Supplementary Materials for

Epidemiological characteristics of pneumococcal disease caused by the additional serotypes covered by the 20-valent pneumococcal conjugate vaccine

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Text S1. Search strategy

("2010/01/01" [Date – Publication]: "3000"[Date – Publication]) AND (pneumococ* OR streptococcus pneumoniae) AND (PPSV23 OR PCV10 OR PCV13 OR serotyp*) AND (invasiv* OR noninvasive OR "pneumonia" OR "otitis media" OR (empyema) OR (rhinosinusitis) OR (sinusitis) OR (peritonitis) OR (osteoarticular infection) OR (hemolytic uremic syndrome) OR (septic arthritis) OR (endocarditis)) NOT ("immunogenicity" OR "immune response") AND ((serotype) AND ((urin*) OR (antigen) OR (detection)))

Table S1. Timeline for PCV use in country and regional NIPs

Country	PCV7	PCV10	PCV13
Argentina			2012
Australia	2005		2010
Austria		2012	
Belgium	2007	2015/2016	2011 (and 2019)
Bengladesh		2015	
Brazil		2010/2016	
Cambodia			2015
Canada			
Alberta	2002		2010
Quebec	2004	2009	2011
Ontario		2009	2010
China	NA	NA	NA
Denmark	2007		2010
Ethiopia		2011	
France	2006		2010
Gambia	2007		2011
Germany	2006	2009 (<10%)	2009
Hong Kong	2009	2010	2011
India	N/A	N/A	N/A
Iran	NA	NA	NA
Israel	2010		2012
Italy	2005-2007		2010-2012
Japan	2011		2013
Kuwait	2006		2010
Malawi			2011
Mozambique		2013	
Netherlands	2006	2011	
Norway	2006		2011
Oman	2008	2010	2012
Portugal	2001	2009	2010
South Africa	2009		2011
South Korea			2010
Spain			
Catalonia	2006*	(2010:<5%)	2010
Galicia			2010
Madrid	2006		2010†
Navarra	2006*	(2010:<1%)	2010‡
Sweden	2009	2010 (~50%)	2010 (~50%)
Taiwan	2005		2015
Tunisia	NA	NA	NA
Turkey	2008		2011
UK	2006		2010
USA	2000		2010

Abbreviations: NA = no PCV in NIP; NIP = national immunization program; PCV = pneumococcal conjugate vaccine.

* Not universal but recommended and uptake around or above 50%.

† Not universal during 2012–2014 but recommended and uptake >75%.

‡ Not universal during 2010–2015 but recommended and uptake >70%.

Table S2. Risk of bias tool

Domain	Category	Risk of bias
1. Sample size	At least 100 isolates	Low
	Less than 100 isolates	High
2. Study population	All participants had equal opportunity to be in the study	Low
	Not all participants had equal opportunity to be included in the study, e.g., patients from specific risk group or severity level were excluded	High
	No description of the study participants	High
3. Study period	More than 1 year	Low
	Less or equal to 1 year	High
4. Serotyping method	Complete serotyping methods given	Low
	Incomplete serotyping methods given	High
	Not reported	High
5. Non-typed isolates proportion	At least 80% of isolates typed	Low
	Less than 80% of isolates typed	High
6. Outcome (proportion, incidence…)	Both numerator and denominator reported	Low
	Missing data	High

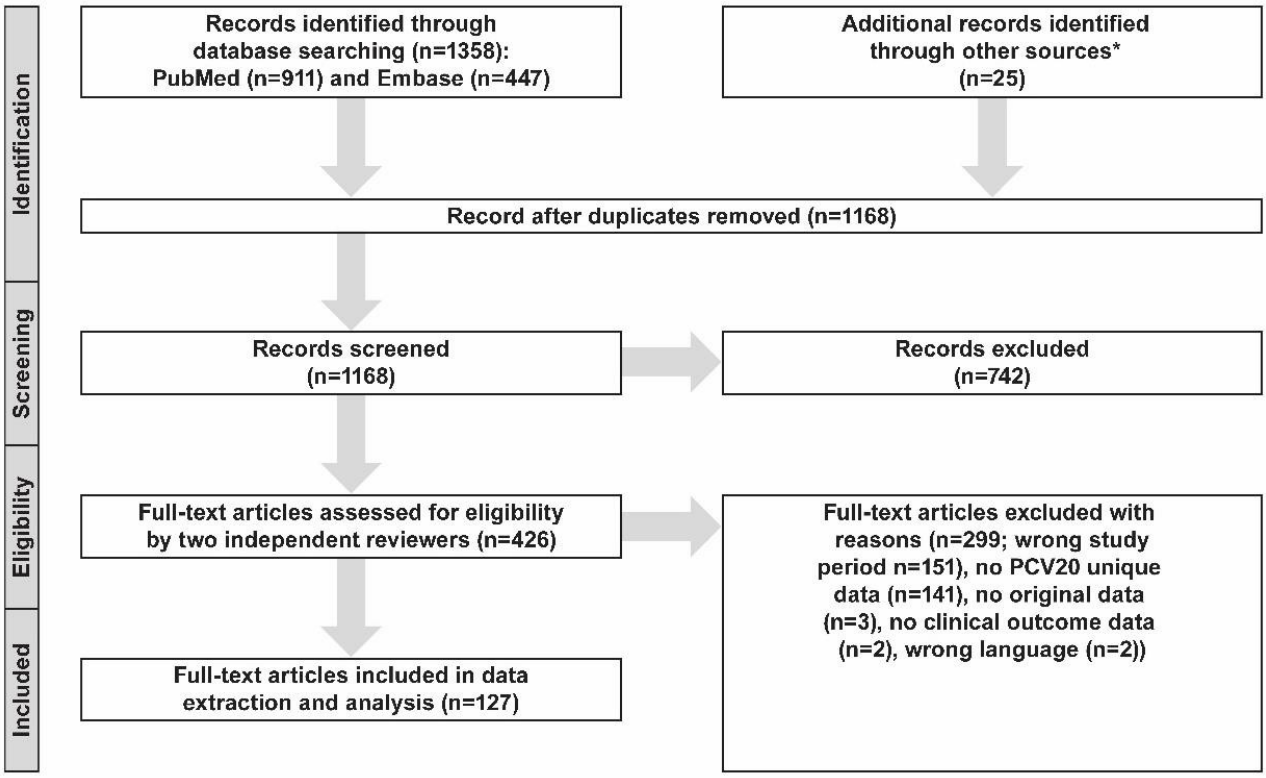


Figure S1. Study selection process: PRISMA flowchart. Proportion of PCV20nonPCV13 and PCV20nonPCV15 serotypes by clinical presentation.
*Records identified through reference list checking.

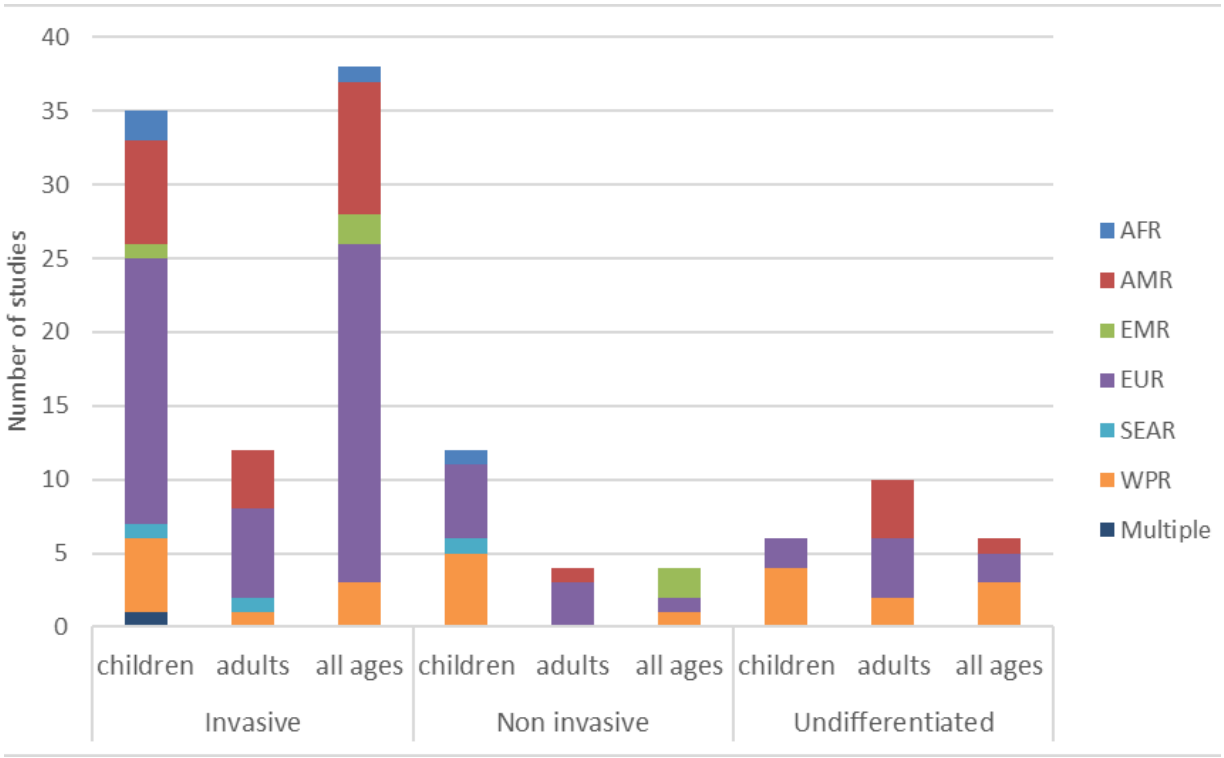


Figure S2. Distribution of studies by clinical presentation type, age group, and WHO region. WHO regions are defined as: AFR, African; AMR, the Americas; EMR, Eastern Mediterranean; EUR, European; SEAR, South-East Asian; WPR, Western Pacific.

Table S3: Description of studies included in the systematic literature review

WHO Region	Country	Reference	Setting	Period	Population	Disease	Outcome
	Portugal	[1]	national	2008 – 2012	<18y	IPD overall	Proportion
	France	[2]	national	2010 – 2014	all ages	meningitis	Proportion
EMR	Oman	[3]	national	2014 – 2016	all ages	IPD overall	Proportion
	UK	[4]	national	2014 – 2018	all ages	IPD overall, bacteremia, other IPD, meningitis, bact. pneumonia	Proportion, Severity
	France	[5]	national	2010 – 2012	<15y	all pneumonia	Proportion
	France	[6]	national	2008 – 2012	>18y	all pneumonia	AMR proportion, Severity, Proportion
	Denmark	[7]	national	2011 – 2011	>15y	bacteremic pneumonia, non-IPD	Proportion
	Israel (Southern)	[8]	regional	2010 – 2013	<2y	AOM	Incidence
	Israel	[9]	national	2010 – 2013	<5y	IPD overall	Incidence
	Israel	[10]	national	2000 – 2016	<5y	bacteremic pneumonia, meningitis, other IPD	Incidence
	UK	[11]	hospital	2008 – 2010	>=16y	non-IPD	Proportion
	US (Alaska)	[12]	regional	2010 – 2013	all ages	IPD overall	Incidence, Proportion
	Canada (Calgary)	[13]	regional	2010 – 2013	>18y; comorbidities	IPD overall	Proportion
	Turkey	[14]	national	2011 – 2014	<18y	IPD overall	Proportion
	Turkey	[15]	national	2015 – 2018	<18y	meningitis, IPD overall, bacteremia	Proportion
	Taiwan	[16]	hospital	2011 – 2015	all ages	all pneumonia	AMR proportion
	Taiwan	[17]	hospital	2011 – 2015	>18y	IPD overall	Proportion
	South Korea	[18]	national	2011 – 2014	<18y	IPD overall	Severity, Proportion
	Taiwan (Northern)	[19]	regional	2010 – 2015	<18y	IPD overall, non-IPD	Proportion
	South Korea	[20]	hospital	2010 – 2013	>19y	all pneumonia	Proportion
WPR	South Korea	[21]	hospital	2015 – 2015	15-91y	IPD + non-IPD	Proportion, AMR proportion

Spain (Catalonia)	[22]	regional	2014 – 2016	>65y	IPD overall	Incidence, Severity
S.Africa	[23]	national	2012 – 2014	<5y; HIV	IPD overall	Proportion
Spain	[24]	hospital	2012 – 2017	0-92y	IPD overall, bacteremic pneumonia, meningitis, bacteremia	Proportion, AMR proportion
France	[25]	national	2014 – 2017	≥18y	IPD overall	Severity, Proportion
Canada	[26]	national	2010 – 2012	all ages	IPD overall	Proportion, AMR proportion
Belgium	[27]	national	2017 – 2018	<16y	IPD overall	Proportion
UK (England and Wales)	[28]	national	2012 – 2017	>65y	IPD overall	Proportion, Incidence
Brazil	[29]	national	2010 – 2012	<5y	IPD overall	Proportion
Spain	[30]	national	2013 – 2015	6mo-6y	non-IPD	Proportion
Spain	[31]	national	2010 – 2011	>18y	non-IPD	AMR proportion, Proportion
China	[32]	hospital	2016 – 2016	<2y	AOM	Proportion
Sweden (Stockholm)	[33]	regional	2011 – 2014	all ages	IPD overall	Incidence, Proportion
Argentina	[34]	national	2012 – 2014	<15y	bacteremic pneumonia	Proportion
Germany	[35]	national	2010 – 2018	<18y	complicated pneumonia	Proportion
Canada	[36]	national	2011 – 2014	all ages	IPD overall	AMR proportion, Proportion
Spain (Navarre)	[37]	regional	2010 – 2013	all ages	IPD overall	Proportion
Australia (Queensl./N.Terr.)	[38]	regional	2005 – 2015	<5y	non-IPD	NA, Proportion
Spain (Catalonia)	[39]	regional	2012 – 2015	<18y	IPD overall	Proportion
Portugal	[40]	national	2012 – 2015	>18y	non-IPD	Proportion
Iran	[41]	hospital	2013 – 2016	<5y	IPD overall	Proportion
Germany	[42]	national	2010 – 2013	all ages	meningitis	Proportion
US	[43]	national	2013 – 2016	≥18y	all pneumonia	Proportion
Spain	[44]	hospital	2012 – 2016	≤17y	meningitis, other IPD, bact.pneumonia, IPD overall, bacteremia	Proportion, AMR proportion

	India	[45]	hospital	2007 – 2017	>18y	IPD overall	Proportion
	Australia	[46]	national	2014 – 2014	all ages	IPD overall	Incidence
	US	[47]	national	2010 – 2011	<18y	meningitis, bact. pneumonia, IPD overall, other IPD, bacteremia	Proportion
AMR	US	[48]	national	2014 – 2017	<18y	IPD overall	Proportion
	Japan (Northern Japan)	[49]	regional	2013 – 2014	all ages	non-IPD	Proportion
	Japan (Hokkaido)	[50]	regional	2016 – 2016	<16y	non-IPD	Proportion
	Japan	[51]	hospital	2011 – 2016	all ages	IPD + non-IPD	Proportion, AMR proportion
	US (Utah)	[52]	regional	2010 – 2012	>18y	IPD overall	Proportion
	Tunisia	[53]	hospital	2012 – 2016	all ages	IPD + non-IPD	Proportion, AMR proportion
	UK (England and Wales)	[54]	national	2016 – 2017	all ages	IPD overall	Proportion, Incidence
	Spain (Madrid)	[55]	regional	2010 – 2015	all ages	IPD overall	Proportion
	Australia	[56]	hospital	1997 – 2016	7-20m	other IPD	Proportion
	Australia (N.Territory)	[57]	regional	2010 – 2013	0-6y	AOM	Proportion
	Canada	[58]	national	2011 – 2015	>16y	all pneumonia	Proportion
	Canada	[59]	national	2010 – 2015	>16y	all pneumonia	Proportion
	Israel (Southern)	[60]	regional	2005 – 2014	3-36mo	bacteremia	Proportion
	Canada (Nunavik)	[61]	regional	2010 – 2016	<5y	IPD overall	Proportion
	France	[62]	national	2012 – 2012	<14y	IPD overall	incidence
	France	[63]	national	2010 – 2012	<16y	meningitis	Proportion
	France	[64]	national	2015 – 2018	3mo-15y	AOM	Proportion
	Germany	[65]	national	2010 – 2017	<18y	complicated pneumonia	Proportion
	Sweden	[66]	hospital	2011 – 2014	all ages	IPD overall	Proportion
Multiple	Hong Kong, Israel, Malawi, S.Africa	[67]	multi-national	NA – NA	<3y	IPD overall	Proportion
	UK (England and Wales)	[68]	national	2010 – 2016	3-59mo	IPD overall, meningitis, other IPD, IPD and LRTI	Severity, Proportion

SEAR	Bangladesh	[69]	hospital	2013 – 2015	<15y; neph. syndr.	other IPD	Proportion
	US (North. California)	[70]	regional	1996 – 2011	>18y; HIV	IPD overall	Proportion
	Canada (North.Alberta)	[71]	regional	2000 – 2014	all ages; asplania	IPD overall	Proportion
	Mozambique (Southern)	[72]	regional	2012 – 2015	<5y	IPD overall	Proportion
	US	[73]	national	2010 – 2012	>18y	non-IPD	Proportion, AMR proportion
	Spain (Galicia)	[74]	regional	2011 – 2012	all ages	IPD overall	AMR proportion, Proportion
	Spain	[75]	hospital	2011 – 2014	>18y	all pneumonia	Proportion
	Kuwait	[76]	national	2006 – 2014	all ages	IPD and LRTI, IPD overall	Proportion
	Kuwait	[77]	national	2010 – 2013	all ages	IPD overall	AMR proportion, Proportion
	UK (Oxfordshire)	[78]	regional	1996 – 2013	all ages	IPD overall	Incidence, Proportion
	US	[79]	national	2010 – 2013	all ages	IPD overall	Proportion
	Japan	[80]	national	2012 – 2014	2mo-15y	IPD overall, IPD + non-IPD, non-IPD	Proportion, AMR proportion
	Bangladesh	[81]	hospital	2014 – 2015	<18y	AOM	AMR proportion, Proportion
AFR	Ethiopia	[82]	hospital	2016 – 2017	<15y	AOM	Proportion
	Japan	[83]	hospital	2011 – 2014	>18y	all pneumonia	Proportion
	Spain (South. Catalonia)	[84]	regional	2010 – 2013	<14y	AOM	Proportion
	US	[85]	national	2000 – 2014	<18y; transplant	IPD overall	Proportion
	US	[86]	hospital	2005 – 2015	<60d	IPD overall	Proportion
	US	[87]	national	2010 – 2015	<2mo	IPD overall	Proportion
	UK	[88]	national	2011 – 2016	all ages	meningitis, IPD overall	NA, Severity, Proportion
	France	[89]	national	2001 – 2017	all ages	IPD overall	Proportion
	UK	[90]	hospital	2013 – 2018	>16y	non-IPD, IPD overall, all pneumonia	Incidence, Proportion

	Brazil (South-Eastern)	[91]	regional	1990 – 2014	all ages	IPD overall	Proportion
	Italy (Apulia)	[92]	regional	2013 – 2015	>65y	non-IPD	Proportion
	US	[93]	national	2010 – 2011	all ages	IPD overall, non-IPD	Proportion, AMR proportion
	Austria	[94]	national	2009 – 2017	all ages	IPD overall	Proportion, Incidence, NA
	Canada (Ontario)	[95]	regional	2010 – 2011	all ages	IPD overall, bacteremic pneumonia, bacteremia	Severity, Proportion
	Spain	[96]	hospital	2011 – 2014	>18y	bacteremic pneumonia	Severity, Proportion
	Spain (Madrid)	[97]	regional	2012 – 2015	all ages	IPD overall	Proportion, AMR proportion
	UK	[98]	national	2010 – 2015	all ages	IPD overall, bacteremia, non-IPD	Proportion, AMR proportion
	Spain	[99]	hospital	2011 – 2015	>18y	bacteremic pneumonia	Proportion
	Portugal	[100]	national	2010 – 2015	<18y	complicated pneumonia	Proportion
	Portugal	[101]	national	2012 – 2015	<18y	IPD overall	Proportion
	Denmark	[102]	national	2010 – 2013	0-3mo	IPD overall	Proportion
	Denmark	[103]	national	2011 – 2014	all ages	IPD overall	Proportion, Incidence
	Norway	[104]	national	2011 – 2012	<5y	IPD overall	Proportion
	Taiwan	[105]	hospital	2012 – 2014	all ages	IPD overall	Proportion
	Taiwan	[106]	national	2007 – 2013	2mo-5y	IPD overall	Proportion
	US	[107]	national	2010 – 2017	>18y	all pneumonia, non-IPD	Proportion, AMR proportion
	Japan (Chiba)	[108]	regional	2016 – 2019	5-15y	all pneumonia	Proportion
	Cambodge	[109]	hospital	2012 – 2018	<5y	IPD overall	Proportion
	Japan	[110]	national	2011 – 2017	all ages	IPD overall	Proportion
	Japan	[111]	national	2016 – 2016	<15y	AOM	Proportion
EUR	Sweden (Southern)	[112]	regional	2016 – 2018	all ages	IPD + non-IPD, non-IPD, AOM	Proportion, AMR proportion
	Germany	[113]	national	2009 – 2018	all ages	IPD overall	Proportion
	Germany	[114]	national	2010 – 2014	all ages	IPD overall	Proportion

England	[115]	national	2002 – 2014	all ages	meningitis, IPD overall, comp.pneumonia, other IPD, bact.pneumo	Proportion, Severity
Spain (Tarragona)	[116]	regional	2012 – 2015	all ages	IPD overall	Proportion
S.Africa	[117]	national	2011 – 2012	all ages	IPD overall	Proportion, Incidence
Netherlands	[118]	national	2004 – 2012	all ages	IPD overall, bact.pneumonia, meningitis	Proportion, Severity
Netherlands	[119]	national	2008 – 2012	>18y	IPD overall	Proportion
UK	[120]	national	2013 – 2014	all ages	IPD overall	Incidence, Proportion
China	[121]	hospital	2011 – 2014	<5y	non-IPD, IPD overall	Proportion
Germany	[122]	national	2010 – 2014	5y:15y	IPD overall	Proportion
Germany	[123]	national	2014 – 2016	<16y	meningitis, IPD overall	Proportion
Canada (Ontario)	[124]	regional	2007 – 2017	all ages	IPD overall	Incidence, Proportion
South Korea	[125]	national	2011 – 2013	<18y	IPD overall	Proportion
Argentina	[126]	national	2013 – 2017	>18y	other IPD, IPD overall, bact. pneumonia, bacteremia, meningitis	Proportion
Israel	[127]	hospital	2010 – 2014	<2mo	AOM	Proportion

*All of the 7 PCV20nonPCV13 serotypes are reported.

Abbreviations: AFR = African Region; AMR (WHO region) = Americas; AMR (outcome) = antimicrobial resistance; Any disease = all *Streptococcus pneumoniae* clinical presentations; AOM = acute otitis media; EMR = Eastern Mediterranean Region; EUR = European Region; IPD = invasive pneumococcal disease; MULTI = multiple regions; SEAR = South-East Asia Region; UK = United Kingdom; US = United States of America; WPR = Western Pacific Region.

Table S4. PCV20nonPCV13 serotype-specific proportion (%) by clinical presentation: number of references (n), median (med.), and minimum and maximum (min–max).

	8		10A		11A		12F		15B/C		22F		33F	
	n	mean (min-max)	n	mean (min-max)	n	mean (min-max)	n	mean (min-max)	n	mean (min-max)	n	mean (min-max)	n	mean (min-max)
Children														
No PCV														
sterile site: IPD overall														
IPD, presentation unspecified[1]		nr	0	nr	1	6 (6–6)	0	nr	1	0 (0–0)	0	nr	0	nr
non-sterile site: non-IPD overall														
non-IPD, presentation specified:														
pneumococcal AOM		nr	0	nr	0	nr	0	nr	1	2.8 (2.8–2.8)	0	nr	0	nr
non-IPD, presentation unspecified		nr	0	nr	0	nr	0	nr	1	3.2 (3.2–3.2)	0	nr	0	nr
PCV10, Initial period														
sterile site: IPD overall														
IPD, presentation specified:														
other IPD[2]	1	2.3 (2.3–2.3)	0	nr	0	nr	1	2.3 (2.3–2.3)	1	7 (7–7)	1	2.3 (2.3–2.3)	0	nr
IPD, presentation unspecified	4	4.1 (0–10.5)	3	2.2 (1.8–11.1)	3	0.9 (0–1.6)	3	1.8 (0–3.6)	3	2.5 (0–2.8)	3	4.6 (2.5–5.6)	2	1.7 (1.4–2)
non-sterile site: non-IPD overall														
non-IPD, presentation specified:														
pneumococcal AOM	1	0.6 (0.6–0.6)	1	0.6 (0.6–0.6)	1	3 (3–3)	1	0 (0–0)	1	5.5 (5.5–5.5)	0	nr	1	0
PCV10, Later period														
sterile site: IPD overall														
IPD, presentation unspecified	1	0 (0–0)	1	13 (13–13)	1	0	1	0 (0–0)	1	8.7 (8.7–8.7)	1	4.3 (4.3–4.3)	1	21.7 (21.7–21.7)

non-sterile site: non-IPD overall														
non-IPD, presentation specified:														
pneumococcal AOM	0	nr	0	nr	1	7.1 (7.1–7.1)	0	nr	0	nr	0	nr	0	nr
PCV13, Initial period														
sterile site: IPD overall														
IPD, presentation specified:														
pneumococcal bacteremia	1	1.2 (1.2–1.2)	0	nr	0	nr	1	15.4 (15.4–15.4)	3	13.6 (4.3–23.1)	2	3.6 (2.2–5)	2	16.9 (8.7–25)
pneumococcal meningitis	0	nr	2	5.1 (3.6–6.5)	0	nr	2	10.7 (7.1–14.3)	3	5.8 (2.4–9.5)	3	1.2 (0–6.5)	3	3.9 (1.2–9.5)
bacteremic pneumococcal pneumonia	3	1.1 (0–2.5)	3	1.1 (0–2.1)	2	1.7 (1.3–2.1)	0	4.7 (4.3–5.1)	3	1.3 (0–6.5)	2	0 (0–2.5)	1	3.2 (3.2–3.2))
other IPD	0	nr	1	9.1 (9.1–9.1)	0	nr	0	nr	1	4.8 (4.8–4.8)	1	4.8 (4.8–4.8)	3	4.8 (4.8–4.8)
IPD, presentation unspecified	18	0.9 (0–11)	27	3.2 (0–11.1)	20	1.4 (0–6.8)	24	2 (0–24.2)	34	7 (0–33.3)	32	4.3 (0–13.2)	28	2.5 (0–11.1)
non-sterile site: non-IPD overall														
IPD, presentation specified:														
pneumococcal AOM	1	3.8 (3.8–3.8)	1	6.5 (6.5–6.5)	3	3.2 (0–18.8)	1	3.2 (3.2–3.2)	2	6.5 (0–12.9)	1	6.5 (6.5–6.5)	3	3.8 (3.2–12.5)
undifferentiated site: pneumo.disease														
pneumo. disease, presentation specified:														
all pneumococcal pneumonia	0	nr	2	5 (0–10.0)	0	nr	2	2.3 (0–4.5)	0	nr	0	nr	2	5.0 (0–10.0)
pneumo. disease, presentation unspecified	1	11.4 (11.4–11.4)	4	2.2 (0–4.3)	3	2.4 (1.9–3.7)	2	0 (0–0.3)	6	7.5 (5.3–13.4)	3	3.7 (2.4–7.7)	3	1 (0.7–2.1)
PCV13, Later period														
sterile site: IPD overall														
IPD, presentation specified:														
pneumococcal bacteremia	3	6.2 (0–11.2)	3	12 (4.7–12.5)	2	2.4 (0–4.7)	3	8.0 (4.7–13.1)	3	9.4 (0–9.6)	2	2.7 (0–5.4)	2	3.9 (0–7.7)
pneumococcal meningitis	3	6.2 (0–8.6)	4	5.8 (3.1–9.9)	1	0 (0–0)	4	4.8 (0–15.1)	3	9.4 (5.6–9.9)	3	6 (0–10.3)	3	5.8 (0–10.3)

bacteremic pneumococcal pneumonia	4	3 (0.5–5.6)	2	4.0 (0.5–7.4)	2	1.3 (0.9–1.6)	4	4.55 (0.5–12.2)	2	4.1 (0–8.1)	4	1.1 (0–6.3)	3	5.9 (0.5–6.6)
other IPD	2	6.2 (4.3–8.0)	2	5.7 (4.3–7.0)	1	8.7 (8.7–8.7)	3	10.7 (0–12.0)	3	8.7 (6–11.4)	2	6.4 (4.3–8.5)	3	7.0 (4.3–8.1)
IPD, presentation unspecified	17	2.4 (0–20)	19	5.8 (0–40)	13	1.4 (0–3.3)	20	6 (0–16.4)	18	5.2 (0–23.1)	17	4.6 (0–11.8)	17	3.3 (0–50)
non-sterile site: non-IPD overall														
non-IPD, presentation specified:														
pneumococcal AOM	1	1.8 (1.8–1.8)	2	6.9 (5.4–8.4)	2	7.3 (5.6–8.9)	2	0.5 (0–0.9)	2	10.6 (7.1–14)	2	3.7 (1.8–5.6)	2	2.3 (0.9–3.6)
non-IPD site unspecified	1	0 (0–0)	2	6.8 (4.8–8.7)	1	1 (1–1)	2	1.5 (0–2.9)	2	11.2 (4.8–17.5)	0	nr	1	0.3 (0.3–0.3)
undifferentiated site: pneumo. disease														
pneumo. disease, presentation specified														
all pneumococcal pneumonia	0	nr	1	1.6 (1.6–1.6)	1	10.9 (10.9–10.9)	0	nr	1	3.1 (3.1–3.1)	1	1.6 (1.6–1.6)	1	1.6 (1.6–1.6)
pneumo. disease, presentation unspecified	1	1 (1–1)	0	nr	2	10.9 (10.8–10.9)	0	nr	2	12.1 (11.3–12.8)	0	nr	2	1.2 (1–1.3)
Adults														
No PCV														
Sterile site: IPD overall														
IPD, presentation unspecified	2	6.0 (4.7–7.3)	2	1.1 (0.3–1.8)	2	0.5 (0–0.9)	2	0.9 (0–1.8)	2	0.2 (0–0.3)	1	0 (0–0)	2	0.5 (0–0.9)
PCV10, Initial period														
Sterile site: IPD overall														
IPD, presentation unspecified	2	10.1 (9.4–10.8)	2	1.7 (1.6–1.8)	2	1.7 (1.6–1.8)	1	2.1 (2.1–2.1)	1	0.7 (0.7–0.7)	2	5.4 (4.2–6.5)	2	2 (1.7–2.3)
PCV13, Initial period														
Sterile site: IPD overall														
IPD, presentation specified:														
bacteremic pneumococcal pneumonia	2	6.8 (5.3–8.3)	3	1.0 (0.7–3.1)	3	3.5 (1.0–10.8)	2	2.7 (1.2–4.2)	3	3.1 (1–4.2)	3	6.2 (3.6–7.5)	1	2.1 (2.1–2.1)
IPD, presentation unspecified	13	2.9 (0.1–22.2)	10	2.1 (0–10)	12	2.9 (0–7.5)	10	2.3 (1–4.3)	13	2.1 (0–8)	15	7.7 (0–13.1)	11	1.7 (0.8–3.1)

non-sterile site: non-IPD overall												
non-IPD site unspecified	5	0.8 (0.5–14.5)	6	1.3 (0.8–3.8)	3	5.8 (5.7–8.1)	2	1 (0.8–1.2)	5	5.3 (3.8–8)	3	3.5 (1.2–6.9)	3	1.2 (0–2.7)
undifferentiated site: pneumo. disease												
pneumo. disease, presentation specified:												
all pneumococcal pneumonia	6	1.8 (0–2.4)	5	0.6 (0–2.5)	7	3.4 (0.6–14.6)	5	1.0 (0–6.5)	5	0.6 (0–2.9)	6	4.6 (2.1–9.3)	5	1.3 (0.6–5.2)
pneumo. disease, presentation unspecified	2	3.3 (2.5–4)	2	3.4 (2.7–4)	2	3.8 (2.5–5)	1	1 (1–1)	2	3.4 (1.3–5.4)	1	3 (3–3)	0	nr
PCV13, Later period												
sterile site: IPD overall												
IPD, presentation specified:												
pneumococcal bacteremia	2	10.1 (6.9–13.2)	1	0 (0–0)	2	4.8 (3.6–5.9)	2	7.3 (6.6–7.9)	1	2 (2–2)	2	5.1 (2–8.2)	2	2.8 (2.0–3.6)
pneumococcal meningitis	2	8.2 (5.1–11.2)	2	3.4 (3.1–3.6)	2	3 (2–4)	2	9.1 (9–9.2)	2	2.1 (1–3.2)	2	5.6 (5.1–6.1)	1	2 (2–2)
bacteremic pneumococcal pneumonia	3	10.6 (5.2–15.6)	2	0.8 (0.7–0.9)	3	2.6 (1.7–3.8)	3	8.1 (3.5–8.8)	2	1.4 (1.2–1.5)	3	4.4 (4.1–8.4)	3	0.9 (0.7–3.9)
other IPD	2	5.1 (0–10.2)	2	3.1 (2–4.2)	1	7.8 (7.8–7.8)	2	8.2 (7.8–8.6)	1	5.9 (5.9–5.9)	2	4.8 (2–7.6)	2	2.1 (0–4.2)
IPD, presentation unspecified	35	13.6 (3.7–50)	15	2.8 (0–5.5)	18	3 (0–5.3)	29	6.5 (0–22.7)	18	1.5 (0–4.5)	25	7.4 (1.6–50)	20	2.6 (0.9–14.5)
non-sterile site: non-IPD overall												
non-IPD, presentation unspecified	4	2 (1.8–5.3)	4	1.8 (0–2.7)	1	0 (0–0)	2	0 (0–3.8)	4	2.1 (0–2.7)	1	1.9 (1.9–1.9)	3	0.5 (0.3–1.9)
undifferentiated site: pneumo. disease												
pneumo. disease, presentation specified:												
all pneumococcal pneumonia	9	20.2 (0.9–50.5)	9	3.2 (0–5.5)	10	5.1 (0.5–16.8)	9	5.8 (0–21.9)	4	1 (0–1.9)	10	4.8 (0.8–13.1)	9	2.7 (0.9–12.7)
pneumo. disease, presentation unspecified	1	2.1 (2.1–2.1)	0	nr	1	11 (11–11)	0	nr	1	6.8 (6.8–6.8)	0	nr	1	0.6 (0.6–0.6)
All ages												
No PCV												
undifferentiated site: pneumo. disease												

pneumo. disease, presentation unspecified	0	nr	1	0.7 (0.7–0.7)	1	2.2 (2.2–2.2)	0	nr	1	1.1 (1.1–1.1)	0	nr	1	0.4 (0.4–0.4)
PCV10, Initial period														
sterile site: IPD overall														
IPD, presentation unspecified	1	3.7 (3.7–3.7)	1	1.6 (1.6–1.6)	1	1.9 (1.9–1.9)	1	1.4 (1.4–1.4)	1	0.7 (0.7–0.7)	1	0.2 (0.2–0.2)	1	0.5 (0.5–0.5)
PCV13, Initial period														
sterile site: IPD overall														
IPD, presentation specified:														
pneumococcal bacteremia	3	9.6 (7.6–11.8)	0	nr	1	3.2 (3.2–3.2)	2	3.9 (3–4.8)	0	nr	3	7.8 (4.4–10.9)	2	5.4 (5.2–5.6)
pneumococcal meningitis	4	1.6 (0.8–2.8)	4	4.5 (2.5–5.7)	4	2.6 (1.8–3.4)	4	11.1 (5.8–13.4)	4	4.3 (2.9–6.3)	3	4 (3.9–5.2)	3	2.2 (1.9–2.3)
IPD, presentation unspecified	14	5.4 (0–15.2)	11	1.5 (0–3.9)	13	2.5 (0–5.6)	11	2.8 (1.1–6.8)	11	2.6 (0.6–16.7)	16	7.2 (0–11.5)	13	2.8 (0.6–4.6)
non-sterile site: non-IPD overall														
non-IPD, presentation unspecified	0	nr	0	nr	1	5.6 (5.6–5.6)	1	0.2 (0.2–0.2)	1	7 (7–7)	1	4.4 (4.4–4.4)	0	nr
undifferentiated site: pneumo. disease														
pneumo. disease, presentation unspecified	1	3.2 (3.2–3.2)	2	3.1 (0.8–5.4)	2	5.15 (1.6–8.7)	0	nr	2	1.75 (1.1–2.4)	1	1.6 (1.6–1.6)	0	nr
PCV13, Later period														
sterile site: IPD overall														
IPD, presentation specified:														
pneumococcal bacteremia	4	15.4 (0–17.4)	3	3.2 (0–4.3)	2	1.5 (0–3.0)	4	6.0 (0–11.6)	1	0 (0–0)	4	6.8 (0–8.9)	3	3.4 (0–3.8)
pneumococcal meningitis	4	9.6 (3.2–12.8)	4	6.2 (5.8–8.3)	2	1.6 (0–3.2)	3	6.8 (0–14)	2	10.5 (4.3–16.7)	4	7.6 (5.4–25)	4	2.9 (0–5.8)
bacteremic pneumococcal pneumonia	2	18 (14–22)	2	1.1 (0–2.1)	1	7 (7–7)	2	6.7 (1.8–11.6)	1	3.5 (3.5–3.5)	2	5.4 (3.5–7.3)	2	4.5 (3.6–5.3)
other IPD	1	11.6 (11.6–11.6)	1	4.8 (4.8–4.8)	0	nr	1	13.5 (13.5–13.5)	0	nr	1	6.6 (6.6–6.6)	1	4.0 (4.0–4.0)
IPD, presentation unspecified	11	15.3 (1.6–31.6)	8	2.5 (0.8–4)	7	2.2 (0–5.6)	10	7 (1.4–13.1)	6	1.8 (0.7–2.8)	10	6.9 (2–8.4)	8	3.5 (0–4.4)
non-sterile site: non-IPD overall														

non-IPD, presentation specified:														
pneumococcal AOM	1	1.4 (1.4–1.4)	0	nr	1	2.8 (2.8–2.8)	0	nr	1	8.5 (8.5–8.5)	0	nr	0	nr
non-IPD, presentation unspecified	1	2.1 (2.1–2.1)	0	nr	1	10.7 (10.7–10.7)	0	nr	1	7.6 (7.6–7.6)	0	nr	1	0.9 (0.9–0.9)

AOM=acute otitis media; IPD=invasive pneumococcal disease; nr=not reported

[1] Refers to cases where the precise clinical presentation was not reported.

[2] Infections of other normally sterile sites (joint fluid, pericardial fluid, peritoneal fluid, infected bone, among others).

Table S5. Meta-analysis of serotype-specific proportion * of IPD isolates from children and adults.

Children	Serotype	N (Studies)	Proportion (95% CI)
	PCV13 NIP, initial period (<3 years)		
	All PCV13	26	50.3 (41.3–59.3)
	PCV20nonPCV13		
	8	22	2.1 (1.3–3.3)
	10A	24	3.5 (2.8–4.4)
	11A	20	1.9 (1.3–2.9)
	12F	24	4.4 (2.6–7.6)
	15B/C	31	7.2 (5.6–9.1)
	22F	25	3.6 (2.5–5.3)
	33F	23	3.2 (2.3–4.6)
	PCV13 NIP, later period (≥3 years)		
	All PCV13	17	44.5 (30.6–59.3)
	PCV20nonPCV13		
	8	19	3.8 (2.5–5.8)
	10A	18	5.9 (4.5–7.7)
	11A	15	1.9 (1.6–2.3)
	12F	20	4.9 (3.2–7.4)
	15B/C	18	6.2 (4.4–8.7)
	22F	20	4.2 (2.7–6.3)
	33F	18	4.4 (3.0–6.4)
Adults	**Serotype**	**N (Studies)**	**Proportion (95% CI)**
	PCV13 NIP, initial period (<3 years)		
	All PCV13	13	49.5 (45.0–57.0)
	PCV20nonPCV13		
	8	10	4.1 (1.6–10.4)
	10A	8	1.8 (1.0–3.5)
	11A	10	3.7 (2.4–5.6)
	12F	7	2.4 (1.5–4.0)
	15B/C	11	2.5 (1.7–3.6)
	22F	13	7.7 (5.9–9.9)
	33F	7	1.8 (1.2–2.7)
	PCV13 NIP, later period (≥3 years)		
	All PCV13	9	27.3 (19.6–36.7)
	PCV20nonPCV13		
	8	13	10.2 (7.6–13.4)
	10A	13	2.4 (1.9–3.0)
	11A	13	2.7 (2.4–3.1)
	12F	13	6.2 (4.7–8.1)
	15B/C	11	1.5 (1.2–2.0)
	22F	13	6.7 (5.7–7.8)
	33F	12	2.5 (1.8–3.4)

* Calculated with a binomial random-effects meta-analytic model for each serotype-specific proportion independently. Consequently, the sum of all PCV20nonPCV13 serotypes may exceed 100%.

Table S6: Sensitivity analysis restricted to studies without moderate or serious risk of bias: Subset meta-analysis of serotype-specific proportion* of IPD isolates from children and adults.

Children	Serotype	N(studies)	Proportion (95%CI)
	PCV13 NIP, Initial period (<3 years)		
	All PCV13	11	56.3 (43.7 – 69.4)
	PCV20nonPCV13		
	8	11	2.3 (1.3 – 4.2)
	10A	13	2.6 (2.1 – 3.4)
	11A	11	2.0 (1.1 – 3.5)
	12F	11	3.2 (0.9 – 10.6)
	15B/C	16	6.6 (4.5 – 9.4)
	22F	14	3.1 (1.6 – 6.1)
	33F	11	2.5 (1.3 – 4.6)
	PCV13 NIP, Later period (≥3 years)		
	All PCV13	10	46.3 (33.0 – 60.1)
	PCV20nonPCV13		
	8	10	3.6 (1.5 – 8.1)
	10A	11	4.4 (3.1 – 6.2)
	11A	10	2.2 (1.9 – 2.6)
	12F	11	4.0 (2.2 – 6.9)
	15B/C	11	5.6 (2.9 – 10.5)
	22F	10	3.1 (1.5 – 6.3)
	33F	11	3.2 (1.7 – 6.2)
Adults	**Serotype**	**N(studies)**	**Proportion (95%CI)**
	PCV13 NIP, Initial period (<3years)		
	All PCV13	7	50.9 (38.8 – 63)
	PCV20nonPCV13		
	8	5	6.1 (1.5 – 21.3)
	10A	2	1.8 (0 – 99.0)
	11A	4	3.6 (1.1 – 10.9)
	12F	2	1.6 (0.5 – 5.0)
	15B/C	5	2.9 (1.3 – 6.5)
	22F	6	10.8 (8.6 – 13.4)
	33F	3	2.5 (1.2 – 5.0)
	PCV13 NIP, Later period (≥3years)		
	All PCV13	6	34.4 (22.6 – 48.5)
	PCV20nonPCV13		
	8	8	9.1 (5.9 – 13.9)
	10A	8	2.2 (1.5 – 3.1)
	11A	8	2.7 (2.5 – 3.0)
	12F	8	6.6 (5.1 – 8.5)
	15B/C	6	1.8 (1.6 – 2.1)
	22F	8	6.6 (5.1 – 8.4)
	33F	7	2.4 (1.3 – 4.5)

Table S7. Incidence rate of PCV20nonPCV13 serotypes per 100,000 person-years (if not stated otherwise).

Sampling site	Clinical presentation	Region	Country	Study period	Age	Reference	8	10A	11A	12F	15B/C	22F	33F
Children													
Sterile site: IPD	IPD, presentation specified												
	Pneumococcal meningitis	EUR	Israel	2008–2016	<5y	[10]	0.1	0.1	nr	0.4	0.1	0.1	0.1
	Bacteremic pneumococcal pneumonia	EUR	Israel	2008–2016	<5y	[10]	0.1	<0.1	nr	0.8	0.1	0.1	0.3
	Other IPD[1]	EUR	Israel	2008–2016	<5y	[10]	<0.1	0.3	nr	1.8	0.6	0.1	0.4
	IPD presentation unspecified[2]	AFR	South Africa	2011–2012	<16y	[117]	0.4	0.1	nr	0.7	0.2	0.2	nr
		AMR	US (Alaska)	2010–2013	<5y	[12]	0.0	1.0	0.5	2.0	3.5	2.0	1.5
		EUR	Austria	2013–2016	<5y	[94]	nr	0.2[3]	nr	nr	0.2[3]	0.1[3]	nr
		EUR	Denmark	2011–2014	<5y	[103]	0.2	nr	0.1	0.6	nr	0.4	0.5
		EUR	Israel	2010–2013	<5y	[9]	nr	nr	nr	3.7	1.1	nr	0.8
		WPR	Australia	2014–2014	<5y	[46]	0.1	0.7	0.3	0.1	1.8	0.4	0.5
Non-sterile site: non-IPD	Non-IPD, presentation specified												

	Pneumococcal AOM	EUR	Israel (South)	2010–2013	<2y	[9]	nr	nr	0.1[4]	nr	0.3[4]	nr	nr
Adults													
Sterile site: IPD	IPD, presentation specified	EUR	Austria	2013–2016	>50y	[94]	0.3[3]	nr	0.2[3]	nr	nr	0.3[3]	nr
		EUR	Denmark	2011–2014	≥65y	[103]	4.8	nr	1.3	2.6	nr	3.8	1.7
		EUR	Spain (Catalonia)	2014–2016	>65y	[22]	2.8	0.8	0.9	2.4	0.3	1.8	0.6
		EUR	UK (Nottingham)	2013–2018	>16y	[90]	2.0	nr	nr	1.1	nr	0.8	nr
		WPR	Australia	2014–2014	≥65y	[46]	0.2	0.1	0.6	0.1	0.5	1.6	0.5
Undifferentiated site	All pneumococcal pneumonia	EUR	UK (Nottingham)	2013–2018	>16y	[90]	6.9	nr	nr	2.1	nr	1.3	nr
All ages													
Sterile site: IPD	IPD, presentation unspecified[2]	AMR	Canada (Ontario)	2011–2017	all	[124]	nr	nr	nr	nr	nr	0.8	nr
		AMR	US (Alaska)	2010–2013	all	[12]	0.8	0.4	0,4	0.7	0.5	1.4	0.4
		EUR	France	2012–2012	all	[62]	nr	nr	nr	1.7	1.5	1.0	nr

Abbreviations: AFR = Africa; AMR = Americas; EUR = Europe; WPR = Western Pacific; nr = not reported; other IPD = any IPD excluding meningitis and bacteremic pneumonia.
[1] Infections of other normally sterile sites (joint fluid, pericardial fluid, peritoneal fluid, infected bone, among others).
[2] Refers to cases where the precise clinical presentation was not reported.
[3] per 100,000 person-months.
[4] per 1,000 population.

Table S8. Proportion (%) of PCV20nonPCV13 serotypes non-susceptible to penicillin or a macrolide or that were multi-drug resistant (MDR)

Age group	Sampling site and clinical pres.	Antibiotic class	Reference	8	10A	11A	12F	15B/C	22F	33F
Children	Sterile site (IPD)									
	IPD presentation unspecified	Penicillin	[44]	0	0	40	0	0	0	nr
	Non-sterile site (Non-IPD)									
	Non-IPD presentation unspecified	Penicillin	[81]	nr	nr	0	nr	0	nr	nr
	Non-IPD presentation unspecified	Macrolide	[81]	nr	nr	60	nr	33	nr	nr
	Undifferentiated site									
	Pneumo. disease presentation unsp.	Penicillin	[80]	nr	nr	nr	nr	nr	0	nr
Adults	Non-sterile site (Non-IPD)									
	Non-IPD presentation unspecified	Penicillin	[31]	nr	0	nr	nr	nr	nr	nr
	Non-IPD presentation unspecified	Macrolide	[31]	nr	5	nr	nr	nr	nr	nr
	Non-IPD presentation unspecified	Penicillin	[73]	nr	1	nr	nr	21	nr	nr
	Non-IPD presentation unspecified	Macrolide	[73]	nr	10	nr	nr	57	nr	nr
	Non-IPD presentation unspecified	Penicillin	[107]	nr	nr	2	nr	nr	0	nr
	Non-IPD presentation unspecified	Macrolide	[107]	nr	nr	30	nr	nr	17	nr
	Non-IPD presentation unspecified	MDR	[107]	nr	nr	2	nr	nr	0	nr
	Undifferentiated site									
	Pneumo. disease presentation unsp.	Penicillin	[6]	0	0	0	0	0	0	0
	Pneumo. disease presentation unsp.	Penicillin	[107]	nr	nr	0	nr	nr	0	nr
	Pneumo. disease presentation unsp.	Macrolide	[107]	nr	nr	41	nr	nr	26	nr
	Pneumo. disease presentation unsp.	MDR	[107]	nr	nr	3	nr	nr	1	nr
All ages	Sterile site (IPD)									
	IPD presentation unspecified	Penicillin	[24]	0	0	25	nr	nr	nr	0
	IPD presentation unspecified	Macrolide	[24]	11	100	0	nr	nr	nr	100
	IPD presentation unspecified	Penicillin	[36]	nr	nr	nr	nr	nr	0	0
	IPD presentation unspecified	Macrolide	[36]	nr	nr	nr	nr	nr	26	79

IPD presentation unspecified	MDR	[36]	nr	nr	nr	nr	nr	1	9
IPD presentation unspecified	Penicillin	[74]	nr	nr	0	nr	nr	nr	nr
IPD presentation unspecified	Macrolide	[74]	2	2	6	nr	3	nr	9
IPD presentation unspecified	Penicillin	[93]	nr	nr	0	nr	8	nr	nr
IPD presentation unspecified	Penicillin	[97]	48	nr	nr	2	2	nr	nr
Non-sterile site (Non-IPD)									
Non-IPD presentation unspecified	Penicillin	[93]	nr	nr	10	nr	39	nr	nr
Non-IPD presentation unspecified	MDR	[98]	4	0	4	nr	0	0	nr
Undifferentiated site									
Pneumo. disease presentation unsp.	Penicillin	[51]	nr	0	nr	nr	22	nr	nr
Pneumo. disease presentation unsp.	Macrolide	[51]	nr	73	nr	nr	100	nr	nr
Pneumo. disease presentation unsp.	Penicillin	[53]	nr	0	33	nr	67	nr	0
Pneumo. disease presentation unsp.	Macrolide	[53]	nr	50	33	nr	33	nr	0
Pneumo. disease presentation unsp.	Penicillin	[112]	nr	nr	5	nr	10	nr	nr
Pneumo. disease presentation unsp.	Macrolide	[112]	nr	nr	3	nr	7	nr	38

Abbreviations: IPD = invasive pneumococcal disease; MDR = multi-drug resistant; nr = not reported.

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