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Pneumococcal Carriage in Sub-Saharan Africa—A Systematic Review

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Abstract

Background: Pneumococcal epidemiology varies geographically and few data are available from the African continent. We assess pneumococcal carriage from studies conducted in sub-Saharan Africa (sSA) before and after the pneumococcal conjugate vaccine (PCV) era.

Methods: A search for pneumococcal carriage studies published before 2012 was conducted to describe carriage in sSA. The review also describes pneumococcal serotypes and assesses the impact of vaccination on carriage in this region.

Results: Fifty-seven studies were included in this review with the majority (40.3%) from South Africa. There was considerable variability in the prevalence of carriage between studies (I-squared statistic = 99%). Carriage was higher in children and decreased with increasing age, 63.2% (95% CI: 55.6–70.8) in children less than 5 years, 42.6% (95% CI: 29.9–55.4) in children 5–15 years and 28.0% (95% CI: 19.0–37.0) in adults older than 15 years. There was no difference in the prevalence of carriage between males and females in 9/11 studies. Serotypes 19F, 6B, 6A, 14 and 23F were the five most common isolates. A meta-analysis of four randomized trials of PCV vaccination in children aged 9–24 months showed that carriage of vaccine type (VT) serotypes decreased with PCV vaccination; however, overall carriage remained the same because of a concomitant increase in non-vaccine type (NVT) serotypes.

Conclusion: Pneumococcal carriage is generally high in the African continent, particularly in young children. The five most common serotypes in sSA are among the top seven serotypes that cause invasive pneumococcal disease in children globally. These serotypes are covered by the two PCVs recommended for routine childhood immunization by the WHO. The distribution of serotypes found in the nasopharynx is altered by PCV vaccination.

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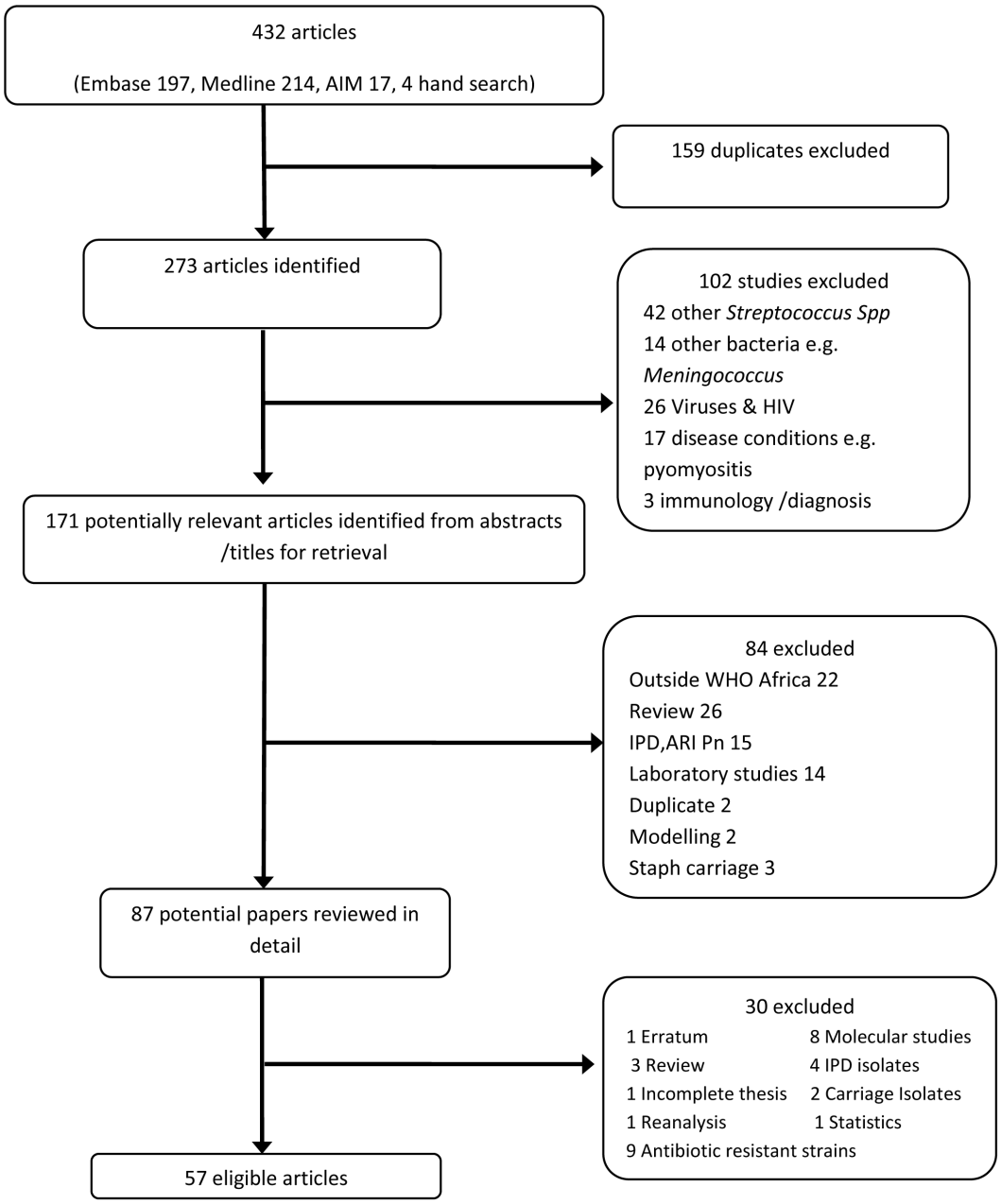
Introduction

The human nasopharynx is the main reservoir for pneumococci. The bacteria which adhere to pharyngeal epithelial cells through epithelial receptor molecules may be acquired very early in life [1,2], and in most children the pneumococcus is present in the nasopharynx at some point in the first few years of life [3]. Carriage is generally higher in developing countries and among economically deprived populations [4,5]. The prevalence of carriage might also vary between developing countries. In one study, Abdullahi et al suggested that colonisation prevalence in East and Southern Africa is substantially lower than in the Gambia [6]. High prevalence have however been reported in Ethiopia and Mozambique.

Carriage is a prerequisite for disease [3,7] and because it is much more common than a disease outcome, it may be a valuable measure of the efficacy of new pneumococcal vaccines [8]. The relation between carriage and disease was first demonstrated in a cohort of infants [9]. Subsequent studies showed that carriage is a risk factor for acute and recurrent otitis media in children [10,11]. Other studies have shown that bacterial carriage densities may be related to the risk of disease in adults and children [12,13], and O'Brien et al have suggested that PCV may reduce carriage density in children [14].

Since the introduction of PCV, several studies have reported a reduction in invasive pneumococcal disease (IPD). However, this is frequently accompanied by a change in the distribution of circulating serotypes. A decrease in vaccine type (VT) IPD and



AIM- African Index Medicus, Pn-pneumonia, IPD- invasive pneumococcal disease, ARI-Acute respiratory infection

Figure 1. Flow chart for eligible articles.
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an increase in non-vaccine type (NVT) IPD have been reported in America [15], Spain [16], Canada [17] and Australia [18]. In particular, serotype 19A has been isolated more frequently after the introduction of PCV 7 [19–22].

This review of pneumococcal carriage in sSA aims to: 1) describe the variability in carriage prevalence across countries in sSA; 2) describe the distribution of serotypes, and 3) assess the impact of pneumococcal vaccination on carriage of VT and NVT serotypes.

Methods

A comprehensive literature search strategy was developed to identify published articles describing pneumococcal carriage in sSA (Appendix S1). The search was conducted in December 2011 using the electronic databases MEDLINE (from 1950), EMBASE (from 1947) and African Index Medicus (AIM). To ensure the retrieval of relevant articles, the search was performed by exploring and combining medical subject headings (MeSH) and free search terms relating to carriage, nasopharyngeal, oropha-

Table 1. Characteristics of studies included in the review (n = 32,253).

First author,(ref)	Country	Year	Age	Population	Swab type	Route	Swabs/person
Central Africa							
Rowe, [47]	CAR	1995	2 m–58 m	opd[a]	c.alginate	NPS	single
Ndip, [48]	Cameron	2004	10 y–21 y	school[b]	ns	OPS	single
East Africa							
Ringertz, [49]	Ethiopia	1987	<5 y	comm	c.alginate	NPS	single
Rusen, [50]	Kenya	1990	<5 y	opd[c]	c.alginate	NPS	single
Joloba, [51]	Uganda	1995	<3 y	opd[d]	c.alginate	NPS	single
Batt, [52]	Tanzania	2000	<7 y	comm	cotton	OPS	single
Scott, [53]	Kenya	2000	<7 y	comm/hosp	dacron	NPS	single
Nyandiko, [54]	Kenya	2003	<42 m	opd[e]	dacron	NPS	single
Abdullahi, [6]	Kenya	2004	all	comm	rayon	NPS	twice
Blossom, [55]	Uganda	2004	20 y–55 y	HIV	BBL	OPS	single
Abdullahi, [56]	Kenya	2006	<5 y	opd[f]	rayon	NPS	single/multiple[g]
Haug, [57]	Ethiopia	2003/6	1 y–5 y	comm	ns	NPS	single
Skalet, [58]	Ethiopia	2006	<10 y	comm	ns	NPS	single
Scott, [27]	Kenya	2004/7	<1 y	EPI	rayon	NPS	single
Southern Africa							
Jacobs, [59]	South Africa	1977	all	hosp[h]	c.alginate	NPS	single
Klugman, [60]	South Africa	1977	<5 y[i]	DCC	c.alginate	NPS	single
Robins-Browne, [61]	South Africa	1981	<12 y	hosp	c.alginate	NPS	single
Oppenheim, [62]	South Africa	1983	<10 y	hosp	c.alginate	NPS	multiple
Frederiksen, [63]	Zambia	1986	<10 y	opd[d]	cotton	OPS	single
Woolfson, [64]	Zambia	1994	<6 y	opd[a]	c.alginate	NPS	single
Mthwalo, [65]	Lesotho	1995	<5 y	comm	c.alginate	NPS	single
Yomo, [66]	Malawi	1995	<5 y	MCH	cotton	both	multiple
Feikin, [67]	Malawi	1997	2 w–59 m	opd[f]	ns	NPS	single
Feikin, [68]	Malawi	1997	2 w–59 m	opd[a]	ns	NPS	multiple
Huebner, [69]	Botswana	1997	2 m–5 y	opd/ward	c.alginate	NPS	single
Gordon, [70]	Malawi	1998	all	ns	cotton	NPS	single
McNally, [36]	South Africa	2001	1 m–59 m	hosp[j]	wire	NPS	single
Cotton, [71]	South Africa	2002	8 w–5 y	HIV	wire	NPS	single
Pemba, [45]	South Africa	2002	adults	HIV	c.alginate	Both	twice
Gill, [45]	Zambia	2003	6 w–18 m	HIV+ve/−ve	c.alginate	NPS	single/multiple[g]
Valles, [72]	Mozambique	2003	<5 y	opd	c.alginate	NPS	Single
von Gottberg, [73]	South Africa	2006	all	hosp[k]	dacron	NPS	single
Mbelle, [28]	South Africa	1999[l]	<1 y	comm	c.alginate	NPS	multiple
Huebner, [74]	South Africa	2000[l]	2 m–5 y	clinic[d]	c.alginate	NPS	single
Mwenya, [75]	Zambia	2002	6 m–14 y	HIV	rayon	NPS	single
Marcus, [76]	South Africa	1993	3 m–8 y	school	c.alginate	NPS	single
West Africa							
Hansman, [77]	Nigeria	1977	ns	opd[a]	ns	NPS	single
Lloyd- Evans, [78]	Gambia	1989	all	comm/hosp	cotton	NPS	single/multiple[g]
Obaro, [30]	Gambia	1995	2 y	comm	ns	NPS	single
Denno, [79]	Ghana	1996	<1 y	opd[e]	wire	NPS	single
Kacou-Ndouba, [80]	Ivory Coast	1997	<5 y	EPI	c.alginate	NPS	single
Obaro, [25]	Gambia	2000	<1 y	EPI	cotton	NPS	twice
Darboe, [81]	Gambia	2001	all	comm	c.alginate	NPS	multiple
Adegbola, [82]	Gambia	2001[l]	3–4 y	comm	c.alginate	NPS	single
Hill, [83]	Gambia	2003/4	all	comm	c.alginate	NPS	single

Table 1. Cont.

First author,(ref)	Country	Year	Age	Population	Swab type	Route	Swabs/person
Hill, [2]	Gambia	2008[l]	<1 y	comm	c.alginate	NPS	multiple
Nwachukwu, [37]	Nigeria	2008[l]	2 m–59 m	EPI	ns	NPS	single
Bere, [84]	Burkina Faso	2000	<5 y	MCH	c.alginate	NPS	single
Cheung, [29]	Gambia	2003	9 m–27 m	comm	ns	NPS	multiple
Kandakai-Olukemi, [85]	Nigeria	2009[l]	15 y–25 y	school	cotton	NPS	single
Mureithi, [86]	Gambia	2009[l]	19 y–50 y	comm	ns	NPS	single
Darboe, [1]	Gambia	2010[l]	<1 y	clinic	c.alginate	NPS	multiple
Donkor, [87]	Ghana	2006	<13 y	hosp[m]	ns	NPS	single
Hill, [88]	Gambia	2010[l]	All	comm	ns	NPS	multiple
Kacou-N'douba, [89]	Ivory Coast	2010[l]	<5 y	ns	ns	ns	single
Ota, [26]	Gambia	2011[l]	<1 y	EPI	c.alginate	NPS	single
Roca, [24]	Gambia	2006/8	All ages	comm	c.alginate	NPS	single

Ref- reference, N-number of individuals, ns- not stated; NPS- Nasopharyngeal swab; OPS- Oropharyngeal swab; c.alginate- Calcium Alginate; w-week, m-months, y-years, comm- community, opd-outpatient department, hosp-hospital, EPI -Expanded programme on immunisation clinic, DCC- day care centre, MCH- mother & child clinic,
[a]any illness,
[b]with respiratory tract infection,
[c]perinatal follow up HIV clinic used control group,
[d]routine check or immunisation,
[e]medical conditions as well as routine checks,
[f]minor illnesses no hospitalisations,
[g]some swabbed once others swabbed more than once,
[h]children and carers sick and well,
[l]adults also swabbed age not specified,
[j]hosp severe pneumonia,
[k]tuberculosis patients,
[l]year published,
[m]patients returning for review after minor illness.
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ryngeal, *Streptococcus pneumoniae*, serotypes, pneumococcal vaccine and specific names of the African countries. Titles and abstracts were reviewed and duplicates, non-relevant studies, and those involving streptococcal infections other than *S. pneumoniae* were excluded (Figure 1). The full texts of potential papers were then screened for eligibility.

Inclusion and exclusion criteria

The review was limited to studies from countries within the sSA region that reported the prevalence of carriage with or without serotyping of the pneumococcal isolates. We used data from both hospital and community based studies that collected swabs from either the nasopharynx or oropharynx. The search was limited to human subjects but there was no restriction on the age of participants, study design or language of publication. Bibliographies of relevant papers and review papers were searched to identify articles that may have been missed in the electronic search.

Data analysis

Data were obtained for the following variables: prevalence of *S. pneumoniae*, country, first author, year the study was conducted (or year of publication if the study year was not reported), age of participants, number of swabs collected per individual, health of the population swabbed, rural or urban setting, and season or months of the year when the study was conducted. The data were entered in an Excel spread sheet and Stata version 12 was used for all analyses. For studies with multiple swabs per individual, only results from the first swab were included in the analysis and for those with interventions, either PCV or other interventions such as antibiotics, only the control arm was included in the analysis. To assess the impact of PCV we used data from randomised trials where PCV was the intervention. The extracted data were reviewed independently by a second reviewer who checked the data to ensure completeness using the template prepared for data extraction.

To describe the prevalence of carriage by age, the studies were grouped as: <5 years (children), 5–15 years (children), and >15 years (adults). Studies that recruited children in both age groups were assigned to the age group 5–15 years. Studies where participants were recruited across child and adult age groups, and where suitable stratified results were unavailable were excluded from the analysis of carriage by age. A random-effects model was used to summarise carriage by age group across the different studies. Studies where the standard error of the prevalence could not be computed were excluded from this analysis. The effects of region, season and urban/rural location on carriage were examined by comparing between studies using random effects model (meta-regression). For each study that reported carriage by gender, the absolute difference in prevalence between males and females (risk difference) was calculated and statistical significance was determined using Fisher's exact test.

Table 2. Pneumococcal carriage prevalence in sub Saharan Africa by age.

A

First author, year	Country	Prevalence	95% CI	% Wt
Hansman, 1977	Nigeria	44.4	34.6 54.2	2.50
Jacobs, 1977	South Africa	41.8	37.6 45.9	2.58
Klugman, 1977	South Africa	58.2	54.6 61.8	2.59
Ringertz, 1987	Ethiopia	89.8	88.0 91.6	2.60
Lloyd- Evans, 1989	Gambia	85.1	83.0 87.2	2.60
Rusen, 1990	Kenya	22.5	13.5 31.6	2.51
Woolfson, 1994	Zambia	71.9	66.4 77.4	2.57
Mthwalo, 1995	Lesotho	59.6	55.4 63.8	2.58
Yomo, 1995	Malawi	47.5	40.6 54.4	2.55
Rowe, 1995	CAR	71.2	66.8 75.6	2.58
Joloba, 1995	Uganda	61.8	54.9 68.7	2.55
Obaro, 1995	Gambia	93.8	90.1 97.5	2.59
Denno, 1996	Ghana	51.4	45.8 57.0	2.57
Kacou-Ndouba, 1997	Ivory Coast	63.3	56.9 69.7	2.56
Feikin, 1997	Malawi	87.0	84.8 89.2	2.59
Huebner, 1997	Botswana	69.1	63.6 74.5	2.57
Feikin, 1997	Malawi	84.0	81.6 86.4	2.59
Gordon, 1998	Malawi	42.0	35.4 48.1	2.56
Mbelle, 1999	South Africa	61.0	54.8 67.2	2.56
Huebner, 2000	South Africa	39.9	34.4 45.4	2.57
Obaro, 2000	Gambia	92.1	88.4 95.8	2.59
Bere, 2000	Burkina Faso	50.7	47.4 54.0	2.59
Adegbola, 2001	Gambia	87.0	80.5 93.5	2.55
McNally, 2001	South Africa	47.6	42.4 52.8	2.57
Darboe, 2001	Gambia	81.0	73.2 88.3	2.53
Cotton, 2002	South Africa	22.2	16.5 27.9	2.56
Hill, 2003	Gambia	93.4	88.7 98.1	2.58
Cheung, 2003	Gambia	86.1	84.0 88.2	2.60
Gill, 2003	Zambia	25.8	23.6 28.1	2.59
Nyandiko, 2003	Kenya	35.9	25.2 46.5	2.48
Valles, 2003	Mozambique	87.0	83.1 90.9	2.58
Haug, 2003	Ethiopia	93.3	88.8 97.8	2.58
Scott, 2004	Kenya	78.0	73.0 83.0	2.57
Abdullahi, 2004	Kenya	57.0	52.4 61.6	2.58
Abdullahi, 2006	Kenya	76.0	65.4 86.6	2.48
Hill, 2008	Gambia	86.0	81.6 90.4	2.58
Nwachukwu, 2008	Nigeria	69.0	58.2 79.8	2.47
Kacou-N'douba, 2010	Ivory Coast	27.5	24.7 30.3	2.59
Darboe, 2010	Gambia	21.0	15.3 26.7	2.56
Overall prevalence		***63.2***	***55.6 70.8***	***100.00***
I^2(%), p-value	*99.33, <0.001*			

B

First author, year	Country	Prevalence	95% CI	% Wt
Robins-Browne, 1981	South Africa	31.0	27.2 34.8	7.80
Oppenheim, 1983	South Africa	24.5	23.0 25.9	7.85
Frederiksen, 1986	Zambia	16.0	11.4 20.6	7.78
Lloyd- Evans, 1989	Gambia	63.0	56.9 69.1	7.72

Table 2. Cont.

B

First author, year	Country	Prevalence	95% CI	% Wt
Marcus, 1993	South Africa	40.6	31.2 49.9	7.54
Scott, 2000	Kenya	37.0	30.2 43.8	7.88
Batt, 2000	Tanzania	10.7	9.0 12.4	7.85
Mwenya, 2002	Zambia	55.0	44.7 65.3	7.47
Hill, 2003	Gambia	86.3	82.5 90.1	7.80
Abdullahi, 2004	Kenya	41.0	36.3 45.7	7.77
Skalet, 2006	Ethiopia	81.7	74.8 88.6	7.68
Donkor, 2006	Ghana	15.3	9.0 21.6	7.71
von Gottberg, 2007	South Africa	53.8	41.7 65.9	7.34
Overall prevalence		***42.6***	***29.9 55.4***	***100.00***
I^2(%), pvalue	*99.34, ,<0.001*			

C

First author, year	Country	Prevalence	95% CI	% Wt
Klugman, 1977	South Africa	15.4	8.2 22.5	7.75
Jacobs, 1977	South Africa	9.9	7.1 12.7	8.08
Lloyd- Evans, 1989	Gambia	20.0	−0.9 40.9	5.65
Gordon, 1998	Malawi	10.8	8.1 13.5	8.08
Darboe, 2001	Gambia	13.0	8.3 17.7	7.97
Pemba, 2002	South Africa	8.8	6.9 10.7	8.11
Hill, 2003	Gambia	60.6	56.4 64.8	8.00
Gill, 2003	Zambia	8.8	7.3 10.3	8.13
Blossom, 2004	Uganda	18.0	14.9 21.1	8.07
Abdullahi, 2004	Kenya	6.4	4.0 8.8	8.10
Mureithi, 2009	Gambia	80.0	66.1 93.9	6.83
Kandakai-Olukemi, 2009	Nigeria	42.0	31.7 52.3	7.36
Darboe, 2010	Gambia	78.0	72.2 83.8	7.88
Overall prevalence		***28.0***	***19.0 37.0***	***100.00***
I^2(%), pvalue	*99.00, <0.001*			

(A) Children <5years, n = 15,879 (B) Children 5–15 years, n = 7,180 (C) Adults >15 years n = 5,350.
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Data from four of the studies were pooled to assess the impact of PCV on overall carriage and the carriage of VT and NVT serotypes among children 9 to 24 months. In all four studies children who received no PCV were compared with children who received at least three doses of PCV. Random effects models were used to estimate the average effect of PCV (DerSimonian-Laird estimate) across studies and to assess the degree of heterogeneity between studies.

Serotypes isolated in each study were ranked in order of prevalence and the five most prevalent serotypes in each study were identified. For each serotype, we determined the proportion of studies in which it was among five most prevalent serotypes.

Quality of the studies

The studies were reviewed for quality using the WHO guidelines for conducting nasopharyngeal studies. The guidelines are for the material used for sample collection, the technique of sample collection, and the transport media [23]. For each study, we identified potential sources of bias in the method of selection of study subjects.

Results

Characteristics of the studies

A total of 57 studies were included in this review (Table 1). Southern Africa contributed the most studies, 23(40.3%). Twenty studies (35.1%) were from West Africa with more than half of these from The Gambia. There were 12(21.1%) and 2(3.5%) studies from East and Central Africa respectively.

The majority of the studies (87.7%) collected nasopharyngeal swabs, only 4(7.0%) collected oropharyngeal swabs, and 2(3.5%) studies collected both. In one study, the anatomical site of sampling was not reported. Calcium alginate was the most

Table 3. Differences in the prevalence of pneumococcal carriage in sub Saharan Africa.

	Prevalence (95%CI)								
	N+	Children <5 years	pvalue	N	Children 5–15 years	pvalue	N	Adults >15 years	pvalue
Region									
East	8	64.5(43.5–85.5)	0.73	4	42.5(−4.2–89.2)	0.72	2	12.2(−61.5–85.9)	0.06
Central	1	71.2		6	36.1(19.6–52.6)		0	-	
Southern	15	56.4(44.8–67.9)		0	-		5	9.3(7.8–10.9)	
West	15	68.8(55.3–82.)		3	54.9(−35.0–144.8)		6	49.3(19.2–79.3)	
Settlement									
Rural	16	80.2(70.5–89.9)	<0.0001	5	55.7(16.1–95.3)	0.26	6	32.9(1.8–63.9)	0.44
Urban	15	53.4(45.2–61.7)		5	35.3(13.4–57.2)		4	19.5(−3.7–42.7)	
Season									
Dry	13	64.7(54.8–74.6)	0.54	5	31.4(11.4–51.3)	na	3	9.6(6.6–12.6)	na
Rainy	6	58.4(31.1–85.9)		0	-		0	-	
Population[a]									
Well	21	69.2(59.5–78.9)	0.11	8	44.3(19.1–69.5)	0.97	9	36.1(13.1–59.1)	0.33
Sick[b]	10	64.3(50.2–78.4)		3	35.5(−1.7–72.7)		0	-	
HIV	1	22.2		1	55.0		2	13.3(−45.1–71.7)	
Year[c]									
Before 2000	19	63.7(54.4–72.9)	0.92	5	34.9(12.4–57.3)	0.39	4	10.8(7.7–13.8)	0.22
After 2000	20	62.8(50.4–75.3)		8	47.5(24.3–70.8)		9	34.8(11.2–58.3)	
Swab route									
NPS	37	64.6(57.1–72.2)	na	11	48.1(32.8–63.3)	0.06	11	31.2(11.9–50.5)	0.67
OPS	0	-		2	13.3(−20.2–46.1)		1	18.0	
Swab type									
WHO[d]	21	60.9(50.5–71.3)		6	45.5(22.1–68.9)		6	22.3(−6.4–51.0)	
Others	10	59.9(44.1–75.8)	0.91	5	36.9. (8.1–65.8)	0.55	6	26.3(3.84–48.9)	0.78

na- not applicable,
[a]excluded studies with both sick and well when prevalence was not available by category.
[b]all illnesses including pneumonia & upper respiratory tract infections.
[c]PCV first licensed 2000,
[d]WHO recommended calcium alginate & Dacro; p-values and prevalences based on meta-regression; N+ = no. of studies;
Data were used from N = 55 studies. Three studies contributed data to all three age groups, five studies contributed to <5 yrs and >15 yrs, 31 studies contributed to <5 yrs only, 10 studies contributed to 5–15 yrs only, and five studies contributed to >15 yrs only. Settlement, season, population, swab route and swab type were not recorded in all studies, and for these variables we have used studies where data were available.
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common type of swab 26 (45.6%). Other types used were cotton 7(12.3%), Dacron 3(5.3%), Rayon 4(7.0%), BBL 1(1.8%) and wire 3(5.3%). Thirteen studies (22.8%) did not report the type of swab that was used.

The majority of the studies (75.4%) were conducted in children, 11(19.3%) involved both children and adults and only 3(5.3%) studies exclusively recruited adults. Most studies (53.0%) were in healthy individuals, 14.0% had both healthy and sick patients, 24.5% were conducted in outpatients, 6.9% in HIV positive populations and in 1.7% the population was not stated. In 15(26.3%) studies, participants were swabbed more than once.

Pneumococcal carriage by age and geographic region

Carriage was highest for children less than 5 years and decreased with age (Table 2 and Figures S1, S2 & S3). High prevalence (>85%) in children were recorded in Ethiopia, Mozambique (only one study) and The Gambia. The Gambia also had the highest prevalence in adults (Table 2). The prevalence of carriage varied considerably between studies. The I^2 index, which assesses heterogeneity between studies, was greater than 99% in all the age categories. In children less than 5 years the prevalence was higher in studies conducted in a rural, rather than urban setting. Carriage was not associated with season, population health, swab type or year (Table 3).

Pneumococcal carriage and gender

Eleven studies reported the prevalence of carriage by gender. Three of these studies reported no association, one study reported a higher prevalence in males compared to females (p = 0.05), and one study reported a higher prevalence in females (OR = 0.61; 95% CI: 0.39–0.95; p = 0.02). From our analysis, there was no significant difference in the risk of carriage between males and females in any of the remaining six studies (Table 4).

Table 4. Prevalence of pneumococcal carriage in Africa by gender.

Country	Ref	Age grp	Prevalence % (n/N)		RD	95%CI	Pvalue
			Male	Female			
Uganda	[51]	Children	62.3 (66/106)	61.2(52/85)	0.01	−0.13,0.15	0.88
Uganda	[55]	Adults	25.9(28/108)	18.3(80/438)	0.08	−0.01,0.17	0.08
South Africa[a]	[36]	Children	ns	ns	-		0.02
South Africa[b]	[45]	Adults	8.8(75/854)	0.0(0/2)	0.09	na	1.00
Ghana	[79]	Infants	47.5 (75/158)	49.7(76/153)	−0.02	−0.13, 0.09	0.73
Nigeria	[37]	Children	(ns/55)	(ns/45)	-	-	0.05
Zambia	[64]	Children	70.9 (93/131)	71.9(92/128)	−0.01	−0.12,0.10	0.88
Kenya[a]	[6]	All ages	ns	ns	-	-	nd
Kenya	[54]	Children	32.3(11/34)	39.5(17/43)	−0.07	−0.29,0.14	0.64
Gambia	[83]	All ages	ns	ns		-	nd
Malawi	[66]	Children	48.9(ns)	46.3(ns)	0.03	-	nd

RD- Risk difference, ns- not stated, nd-no difference reported in paper, na – not applicable, Ref-reference,
[a]OR = 0.61 (95% CI: 0.39, 0.95),
[b]HIV infected mineworkers 99.8% male, p-value based on Fisher's exact test.
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PCV and pneumococcal carriage

Seven studies from three countries (The Gambia, Kenya and South Africa) assessed the association between PCV and carriage. One study from the Gambia was a village cluster randomised trial with adults and older children in 10 villages receiving one dose of PCV 7, and adults and older children in 11 control villages receiving meningococcal serogroup C vaccine. In both arms of the trial, infants aged between 2 and 11 months received three doses of the vaccine given at monthly intervals, and children aged between 12 and 30 months received two doses at one month interval between doses. Infants born during the study received three doses of the vaccine given monthly at the ages 2, 3, and 4 months [24]. The other six studies compared carriage in vaccinated and unvaccinated children using data from individually randomised control trials (RCTs). Four of these studies collected carriage data on all children that participated in the trial [25–28] while two studies used data from a subsample of children enrolled in the original trial [29,30] (Table 5).

The participants in all the PCV studies were children from the general population presenting at infant welfare clinics for immunisation, except for the village cluster randomized trial which recruited children and adults in the community. Carriage of vaccine type (VT) serotypes was reduced by vaccination, while carriage of non-vaccine type serotypes was greater among vaccinated children (Figure 2 & Table 5). The prevalence of overall carriage was not affected by vaccination.

Pneumococcal carriage serotypes in Africa

Twenty eight (49.1%) of the studies had collected data on serotypes and in total 6904 isolates were serotyped in these studies. The seven studies with PCV intervention were excluded from this analysis. There were 70 serotypes and serogroups. Serotype 19F was among the five most prevalent serotypes in 14/21 studies, serotype 6B in 13/21, serotype 14 in 13/21, serotype 6A in 11/21 and serotype 23F in 9/21 studies. Some studies only described serogroups, and in these studies serogroups 19 and 6 were the most common. In the PCV 9 vaccine trial in South Africa, serotypes 6B, 19F and 23F were the most common vaccine serotypes in both vaccinated (6B 3.3%, 19F 7.8%, 23F 2.9%) and control (6B 11.7%, 19F 13.4%, 23F 5.8%) groups, and serotype 6B and 19F were significantly less frequent in the PCV 9 vaccinated children. 15 (9.1%), 6A (5.8%) and 19A (2.9%) were the most common NVT serotypes/serogroup in the vaccinees, with serogroup 15 significantly increased in vaccinated compared to control children (9.1% versus 3.8%, p value 0.017) [28].

In The Gambia, the carriage study during the PCV 9 trial found that serotype 19F (11.5%) was again the most common VT serotype isolated and serogroup 15 was the most common NVT, and more prevalent in the PCV 9 vaccinated children (11.8% versus 8.5%, $P<0.05$). When the study children were swabbed a second time about 10 months later, NVT serotypes 10, 21 and 35B were isolated more frequently from PCV 9 vaccinated children than controls. There was no longer any difference between the groups for carriage of serotype 19F [29]. In the cluster randomised trial conducted in The Gambia, serotypes 23F, 6A, 6B, 3, 11 and 7C were the most common serotypes before vaccination and serotypes 3, 11, 19F and 6A were the most common serotypes after vaccination [24].

Discussion

This systematic review of pneumococcal carriage in sSA summarises the prevalence of carriage, distribution of serotypes and the effect of PCV on carriage. The majority of the studies were from Southern and West Africa, particularly South Africa and the Gambia. There were only two studies from Central Africa.

We found that the prevalence of pneumococcal carriage in sSA is generally high but there is much variation between countries, particularly among older age groups. Carriage was higher in children than adults as reported outside sSA [31,32].

A small number of studies conducted outside sSA have reported a higher prevalence of carriage in males compared to females [33–35]. However, in this review gender was not associated with

Table 5. Studies of pneumococcal conjugate vaccination and carriage in Africa (n = 9,549).

							Trial arm n/N (%)			
1st Author	**Year**	**Country**	**Valency, Study design**	**Age PCV administered (w/m/y)**	**Age swabbed (w/m/y)**	**Serotypes**	**PCV[b+c]**		**RD**	**pvalue**
SK Obaro	1995	Gambia	PCV 5	2, 3,4 w			**PCV^{3+1}**	**Control**		
			PPV	18 m						
			RCT[a]		24 m	Overall	22/26(84.6)	150/160(93.8)	−0.09	0.112
						VT	13/26(50.0)	144/160(90.0)	−0.40	<0.001
						NVT	20/26(76.9)	68/160(42.5)	0.34	0.001
N.Mbelle	1999	S. Africa	PCV 9	6, 10,14 w			**PCV^{3}**	**Control**		
			RCT		6 w	Overall	64/250(25.6)	74/250(29.6)	−0.04	0.368
					10 w	Overall	110/249(44.2)	109/249(43.8)	0.004	1.000
					14 w	Overall	115/246(46.7)	127/247(51.4)	−0.05	0.322
					9 m	Overall	130/242(53.7)	145/239(60.7)	−0.07	0.140
						VT[d]	43/242(17.8)	86/239(36.0)	−0.18	<0.001
						NVT	87/242(36.0)	59/239(24.7)	0.11	0.008
SK Obaro	2000	Gambia	PCV 9	2, 3, 4 m			**PCV^{3}**	**Control**		
			RCT		5 m	Overall	92/100(92.0)	94/102 (92.2)	−0.002	1.000
						VT	54/100(54.0)	64/102 (62.7)	−0.09	0.253
						NVT	45/100 (45.0)	33/102 (32.4)	0.13	0.083
					9 m	Overall	83/98 (84.7)	87/99(87.9)	−0.03	0.541
						VT	61/98(62.2)	74/99(74.7)	−0.13	0.067
						NVT	28/98(28.6)	16/99(16.2)	0.12	0.041
YB.Cheung	2003	Gambia	PCV 9	2, 3, 4 m			**PCV^{3}**	**Control**		
			nested		9–15 m	Overall	943/1078(87.5)	914/1061(86.1)	0.01	0.371
			Cohort,			VT	237/1051(22.5)	416/1041(40.0)	−0.17	<0.001
			RCT			NVT	449/1051(42.7)	280/1041(26.9)	0.16	<0.001
					21–27 m	Overall	793/967(82.0)	813/961(84.6)	−0.03	0.143
						VT	230/922(24.9)	381/925(41.2)	−0.16	<0.001
						NVT	373/922(40.5)	242/925(26.2)	0.14	<0.001
J. A Scott*	2004/7	Kenya	PCV 7	0 or 6 & 10, 14 w			**PCV^{3+1e}**	**PCV^{3+1f}**		
			PCV7/PPV	36 w	18 w	Overall[g]	205/263(78.0)	-		
			RCT			VT	ns(25.0)	ns(31.0)	−0.06	0.280
					36 w	Overall[g]	188/244(77.0)	-		
						NVT	ns(62.0)	ns(51.0)	0.11	0.250
M.Ota*	2011	Gambia	PCV 7	2, 3, 4 m			**PCV^{3+1}**	**PCV^{1+1}**		
			PPV	10 m	5 m	Overall	177/215(82.3)	178/217(82.0)	0.003	1.000
			RCT			VT	29/215(13.5)	43/217(19.8)	−0.06	0.093
						NVT	151/215(70.2)	138/217(63.6)	0.07	0.153
					11 m	Overall	143/200(71.5)	155/203(76.4)	−0.05	0.307
						VT	20/200(10.0)	41/203(20.2)	−0.10	0.005
						NVT	123/200(61.5)	117/203(57.6)	0.04	0.478
					15 m	Overall	159/194(82.0)	181/205(88.3)	−0.06	0.090
						VT	24/194(12.4)	38/205(18.5)	−0.06	0.098
						NVT	136/194(70.1)	149/205(72.7)	−0.03	0.581
A.Roca*	2003/8	Gambia	PCV 7	All ages			**PCV^{1}**	**Control**		
			clustered		2–5 y[h]	Overall	79/90(87.8)	53/59(89.8)	−0.02	0.796

Table 5. Cont.

							Trial arm n/N (%)			
1st Author	Year	Country	Valency, Study design	Age PCV administered (w/m/y)	Age swabbed (w/m/y)	Serotypes	PCV[b+c]		RD	pvalue
			RCT			VT	18/90(20.0)	17/59(28.8)	−0.09	0.239
						NVT	61/90(67.6)	39/59(66.1)	0.02	0.860
					2–5 y[i]	Overall	23/30(76.7)	30/38(78.9)	−0.02	1.000
						VT	4/30(13.3)	9/38(23.7)	−0.10	0.360
						NVT	19/30(63. 6)	23/38(60.5)	0.03	1.000

w-weeks, m-months, y-years, RD- Risk difference- Risk in the PCV vaccinated group minus the risk in the control group calculated in Stata, PPV-Polyvalent polysaccharide vaccine, ns- not stated,
[a]children who received PCV 5 in an RCT and controls matched with age and place of residence who did not receive PCV, PCV[b+c] received b+c doses of PCV doses with
[b]for the primary series and
[c]for booster dose,
[d]includes vaccine associated serotypes.
[e]received PCV7 at 6, 10 and 14 weeks,
[f]received PCV7 at 6, 10 and 14 weeks or at 0, 10 and 14 weeks,
[g]Overall carriage for both groups,
[h]4–6 months after vaccination,
[i]22 months after vaccination;
*these three studies were not included in the meta-analysis (in these 3 studies, both groups received PCV).P-value obtained using Fisher's exact test.
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carriage in 9/11 studies, and in two studies carriage was more common among females [36,37]. One of these studies was conducted in South Africa among children 1–59 months with severe pneumonia, 67.3% of whom were HIV positive and another was in Nigeria in children 1–4 years who presented for regular check-up or immunisation, some of whom had a cough and a cold.

The five serotypes that were most common in this review are among the seven that cause most global IPD in children; PCV 10 and PCV 13 will cover at least 70% of the cases of IPD caused by these serotypes [38,39]. The other two serotypes, serotypes 1 and 5, are rarely isolated from carriage studies, although they are often associated with pneumococcal disease epidemics [40–42]. Serotypes also differ in their ability to cause invasive pneumococcal disease [43].

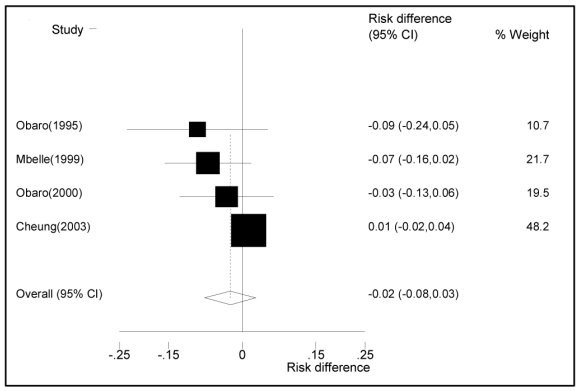
It has been suggested that the impact of PCV on disease can be determined by pneumococcal carriage studies because it is newly acquired serotypes that lead to disease [9]. In this review, studies that assessed the impact of PCV on carriage generally showed a decrease in carriage of VT and an increase in NVT serotypes, with no change in the overall prevalence of carriage. One study in this review, and one in native Indians have shown a gradual decrease in overall carriage following vaccination [24,35]. Continuous surveillance of circulating serotypes will be important as countries introduce PCV.

Nasopharyngeal swabs are more sensitive for *S.pneumoniae* than the oral swabs [44,45]. The prevalence of carriage is therefore likely to be underestimated in the four studies that used oral swabs. The different lab methods used might also have been responsible for some of the variability in the prevalence of carriage reported in this review. WHO recommends calcium alginate or Dacron polyester swabs since cotton swabs suppress the pneumococcus [23]. However, only half of the studies (50.9%) followed the WHO guidelines, and in 13 (22.4%) the type of swab was not stated.

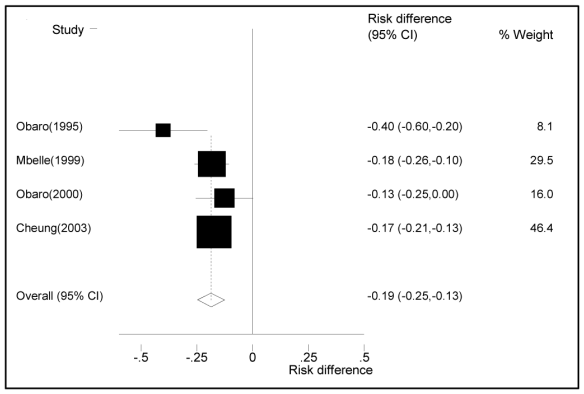
Another source of variation between studies is the prevalence of antibiotic use, since antibiotics might reduce carriage [46]. Some studies excluded those individuals who had taken antibiotics from their analysis. However, even when these individuals were excluded, often different periods were used to define prior use.

We have combined results from all available published studies irrespective of the study population (unpublished studies were not included in this review). Study participants were recruited from the community, day care centres, schools and outpatient clinics and hospital wards. Hospital patients may have higher carriage than the rest of the population, particularly if they were admitted for pneumonia. Generally, we expect selection bias to be less in studies conducted in the community compared with studies that use outpatient clinics. In this review, 57.9% of the studies were conducted in hospital/clinic settings and 35.1% of the studies in the community.

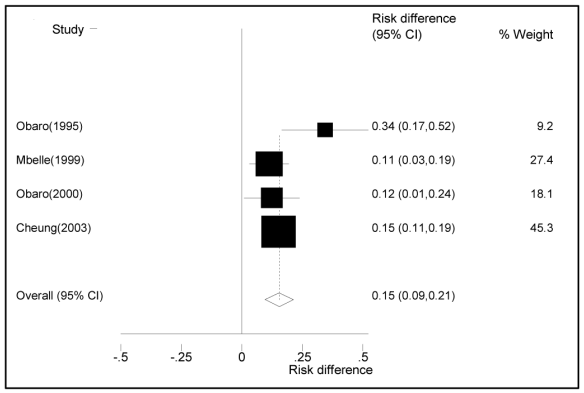
We have summarised available data on pneumococcal carriage in sub Saharan Africa. There remain unexplained differences in carriage within the region, and multi centre studies may provide reasons for some of the differences seen. Pneumococcal carriage studies can show indirect effects of PCV by showing changes in unvaccinated age groups and can supplement disease surveillance studies as PCV is introduced in the region.



B Carriage of vaccine type serotypes



C Carriage of non-vaccine type serotypes



The meta-analysis includes a subset of data from four individually randomized studies where children in the vaccinated arm received at least three doses of PCV and children in the control arm were not vaccinated. Only children less than 2 years were included in this analysis-PCV9; Mbelle(1999) carriage at 9 months (vaccine type serotypes includes vaccine associated serotypes), Obaro(1995) carriage at 24months-PCV 5, Obaro(2000) carriage at 9 months- PCV 9 and Cheung carriage at 9-15months- PCV 9

Figure 2. A comparison of pneumococcal carriage in vaccinated and unvaccinated children aged 9–24 months. A positive risk difference indicates higher prevalence in the vaccinated arm.
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Supporting Information

Figure S1 Pneumococcal carriage in children <5 years. (Forest plot).
(TIF)

Figure S2 Pneumococcal carriage in children 5–15 years. (Forest plot).
(TIF)

Figure S3 Pneumococcal carriage in adults >15 years. (Forest plot).
(TIF)

Checklist S1 Prisma checklist.
(DOC)

Appendix S1 Search terms.
(DOCX)

Protocol S1 Study Protocol.
(DOCX)

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Author Contributions

Conceived and designed the experiments: EU AH RA. Performed the experiments: EU AH. Analyzed the data: EU AH CB. Contributed reagents/materials/analysis tools: EU AH CB RA. Wrote the paper: EU CB RA AH.

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