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Effect of the 13-valent pneumococcal conjugate vaccine on pneumococcal carriage in rural Gambia 10 years after its introduction: A population-based cross-sectional study

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ABSTRACT

Background: Sub-Saharan Africa has a high burden of pneumococcal diseases. Pneumococcal carriage precedes invasive disease and transmission. The introduction of pneumococcal conjugate vaccines (PCVs) has significantly reduced global vaccine-type (VT) pneumococcal disease, but data on PCVs' long-term impact on VT serotypes in Africa are limited. We aimed to evaluate PCV13's long-term effect on pneumococcal carriage in rural Gambia.
Methods: From January to November 2022, we conducted a population-based, cross-sectional pneumococcal carriage survey in Central and Upper River Regions of The Gambia. We collected data on demographic characteristics, clinical history, risk factors, and PCV status. Nasopharyngeal swabs were taken from randomly selected household members of all ages. *Streptococcus pneumoniae* was isolated and serotyped using standard methods. We measured the prevalence of pneumococcal carriage by specific age groups, PCV13 vaccination status, and the proportions of different pneumococcal outcomes among carriers. We performed multivariable logistic regression to examine factors associated with VT carriage.
Results: Overall, 4087 participants were enrolled; the prevalence of pneumococcal carriage was 32.1% (95% CI: 29.34% – 35.03%). The estimated prevalence of PCV13 VT carriage was 6.4% (95% CI: 5.48% - 7.47%). Children aged 5–9 years had the highest VT carriage prevalence at 13.6% (95% CI: 10.34% - 17.56%). Among fully PCV-vaccinated children under 10, the odds of VT carriage in 5–9-year-olds were 1.60 times higher than in infants aged 0–11 months [AOR = 1.60, 95% CI:1.06–2.41]. The prevalence of VT carriage was similar among fully PCV-vaccinated and unvaccinated children under 10 years of age. Serotypes 19F, 3 and 6A were the most abundant VTs; 19F and 3 were the most prevalent among <5 and 5–14-year-old children, respectively.
Conclusions: Ten years after the introduction of PCV13 in the Gambia, residual VT carriage persists, particularly in age groups in whom direct protection from immunization in infancy has waned. A booster dose or catch-up vaccinations could aid control of VT circulation.

1. Introduction

Pneumococcal carriage is a required precursor for invasive pneumococcal disease (IPD) and pneumococcal transmission [1]. The introduction of pneumococcal conjugate vaccines (PCVs) into routine immunization programs has led to a substantial decrease in the overall incidence of IPD and IPD attributed to vaccine type (VT) serotypes globally [2]. For example, among children under 5 years old, the

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incidence of IPD declined by 80% (95% CI: 69% - 87%) in The Gambia [3], 68% (95% CI: 40% - 83%) in Kenya [4], 64% (95% CI: 59% - 68%) in the USA [5], and 56% (95% CI: 53% - 47%) in the UK [6]. The impact of PCVs can be measured directly through the reduction in disease endpoints or indirectly through changes in nasopharyngeal (NP) carriage of VT serotypes in both vaccinated and unvaccinated individuals [7]. A reduction in the carriage of VT serotypes among vaccinated individuals can reduce transmission in the population, resulting in indirect or herd protection. As PCV programs mature, community-level indirect protection becomes a more important component of the overall programmatic impact of PCV than individual-level direct protection [8].

The impact of PCV on IPD and NP carriage as a combined measure of direct and herd effects in different age groups has been well-established in developed countries [9–12]. Although Sub-Saharan Africa has one of the highest burdens of pneumococcal disease [13], very few studies evaluating the impact of PCV on IPD have been conducted in these countries [4,14–16]. Resource challenges and the high cost of establishing long-term IPD surveillance in low- and middle-income countries (LMICs), especially in sub-Saharan Africa, have been cited as a major difficulty in establishing and sustaining pneumococcal disease surveillance systems [17–19]. Pneumococcal carriage studies have been used as an alternative method to evaluate the impact of PCVs and monitor pneumococcal serotypes in LMICs [20]. The decrease in VT carriage following the introduction of a PCV has been associated with the decline in vaccine-type disease, as carriage serves as a precursor to disease [20].

The Gambia was among the early adopters of a PCV in Africa. It introduced PCV7 into its routine Essential Program on Immunization (EPI) using a three-dose schedule without a booster dose (i.e. a '3p + 0' schedule) in August 2009, which was subsequently replaced with PCV13 in May 2011. Vaccination coverage for PCV in The Gambia is high, with estimates from the World Health Organization (WHO) and the United Nations Children's Fund (UNICEF) in 2018 indicating that the rates are 98% for the first dose of PCV and 93% for the third dose [21]. A recent report on findings from carriage surveys conducted in the study setting in 2009, 2015, and 2017 indicates that although VT carriage has substantially decreased, especially in young children, residual VT carriage persists. Compared to the baseline carriage in 2009, the VT carriage rates in 2017 declined from 42.6% to 17.5% among those aged 0–4 years, from 16.6% to 15.8% for ages 5–14 years, increased from 6.4% to 7.1% for individuals aged 15–44 years, and remained at 4.5% for both 2009 and 2017 for those aged ≥45 years [22]. However, limited data exist on the impact of PCV13 on VT carriage after ten years of routine use in a high-transmission setting.

Therefore, The Gambia, with its long history of PCV13 use, high PCV vaccination coverage, and over a decade of robust IPD surveillance, along with several studies on pneumococcal carriage [22], offers a suitable setting to evaluate the long-term impact of PCV on pneumococcal carriage in a high-transmission setting. We assessed the impact of PCV13 on pneumococcal carriage in rural Gambia a decade after its routine implementation.

2. Methods

Study setting and population.

The Gambia is a small country located in West Africa, home to around 2.4 million residents. The Central River Region (CRR) and Upper River Region (URR) are situated in the eastern part of the country. The Medical Research Unit The Gambia at the London School of Hygiene & Tropical Medicine manages the Basse and Fuladu West Health and Demographic Surveillance Systems (BHDSS and FWHDSS) in the URR and CRR, respectively. In 2022, the population of BHDSS was 206,429, distributed across 224 villages, and the FWHDSS population was 116,299, distributed across 217 villages. The BHDSS population is predominantly young, with approximately two-thirds of individuals under 25 and only 4% over 60 years old. Children aged under 5 years make up about 15% of the total population. The population consists of a higher number of females (54%) than males, with those aged 5–9 years being the most populous age group (Fig. 1). The age structure of the FWHDSS population is similar to that of the BHDSS. Approximately 8000 births occur each year in the combined BHDSS and FWHDSS populations. The primary ethno-linguistic groups in the region are the Fula and Serahule. The area features Guinea Savannah vegetation and experiences two distinct seasons: a hot, dry season from November to May and a rainy season from June to October. Groups of families typically reside together in a living arrangement known as a compound. On average, compounds consist of 38 individuals and are headed by a single adult male or female [23]. The coverage of three doses of PCV by 12 months of age in the study area is estimated to be 92% [24].

2.1. Study design

This study was nested within the Pneumococcal Vaccine Schedules (PVS) trial, which is ongoing in CRR and URR. PVS (trial number: ISRCTN15056916||http://www.isrctn.org/. registered on 15 November 2018) is a cluster-randomized trial testing the non-inferiority of an alternative two-dose PCV delivery schedule to the routine three-dose delivery EPI schedule. From January to November 2022, three years after PVS started, we conducted a population-based, cross-sectional pneumococcal carriage survey in CRR and URR. The protocol for the PVS trial has been published elsewhere [24].

2.2. Participant selection and sampling

A sampling frame consisting of residents of all ages was obtained from the BHDSS and FWHDSS. A Demographic Surveillance Systems (DSS) resident was defined as someone who had lived in the area covered by the DSS for over four months, as verified by DSS records or a household visit with confirmation from the household or compound head. For infants, residency was defined as being born to or cared for by a parent or guardian who had been resident for more than four months or intended to be resident for that duration. Residency was confirmed by DSS records or a household visit with input from the household or compound head. We used the DSS to determine population sizes for clusters, villages, compounds, and households and as a source for identifying members of a household. A household was defined as a group of individuals living together (related or unrelated) who share the same cooking pot or meal. The BHDSS and FWHDSS cover 68 geographic clusters and 441 villages. We utilized a three-stage sampling method, using probability proportional to size, to randomly select two villages from each of the 68 clusters. We then randomly selected three compounds from each village and ten individuals from each compound. A cluster consists of a group of villages that share the same Reproductive and Child Health (RCH) clinic. A compound comprised multiple different households. A household member includes others living within the same compound who share or eat from the same cooking pot. Within each compound, one household was randomly chosen, and within that household, ten household members were selected according to the stratified age-structure ratio 2:2:2:1:1:1:1 (0–11 months, 12–23 months, 24–59 months, 5–9 years, 10–14 years, 15–44 years, and ≥ 45 years). If a participant from a specific age group was unavailable, or if the needed proportion was not met in the selected household, the required individual was chosen from another randomly selected household within the compound. This process was repeated until the required number of participants was reached in the chosen compound.

2.3. Data collection

Field workers were trained for two weeks using a standardized pneumococcal carriage questionnaire (Additional files 1&2). At the outset, community sensitization meetings were held across 68 clusters, where trained study personnel, proficient in the local languages, shared details about the study and addressed any inquiries. Subsequently,

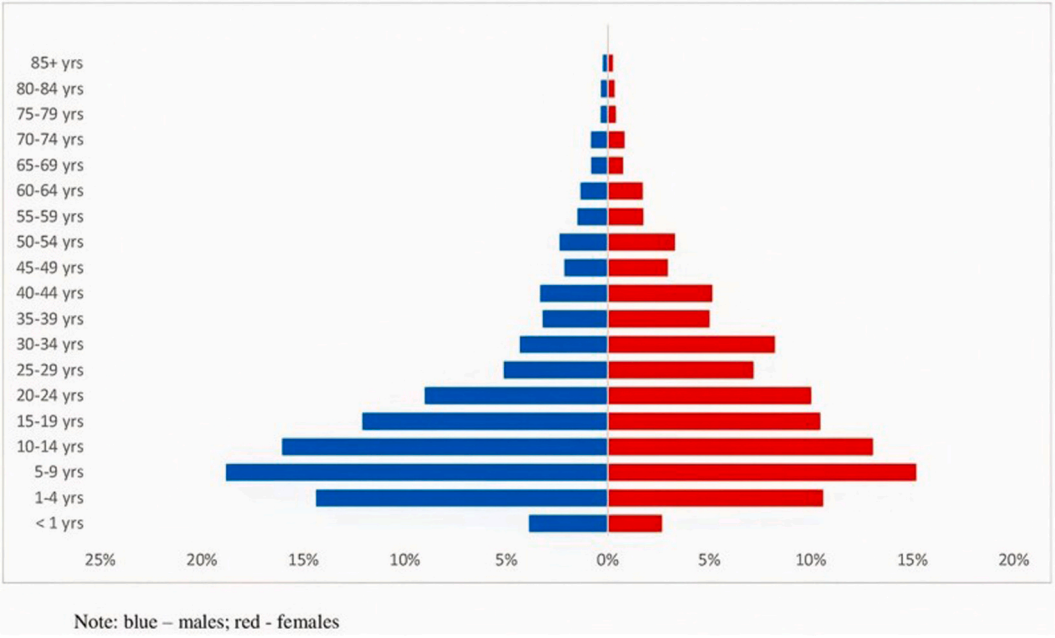

Fig. 1. Age and sex distribution of the Basse Health and Demographic Surveillance System, December 2020. Source: [25].

trained field workers visited each randomly selected household, outlined the study to prospective participants, and obtained written informed consent for their participation in the study. Parents or guardians from the community provided consent for themselves and on behalf of child participants (age <18 years). Child participants aged 12–17 years also provided assent. We recorded demographic information, PCV vaccination status, and completed a short questionnaire on risk factors for carriage. Demographic variables collected included age, sex, ethnicity, and household composition. Variables assessed for pneumococcal risk factors included bed sharing with a child, cooking methods, cooking locations, exposure to household cigarette smoke, recent symptoms of upper respiratory infections, and antibiotic use within two weeks prior to sampling. Demographic data were obtained and verified from the DSS database. We determined the PCV status of every child in the household. Vaccination status was verified from records in the infant welfare card (IWC). If a parent reported their child as PCV vaccinated in the absence of an IWC, standardized questions such as age, site and route of vaccination were asked to ascertain the veracity of the claim. A further check was made through our Real-time Vaccine data collection System (RVS). The RVS is an electronic vaccination recording system which has been in use since 2011 to collect vaccination data at Reproductive and Child Health clinics in real-time in the BHDSS and FWHDSS [26]. A person was deemed PCV13 vaccinated if the individual had received at least two doses of PCV13 before data collection. The rationale for this definition was based on the number of doses received for immune protection rather than the specific age at which they were administered, indicating a broader approach to assessing vaccination coverage. Data were collected electronically using a customized application.

2.4. Nasopharyngeal sample collection, transport, and storage

A single nasopharyngeal specimen per participant was collected using nylon-tipped flexible nasopharyngeal flocked swabs following WHO guidelines [27]. The swabs were immediately inserted into a vial of skim-milk tryptone glucose glycerol (STGG) transport medium and then placed in a specimen bag. The packaged sample was placed between two inner layers of foam in a specimen cold box, transported within 8 h of collection at 2°C - 8°C, and stored at −80°C at the Basse Medical Research Centre Laboratory.

2.5. Laboratory analysis

S. pneumoniae was identified by its distinct alpha hemolytic colony morphology on blood agar, susceptibility to optochin and bile solubility. Serotyping was performed using a WHO-standardized isolate latex agglutination serotyping method, consistent with the protocol described by Satzke et al. [27]. A positive reaction was indicated by agglutination. A positive serum factor reaction was interpreted using the key to pneumococcal factor sera. We utilized the Quellung method [28] to confirm serotyping when the results of the latex agglutination were inconclusive. Pneumococcal isolates that did not react with any of the pooled antisera were deemed non-typeable (NT). VT serotypes were defined as serotypes included in PCV13 (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F), and VT carriage was defined as the detection of pneumococci serotypes included in PCV13. Non-VT (NVT) was defined as the detection of pneumococci serotypes not included in PCV13. NVT pneumococci included non-encapsulated pneumococci. Nasopharyngeal pneumococcal carriage of any type (any *S. pneumoniae*) was defined as carriage of any pneumococcus, including NTs. In instances where multiple pneumococcal serotypes were detected, the presence of VT pneumococci did not preclude the reporting and inclusion of NVT in the analysis. All laboratory work was performed at MRC Basse Laboratories. A detailed description of the laboratory methods is provided in the Supplemental Material Section A.

2.6. Statistical power and sample size

The carriage survey was designed to estimate population-level pneumococcal carriage prevalence in addition to determining the difference in age-specific VT carriage prevalence, especially between age groups 5–14 years and <5-year-olds. A sample size of 4080 from 68 clusters of 60 individuals per cluster in a ratio of 36:12:12 (<5 years, 5–14 years, ≥15 years) was chosen to provide >90% power to detect an absolute PCV13 VT carriage difference of at least 6% between age group 5–14 years and <5-year-olds. The 6% absolute difference was selected based on findings from a previous study in The Gambia [29].

2.7. Statistical considerations

A descriptive analysis of background characteristics and risk factors

for carriage was performed. Age-specific probability weights to account for oversampling in the younger age group at the design stage were applied to calculate population-level estimates. We used design weights to account for clustering, and the analyses were conducted using the svyset commands in STATA. The age-stratified prevalence of VT *S. pneumoniae* was calculated with 95% confidence intervals (CI). The overall VT carriage prevalence was determined among vaccinated and unvaccinated groups. A similar analysis was also performed for non-VT serotypes and any pneumococcal isolates. Both the overall and age-specific prevalence of specific PCV13 VT serotypes were measured to determine if (a) specific serotypes are potentially acting as reservoirs and (b) there are age-associated differences in serotype carriage. A sensitivity analysis was performed to determine any effect of the number of PCV doses received on VT pneumococcal carriage. We performed univariable and multivariable logistic regression analysis to examine risk factors associated with overall pneumococcal carriage and VT carriage. Variables with *p*-values <0.1 in the univariable logistic regression model were included in the multivariable model. Age and sex were included in both analyses as a priori variables to account for their potential confounding effect. Age was treated as a categorical variable using predefined age categories based on established age-related differences in pneumococcal carriage. The 0–11 age group was chosen as the reference group to enhance interpretation and comparison with younger and older children.

2.8. Ethical approval

The study was approved by the Gambia Government/MRC Joint Ethics Committee (ref: 28705) and by the LSHTM Ethics Committee (ref: 28705). Written informed consent to participate was obtained from all enrolled participants.

3. Results

3.1. Characteristics of the study participants

Overall, 4087 participants from 1594 households residing in 1391 compounds across 441 villages were enrolled in the pneumococcal carriage survey. Only 51/4138 (1.2%) declined to consent to participate. Nasopharyngeal swabs (NPS) were collected from all enrolled participants. There were missing values for the following variables: NPS culture results (1), cooking method (27), cooking location (13), and experiencing a runny nose in the previous two weeks prior to the survey (12). We validated 95% (2319/2455) and 93% (2669/2862) of the PCV vaccination status of child participants aged <5 years and <10 years, respectively. More than half (60%) of the participants were aged less than 5 years. There were slightly more females (52%) than males, and 55% of the samples were collected during the rainy season. About half of the households had 20–49 members, and the majority (99%) used firewood for cooking. Sixty-nine percent (69%) of participants reported experiencing respiratory symptoms, and 26% reported antibiotic use in the two weeks prior to the survey (Table 1).

3.2. Pneumococcal carriage

The overall estimated carriage prevalence of any pneumococci was 32.1% (95% CI: 29.34% - 35.03%). Carriage decreased with age, and those aged 0–11 months had the highest estimated prevalence of any pneumococcal carriage (69%). Non-typeable pneumococcal isolates accounted for <2% of all pneumococci. The estimated prevalence of NVT carriage was 24.1%, and prevalence decreased with age. Among children under 10 years old, the prevalence of any pneumococcal carriage was higher among those who had received fewer than two doses of PCV [72.9% (95% CI: 66.39% - 78.68%)] compared to those who had received at least two doses of PCV [52.1% (95% CI: 48.59% - 55.70%)] (Table 2).

Table 1
Socio-demographic characteristics of participants with overall pneumococcal nasopharyngeal carriage in a cross-sectional carriage survey, BHDSS and FWHDSS (combined) conducted in 2022 ($N = 4087$).

Characteristics		N = 4087 n (%)	#Carriage prevalence n (%)	p-value
Age in months (m) or years (yrs)				
	0–11 m	820 (20.0)	566 (69.0)	<0.01
	12–23 m	817 (20.0)	533 (65.2)	
	24–59 m	818 (20.0)	462 (56.5)	
	5–9 yrs	407 (10.0)	156 (38.4)	
	10–14 yrs	408 (10.0)	130 (31.9)	
	15–44 yrs	409 (10.0)	67 (16.4)	
	≥ 45 yrs	408 (10.0)	48 (11.8)	
Sex				
	Male	1966 (48.1)	1022 (38.8)	<0.01
	Female	2121 (51.9)	940 (27.9)	
Ethnicity				
	Fula	2434 (59.6)	1097 (30.0)	0.01
	Serahule	611 (15.0)	373 (42.5)	
	Mandinka	762 (18.6)	379 (34.7)	
	Wolof	256 (6.2)	104 (23.7)	
	Others	24 (0.6)	9 (30.8)	
Season				
	Dry	1840 (45.0)	887 (28.8)	<0.01
	Rainy	2247 (55.0)	1075 (37.2)	
[a]Doses of PCV in <5 year olds				
	0	51 (2.2)	27 (55.3)	
	1	279 (12.0)	213 (76.8)	<0.01
	2	584 (25.2)	367 (60.8)	
	3	1405 (60.6)	869 (58.8)	
[b]Doses of PCV in <10 year olds				
	0	51 (1.9)	27 (55.2)	
	1	281 (10.5)	214 (75.9)	<0.01
	2	599 (22.4)	374 (59.6)	
	3	1738 (65.1)	995 (50.6)	
Household size				
	0–19	1229 (30.1)	517 (29.3)	0.16
	20–49	2039 (49.9)	1006 (33.2)	
	≥ 50	819 (20.0)	439 (34.4)	
Bed-sharing with a child aged <10 yrs				
	Yes	1920 (47.0)	924 (31.6)	0.54
	No	2167 (53.0)	1038 (32.8)	
*Cooking method				
	Firewood	4029 (98.6)	1934 (32.1)	0.07

(continued on next page)

Table 1 (*continued*)

Characteristics		N = 4087 n (%)	#Carriage prevalence n (%)	p-value
Age in months (m) or years (yrs)				
	Charcoal/ Other	31 (0.8)	9 (19.4)	
*Cooking location				
	Inside	2600 (63.6)	1218 (29.7)	<0.01
	Outside	124 (3.0)	61 (30.7)	
	Inside & outside	1350 (33.0)	673 (36.4)	
Smoker in the household				
	Yes	1538 (37.6)	719 (32.2)	0.97
	No	2549 (62.4)	1243 (32.1)	
*Has had a runny nose within the past two weeks				
	Yes	2816 (68.1)	1508 (38.1)	<0.01
	No	1259 (30.9)	445 (23.2)	
Took antibiotics in the last two weeks				
	Yes	1069 (26.2)	571 (34.0)	0.05
	No	3018 (73.8)	1391 (31.4)	

Estimates are the weighted prevalence and proportions, and *p*-values are calculated using a chi-square test adjusted for village-level clustering.
NVT included non-encapsulated pneumococci.
[a] We could not determine the PCV vaccine status of 5% (2319/2455) of children aged <5 years.
[b] We could not determine the PCV vaccine status of 7% (2669/2862) of children aged <10 years.
[*] Missing values - cooking method = 27/4087 (0.7%), cooking location = 13/4087 (0.3%), Has had a runny nose within the past two weeks = 12/4087 (0.3%), NPS culture results = 1.

3.3. Age-stratified prevalence of VT carriage

Overall, the prevalence of VT carriage in all age groups was 6.4% (95% CI: 5.48% - 7.47%). Those aged 5–9 years had the highest prevalence of VT carriage [13.6% (95% CI: 10.34% - 17.56%)], followed by those aged 0–11 months [10.5% (95% CI: 8.53% - 12.83%)]. Vaccine-type prevalence was very low among those aged ≥15 years, ranging from 0.83% to 4.69%. The VT carriage prevalence was similar in the 5–14 age group [11.1% (95% CI: 8.93 % – 13.68%)] and in those aged 0–4 [10.1 % (95% CI: 8.71% – 11.72%)]. Among pneumococcal carriers, the prevalence of VT carriage was notably higher (almost double) in the 5–14-year-old group, at 31.5% (95% CI: 26.37% - 37.15%) compared to those aged 0–4 years with a prevalence of 16.8% (95% CI: 14.61% - 19.22%). (Table 2).

3.4. PCV13 vaccination status and VT carriage

Among the enrolled participants aged <10 years, 87% had received at least 2 doses of PCV (Table 1). We found strong evidence that the prevalence of VT carriage increases with age among PCV13-vaccinated children (defined as those who received at least two doses of PCV) under the age of 10 years. Among these PCV13-vaccinated children, the prevalence of VT carriage was 14.1% in those aged 5 to 9 years, compared to 9.3% in infants aged 0 to 11 months (*p*-value = 0.02, Table 3). Among children under 10 years old, VT carriage prevalence was slightly higher in those who received fewer than two doses of the

Table 2
Pneumococcal carriage prevalence by specific age groups in a cross-sectional carriage survey, BHDSS and FWHDSS (combined), conducted in 2022 (*N* = 4087).

Characteristic		Serotype (n)	[a]Population-level Prevalence (%) (95 % CI)	[a]Proportion among carriers (%) (95% CI)
Overall				
		VT (350)	6.4 (5.48–7.47)	20.0 (17.48–22.65)
		NVT (1544)	24.1 (21.87–26.39)	74.9 (71.87–77.73)
		NT (68)	1.7 (1.15–2.36)	5.1 (3.67–7.16)
		Any Spn (1962)	32.1 (29.34–35.03)	
Age(m, yrs)				
	0–11 m			
		VT (86)	10.5 (8.53–12.83)	15.2 (12.42–18.46)
		NVT (466)	56.8 (52.54–61.02)	82.3 (79.02–85.22)
		NT (14)	1.7 (0.97–2.97)	2.5 (1.42–4.28)
		Any Spn (566)	69.0 (64.51–73.21)	
	12–23 m			
		VT (72)	8.8 (6.98–11.07)	13.6 (10.75–16.84)
		NVT (449)	55.0 (50.54–59.23)	84.2 (80.74–87.20)
		NT (12)	1.5 (0.85–2.53)	2.3 (1.30–3.87)
		Any Spn (533)	65.2 (60.69–69.53)	
	24–59 m			
		VT (85)	10.4 (8.49–12.65)	18.4 (15.19–22.10)
		NVT (361)	44.1 (40.15–48.19)	78.1 (74.34–81.51)
		NT (16)	1.9 (1.16–3.29)	3.5 (2.07–5.73)
		Any Spn (462)	56.5 (51.98–60.87)	
	#0–4 yrs			
		VT (243)	10.1 (8.71–11.72)	16.8 (14.61–19.22)
		NVT (1276)	48.3 (45.03–51.68)	80.2 (77.72–82.44)
		NT (42)	1.8 (1.22–2.69)	3.0 (2.06–4.43)
		Any Spn (1561)	60.3 (56.49–63.97)	
	5–9 yrs			
		VT (55)	13.6 (10.34–17.56)	35.3 (27.78–43.53)
		NVT (94)	23.1 (19.11–27.76)	60.3 (51.68–68.24)
		NT (7)	1.7 (0.83–3.53)	4.4 (2.21–9.01)
		Any Spn (156)	38.4 (33.52–43.57)	
	10–14 yrs			
		VT (35)	8.6 (6.17–11.82)	26.9 (20.10–35.04)
		NVT (84)	20.6 (16.72–24.09)	64.6 (56.32–72.11)
		NT (11)	2.7 (1.51–4.77)	8.5 (4.73–14.68)
		Any Spn (130)	31.9 (27.01–37.14)	
	#5–14 yrs			
		VT (90)	11.1 (8.93–13.68)	31.5 (26.37–37.15)
		NVT (178)	21. 9 (18.87–25.22)	62.2 (56.05–68.01)
		NT (18)	2.2 (1.35–3.58)	6.3 (3.84–10.08)
		Any Spn (286)	35.2 (31.31–39.23)	
	15–44 yrs			
		VT (7)	1.7 (0.83–3.51)	10.4 (5.21–19.86)

(*continued on next page*)

Table 2 (*continued*)

Characteristic		Serotype (n)	[a]Population-level Prevalence (%) (95 % CI)	[a]Proportion among carriers (%) (95% CI)
		NVT (54)	13.2 (9.99–17.25)	80.6 (70.72–87.72)
		NT (6)	1.5 (0.66–3.21)	9.0 (4.22–18.00)
		Any Spn (67)	16.4 (12.56–21.08)	
	≥ 45 yrs			
		VT (10)	2.5 (1.27–4.69)	20.8 (11.16–35.54)
		NVT (36)	8.8 (6.44–11.98)	75.0 (60.17–85.63)
		NT (2)	0.5 (0.12–1.94)	4.2 (1.02–15.45)
		Any Spn (48)	11.8 (8.99–15.25)	

Missing value - NPS culture results = 1.
VT; PCV13 vaccine-type serotypes.
NVT: Non-PCV13 serotypes.
NT: Non-typeable pneumococci.
Any Spn: Any pneumococcal serotype, including non-typeable.
NVT included non-encapsulated pneumococci.
[a] Estimates are the weighted proportions and prevalence with 95 % CIs adjusted for clustering at the village level.
[#] Aggregated estimates in those aged <5 years and those aged 5–14 years.

Table 3
Prevalence of PCV13 vaccine-serotype carriage among PCV-vaccinated children aged <10 years in a cross-sectional carriage survey, BHDSS and FWHDSS (combined) conducted in 2022 ($N = 2337$).

Characteristics		**[a]VT Carriage prevalence %**	**95 % CI**	***P* value**
Age in months (m) or years (yrs)				
	0–11 m	9.3	6.92–12.33	0.02
	12–23 m	9.0	7.12–11.33	
	24–59 m	10.3	8.34–12.65	
	5–9 yrs	14.1	10.63–18.52	

P-value was calculated using a chi-square test adjusted for village-level clustering.
[a] Estimates are the weighted prevalence with 95 % CIs adjusted for village-level clustering.

PCV, at 13.4% (95% CI: 9.74% - 18.18%) compared to PCV13-vaccinated children at 11.3% (95% CI: 9.59% - 13.36%). The confidence intervals overlapped between the two groups (Supplementary Table ST5). In the under-five age group, the prevalence of VT carriage did not differ substantially between PCV-vaccinated children at 9.9% (95% CI: 8.40% – 11.67%) and unvaccinated children at 13.8% (95% CI: 10.06% – 18.72%) with overlapping confidence intervals (ST6 of the Supplemental Material). Among the PCV-vaccinated children aged <10 years, the number of doses did not affect the prevalence of VT carriage. Among those vaccinated with two doses ($N = 599$), the prevalence of VT carriage was 12.7% (95% CI: 9.79% - 16.25%), compared to 11.0% (95% CI: 9.08% - 13.41%) for those who received three doses ($n = 1737$), with confidence intervals that overlapped (see ST5 of the Supplemental Material). Similarly, among PCV-vaccinated children under 5 years old, there was no substantial difference in prevalence of VT carriage between those who received two doses at 12.6% (95% CI: 9.63% – 16.33%) and three doses at 9.0% (95% CI: 7.31% – 11.15%) with overlapping confidence intervals (ST6 of the Supplemental Material).

3.5. Age-specific prevalence of PCV13 VT pneumococcal carriage

Serotypes 19F (1.7%), 3 (1.7%), and 6A (1.0%) were the most abundant vaccine-type (VT) serotypes, together making up nearly two-thirds of the estimated VT population serotypes. 19F, 3, and 6A proportions among all PCV13 VT carriers were 30.2%, 19.2%, and 10.7%, respectively. Serotype 7F was the only VT that was not isolated from any sample. While serotype 19F was the most prevalent serotype among those under 5 years of age, serotype 3 was the most dominant in the 5 to 14-year-old group. Among individuals aged 15 years and older, no cases of carriage were found for serotypes 1, 4, 5, 18C, and 19A (Fig. 2 and supplementary Table ST2).

3.6. Factors associated with VT and overall pneumococcal carriage

Among PCV-vaccinated children under 10 years, an increase in age and the dry season were associated with higher odds of VT pneumococci carriage (Table 4). After adjusting for age, sex, and other covariates, the odds of VT pneumococcal carriage were 1.60 times greater among PCV-vaccinated children aged 5–9 years compared to PCV-vaccinated infants aged 0–11 months (AOR = 1.60, 95% CI: 1.06–2.41). In comparison to the rainy season, the odds of VT pneumococci carriage were 1.97 times higher during the dry season (AOR = 1.97, 95% CI: 1.34–2.89). Increasing age was associated with lower odds of VT carriage in all age groups. Conversely, the dry season (AOR = 1.87, 95% CI: 1.30–2.69) and co-sleeping with a child under 10 years (AOR = 1.62, 95% CI: 1.20–2.18) were linked to higher odds of VT carriage (Table ST8 in the Supplemental Material). Increasing age and recent antibiotic use (AOR = 0.60, 95% CI: 0.49–0.81) were associated with lower odds of overall pneumococcal carriage. However, the dry season (AOR = 2.26, 95% CI: 1.64–3.11), using firewood for cooking (AOR = 2.06, 95% CI: 1.11–3.86), experiencing a runny nose within the last two weeks prior to sampling (AOR = 1.63, 95% CI: 1.29–2.05), and living in a household that utilizes both indoor and outdoor cooking methods (AOR = 1.34, 95% CI: 1.09–1.66) were associated with a higher risk of overall pneumococcal colonization (Supplementary Table ST9).

4. Discussion

Ten years after the introduction of PCV13 in the Gambia, substantial reductions in VT carriage have been observed in children, with significant indirect effects in unvaccinated adults. School-aged children, particularly those aged 5–9 years, were found to be key reservoirs of VT carriage. We found strong evidence that VT carriage prevalence increases with age among PCV-vaccinated children under 10 years. The odds of VT pneumococcal carriage were 1.60 times higher among PCV-vaccinated children aged 5–9 years compared to those aged 0–11 months. This may suggest that despite the high coverage of PCV vaccination in this setting, the protection offered by PCV has waned in this age group. This finding is consistent with a report from a study in Australia, which observed a substantial waning of protection from PCV when children entered the toddler stage [30]. Studies conducted in high-transmission settings in Blantyre, Malawi, and Kilifi, Kenya, have reported a decline in PCV-induced antibody levels within the first year of life among children under five years of age [31,32]. Notably, Kenya, Malawi, and The Gambia implement 3p + 0 PCV schedules (i.e., three doses of PCV administered in early childhood without a booster). The absence of a booster dose could potentially result in a rapid decline in serological immunity [33]. Furthermore, the high prevalence of VT carriage in 5–9-year-olds may reflect the social contact behaviours of school-aged children. The positive correlation between close physical contacts, such as those that occur in subpopulations, and pneumococcal infections is well documented [34–37]. Children aged 5–9 years are very active and often mix a lot with others in their age group as well as with different age groups [23]. This suggests a significant risk for the transmission of respiratory pathogens such as *S. pneumoniae*, which are spread through close contact. Le Polain de Waroux et al. found that compared to non-carriers, adults who had pneumococcal carriage had more than double daily close contact with young children [35]. The

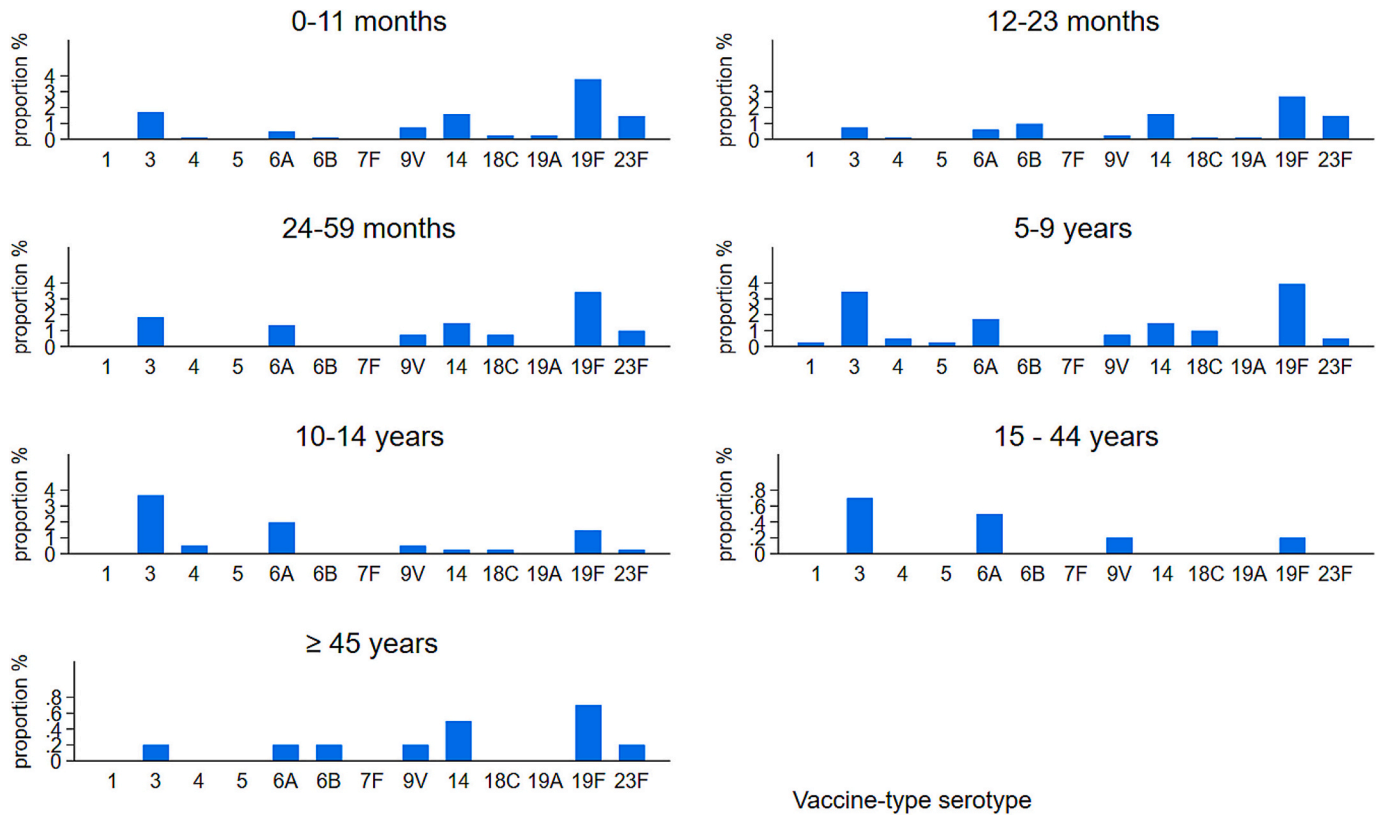

Fig. 2. Age-specific prevalence of vaccine-type pneumococci.

argument for including a booster dose in the PCV schedule for high-transmission settings to control pneumococcal transmission is compelling.

In the 0–4 age group, the prevalence of VT carriage decreased from 42.6% in 2009 to 10.1% in 2022, signifying a relative reduction of 76% and an absolute reduction of approximately 33%. This represents a further decrease from the 62% relative reduction observed in 2017 [22]. Similarly, comparing 2009 to 2022, there was a 33% (16.6% vs 11.1%), 73% (6.4% vs 1.7%), and 44% (4.5% vs 2.5%) relative reduction in VT carriage prevalence among those aged 5–14, 15–44, and 45 and older, respectively [22]. Our findings of a 76% reduction in VT carriage among 0–4-year-olds closely align with the 74% and over 75% reductions observed in Kilifi, Kenya [38], and rural western Gambia [29] following 6 and 10 years of PCV pressure in these settings, respectively. The substantial indirect effect on VT carriage in adults, particularly in the 15–44 age group, is comparable to that observed in South Africa [39], Kenya [38], and previously in The Gambia [22,29]. This indicates that overall protection largely appears to be driven by herd effect in this setting.

Although the overall estimated VT carriage prevalence of 6.4% was lower than the 11.0% noted in 2017 in this setting [22] and the 10.2% recorded in 2016 in rural western Gambia [29], it remains higher than those observed at various time points less than five years after vaccination in the UK (0.7%) [40], Belgium (5.4%) [41] France (6.5%) [42] and the USA (4.8%) [43]. However, it is important to note that the countries mentioned above all have low transmission rates. While a recent report indicates a near elimination of VT IPD among children under 5 years in the current study setting [3], the residual VT carriage observed in our study characterizes a potential, persistent reservoir population of vaccine-serotype pneumococci, suggesting ongoing VT transmission. Serotype 19F (30.2%), 3 (19.2%), and 6A (10.7%) were the predominant serotypes of PCV13 vaccine-type (VT) identified, collectively representing nearly two-thirds of all VT serotypes. Serotype 19F continues to be the residual VT pneumococci in children aged 0–4 years, while serotype 3 remains prevalent in those aged 5–14 years, consistent with previous estimates in both this setting [22] and rural western Gambia [29]. Serotype 19F is recognized for its prolonged carriage duration in infants, potentially increasing its transmission risk [44]. It has also been linked to antimicrobial resistance, particularly to penicillin and macrolides [45]. Infants have shown carrier-induced hyporesponsiveness to PCV13 against serotype 19F [46]. A recent study conducted in South Africa indicated that the 1p + 1 schedule was associated with nearly a threefold reduction in the prevalence of 19F colonization at 15 months of age compared to the 2p + 1 schedule [47]. Although a previous report has shown that serotype 3 has a short duration of carriage (approximately 10 days), it also has a high rate of acquisition [48]. IPD caused by serotype 3 has been associated with high mortality and long-term complications [49–51]. We detected serotype 1 among participants aged 5–9 years. Serotype 1, similar to serotype 3, exhibits high invasiveness and is a significant cause of IPD globally, particularly in LMICs [52,53]. It is rarely detected in carriage, even in settings with high pneumococcal prevalence [54], and has often been associated with outbreaks and epidemics, especially in confined communities and particularly in vulnerable populations [52,55]. The persistence of serotype 3 carriage and the detection of serotype 1 in 5–14-year-olds, identified as the primary reservoir of pneumococcal carriage in this population, is a public health concern.

This finding reinforces the importance of catch-up vaccination for school-aged children and supports the inclusion of booster doses in PCV schedules in rural Gambia.

Among children aged under 5 years and up to 10 years, we found no evidence of a difference in VT carriage between PCV-vaccinated and unvaccinated children. This indicates that after 12 years of PCV pressure in rural Gambia, significant herd protection against VT carriage has developed in unvaccinated individuals. This observation is consistent with findings in Lao PDR [56], Kenya [38], and South Africa [57]. This finding offers significant local evidence of herd protection and supports the consideration of a reduced-dose PCV schedule for young children.

Table 4
Risk factors associated with PCV13 VT pneumococci carriage among PCV-vaccinated children[#] aged <10 years, obtained from a multivariable logistics regression model (N = 2337).

Characteristics		Crude Odds Ratio (95 % CI)	P-value	[a]Adjusted Odds Ratio (95 %CI)	p-value
Age in months (m) or years (yrs)					
	0–11 m	1 (Reference)		1 (Reference)	
	12–23 m	0.97 (0.65–1.43)	0.87	0.97 (0.65–1.44)	0.87
	24–59 m	1.12 (0.78–1.60)	0.52	1.13 (0.79–1.63)	0.50
	5–9 yrs	1.61 (1.07–2.42)	0.02	1.60 (1.06–2.41)	**0.02**
Sex					
	Female	1 (Reference)		1 (Reference)	
	Male	0.93 (0.65–1.34)	0.72	0.93 (0.64–1.34)	0.71
Ethnicity					
	Fula	3.88 (0.46–32.68)			
	Serahule	5.62 (0.59–52.90)			
	Mandinka	6.05 (0.62–58.05)	0.18		
	Wolof	3.74 (0.36–38.50)			
	Others	1 (Reference)			
Season					
	Rainy	1 (Reference)		1 (Reference)	
	Dry	1.98 (1.35–2.89)	<0.01	1.97 (1.34–2.89)	**<0.01**
Household size					
	0–19	1 (Reference)			
	20–49	0.79 (0.50–1.17)	0.64		
	≥ 50	0.93 (0.58–1.51)			
Cooking method					
	Charcoal/ Other	1 (Reference)			
	Firewood	4.52 (0.55–36.96)	0.16		
Cooking location					
	Inside	1 (Reference)			
	Outside	1.02 (0.40–2.55)			
	Inside & outside	1.09 (0.74–1.63)	0.65		
Smoker in the household					
	No	1 (Reference)			
	Yes	1.03 (0.74–1.44)	0.86		
Has had a runny nose in the last two weeks					
	No	1 (Reference)			
	Yes	1.12 (0.72–1.74)	0.62		
Took antibiotics in the last two weeks					
	No	1 (Reference)			
	Yes	0.76 (0.51–1.15)	0.19		

95 % confidence intervals adjusted for village-level clustering.
- PCV-vaccinated children - Children who have been vaccinated with ≥2 doses of PCV13.
[a] Adjusted odds ratio: adjusted for age, sex, and season.

However, despite the high coverage of PCV vaccinations in the study setting, the residual carriage in older children indicates that implementing catch-up campaigns for this age group could positively impact the reduction of persistent VT carriage.

Our study has several strengths. First, it is a large population-based study with a random selection of participants of all ages, making our results applicable to the population in rural Gambia. Second, our data collection covered both dry and rainy seasons, allowing us to measure seasonal variation. Third, through our real-time vaccination record system (RVS), we validated the vaccination status of 95% of children under 5 years and 93% of those under 10 years, excluding individuals with missing PCV vaccination status from the vaccine-related analysis. This high degree of validation ensures that our results are robust. Lastly, we successfully serotyped a high percentage of isolated pneumococcal samples, with approximately 2 % being non-typeable.

Despite this, our study has some limitations. The use of molecular methods could have improved the detection of *S. pneumoniae* carriage compared to the conventional culture method. Additionally, differences in methodologies, such as laboratory techniques and the quality of nasopharyngeal collection methods between our study and previous carriage studies in the same setting,which served as a reference for comparing changes in VT carriage over time,may have influenced the reported secular trend in overall pneumococcal transmission.

5. Conclusion

We found that in rural Gambia, children aged 5–14 years, particularly those aged 5–9 years, were the main reservoir for VT pneumococcal carriage. We identified serotype 3 as the key persisting VT reservoir among school-aged children. Although VT carriage has decreased substantially due to both direct and herd effects in rural Gambia, residual VT carriage persists twelve years after the introduction of PCV into routine EPI services, particularly in age groups in whom direct protection from immunization in infancy may have waned. Our findings provide important local evidence and support the consideration of a booster dose in a reduced-dose PCV schedule for young children or strategic catch-up vaccinations for older children in this and other high-transmission settings.

Abbreviations

BHDSS	Basse Health and Demographic Surveillance System
FWHDSS	Fuladu West Health and Demographic Surveillance Systems
DSS	Demographic Surveillance System
PVS	Pneumococcal Vaccine Schedules trial
MRCG	The Medical Research Council Unit The Gambia
PCV	Pneumococcal Conjugate Vaccine
NPS	Nasopharyngeal Swab
VT	Vaccine-type serotype
WHO	World Health Organization
UNICEF	United Nations International Children's Fund

Authors' contributions

IO, GM, EM, and SF conceived and designed the surveys. IO and EM coordinated the fieldwork. OB, MM, and RS conducted the microbiological analyses. IO analyzed the data and interpreted the findings. IO wrote the first draft of the manuscript. KvZ, GS, BG, JB, SF, NIM, and GAM reviewed drafts and provided input. All authors contributed to and approved the final version of the manuscript.

CRediT authorship contribution statement

Isaac Osei: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Emmanuel Mendy:** Writing – review & editing, Project administration, Methodology, Investigation, Data curation. **Kevin van Zandvoort:** Writing – review & editing, Supervision, Investigation. **Golam Sarwar:** Writing – review & editing, Supervision, Methodology, Data curation. **I. Mohammed Nuredin:** Writing – review & editing, Supervision, Data curation. **Jane Bruce:** Writing – review & editing, Supervision, Methodology. **Ousman Barjo:** Writing – review & editing, Validation, Supervision, Methodology, Investigation, Data curation. **Minteh Molfa:** Writing – review & editing, Validation, Supervision, Methodology, Investigation, Data curation. **Rasheed Salaudeen:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Investigation, Data curation. **Brian Greenwood:** Writing – review & editing, Supervision, Conceptualization. **Stefan Flasche:** Writing – review & editing, Supervision, Conceptualization. **Grant A. Mackenzie:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Funding acquisition, Data curation, Conceptualization.

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Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2025.127181.

Data availability

Data will be made available on request.

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