IJID Regions 10 (2024) 240–247

Contents lists available at ScienceDirect

IJID Regions

journal homepage: www.elsevier.com/locate/ijregi

Prevalence of prolonged otitis media with effusion among 2 to 3 years old Cameroonian children in the era of 13-valent pneumococcal conjugate vaccines

John Njuma Libwea[1,2,3,*], Viviane Armelle Ngomba[3], Nadesh Ashukem Taku[4,5], Chanceline Bilounga Ndongo[3], Bernadette Dorine Ngono Noah[3], Ninying Fointama[6], Marie Kobela[2,6], Heini Huhtala[1], Emilienne Epee[3,6], Sinata Koulla-Shiro[6], Paul Koki Ndombo[4,6]

[1] Health Sciences Unit, Faculty of Social Sciences, Tampere University, Tampere, Finland
[2] Expanded Programme on Immunization, Yaoundé, Cameroon
[3] Directorate for disease control, epidemics and pandemics, Ministry of Public Health, Yaoundé, Cameroon
[4] Mother & Child Centre (MCH), Chantal Biya Foundation, Yaoundé, Cameroon
[5] Faculty of Sciences, Department of Microbiology, University of Buea, Buea, Cameroon
[6] Faculty of Medicine and Biomedical Sciences, University of Yaoundé 1, Yaoundé, Cameroon

ARTICLE INFO

Keywords:
PCV13
Vaccinated children
Otitis media
Unvaccinated children
Attributable proportion
Cameroon

ABSTRACT

Objectives: There is data scarcity on the overall effects of pneumococcal conjugate vaccines (PCVs) on otitis media (OM) in low- and middle-income countries. The impact of the 13-valent PCV (PCV13) program on OM was evaluated in Cameroon where infant vaccination was implemented in July 2011 using a 3-dose primary series at 6, 10 and 14 weeks of age.

Methods: Through community-based surveillance, we used a retrospective cohort study design to assess OM prevalence among PCV13-vaccinated children aged 24 to 36 months in 2015. This was compared with a 2013 age-matched cohort of PCV13-unvaccinated children. OM was diagnosed by clinical inspection for chronic suppurative OM (CSOM) and tympanometry for OM with effusion (OME). CSOM was defined as draining of the middle ear with duration of more than 2 weeks and prolonged OME was defined as a flat 'type B' tympanogram. PCV13-vaccinated and PCV13-unvaccinated cohorts were compared by calculating prevalence odds ratios for OM and baseline characteristics.

Results: Altogether, 111 OM cases were identified; 42/433 (9.7%) in the PCV13-unvaccinated in 2013 and 69/413 (16.7%) in the PCV13-vaccinated cohort in 2015. In the 2013 baseline survey, 3/433 (0.7%) children were identified with unilateral CSOM compared to 9/413 (2.2%) in the PCV13-vaccinated cohort in 2015. Bilateral prolonged OME was diagnosed in 7/433 (1.6%) PCV13-unvaccinated children and in 12/413 (2.9%) in PCV13-vaccinated children. Proportions of children with unilateral prolonged OME were 31/433 (7.2%) in the PCV13-unvaccinated group compared with 48/413 (11.6%) in the PCV13-vaccinated group. Multivariate logistic regression analysis showed evidence that PCV13-vaccinated children in 2015 had 40% less risk of contracting OM compared to PCV13-unvaccinated children in 2013 (adjusted prevalence odds ratios = 0.60 [95% confidence interval: 0.38 to 0.94], $P = 0.025$). Additionally, attributable proportion estimates show that, 58% of OM infections among the PCV13-vaccinated group would still have occurred despite PCV13 vaccination.

Conclusion: Our findings provide significant evidence on the effect of PCV13 in decreasing OM or OME among children in this age group. It also supports justification for government's continuation of PCV13 immunization program in the absence of GAVI's funding. Further research is needed to assess the long-term impact of the PCV13 program on in OM Cameroon.

* Corresponding author.
E-mail addresses: Libwea_j@yahoo.com (J. Njuma Libwea), ngombacm@yahoo.com (V.A. Ngomba), takuashukem@yahoo.com (N.A. Taku), bilounga_chance@yahoo.fr (C.B. Ndongo), ngonodorine@gmail.com (B.D. Ngono Noah), ninyingfuh@gmail.com (N. Fointama), mariekobela2006@yahoo.fr (M. Kobela), heini.huhtala@tuni.fi (H. Huhtala), epeeemilienne@gmail.com (E. Epee), koullasinata@yahoo.fr (S. Koulla-Shiro), koki_paul@hotmail.com (P.K. Ndombo).

https://doi.org/10.1016/j.ijregi.2023.11.009
Received 3 April 2023; Received in revised form 8 November 2023; Accepted 12 November 2023

Introduction

Middle ear infections are a predominant cause for healthcare visits in the early years of life [1]. Otitis media (OM) is a very common middle ear infection in children globally, contributing to excessive antibiotic consumption in most countries and to a substantial burden of deafness and suppurative complications in developing countries [2]. Peak incidence period of the disease is reported to occur between the ages of 6 and 11 months based on data mostly from high-income nations. Moreover, an estimated 70% of children aged under 5 years worldwide do encounter at least one episode of OM before their fifth birthdays [3]. The most frequent bacterial pathogen associated with OM is *Streptococcus pneumoniae*, followed by non-typeable *Haemophilus influenza* and *Moraxella catarrhalis* [4]. These three pathogens are reported to account for more than 95% of all OM cases with a bacterial etiology, although viral infections may play a role in the pathophysiology [4]. The type of OM disease witnessed in developed countries differs widely to what pertains in developing countries [2]. The major differences seem to be the frequency of complications and sequelae such as hearing loss due to chronic suppurative OM (CSOM) or OM with effusion (OME) reported in developing countries, rather than the incidence of acute OM (AOM) frequently reported in developed countries [2].

The frequent occurrence of OM in children under 5 years of age and the associated direct and indirect cost is a heavy toll to both parents and the healthcare providers [5]. Even when parents do not seek medical care for a child, they may still need to be absent from work to care for them [1]. In some countries, costs related to parental loss of productivity have been reported to represent a 50% average relative to the total costs of OM, depending on country, age, and number of previous episodes [5]. As such, the use of currently available and future vaccine formulations to prevent OM is considered the most promising approach to affect disease burden and complications, both in developed and developing countries [2].

Prior to the availability of the 13-valent pneumococcal conjugate vaccine (PCV13) in 2010, studies using previous PCV formulations (PCV7 or the investigational prototype PCV11) involving over 54000 children under 5 years old in randomized control trials conducted in the USA and Europe demonstrated modest to insignificant protection against AOM [6]. In 2001, a 6% vaccine efficacy was reported in the Finnish OM (FinOM) trial using the PCV7 with endpoint of reducing the number of vaccine-type AOM episodes [7]. Another efficacy trial using PCV7 in Northern California, USA (with the endpoints of preventing invasive pneumococcal disease [IPD] and clinical episodes of AOM) had a 7.8% efficacy against AOM [8]. Both the Finnish and California studies demonstrated the PCV's potential role in reducing the bacterial causes of OM in immunized subjects, although the vaccine impact has been suggested to be overshadowed by an overall increase in non-PCV7 serotypes [7,8]. These findings were corroborated by reports from three other randomized control trials (PCV7-OMPC, Native American and POET), which also estimated endpoints of AOM incidences [6]. However, AOM is described as a transient state of ear disease and its assessment is suggested not to sufficiently represent the actual OM burden in a developing country-perspective: defined by assessing OM sequelae including OME, recurrent, non-responsive, and chronic OM [6].

Further, a prospective-based active surveillance study in Israel reported dramatic reductions in endpoints of rates of pneumococcal and overall OM in children <2 years old, resulting in near-elimination of PCV13 serotypes following sequential introduction of PCV7 and PCV13 [9]. Another observational study in the United Kingdom including an endpoint of overall OM incidence reported first a 22% significant reduction in OM in children aged <10 years using the PCV7 and an additional 19% reduction after PCV13 introduction [10].

In Sub-Saharan Africa, where most of the OM disease burden and sequelae are reported [2], PCV effectiveness or impact studies of any OM endpoints are yet to be documented; as most studies have focused on the impact of the vaccines on pneumonia, carriage and IPD [11]. PCV's impact on nasopharyngeal colonization plays an important role against bacteria causing IPD and mucosal infections such as OM [12].

In July 2011, Cameroon introduced the PCV13 which is administered following the Expanded Program on Immunization (EPI) 3-dose schedule to infants at 6, 10 and 14 weeks of age. Two studies on children aged from 2 to 3 years in Cameroon from the same population conducted in 2013 and 2015 respectively, on nasopharyngeal carriage prevalence demonstrated a slight increase in non-PCV13 type carriage and a remarkable increase in *Moraxella catarrhalis* and *Haemophilus influenzae* [13]. Additionally, the overall proportion of PCV13-serotypes in carriage was 18.0% for the PCV13-vaccinated group in 2015 and 21.2% for the PCV13-unvaccinated group in 2013 [13]. Also, earlier we conducted a study on baseline prevalence of OM in 2013 sampling 24 to 36 months old PCV13-unvaccinated children in which an OM disease prevalence of 9.7% was reported [14]. In this study, we investigated the impact of the PCV13 on OM as case-defined (CSOM and prolonged OME), by comparing the prevalence of OM in PCV13-vaccinated to that of PCV13-unvaccinated children.

Methods

Study design

We used a retrospective cohort design in which two rounds of community-based surveillance surveys were conducted. First in the year 2013 to assess the prevalence of OM in PCV13-unvaccinated subjects and 2 years later, in 2015 PCV13-vaccinated subjects were sampled, using the same sampling methods [14].

Study population and study areas

We targeted children born between June 2010 and June 2011 (baseline data) and between June 2012 and June 2013 (comparison data). Cameroon had an annual birth cohort of approximately 856,000 according to the 2016 report of The Vaccine Alliance – GAVI (www.gavi.org/country/cameroon). Selection of subjects was done systematically following the World Health Organization (WHO) cluster sampling method and guided by the inclusion and exclusion criteria. The study areas have been earlier described [14]. Briefly, they included localities situated within an 80 km radius from Yaoundé, Cameroon's capital city. Yaoundé and its surroundings harbored a population of over 3.5 million, out of which 18% were children aged under 5 years, based on 2010 National Population Census.

The study areas were chosen as they host a group of health institutions involved with invasive disease sentinel surveillance. Study areas had been partitioned into 40 communities (clusters) using the health map and with each cluster hosting at least one health center/clinic, either public or private [14]. The starting household within the cluster was selected after spinning a pen, usually at a central location in the community. As previously reported during the 2013 baseline study, selection of participating household was done systematically after every 10^{th} household within a cluster and the first household was selected following the direction of pointer of a flipped pen at a central location within a cluster. An eligible participant was selected per household, and in an event where there was more than a single eligible participant in one household, selection was done according to birth order. Additionally, in an event where there was no eligible participant in a supposed eligible household, the next household was automatically considered. In total, the target was to enroll at least 25 children per "cluster" [14].

Using the sample size calculator (http://www.raosoft.com/samplesize.html), we estimated to sample at least 277 participants during each study period using the following assumptions: (i) that the estimated prevalence of OM in the unvaccinated population was 15% based on data from neighboring Nigeria [15]; (ii) impact of the PCV13 estimated to bring at least a 50% reduction, i.e., a 7.5% OM prevalence in the vaccinated group (second round); (iii) Alpha (Significance

level) = 5%; and (iv) Power (i.e., percentage chance of detecting any difference in OM prevalence between the PCV13-vaccinated and PCV13-unvaccinated groups) = 80%. Allowing some non-evaluable subjects with missing data (10%), a minimum of 600 children aged 24 to 36 months were targeted to constitute our sample size for the entire study.

Inclusion and exclusion criteria

Those included in the study were children aged from 24 to 36 months, residing in the study area for at least 6 months, availability of parental signed consent and subjects who were PCV-unvaccinated (for the baseline group in 2013). In 2013, enrolment was restricted to those who had not received any doses of the PCV as was confirmed from child's vaccination card or registers. Children had to have at least two documented doses of PCV13 in order to be eligible for inclusion in the comparison group in 2015.

Data collection

The data collection process during the baseline study had earlier been reported [14] and in the 2015 study the procedure was similar. Briefly, inspection to detect draining ears in subjects was done first, followed by tympanometry. Clinical and visual examination involved a thorough inspection of the external ear structure for signs of drainage or cerumen accumulation in the outer third of the ear canal as previously recommended [14]. Using a Welch Allyn with Siegel's speculum, pneumatic otoscopy was done and many of the subjects had cerumen stacked in the middle ear, but we lacked sufficient material to clean earwax at field conditions during the baseline study [14]. Tympanometry was performed using the middle ear analyzer Grason Stadler tympanometer (GSI-38 Autotymp, Grason-Stadler Inc., Milford, NH, USA). Tympanograms were recorded with a 226 Hz probe tone with a pressure varying from +200 deca Pascals (daPa) to −400 daPa in a time of 7 seconds. We did not perform tympanometry on draining ears. As earlier reported, study-specific case report forms were used for parental interviews to obtain socio-demographic and clinical history of study subjects [14].

Otitis media case definitions

In this study and using the same criteria as previously defined in the 2013 baseline cohort [14], ears observed by clinical inspection with draining and from parental reporting to have lasted more than 2 weeks were considered as CSOM based on the WHO's criteria [16]. We defined prolonged OME as 'type B' tympanogram with no peak as observed in tympanometry. Dry tympanic membrane perforation was denoted when the ear canal volume (ECV) was >1.0 cm^3, in an event of a flat curve. For each subject, one of the following mutually exclusive categories was assigned: CSOM, dry perforation, bilateral prolonged OME, unilateral prolonged OME and healthy ears. We considered subjects with the first four categories to have OM or its complications [14].

Interpretation and classification of tympanograms

The tympanograms were independently interpreted by two researchers in retrospect, as was previously reported [14]. In an event of discordance in the interpretation, a third researcher interpreted for a final decision. The tympanograms (Supplementary Table 1) were categorized following a modified version of Liden & Jerger's classification, as we earlier reported [14], in which flat 'type B' tympanograms indicated the presence of middle ear fluid. Tympanograms with curve types A, As, C, or Cs suggested absence of middle ear fluid. High external ear canal volume (ECV >1.0 cm^3) with a 'flat curve' was interpreted as perforation of the tympanic membrane i.e., "type P" tympanogram. Curves with erroneous peaks due to artefacts or movements of the child and curves with ECV below 0.3 cm^3 without any recording of a normal curve were interpreted as failed or 'type F' tympanogram [14].

Methodological approach

As previously reported [14], many children had occluded ear canals due to earwax accumulation and therefore, produced a false flat type B tympanogram curve with low ear canal volume (ECV). We resolved this by examining the distributions of the ECV measurements by tympanogram type, and observed that higher proportion of the initial 'type B' tympanograms had low ECV values i.e., 0.3 cm^3 and 0.4 cm^3 in comparison to other tympanogram types. We interpreted this difference to be probably due to earwax accumulation resulting in flat tympanograms. Based on the distribution of the ECV values in 'other type' tympanograms with discernible curves (A, As, C and Cs), it was evident that 90% of these were in the ECV categories of between 0.5 cm^3 to 1.2 cm^3, and 10% were distributed between the ECV categories <0.5 cm^3. Therefore, we adjusted the number of original 'type B' tympanograms with ECV values below 0.5 cm^3 to follow the same ECV distribution for the aforementioned categories [14]. It was in this respect that the adjustment was done i.e., of all flat curves, only 10% with lower ECV values were true positive "type B". The same approach was used for the 2013 (PCV13-unvaccinated) group [14].

Statistical analyses

The prevalence of OM in PCV13-vaccinated children in 2015 who had received at least two doses of PCV13 was compared with that of children with no PCV13 vaccination in 2013. Additionally, we explored associations between OM prevalence and potential risk factors. The chi-square test was used to compare differences between OM prevalence and baseline characteristics of PCV13-vaccinated and PCV13-unvaccinated groups (Table 1). In the multivariate logistic regression analyses (Table 2), variables with *P*-values ≤0.05 were entered to obtain the adjusted prevalence odds ratios (PORs). More so, two sensitivity analyses were performed; (a) to find out if there were possible differences in OM prevalence between subjects who had received 2 and 3 PCV13 doses, and (b) to determine if there were differences in the strength of association between OM prevalence and potential risk factors i.e., in the multivariate regression analysis where subjects with ECV values < 0.5 cm^3 and having "type B" tympanograms initially adjusted for were excluded (Supplementary Table 2). We computed PORs and prevalence difference (PD) with their 95% CI at a statistical significance level of 5%. PD was estimated by subtracting the prevalence in the PCV13-unvaccinated group from that in the PCV13-vaccinated group. Moreover, to extrapolate the burden of OM to the general population and account for the possibility of year-to-year variability in disease, weighted averages were estimated by PCV13 vaccination coverage in years 2013, 2014 and 2015. To obtain the weighted average, we used the WHO's and United Nations Children's Fund (UNICEF) estimates of national immunization coverage (WUENIC) where PCV13 uptake for year 2013, 2014 and 2015 were 88%, 83% and 77%, respectively [17]. Firstly, we considered the OM prevalence amongst the PCV13-vaccinated cohort (16.7%) as the weighted data point or base weight (0.167). Secondly, the base weight was then multiplied by each of the WUENIC PCV13 uptake values for 2013, 2014 and 2015, to get individual weighted scores. Finally, the weighted scores of each of the 3 years were then summed up and divided by 3 to get the weighted average. Further, we considered the attributable proportion (AP) otherwise described as the attributable risk percent which is used to quantify the public health impact of causative factor or an exposure (in this context PCV13) to an outcome (in this case, OM) in a specific population overtime. In imputing the AP, two assumptions were considered: (a) that the occurrence of OM in the unexposed group represents the baseline or expected risk of the disease; (b) if the risk of disease in the exposed group is higher than risk of disease in the unexposed group, then difference can be attributed to the

Table 1
Baseline characteristics and clinical outcome in PCV13-vaccinated (N = 413) and PCV13-unvaccinated (N = 433) 2 to 3 years old children screened for otitis media in Yaoundé, Cameroon.

Characteristics/ Clinical outcome	PCV13-vaccinated		PCV13-unvaccinated		*P*-value[a]
	N	%	N	%	
Gender of child					0.207
Male	212	51.3	241	55.7	
Female	201	48.7	192	44.3	
Age (group) of child in months					**< 0.001**
24 to 29	154	37.3	157	36.3	
30 to 35	44	10.7	110	25.4	
36	215	52.0	166	38.3	
No. of siblings living in same home ≤18 years					0.016
One	45	10.9	77	17.8	
Two	99	24.0	100	23.1	
≥ Three	269	65.1	256	59.1	
No. of siblings sleeping in same bedroom ≤18 years					**< 0.001**
Alone	37	9.1	172	39.7	
One	65	15.7	143	33.0	
Two	140	33.9	84	19.4	
≥ Three	171	41.3	34	7.9	
Otitis media status					**0.003**
Healthy	344	83.3	391	90.3	
Otitis positive	69	16.7	42	9.7	
History of previous otitis media					**0.021**
No	392	90.6	392	90.5	
Yes	21	9.4	41	9.5	
Breastfeeding period					**0.012**
≤6 months or not breastfed	21	5.2	38	8.9	
≤12 months	145	36.1	179	41.7	
>12 months	236	58.7	212	49.4	
Antibiotic use when child is sick					**0.001**
No	185	46.0	149	34.7	
Yes: with /without medical report	217	54.0	280	65.3	
Noticed any current URTI					**< 0.001**
No	365	90.8	341	79.5	
Yes	32	8.0	48	11.2	
Unknown	05	1.2	40	9.3	
Parental educational level					**0.001**
≤Primary school	183	45.5	147	34.3	
≥Secondary school	179	44.5	211	49.2	
≥University education	40	10.0	71	16.6	
Parental smoking status					0.588
Non-smokers	374	86.4	358	86.7	
Smokers	59	13.6	55	13.3	
Using wood/cool as household cooking fuel					**< 0.001**
No	98	24.7	128	29.6	
Yes	311	75.3	305	70.4	

N = number; PCV13 = 13-valent pneumococcal conjugate vaccines; % = percent; URTI = Upper respiratory tract infection.

[a] In bold denotes *P*-values less than 0.05.

exposure (PCV13). AP = (risk in the exposed group – risk in the unexposed group) divided by risk in the exposed group multiplied by 100%. Statistical analyses were performed using the International Business Machines (IBM) corporation's Statistical Package for Social Sciences (SPSS) version 25.0.

Results

Study population

A total of 846 children aged from 24 to 36 months were included in the analysis, consisting of 433 children in 2013 baseline (PCV13-unvaccinated) and 413 children in 2015 (PCV13-vaccinated) groups. Apart from those who refused to participate, the remainder were excluded either for not having a tympanogram or outside the age range of 24 to 36 months or due to lack of signed parental consent (Figure 1). All children in PCV13-vaccinated group had received at least two doses of the vaccine and WUENIC vaccine coverage was 77% in the year 2015 for fully vaccinated children i.e., three complete PCV13 doses received [17]. However, sensitivity analysis showed no statistically significant difference in OM prevalence between subjects who had received either two or three PCV13 primary doses, as previously reported [18]. There were 111 cases of OM in total (Figure 1).

Point estimates for otitis media prevalence in both PCV13-unvaccinated and PCV13-vaccinated groups

A diagnosis for OM or its complications (excluding AOM) was obtained for 42/433 (9.7%) of PCV13-unvaccinated children compared with 69/413 (16.7%) in PCV13-vaccinated children (PD = 7% [95% CI: 2.5 to 11.6], $P = 0.003$). This included 3/433 (0.7%) children identified with unilateral CSOM in the baseline survey in 2013, compared with 9/413 (2.2%) in subjects with CSOM in the PCV13-vaccinated group in 2015 (PD 1.5% [95% CI: −0.2 to 3.5], $P = 0.067$). Bilateral prolonged OME was diagnosed in 7/433 (1.6%) PCV13-unvaccinated children and 12/413 (2.9%) of PCV13-vaccinated children (PD = 1.3% [95% CI: −0.8 to 3.6%], $P = 0.2013$). Proportions of children with unilateral prolonged OME were 31/433 (7.2%) amongst the PCV13-unvaccinated group

Table 2
Factors associated with OM in PCV13-vaccinated (N = 413) and PCV13-unvaccinated (N = 433) in children aged 2 to 3 years in Yaoundé, Cameroon.

Characteristics/Clinical outcome	OM prevalence N (%)	Univariate analyses			Multivariate analyses[a]		
		POR	95% CI	*P*-value	Adjusted POR	95% CI	*P*-value
Vaccine cohort							
PCV13-Unvaccinated (2013)	42/433 (9.7)	1.0			1.0		
PCV13-Vaccinated (2015)	69/413 (16.7)	1.87	1.239-2.814	0.003	0.60	0.382-0.936	0.025
Age (group) of child in months							
24 to 29	43/311 (13.8)	1.0					
30 to 36	68/535 (12.7)	0.91	0.602-1.368	0.643			
No. of persons living in same household ≤18 years							
One	18/122 (14.8)	1.0					
Two	30/199 (15.1)	1.27	0.721-2.234	0.409			
≥Three	63/525 (12.0)	1.30	0.814-2.081	0.271			
No. of siblings sleeping in same bedroom							
One	26/208 (12.5)	1.0					
Two	35/224 (15.6)	1.21	0.696-2.102	0.500			
≥ Three	52/414 (12.6)	1.01	0.608-1.663	0.983			
Previous otitis media history							
No	98/759 (12.9)	1.0					
Yes	13/87 (14.9)	1.19	0.633-2.217	0.596			
Breastfeeding period							
≤6 months or not breastfed	8/59 (13.6)	1.0					
≤12 months	43/331 (13.0)	0.95	0.423-2.146	0.905			
>12 months	60/456 (13.2)	0.97	0.437-2.135	0.932			
Antibiotic use when child is sick							
No	14/173 (8.1)	1.0			1.0		
Yes: with / without medical report	97/693 (14.0)	0.52	0.291-0.941	0.030	0.67	0.354-1.253	0.207
Noticed any current symptoms of URTI							
No	88/718 (12.3)	1.0			1.0		
Yes	22/82 (26.8)	2.63	1.534-4.491	0.001	5.10	0.683-37.972	0.067
Unknown	1/45 (2.2)	0.16	0.022-1.196	0.074	14.16	1.825-109.82	0.011
Parental educational level							
≤Primary education	45/333 (13.5)	1.0					
≥Secondary education	56/402 (13.9)	1.53	0.767-3.248	0.215			
≥Tertiary education	10/111 (9.0)	1.64	0.805-3.320	0.174			

CI = confidence interval; N = number; OM = otitis media; POR = prevalence odds ratio; PCV13 = 13-valent pneumococcal conjugate vaccine; URTI = upper respiratory tract infection; % = percentage.
[a] OR was adjusted for symptoms of URTI and antibiotic usage.

compared with 48/413 (11.6%) in the PCV13-vaccinated group (PD = 4.4% [95% CI: 0.5 to 8.4], $P = 0.028$). There was no significant difference in the proportions of subjects with unilateral dry tympanic membrane perforation (ECV >1.0 cm^3) between the two groups, 0.2% and 0%, respectively (PD = 0.2% [95% CI: −0.7 to 1.2], $P = 0.365$).

Multivariate analyses and attributable proportion estimates

The crude estimates from logistic regression analyses showed that PCV13-vaccinated children were significantly associated with more OM (POR = 1.87 [95% CI: 1.24 to 2.81], $P = 0.003$) compared to PCV13-unvaccinated children. However, in the multivariate analyses adjusting for significant baseline risk factors in Table 2, we found a statistically significant evidence that PCV13-vaccinated children in 2015 had 40% less risk of contracting OM compared to PCV13-unvaccinated children in 2013 (adjusted POR = 0.60 [95%CI: 0.38 to 0.94], p = 0.025). Also, a statistically significant association was observed between reportedly "unknown symptoms of upper respiratory tract infections" and OM (adjusted POR = 14.16 [95% CI: 1.83 to 109.842], $P = 0.011$). Additionally, in the sensitivity analysis non-significant results were found for OM prevalence between the PCV13-vaccinated and unvaccinated groups as well as for the other risk factors assessed (Supplementary Table 2). Besides, the estimated OM prevalence weighted average by vaccination coverage to account for possible seasonal variations across years 2013, 2014 and 2015 was 14.8%, a value closed to the 16.7% reported for among the PCV13-vaccinated cohort in 2015. Further, a 42% attributable proportion estimate was obtained i.e., 42% of OM infection among the PCV13-vaccinated group might be attributable to PCV13 vaccination. The remainder (58%) of OM infections in the vaccinated group would have still occurred even without the vaccine.

Discussion

Our surveillance found a statistically significant evidence that PCV13-vaccinated children in 2015 had a forty percent less risk of contracting OM compared to PCV13-unvaccinated children in 2013, despite the significantly higher prevalence of OM in the 2015 cohort. Our findings corroborate results from a recent systematic review study which found a considerable effect of the PCVs in reducing OM in children under 5 years old in several countries [19]. This supports the broader public health value of implementing PCVs in national immunization programs, and the continuation of public financing, when GAVI's funding ends [20].

However, differences in baseline epidemiology and disease incidence, study design, case definitions, case ascertainment, and local or regional practices make it difficult to compare the results of clinical trials/observational studies of PCV efficacy/effectiveness or impact analyses [6,7,21–23]. Previous studies have primarily evaluated vaccine effectiveness on the endpoint of AOM incidence, whereas we assessed PCV13 impact on the prevalence of CSOM, prolonged OME and dry perforation. As a result, such discrepancies may limit our ability to extensively compare our findings to previous research from other global regions. Nonetheless, our findings share some similarities with those from an Australian community-based cross-sectional study of indigenous population of children under the age of 36 months [22]. In that study, the researchers used a similar categorization of middle ear statuses as we did (including healthy ears, OM without perforation, OM

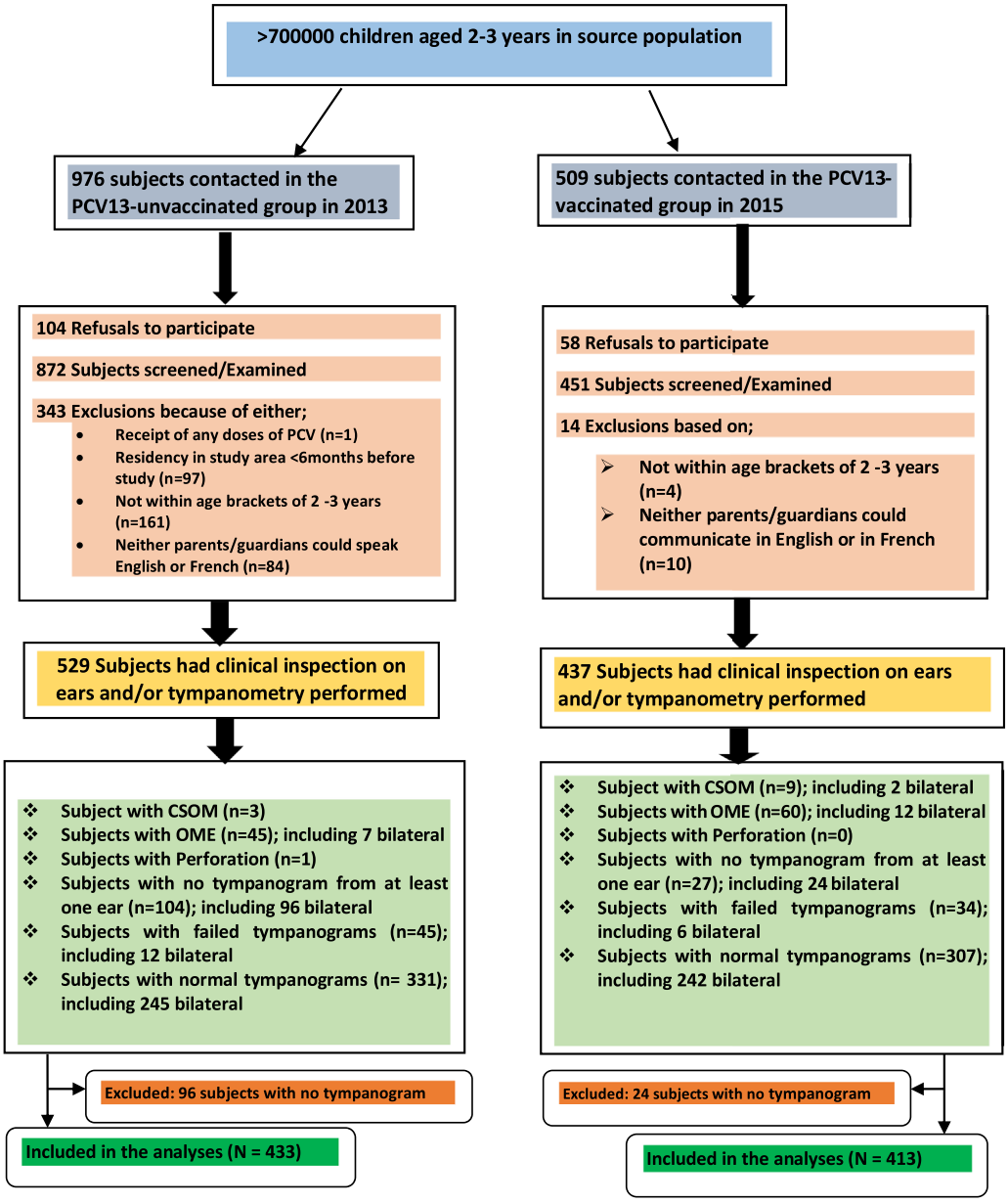

Figure 1. Study profile of subjects on the assessment of PCV13 effect on otitis media.
(*CSOM = chronic suppurative otitis media; OME = Otitis media with effusion; n = number of subjects with specific outcomes; PCV13 = 13-valent pneumococcal conjugate vaccine*).

with perforation, dry perforation and CSOM). Subjects vaccinated with the 10-valent pneumococcal *Haemophilus influenzae* Protein-D conjugate vaccine (PHiD-CV10) had less CSOM than those vaccinated with PCV7 [22]. However, there was a simultaneous increase in asymptomatic OME in these subjects, so the overall risk of OM was similar between the two groups [22].

Our findings could be explained by a variety of factors. First, differences in the patho-physiology of AOM or OME/CSOM, compared to that of IPD, such as bacteremia and meningitis, may be a contributing factor [23]. The polymicrobial nature of AOM or OME/CSOM disease may play a role, as it is believed that even if high efficacy and effectiveness could be obtained, protection against pneumococcal OM alone would have only a limited impact on the overall burden of OM disease [6,7]. This signifies that PCV may offer only limited protection against OME/CSOM. It is unclear whether the infants were exposed to a preceding viral upper respiratory tract infection or early AOM episodes prior to vaccination, giving that children in low-resource settings are more exposed than those in more affluent communities to experience bacterial nasopharyngeal colonization shortly after birth [23]. In addition, nasopharyngeal carriage not only provides an ecological niche for *S. pneumoniae,* but also for other pathogens that can cause middle ear infection [21]. PCV vaccination prior to this chain of patho-physiological events may play a significant role in preventing recurrent and complicated infections in otitis-prone children [23]. But, once this chain of events has commenced, PCV vaccination is thought to have little or no effect [23]. Previous studies, however, have found no correlation between early vaccine-type AOM and an increased risk of subsequent AOM when compared to AOM caused by other confirmed bacterial etiologies [24]. This supports the hypothesis that the higher OME prevalence among PCV13-vaccinated subjects in our study may have resulted from other bacterial etiology or the replacement of PCV13 serotypes by non-PCV13-type pneumococci, when compared to the PCV13-unvaccinated. Hence, it is likely that the predominance of non-vaccine type pneumococci and/or other pathogens were primarily responsible for the

unexpectedly higher OM prevalence amongst the PCV13-vaccinated group in our study.

Furthermore, the lack of indirect effects or vaccine waning effects in children as they get older may be consistent with our findings, especially since the PCV13 is being rolled-out using the 3+0 EPI primary dose-schedule with no booster [25]. The possible vaccine waning effects after the first year of life [25], and an increasing OM prevalence among the PCV13-vaccinated supports recommendation that a booster dose be introduced to counter observations of waning immunological effects over time [26]. This could be achieved by shifting to a 2 +1 schedule in which the third dose is given at 9- to 12-months of age may be more effective [26].

To the best of our knowledge, this is Africa's first study to assess the impact of PCV13 on the prevalence of prolonged OME and CSOM. However, we are aware of some constraints. As previously stated, AOM findings obtained using pneumatic otoscopy were not reported here because they were not evaluated in the same way in both groups. AOM is a serious problem worldwide [1], but in a low-resource setting like Cameroon, it often goes unnoticed in affected children [2]. Hence, we needed to define endpoints in our assessment that were realistic and reflective of local practices. More so, concerns from misclassification bias could not be ruled out i.e., the possibility of misinterpreting a 'type F' or 'type P' tympanogram for a true prolonged OME (type B), as they all produced graphically a "flat curve" as previously indicated [14]. In addition, because we did not have the possibility to examine the microbiology of OM disease causing serotypes, direct evidence of disease replacement of vaccine types by non-vaccine type pneumococci or other bacteria could not be ascertained. However, a study on nasopharyngeal carriage prevalence in same population and age group found a slight increase in non-PCV13 type carriage as well as a significant increase in *Moraxella catarrhalis* and *Haemophilus influenzae* [13], which share the same ecological niche with the pneumococcus.

In developing countries, studies evaluating the impact of PCV13 infant vaccination on invasive pneumococcal diseases, pneumonia and nasopharyngeal carriage endpoints yielded vaccine impact estimates comparable to those obtained from high-income countries [11,27–29]. This study estimated the impact of the PCV13 program on CSOM, prolonged OME and dry perforation, which had not previously been measured in Africa, and found a significant difference in the risk of contracting OM between the PCV13-vaccinated group and the PCV13-unvaccinated group. These findings should contribute to the possibility that PCV programs have potential ability to effect appropriate immunogenic response against otitis in children who were vaccinated in infancy, although the development of indirect effects maybe slow to interrupt the transmission of vaccine-type carriage [23].

In conclusion, our study found significant evidence that PCV13-vaccinated children in 2015 were associated with lower odds of prolonged OME and CSOM compared to PCV13-unvaccinated children in 2013, despite a reportedly higher number of OM cases among those vaccinated. However, confounding due to unknown factors or the replacement with non-PCV13 serotypes or other bacteria may rapidly outweigh a positive effect. Another possibility could be waning immunity in PCV13-vaccinated children with a 3+0 schedule, despite a reported vaccine uptake of >75% over time. More research is needed to assess these findings and potential causes, as well as to monitor the long-term impact of PCV13 program implementation on the epidemiology of pneumococcal diseases, including otitis media in African settings.

Declarations of competing interest

Authors have no competing interests.

Funding

This work was supported in part by small research grants from the International Society of Infectious Disease (ISID) for data collection in 2015. All research materials were provided by the Finnish Institute for Health and Welfare (THL). Neither ISID nor THL were involved in the study design, collection, analysis and interpretation of the data, the writing of the report, and the decision to submit the article for publication.

Ethical considerations

The Institutional Review Boards (IRBs) of the Cameroon National Ethics Committee and the Yaoundé Gynaecology, Obstetric and Paediatric Hospital, approved the study. Signed informed consent forms were obtained from all parents. Additional permission for the study was obtained from local and administrative leaders.

Acknowledgements

We sincerely extend our gratitude to all the study participants, study personnel and other collaborators for the immense assistance we received during the conduct of this study. We are particularly indebted to Ms. Päivi Siren (THL, Finland) and Ms. Sandrine Bebey (MCH, Cameroon) for coordinating the logistics and transportation of research materials to and from Cameroon, respectively.

Author contributions

Conceived, planned and designed the study: JNL; participated and supervised local data collection: JNL, TNA, VAN, CBN, BBNN, NF, MK, EE, PKN, MK and SKS; Contributed logistics: MK, SKS, PKN and JNL; Drafted the manuscript: JNL; significantly contributed to the revised and final versions of the manuscript: JNL, NAT, VAN, CBN, BBNN, NF, MK, EE, SKS and PKN.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijregi.2023.11.009.

References

[1] Rovers MM. The burden of otitis media. *Vaccine* 2008;**26**:G2–4. doi:10.1016/j.vaccine.2008.11.005.
[2] Vergison A, Dagan R, Arguedas A, Bonhoeffer J, Cohen R, DHooge I, et al. Otitis media and its consequences: beyond the earache. *Lancet Infect Dis* 2010;**10**:195–203. doi:10.1016/S1473-3099(10)70012-8.
[3] Speets A, Wolleswinkel J, Cardoso C. Societal costs and burden of otitis media in Portugal. *J Multidiscip Healthc* 2011;**4**:53–62. doi:10.2147/JMDH.S17529.
[4] Dagan R, Leibovitz E, Greenberg D, Bakaletz L, Givon-Lavi N. Mixed pneumococcal-nontypeable haemophilus influenzae otitis media is a distinct clinical entity with unique epidemiologic characteristics and pneumococcal serotype distribution. *J Infect Dis* 2013;**208**:1152–60. doi:10.1093/infdis/jit289.
[5] Capra AM AM, Lieu TA, Black SB, Shinefield HR, Martin KE, Klein JO. Costs of otitis media in a managed care population. *Pediatr Infect Dis J* 2000;**19**:354–5. doi:10.1097/00006454-200004000-00019.
[6] Fletcher MA, Fritzell B. Pneumococcal conjugate vaccines and otitis media: an appraisal of the clinical trials. *Int J Otolaryngol* 2012;**2012**:312935. doi:10.1155/2012/312935.
[7] Eskola J, Kilpi T, Palmu A, Jokinen J, Eerola M, Haapakoski J, et al. Efficacy of a pneumococcal conjugate vaccine against acute otitis media. *N Engl J Med* 2001;**344**:403–9. doi:10.1056/NEJM200102083440602.
[8] Fireman B, Black SB, Shinefield HR, Lee J, Lewis E, Ray P. Impact of the Pneumococcal Conjugate Vaccine on otitis media. *Pediatr Infect Dis J* 2003;**22**:10–16. doi:10.1097/00006454-200301000-00006.
[9] Ben-Shimol S, Givon-Lavi N, Leibovitz E, Raiz S, Greenberg D, Dagan R. Near-elimination of otitis media caused by 13-valent Pneumococcal Conjugate Vaccine (PCV) serotypes in southern israel shortly after sequential introduction of 7-valent/13-valent PCV. *Clin Infect Dis* 2014;**59**:1724–32. doi:10.1093/cid/ciu683.
[10] Lau WCY, Murray M, El-Turki A, Saxena S, Ladhani S, Long P, et al. Impact of pneumococcal conjugate vaccines on childhood otitis media in the United Kingdom. *Vaccine* 2015;**33**:5072–9. doi:10.1016/j.vaccine.2015.08.022.
[11] Madhi SA, Nunes MC. The potential impact of Pneumococcal Conjugate Vaccine in Africa: considerations and early lessons learned from the South African experience. *Hum Vaccin Immunother* 2016;**12**:314–25. doi:10.1080/21645515.2015.1084450.
[12] Bergenfelz C, Hakansson AP. Streptococcus pneumoniae otitis Media pathogenesis and how it informs our understanding of vaccine strategies. *Curr Otorhinolaryngol Rep* 2017;**5**:115–24. doi:10.1007/s40136-017-0152-6.

[13] Njuma Libwea J, Gröndahl-Yli-Hannuksela K, Kobela M, Toropainen M, Nyholm O, Ndombo PK, et al. Prevalence of pneumococcal nasopharyngeal colonization and serotypes circulating in Cameroonian children after the 13-valent pneumococcal conjugate vaccine introduction. *Int J Infect Dis* 2020;**98**:113–20. doi:10.1016/j.ijid.2020.06.048.

[14] Njuma Libwea J, Kobela M, Ndombo PK, Syrjänen RK, Huhtala H, Fointama N, et al. The prevalence of otitis media in 2–3 year old Cameroonian children estimated by tympanometry. *Int J Pediatr Otorhinolaryngol* 2018;**115**:181–7.

[15] Amusa YB, Ijadunola IKT, Onayade OO. Epidemiology of otitis media in a local tropical African population. *West Afr J Med* 2005;**24**:227–30. doi:10.4314/wajm.v24i3.28202.

[16] World Health Organization *Chronic suppurative otitis media - Burden of Illness and Management Options*. Geneva: World Helath Organization; 2004.

[17] World Health Organization *Cameroon: WHO and UNICEF estimates of immunization coverage : 2017 revision*. Geneva: World Helath Organization; 2018.

[18] Loo JD, Conklin L, Fleming-Dutra KE, Knoll MD, Park DE, Kirk J, et al. Systematic review of the indirect effect of pneumococcal conjugate vaccine dosing schedules on pneumococcal disease and colonization. *Pediatr Infect Dis J* 2014;**33**:S161–71. doi:10.1097/INF.0000000000000084.

[19] Marra LP, Sartori AL, Martinez-silveira MS, Toscano CM, Andrade AL. Effectiveness of pneumococcal vaccines on otitis media in children: a systematic review. *Value Health* 2022;**25**:1042–56. doi:10.1016/j.jval.2021.12.012.

[20] Ojal J, et al. Sustaining pneumococcal vaccination after transitioning from Gavi support: a modelling and cost-effectiveness study in Kenya. *Lancet Glob Health* 2019;**7**:e644–54. doi:10.1016/S2214-109X(18)30562-X.

[21] Auranen K, Syrjänen R, Leino T, Kilpi T. New pneumococcal carriage acquired in association with acute respiratory infection is prone to cause otitis media. *PLoS One* 2016;**11**:e0156343. doi:10.1371/journal.pone.0156343.

[22] Leach AJ, Wigger C, Andrews R, Chatfield M, Smith-vaughan H, Morris PS. Otitis media in children vaccinated during consecutive 7-valent or 10-valent pneumococcal conjugate vaccination schedules. *BMC Pediatr* 2014;**14**:200. doi:10.1186/1471-2431-14-200.

[23] Schilder AGM, Chonmaitree T, Cripps AW, Rosenfeld RM, Casselbrant ML, Haggard MP, et al. Otitis media. *Nat Rev Dis Primers* 2016;**2**:1–19. doi:10.1038/nrdp.2016.63.

[24] Palmu AAI, Jokinen JT, Kaijalainen T, Leinonen M, Karma P, Kilpi TM. Association of clinical signs and symptoms with pneumococcal acute otitis media by serotype - implications for vaccine effect. *Clin Infect Dis* 2005;**40**:52–7. doi:10.1086/426446.

[25] Fortanier AC, Venekamp RP, Wb Boonacker C, Hak E, Gm Schilder A, Am Sanders E, et al. Pneumococcal conjugate vaccines for preventing acute otitis media in children. *Cochrane Database Syst Rev* 2019;**5**:CD001480. doi:10.1002/14651858.CD001480.pub5.

[26] Soeters HM, Kambiré D, Sawadogo G, Ouédraogo-Traoré R, Bicaba B, Medah I, et al. Impact of 13-valent Pneumococcal Conjugate Vaccine on pneumococcal meningitis, Burkina Faso, 2016–2017. *J Infect Dis* 2019;**220**:S253–62. doi:10.1093/infdis/jiz301.

[27] Grant LR, Hammitt LL, O'Brien SE, Jacobs MR, Donaldson C, Weatherholtz RC, et al. Impact of the 13-valent pneumococcal conjugate vaccine on pneumococcal carriage among American Indians. *Pediatr Infect Dis J* 2016;**35**:907–14. doi:10.1097/INF.0000000000001207.

[28] Roca A, Bojang A, Bottomley C, Gladstone RA, Adetifa JU, Egere U, et al. Effect on nasopharyngeal pneumococcal carriage of replacing PCV7 with PCV13 in the Expanded Programme of Immunization in The Gambia. *Vaccine* 2015;**33**:7144–51. doi:10.1016/j.vaccine.2015.11.012.

[29] von Gottberg A, De Gouveia L, Tempia S, Quan V, Meiring S, Von Mollendorf C, et al. Effects of vaccination on invasive pneumococcal disease in South Africa. *N Engl J Med* 2014;**371**:1889–99. doi:10.1056/NEJMoa1401914.