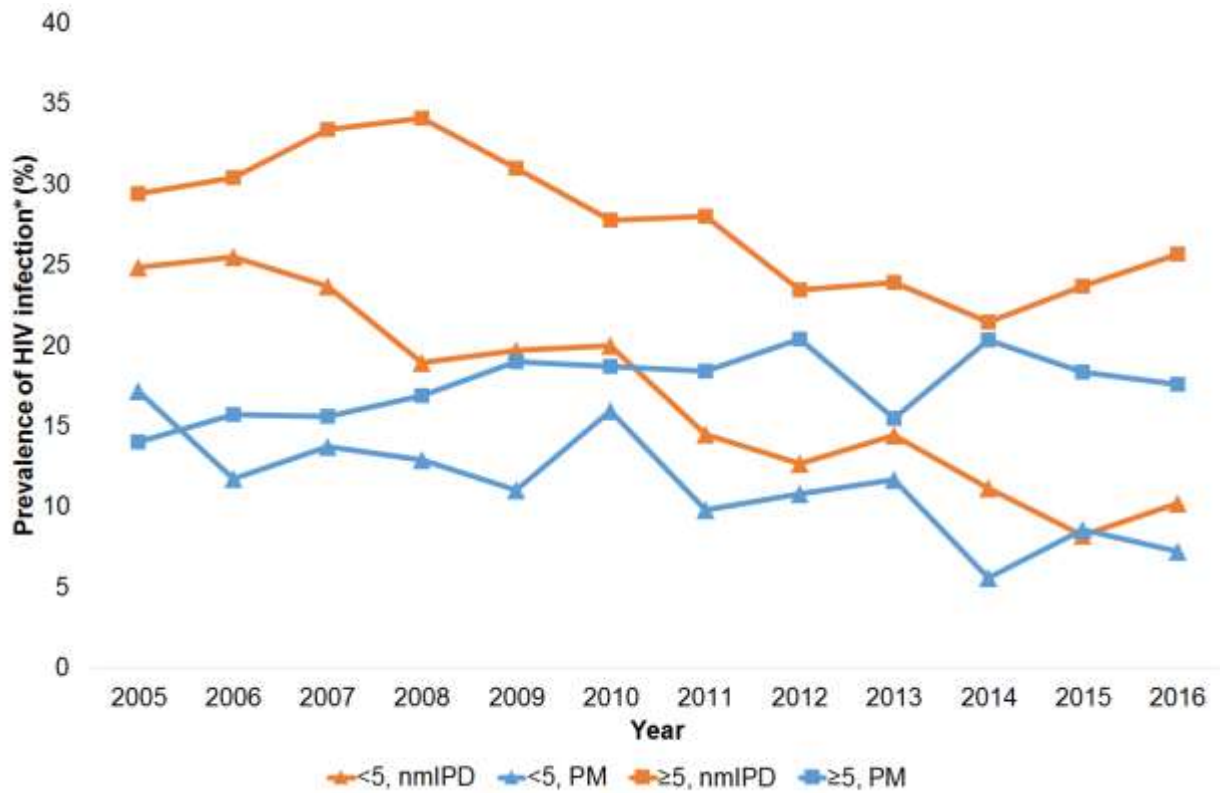
a Percentage effect difference calculated as the rate ratio of the interaction term for PCV period (2016 vs. 2005-2008) and syndrome (PM vs. nmIPD) term minus 1 multiplied by 100

b Model adjusted by serotype groups: PCV7, additional PCV13 and non-PCV13 serotypes.

c Model adjusted by age groups: individuals <5 and ≥5 years of age.

d Model adjusted by serotype and age groups.

**Supplementary Figure 2.** Prevalence of HIV infection amongst non-meningitis invasive pneumococcal disease (nmIPD) and pneumococcal meningitis (PM) cases from GERMS-SA enhanced surveillance sites by age, 2005-2016, South Africa.



**Supplementary Table 5.** Comparison of the characteristics of patients with pneumococcal meningitis (PM) and non-meningitis invasive pneumococcal disease (nmIPD) for the pre-PCV period (2005-2008).

Variable	PM	nmIPD	Univariate analysis		Multivariable analysis	
	n/N (%)	n/N (%)	OR (95% CI)	P-value	aOR (95% CI)	P-value
<b>Sex (N=8,773)</b>						
Female	1,151/2,214 (52)	3,301/6,559 (50)	1.1 (1.0-1.2)	0.05	-	-
Male	1,063/2,214 (48)	3,258/6,559 (50)	Reference	-	-	-
<b>Age (N=8,711)</b>						
<1 years	533/2,183 (24)	1,062/6,528 (16)	<b>1.6 (1.4-1.9)</b>	<b>&lt;0.01</b>	<b>1.5 (1.2-1.9)</b>	<b>&lt;0.01</b>
1-14 years	476/2,183 (22)	1,551/6,528 (24)	Reference	-	Reference	-
15-64 years	1,145/2,183 (53)	3,690/6,528 (57)	1.0 (0.9-1.1)	0.86	0.8 (0.7-1.0)	0.12
>64 years	29/2,183 (1)	225/6,528 (3)	<b>0.4 (0.3-0.6)</b>	<b>&lt;0.01</b>	0.5 (0.2-1.4)	0.19
<b>Province (N=8,853)</b>						
Eastern Cape	135/2,233 (6)	111/6,620 (2)	<b>5.2 (3.9-7.0)</b>	<b>&lt;0.01</b>	<b>4.5 (2.5-8.0)</b>	<b>&lt;0.01</b>
Free State	162/2,233 (7)	386/6,620 (6)	<b>1.8 (1.4-2.3)</b>	<b>&lt;0.01</b>	<b>2.0 (1.4-2.8)</b>	<b>&lt;0.01</b>
Gauteng	960/2,233 (43)	3,863/6,620 (58)	1.1 (0.9-1.3)	0.40	<b>1.6 (1.3-2.1)</b>	<b>&lt;0.01</b>
KwaZulu-Natal	346/2,233 (16)	1,027/6,620 (16)	<b>1.5 (1.2-1.8)</b>	<b>&lt;0.01</b>	1.4 (1.0-2.0)	0.09
Limpopo	82/2,233 (4)	60/6,620 (1)	<b>5.9 (4.1-8.5)</b>	<b>&lt;0.01</b>	<b>4.9 (2.3-10.4)</b>	<b>&lt;0.01</b>
Mpumalanga	155/2,233 (7)	102/6,620 (2)	<b>6.6 (4.9-8.7)</b>	<b>&lt;0.01</b>	<b>10.8 (6.1-18.9)</b>	<b>&lt;0.01</b>
Northern Cape	62/2,233 (3)	83/6,620 (2)	<b>3.2 (2.2-4.6)</b>	<b>&lt;0.01</b>	<b>3.8 (2.0-7.1)</b>	<b>&lt;0.01</b>
North West	104/2,233 (5)	9/6,620 (0)	<b>49.8 (24.8-100.0)</b>	<b>&lt;0.01</b>	<b>21.2 (4.0-111.5)</b>	<b>&lt;0.01</b>
Western Cape	227/2,233 (10)	979/6,620 (15)	Reference	-	Reference	-
<b>HIV status (N=5,477)</b>						
Uninfected	278/1,224 (23)	764/4,253 (18)	Reference	-	Reference	-
Infected	946/1,224 (77)	3,489/4,253 (82)	<b>0.7 (0.6-0.9)</b>	<b>&lt;0.01</b>	<b>0.7 (0.6-0.9)</b>	<b>&lt;0.01</b>
<b>Serotype group<sup>a</sup> (N=6,723)</b>						
Non-PCV13	523/1,861 (28)	1,128/4,862 (23)	<b>1.3 (1.1-1.5)</b>	<b>&lt;0.01</b>	<b>1.4 (1.1-1.7)</b>	<b>&lt;0.01</b>
PCV13	1,338/1,861 (72)	3,734/4,862 (77)	Reference	-	Reference	-
<b>Duration of hospital stay (N=7,354)</b>						
0 – 5 days	676/1,767 (38)	2,422/5,587 (43)	Reference	-	Reference	-
≥6 days	1,091/1,767 (62)	3,165/5,587 (57)	<b>1.2 (1.1-1.4)</b>	<b>&lt;0.01</b>	<b>2.4 (1.9-3.0)</b>	<b>&lt;0.01</b>
<b>Pre-disposing conditions<sup>b</sup> (N=7,384)</b>						
Absent	1,581/1,771 (89)	4,530/5,613 (81)	Reference	-	Reference	-
Present	190/1,771 (11)	1,083/5,613 (19)	<b>0.5 (0.4-0.6)</b>	<b>&lt;0.01</b>	<b>0.4 (0.3-0.6)</b>	<b>&lt;0.01</b>
<b>Smoking (N=8,853)</b>						
No	2,150/2,233 (96)	6,165/6,620 (93)	Reference	-	-	-
Yes	83/2,233 (4)	455/6,620 (7)	<b>0.5 (0.4-0.7)</b>	<b>&lt;0.01</b>	-	-
<b>Antibiotic use 24 hours prior to admission (N=5,341)</b>						
No	1,207/1,295 (93)	3,954/4,046 (98)	Reference	-	Reference	-
Yes	88/1,295 (7)	92/4,046 (2)	<b>3.1 (2.3-4.2)</b>	<b>&lt;0.01</b>	<b>2.3 (1.5-3.5)</b>	<b>&lt;0.01</b>
<b>Antibiotic use during admission (N=8,504)</b>						
No	459/2,126 (22)	1,130/6,378 (18)	Reference	-	-	-
Yes	1,667/2,126 (78)	5,248/6,378 (82)	<b>0.8 (0.7-0.9)</b>	<b>&lt;0.01</b>	-	-
<b>Outcome of hospitalization (N=7,283)</b>						
Discharged	988/1,767 (56)	4,250/5,516 (77)	Reference	-	Reference	-



Died	779/1,767 (44)	1,266/5,516 (23)		<b>2.6 (2.4-3.0)</b>	<b>&lt;0.01</b>		<b>5.0 (4.0-6.4)</b>	<b>&lt;0.01</b>	
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OR-odds ratio, 95%CI-95% confidence interval<sup>a</sup> Serotype groups classified by 13-valent pneumococcal conjugate vaccine. Non-PCV: all serotypes not in PCV13, compared to serotypes in PCV13-4, 6B, 9V, 14, 18C, 19F, 23F, 1, 3, 5, 7F and 19A. <sup>b</sup> Pre-disposing conditions defined as any one or more of the following: burns, chronic lung disease (including asthma, chronic obstructive pulmonary disorder, cystic fibrosis), chronic liver disease, chronic renal disease, cardiac conditions (including valvular disease and heart failure), cerebrovascular accident, stroke, neuromuscular diseases, cerebral palsy, metabolic diseases (including diabetes mellitus), head injury, surgery, cerebrospinal fluid leaks, ventricular shunts, cochlear implants, primary immunodeficiency conditions, complement deficiency, immunosuppression treatment (steroids/chemo/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.

**Supplementary Table 6.** Comparison of the characteristics of patients with pneumococcal meningitis (PM) and non-meningitis invasive pneumococcal disease (nmIPD) for the post-PCV period (2013-2016).

Variable	PM	nmIPD	Univariate analysis		Multivariable analysis	
	n/N (%)	n/N (%)	OR (95% CI)	P-value	aOR (95% CI)	P-value
<b>Sex (N=3,912)</b>						
Female	578/1,145 (51)	1,373/2,767 (50)	1.0 (0.9-1.2)	0.63	-	-
Male	567/1,145 (50)	1,394/2,767 (50)	Reference	-	-	-
<b>Age (N=3,896)</b>						
<1 years	182/1,139 (16)	299/2,757 (11)	<b>2.1 (1.6-2.8)</b>	<b>&lt;0.01</b>	<b>1.9 (1.3-2.9)</b>	<b>&lt;0.01</b>
1-14 years	126/1,139 (11)	441/2,757 (16)	Reference	-	Reference	-
15-64 years	812/1,139 (71)	1,819/2,757 (66)	<b>1.6 (1.3-1.9)</b>	<b>&lt;0.01</b>	1.0 (0.7-1.4)	0.95
>64 years	19/1,139 (2)	198/2,757 (7)	<b>0.3 (0.2-0.6)</b>	<b>&lt;0.01</b>	<b>0.2 (0.1-0.4)</b>	<b>&lt;0.01</b>
<b>Province (N=3,923)</b>						
Eastern Cape	128/1,148 (11)	107/2,775 (3.9)	<b>6.5 (4.7-9.2)</b>	<b>&lt;0.01</b>	<b>7.7 (4.7-12.5)</b>	<b>&lt;0.01</b>
Free State	53/1,148 (5)	115/2,775 (4.1)	<b>2.5 (1.7-3.7)</b>	<b>&lt;0.01</b>	<b>3.0 (1.8-5.0)</b>	<b>&lt;0.01</b>
Gauteng	432/1,148 (38)	1,280/2,775 (46.1)	<b>1.8 (1.4-2.4)</b>	<b>&lt;0.01</b>	<b>1.4 (1.0-2.0)</b>	<b>0.03</b>
KwaZulu-Natal	164/1,148 (14)	413/2,775 (14.9)	<b>2.2 (1.6-2.9)</b>	<b>&lt;0.01</b>	<b>1.8 (1.2-2.7)</b>	<b>&lt;0.01</b>
Limpopo	48/1,148 (4)	43/2,775 (1.5)	<b>6.1 (3.8-9.7)</b>	<b>&lt;0.01</b>	<b>4.8 (2.3-9.9)</b>	<b>&lt;0.01</b>
Mpumalanga	80/1,148 (7)	108/2,775 (3.9)	<b>4.1 (2.8-5.8)</b>	<b>&lt;0.01</b>	<b>2.2 (1.2-3.9)</b>	<b>0.01</b>
Northern Cape	47/1,148 (4)	110/2,775 (4)	<b>2.3 (1.6-3.5)</b>	<b>&lt;0.01</b>	<b>2.3 (1.4-3.9)</b>	<b>&lt;0.01</b>
North West	99/1,148 (9)	68/2,775 (3)	<b>8.0 (5.5-11.6)</b>	<b>&lt;0.01</b>	<b>25.1 (11.3-55.9)</b>	<b>&lt;0.01</b>
Western Cape	97/1,148 (8)	531/2,775 (19)	Reference	-	Reference	-
<b>HIV status (N=3,000)</b>						
Uninfected	268/888 (30)	755/2,112 (36)	Reference	-	-	-
Infected	620/888 (70)	1,357/2,112 (64)	<b>1.3 (1.1-1.5)</b>	<b>&lt;0.01</b>	-	-
<b>Serotype group<sup>a</sup> (N=3,168)</b>						
Non-PCV13	684/927 (74)	1,429/2,241 (64)	<b>1.6 (1.3-1.9)</b>	<b>&lt;0.01</b>	<b>1.6 (1.3-2.0)</b>	<b>&lt;0.01</b>
PCV13	243/927 (26)	812/2,241 (36)	Reference	-	Reference	-
<b>Duration of hospital stay (N=3,627)</b>						
0 – 5 days	357/1,046 (34)	1,079/2,581 (42)	Reference	-	Reference	-
≥6 days	689/1,046 (66)	1,502/2,581 (58)	<b>1.4 (1.2-1.6)</b>	<b>&lt;0.01</b>	<b>3.2 (2.4-4.2)</b>	<b>&lt;0.01</b>
<b>Pre-disposing conditions<sup>b</sup> (N=3,856)</b>						
Absent	894/1,100 (81)	1,785/2,706 (66)	Reference	-	Reference	-
Present	206/1,100 (19)	921/2,706 (34)	<b>0.4 (0.4-0.5)</b>	<b>&lt;0.01</b>	<b>0.4 (0.3-0.6)</b>	<b>&lt;0.01</b>
<b>Smoking (N=3,923)</b>						
No	1,045/1,148 (91)	2,444/2,775 (88)	Reference	-	-	-
Yes	103/1,148 (9)	331/2,775 (12)	<b>0.7 (0.6-0.9)</b>	<b>0.01</b>	<b>0.7 (0.5-1.0)</b>	<b>0.03</b>
<b>Antibiotic use 24 hours prior to admission (N=2,995)</b>						
No	781/859 (91)	2,057/2,136 (96)	Reference	-	Reference	-
Yes	78/859 (9)	79/2,136 (4)	<b>2.6 (1.9-3.6)</b>	<b>&lt;0.01</b>	<b>2.3 (1.6-3.5)</b>	<b>&lt;0.01</b>
<b>Antibiotic use during admission (N=3,557)</b>						
No	51/1,027 (5)	226/2,530 (9)	Reference	-	Reference	-
Yes	976/1,027 (95)	2,304/2,530 (91)	<b>1.9 (1.4-2.5)</b>	<b>&lt;0.01</b>	<b>1.7 (1.0-2.7)</b>	<b>0.03</b>
<b>PCV status (N=3,328)</b>						
Not vaccinated	791/949 (83)	1,967/2,379 (83)	Reference	-	-	-

Partial for age	115/949 (12)	371/2,379 (16)	<b>0.8 (0.6-1.0)</b>	<b>0.02</b>	-	-
Complete for age	43/949 (5)	41/2,379 (2)	<b>2.6 (1.7-4.0)</b>	<b>&lt;0.01</b>	-	-
<b>Outcome of hospitalization (N=3,676)</b>						
Discharged	594/1,044 (57)	1,886/2,561 (74)	Reference	-	Reference	-
Died	450/1,044 (43)	675/2,561 (26)	<b>2.1 (1.8-2.5)</b>	<b>&lt;0.01</b>	<b>4.3 (3.2-5.6)</b>	<b>&lt;0.01</b>

OR-odds ratio, 95%CI-95% confidence interval <sup>a</sup> Serotype groups classified by 13-valent pneumococcal conjugate vaccine. Non-PCV: all serotypes not in PCV13, compared to serotypes in PCV13-4, 6B, 9V, 14, 18C, 19F, 23F, 1, 3, 5, 7F and 19A. <sup>b</sup> Pre-disposing conditions defined as any one or more of the following: burns, chronic lung disease (including asthma, chronic obstructive pulmonary disorder, cystic fibrosis), chronic liver disease, chronic renal disease, cardiac conditions (including valvular disease and heart failure), cerebrovascular accident, stroke, neuromuscular diseases, cerebral palsy, metabolic diseases (including diabetes mellitus), head injury, surgery, cerebrospinal fluid leaks, ventricular shunts, cochlear implants, primary immunodeficiency conditions, complement deficiency, immunosuppression treatment (steroids/chemo/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.

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