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Effect of pneumococcal conjugate vaccine on prevalence of otitis media with effusion among children in Vietnam

Michiko Toizumi [a,b,1], Chisei Satoh [c,1], Billy J. Quilty [d], Hien Anh Thi Nguyen [e], Lina Madaniyazi [a,b], Lien Thuy Le [f], Chris Fook Sheng Ng [b,g], Minoru Hara [h], Chihiro Iwasaki [a], Mizuki Takegata [a], Noriko Kitamura [b], Monica Larissa Nation [i], Catherine Satzke [i,j,k], Yoshihiko Kumai [c], Hung Thai Do [f], Minh Xuan Bui [l], Kim Mulholland [i,j], Stefan Flasche [d], Duc Anh Dang [e], Kenichi Kaneko [c], Lay-Myint Yoshida [a,b,*]

[a] Department of Pediatric Infectious Diseases, Institute of Tropical Medicine, Nagasaki University, Nagasaki, Japan
[b] School of Tropical Medicine and Global Health, Nagasaki University, Nagasaki, Japan
[c] Department of Otorhinolaryngology, Nagasaki University Hospital, Nagasaki, Japan
[d] Centre for Mathematical Modelling of Infectious Diseases, London School of Hygiene and Tropical Medicine, London, UK
[e] National Institute of Hygiene and Epidemiology, Hanoi, Viet Nam
[f] Department of Bacteriology, the Pasteur Institute in Nha Trang, Nha Trang, Viet Nam
[g] Department of Global Health Policy, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan
[h] Department of Otorhinolaryngology, Kamio Memorial Hospital, Tokyo, Japan
[i] Infection and Immunity, Murdoch Children's Research Institute, Melbourne, Australia
[j] Department of Paediatrics, The University of Melbourne, Melbourne, Australia
[k] Department of Microbiology and Immunology, The University of Melbourne at the Peter Doherty Institute for Infection and Immunity, Melbourne, Australia
[l] Khanh Hoa Health Service, Nha Trang, Viet Nam

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ABSTRACT

Purpose: Otitis media with effusion (OME) is common in young children and is associated with *Streptococcus pneumoniae* infection. We aimed to determine the impact of pneumococcal conjugate vaccine (PCV) introduction on the prevalence of OME and OME associated with vaccine-type (VT) or non-VT.
Methods: Population-based cross-sectional surveys were conducted in pre- (2016) and post-PCV periods (2017, 2018, and 2019) at selected communes in Nha Trang, Vietnam. For each survey, we randomly selected 60 children aged 4–11 months and 60 aged 14–23 months from each commune. Nasopharyngeal sample collection and tympanic membrane examination by digital otoscope were performed. *S. pneumoniae* was detected and serotyped by *lytA* qPCR and microarray. Odds ratios (OR) and 95% confidence intervals (CIs) were calculated using Firth's logistic regression, stratified by age group.
Results: Over the four surveys, 2089 children had a bilateral ear examination. Compared to pre-PCV, the prevalence of OME reduced in 2018 (OR 0.51, 95 %CI 0.28–0.93) and in 2019 (OR 0.53, 95 %CI 0.29–0.97) among the <12-month-olds, but no significant reduction among the 12–23-month-olds. The prevalence of OME associated with VT pneumococcus decreased in 2018 and 2019 (2018: OR 0.14, 95 %CI 0.03–0.55; 2019: OR 0.20, 95 %CI 0.05–0.69 in the <12-months-olds, 2018: OR 0.05, 95 %CI 0.00–0.44, 2019: OR 0.41, 95 %CI 0.10–1.61 in the 12–23-months-olds). The prevalence of OME associated with non-VT pneumococcus increased in the 12–23-month-olds in 2017 (OR 3.09, 95 %CI 1.47–7.45) and returned to the pre-PCV level of prevalence in 2018 and 2019 (OR 0.94, 95 %CI 0.40–2.43 and 1.40, 95 %CI 0.63–3.49).
Conclusion: PCV10 introduction was associated with a reduction of OME prevalence in infants but not in older children.

Abbreviations: AOM, acute otitis media; CI, confidence interval; Hib, *Haemophilus influenzae* type-b vaccine; MCV, measles containing vaccine; NTHi, non-typeable *Haemophilus influenzae*; OME, otitis media with effusion; OR, odds ratio; PHiD-CV, pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine; VT, vaccine type.

* Corresponding author at: Department of Pediatric Infectious Diseases, Institute of Tropical Medicine, Nagasaki University, 1-12-4 Sakamoto, Nagasaki 852-8523, Japan.
E-mail address: lmyoshi@nagasaki-u.ac.jp (L.-M. Yoshida).

[1] These authors contributed equally to this work.

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1. Introduction

Otitis media with effusion (OME), defined as the presence of fluid in the middle ear without any signs or symptoms of acute ear infection, commonly occurs and persists in young children [1]. Approximately 80% of children have experienced OME by the age of four years [2]. Recurrent OME occurs in 30–40% of children and 5–10% of episodes last a year or longer [3]. Persistent OME can lead to complications, such as hearing loss and damage to the tympanic membrane [4].

Nasopharyngeal infection, sometimes followed by acute otitis media (AOM), can trigger or maintain inflammation in the middle ear of young children [5]. *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, Respiratory Syncytial virus, rhinovirus, parainfluenza viruses, and influenza virus are the common primary infectious pathogens [6]. Other factors inducing inflammation can be involved, such as pollution, smoking, gastro esophageal reflux disease, and allergy [5], and it is also influenced by otolaryngo-morphological factors such as Eustachian tube function and adenoid hypertrophy [1].

The latest Cochrane review [7] including 15 publications of 11 trials reported that administration of the licensed seven-valent pneumococcal conjugate vaccine (PCV7) and ten-valent PCV (PCV10) during early infancy largely reduced the relative risk of pneumococcal AOM, not only AOM attributed to vaccine serotype but both vaccine type (VT) and non-vaccine type (non-VT) of pneumococcal AOM [8,9]. However, the effects of these vaccines on all-cause AOM was uncertain [7].

Few studies have investigated the effect of PCV on the prevalence or incidence of actively screened OME in a community [10,11]. Thus this study was conducted to determine the yearly change in the prevalence of OME, OME with pneumococcal carriage in the nasopharynx (VT and non-VT) or OME without pneumococcal carriage after PCV10 introduction. Nasopharyngeal pneumococcal colonisation is considered to be a prerequisite to and may remain after the development of pneumococcal nasopharyngeal or middle ear infection which can be followed by middle ear effusion [12]. Also, nasopharyngeal infection can trigger inflammation to induce increased secretions responsible for middle ear effusion even without direct infection to the middle ear [5]. Therefore, we assumed that OME with pneumococcal carriage is a proxy of OME caused in association with pneumococcal infection or colonisation. Our study population was children aged <24 months, in Nha Trang, Vietnam, where PCV10 was introduced in 2017 as part of a PCV trial [13], and described the direct and indirect effect of PCV on the prevalence of OME among young children.

2. Methods

2.1. Study design

The community-based cross-sectional surveillance of OME was conducted in 2016 (pre-PCV), and post-PCV period (2017, 2018, and 2019), nested in the pneumococcal carriage surveys of the PCV trial [15].

2.2. Study area and participants' enrollment

The study site, Nha Trang, consists of 27 communes; the smallest administrative unit in which health and educational services are provided. Each commune has a commune health center that provides a range of basic health services, except for commune Phước Đ ng (Fig. 1), that has two commune health centers, the main and satellite ones. The study area of the surveys in 2017, 2018 and 2019 consisted of six communes and PCV10 (Synflorix™, GlaxoSmithKline [14]) was introduced as part of the ongoing PCV clinical trial [15]. Starting in February 2017, all children aged <37 months were vaccinated in a catch-up campaign. Routine PCV10 vaccination was introduced in March 2017. Children in the six communes received PCV10 given as a 2p + 1 schedule (2, 4, 12 months). The survey in 2016 was conducted only in a subset of the study area; two communes (Vĩnh Thạnh and Vĩnh Hải) and the main section of commune Phước Đ ng (Fig. 1). The prevalence of OME and pneumococcal carriage in the nasopharynx in the 2016 survey before PCV introduction were published previously and used as baseline prevalence in this study [15].

For each survey, 60 children aged 4–11 months and 60 aged 14–23 months from each commune were randomly selected using the registration records. As for commune Phước Đ ng, 40 and 20 each from the main and satellite part were randomly selected. Home visits were conducted to obtain informed consent prior to examination and interview. Sample collection took place at respective commune health centers in October 2016, November 2017, October 2018, and October 2019. Due to the gap of planned and actual date of data/sample collection, 34 children between 12 and 13 months old, originally planned for the younger group, were included in the 12–23 month-old group.

2.3. Data collection and laboratory testing

Using a structured interview form, a trained healthcare worker from each commune health center interviewed the guardian of each participant in order to collect demographic and social information including the child's sex, date of birth, and number of PCV doses received. A nasopharyngeal swab sample was collected using a paediatric nylon flocked swab and placed in one millilitre of skim-milk tryptone glucose glycerol (STGG) transport medium following WHO guidelines [16]. Samples were sent to the Pasteur Institute of Nha Trang where they were screened for pneumococci using quantitative PCR (qPCR) for the autolysin-encoding gene (*lytA*) of *S. pneumoniae* [17]. Samples that were *lytA* positive (Cycle threshold (Ct): value < 35) or equivocal (Ct value: 35–40) were cultured on selective agar. DNA was extracted from samples with alpha-haemolytic growth using the QIAcube HT platform (Qiagen, Hilden, Germany) [18]. DNA was sent to the Murdoch Children's Research Institute, Melbourne, Australia, for molecular serotyping by microarray (Senti-SP v1.5, BUGS Bioscience, London, UK; https://bugsbio.org) [18]. VT serotypes were defined as the serotypes contained in the PCV10 vaccine (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F). All other serotypes were considered non-VTs, including non-encapsulated lineages such as NT2 and NT3b [19]. In this study, we defined pneumococcus carriage as detection of pneumococcus including both colonisation and infection which we could not differentiate. OME associated with VT pneumococcal carriage was defined as OME with detection of at least one VT serotype. OME associated with non-VT pneumococcal carriage was defined as OME with detection of *S. pneumoniae* and all the strains were non-VT serotype.

2.4. Assessment of the tympanic membrane

Three otolaryngologists conducted the ear examination and each was allocated to each of the three areas: two communes and the main section of one commune (Vĩnh Thạnh, Vĩnh Hải, and Phước Đ ng-main: in 2016, 2017, 2018, and 2019), one commune and the satellite section of one commune (Phước Hải and Phước Đ ng-satellite: in 2017, 2018, and 2019), and two com-

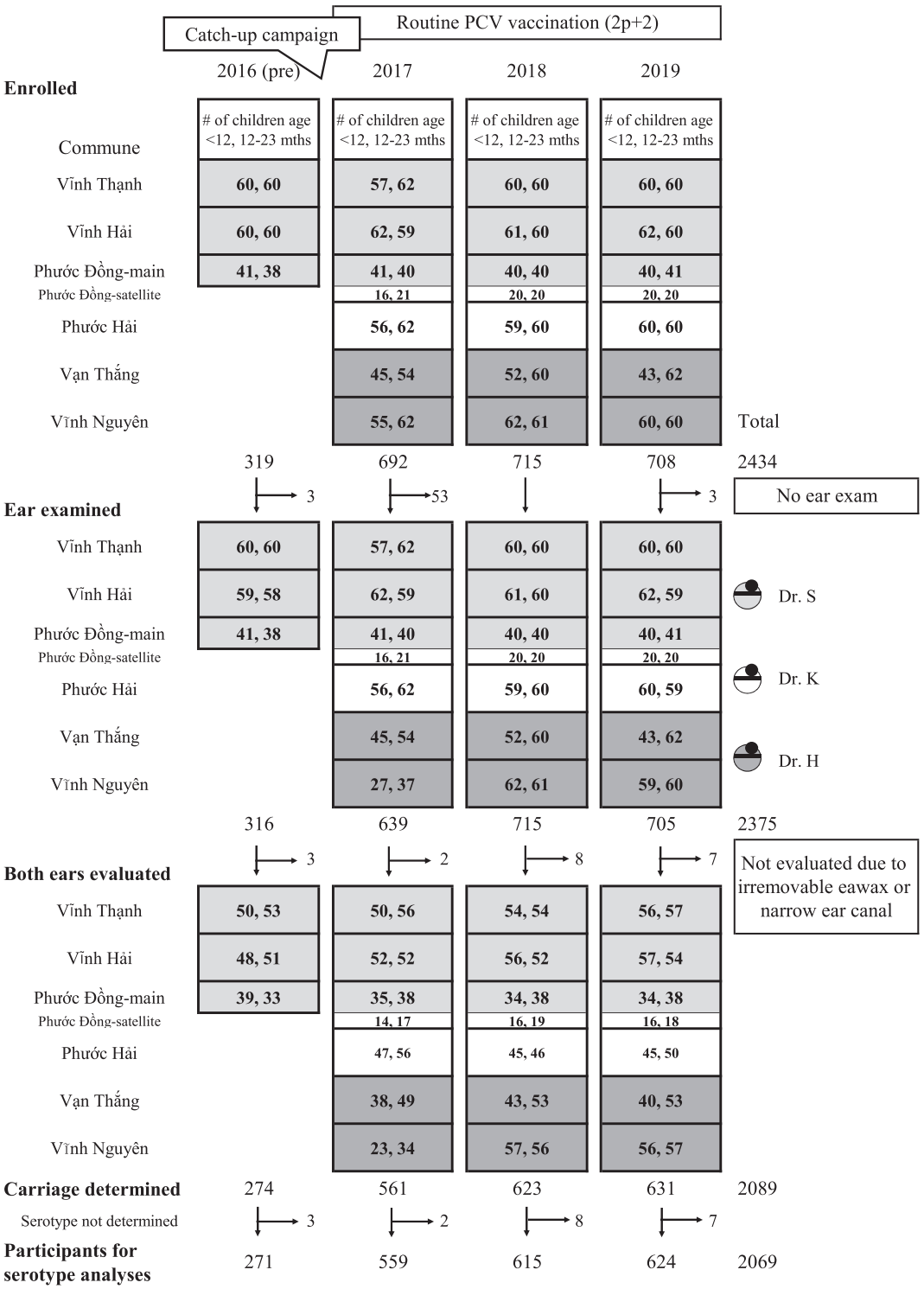

Fig. 1. Flow chart of enrollment, ear examination, and evaluation of the surveys 2016, 2017, 2018, and 2019. Light gray area (commune Vĩnh Thạnh, Vĩnh Hải, and the main part of commune Phước Đ ng) were targeted for the sensitivity analysis (Supplement table).

munes (Vạn Th ng and Vĩnh Nguyên in 2017, 2018, and 2019), respectively (Fig. 1). They examined the ear canal and tympanic membrane of each child using a digital otoscope (Digital Macro-View™ Otoscope, Welch Allyn, Skaneateles Falls, NY). Middle ear effusion was also evaluated using the attached insufflation bulb for pneumatic otoscopy. Earwax was removed before observation of the tympanic membrane where necessary and possible. Digital otoscope videos were recorded. The otolaryngologist who examined the ears assessed and categorised the status of the tympanic membrane. The assessments and categorisations were confirmed based on the recorded otoscopic videos independently by the other two otolaryngologists. If there were any disagreements regarding the assessments and categorisations, the discrepancies were resolved through discussions between the otolaryngologists. The interrater reliability among the three otolaryngologists for assessment and categorisation of each ear of the children was

evaluated using the Kappa statistic [20]. They assessed the otoscopic videos after each survey and there was no blinding for the survey years. We categorised the middle ear status as follows: normal, OME, AOM with apparent signs or symptoms of acute ear infection: fever, irritability, or sleeplessness, otorrhea, atelectasis, perforation, or others. OME was defined as the presence of fluid in the middle ear without any apparent signs or symptoms of acute ear infection [1]. OME detected in either of both ears was regarded as OME in this analysis.

2.5. Ethical considerations

The Institutional Review Boards of the National Institute of Hygiene and Epidemiology, Hanoi, Vietnam (approval number VN01057), and the Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, approved this study (approval number 16060291). Written informed consent was obtained from all parents or guardians before enrollment.

2.6. Statistical analysis

The prevalence of OME, OME associated with VT or non-VT pneumococcal carriage in the nasopharynx, and OME associated with no pneumococcal carriage were analysed in children aged < 12 months and 12–23 months for each survey. Additionally, we report VT, non-VT, and no pneumococcal carriages for each age group to show changes in carriage alone compared to changes in carriage associated with OME. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for each outcome by comparing the post-PCV odds (2017, 2018, and 2019) with the pre-PCV (2016) odds, using Firth's logistic regression model [21].

The numbers of communes surveyed in 2017–2019 were more extensive than in 2016. To check if our results could be affected by this difference in coverage, we performed a sensitivity analysis by restricting all participants to the same communes surveyed in 2016 (Fig. 1).

P values < 0.05 were considered statistically significant. Statistical analyses were conducted using R 4.0.4 and Stata version 14.2 [22].

3. Results

3.1. Characteristics of the participants

A total of 2434 children were enrolled to the four annual pneumococcal carriage surveys (2016–2019) of the PCV trial (Fig. 1). Among them, 59 did not receive the ear examination (53 in the 2017 survey because the otolaryngologist could not reach Vĩnh Nguyên commune due to an incoming typhoon at the study area and six went back home before ear examination) and 286 children had irremovable earwax or narrow ear canals in either or both ears and they were excluded from this OME study. The remaining 2089 (86%) children completed the bilateral ear examination and were included in the study: 274, 561, 623, and 631 in 2016, 2017, 2018, and 2019, respectively.

Of the 2089 children, 54% (n = 1129) were boys, and the median age at examination was 14.1 months (interquartile range, 8.3–18.9) (Table 1). Nearly all children (n = 271, 99%) were unvaccinated in 2016 (Table 1). For the post-PCV surveys, most (69–87%) of the children in the <12-month-olds had received two doses of PCV, while most in the 12–23 month-olds had been vaccinated two times in 2017 (88%) or three times in 2018/2019 (79–80%). This was because the 12–23-month-old children in 2017 were vaccinated by the catch-up campaign and those in 2018/2019 were immunized through routine vaccination (Table 2).

3.2. The prevalence of OME

Among the 2089 children, 308 had uni or bilateral OME (Table 3). Five with acute otitis media, three with otorrhea, two with perforation, one after left mastoidectomy, and 1770 without any abnormal findings were regarded as non-OME. The weighted mean of Kappa score for the inter-observer agreement among the three otolaryngologists was 0.82, indicating substantial agreement among them. The prevalence of OME in all children aged <24 months were 17.2% (95% confidence interval [CI] 12.9–22.1%), 19.8% (16.6–23.3%), 10.4% (8.1–13.1%), and 13.5% (10.9–16.4%) in 2016, 2017, 2018, and 2019, respectively. Outcomes stratified by age group (aged <12 and 12–23 months) are shown in Table 4.

3.3. Change in the prevalence of OME associated with VT pneumococcal carriage in the nasopharynx, with non-VT pneumococcal carriage, and with no pneumococcal carriage

Among the 2089 children enrolled and tested for pneumococcal carriage, 664 (31.8%) were positive. Twenty samples were excluded from VT and non-VT carriage analyses as the pneumococcal serotype could not be determined (Fig. 1). Among 93 serotype determined samples in pre-PCV, 6A was the most (n = 30), following 19F (n = 18), NT2 (n = 17), 6B (n = 16), 23F (n = 11), 14 (n = 4), 15A (n = 3), 15B/C (n = 3), 9 V (n = 1), 19A (n = 1) and NT2/NT3b (n = 1). Approximately half (49.5%) of them were PCV10 type.

Among the <12 month-olds, the prevalence of OME reduced in post-PCV in 2018 (OR 0.51, 95% CI 0.28–0.93) and 2019 (OR 0.53, 95% CI 0.29–0.97). In contrast, there was no reduction in OME among the 12–23 month-olds (OR 0.61, 95% CI 0.35–1.05 in 2018; OR 0.94, 0.57–1.59 in 2019) (Table 4 and Fig. 2). OME with VT pneumococcal carriage reduced in both age groups, with a greater reduction from 2016 to 2019 in the <12 month-olds (OR 0.20, 95% CI 0.05–0.69) than in the 12–23 month-olds (OR 0.41, 95% CI 0.10–1.60). The prevalence of OME with non-VT pneumococcal carriage increased clearly in 2017 (OR 3.09, 95% CI 1.47–7.45) and then returned to the 2016 baseline prevalence in 2018 (OR 0.94, 95% CI 0.40–2.43) and 2019 (OR 1.40, 95% CI 0.63–3.49) in the 12–23 month-olds, while the increase in 2017 was slight

Table 1
Characteristics of the participants in each survey in 2016, 2017, 2018, and 2019.

Characteristics	Number (%)	2016 (pre-PCV) [17] (n = 274)	2017 (n = 561)	2018 (n = 623)	2019 (n = 631)	Total (n = 2089)
Sex						
	Boy	150 (54.7)	291 (51.9)	350 (56.2)	338 (53.6)	1129 (54)
	Girl	124 (45.3)	270 (48.1)	273 (43.8)	293 (46.4)	960 (46)
Age						
	<12 months	137 (50.0)	259 (46.2)	305 (49.0)	304 (48.2)	1005 (48.1)
	12-23 months	137 (50.0)	302 (53.8)	318 (51.0)	327 (51.8)	1084 (51.9)

Table 2
Number and proportion of the participants who had taken each number of doses of pneumococcal conjugate vaccine before each survey in 2016, 2017, 2018, and 2019, by age group.

Number of doses of PCV taken before the survey	Year	2016 (n = 274)N (%)		2017 (n = 561)N (%)		2018 (n = 623)N (%)		2019 (n = 631)N (%)		Total (n = 2089)N (%)	
	Age group	<12 m	12–23 m	<12 m	12–23 m	<12 m	12–23 m	<12 m	12–23 m	<12 m	12–23 m
0		135 (98.5)	136 (99.3)	12 (4.6)	24 (8.0)	6 (2.0)	10 (3.1)	21 (6.9)	13 (4.0)	174 (17.3)	183 (16.9)
1		1 (0.7)	0 (0.0)	42 (16.2)	11 (3.6)	34 (11.2)	24 (7.6)	47 (15.5)	17 (5.2)	124 (12.3)	52 (4.8)
2		0 (0.0)	1 (0.7)	205 (79.2)	265 (87.8)	264 (86.6)	30 (9.4)	226 (74.3)	37 (11.3)	695 (69.2)	333 (30.7)
3		0 (0.0)	0 (0.0)	0 (0.0)	2 (0.7)	1 (0.3)	253 (79.6)	10 (3.3)	258 (78.9)	11 (1.1)	513 (47.3)
4*		1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	2 (0.6)	1 (0.1)	3 (0.3)

*Children got another dose of PCV outside of the trial in parental discretion.

Table 3
Diagnosis by otoscopic examination in each survey.

Ear diagnosis (number)	Survey				
	2016 [14]	2017	2018	2019	Total
OME	47	111	65	85	308
Otorrhea	0	1	1	1	3
Normal	227	448	553	542	1,770
AOM	0	1	1	3	5
Perforation	0	0	2	0	2
Other	0	0	1*	0	1*
Total	274	561	623	631	2,089

OME; otitis media with effusion, AOM; acute otitis media.
*One "other" case was after left mastoidectomy.

(OR 1.32, 95% CI 0.50–3.99) and the change in the prevalence was not obvious throughout the surveys in the <12 month-olds (OR 1.12, 95% CI 0.43–3.38 in 2018; OR 0.69, 95% CI 0.24–2.21 in 2019). On the other hand, in 2019, VT pneumococcal carriage in the nasopharynx in both age groups reduced compared to in 2016 among the <12 month-olds (OR 0.22, 95% CI 0.10–0.43) and among the 12–23 month-olds (OR 0.25, 0.13–0.50) (Fig. 3). Non-VT pneumococcal carriage increased in 2017 (OR 1.64, 95% CI 1.05–2.63) and prevalence higher than in 2016 (33–34%) was maintained during 2018–2019 in the 12–23 month-olds. An increase in non-VT pneumococcal carriage was also seen in the <12 month-olds (OR 2.01, 95% CI 1.13–3.77) in 2018, however, the increase was not persistent. The prevalence of OME with no pneumococcal carriage was relatively stable throughout the surveys in both age groups.

The prevalence and ORs in the main analysis were comparable with those in the sensitivity analysis targeting only commune Vĩnh Thạnh, Vĩnh Hải, and the main part of commune Phước Đ ng, the 2016 survey area (Supplemental Table).

4. Discussion

There are very few data of OME actively screened in a community and none examined the effect of PCV on it at a community level. This study investigated the direct and indirect (herd) effect of PCV10 introduction on the prevalence of OME detected by active screening in a community. We found that the prevalence of OME had reduced following the introduction of PCV10 in children aged <12 months, however, not in those aged 12–23 months. Categorising OME by the presence of pneumococcal carriage in the nasopharynx, OME with VT pneumococcal carriage reduced, reflecting the reduction of VT pneumococcal carriage by the PCV introduction. While, OME with non-VT pneumococcal carriage increased in the following year after the PCV introduction and before returning to the pre-PCV prevalence in the later years, the increase in non-VT pneumococcal carriage was sustained through to 2019 in the 12–23 month-olds.

Two previous studies investigated the effect of pneumococcal vaccine on OME prevalence actively surveyed in a community study cohort. In Finland, data from a randomised controlled double-blind trial were analysed for the direct effect of vaccination against OME during follow-up visits at the age of seven and 24 months [10]. The odds ratio for OME was 0.90 (95% CI 0.69–1.19) in a PCV7-vaccinated group compared to a control group. There was no evidence of an age-dependent association with the vaccine effect (0.84, 95% CI 0.58–1.21 at 7-month and 1.00, 95% CI 0.66–1.51 at 24-month visit). The other study compared birth cohorts before and after PCV7 and Pneumococcal Polysaccharide Vaccine introduction among Aboriginal children in remote Australia [11]. Most vaccinees (96%) and comparison subjects (100%) had experienced OME by six months of age. The authors discussed

Table 4
The prevalence of OME with VT pneumococcal carriage in the nasopharynx, with non-VT pneumococcal carriage, and with no pneumococcal carriage in each survey and the odds ratios in 2017, 2018 and 2019 compared with those in 2016 by age group.

Younger group: age < 12 months		Prevalence (95 %CI) (%)								Odds ratio (95 %CI)		
		N	2016	N	2017	N	2018	N	2019	2017 vs 2016	2018 vs 2016	2019 vs 2016
OME	OME	137	16.1 (10.3–23.3)	259	14.3 (10.3–19.1)	305	8.9 (5.9–12.6)	304	9.2 (6.2–13.0)	0.87 (0.49–1.55)	0.51 (0.28–0.93)	0.53 (0.29–0.97)
	OME with VT pneumococcus carriage	137*	5.1 (2.1–10.2)	258*	2.3 (0.9–5.0)	302*	0.7 (0.1–2.4)	303*	1.0 (0.2–2.9)	0.45 (0.15–1.32)	0.14 (0.03–0.55)	0.20 (0.05–0.69)
	OME with non-VT pneumococcus carriage	137*	3.6 (1.2–8.3)	258*	5.0 (2.7–8.5)	302*	4.3 (2.3–7.3)	303*	2.6 (1.1–5.1)	1.32 (0.50–3.99)	1.12 (0.43–3.38)	0.69 (0.24–2.21)
	OME with no pneumococcus carriage	137	7.3 (3.6–13.0)	259	6.9 (4.2–10.8)	305	3.9 (2.0–6.8)	304	5.3 (3.0–8.4)	0.93 (0.43–2.11)	0.52 (0.22–1.23)	0.69 (0.32–1.59)
Carriage	VT pneumococcus carriage	137*	17.5 (11.6–24.9)	258*	6.2 (3.6–9.9)	302*	3.6 (1.8–6.4)	303*	4.3 (2.3–7.2)	0.32 (0.16–0.61)	0.18 (0.08–0.37)	0.22 (0.10–0.43)
	non-VT pneumococcus carriage	137*	10.9 (6.3–17.4)	258*	14.3 (10.3–19.2)	302*	20.2 (15.8–25.2)	303*	13.2 (9.6–17.5)	1.34 (0.72–2.58)	2.01 (1.13–3.77)	1.21 (0.66–2.33)
	no pneumococcus carriage	137	71.5 (63.2–78.9)	259	79.2 (73.7–83.9)	305	75.4 (70.2–80.1)	304	82.2 (77.5–86.4)	1.51 (0.94–2.43)	1.22 (0.78–1.92)	1.84 (1.15–2.95)
Older group: age 12–23 months		Prevalence (95%CI) (%)								Odds ratio (95%CI)		
		N	2016	N	2017	N	2018	N	2019	2017 vs 2016	2018 vs 2016	2019 vs 2016
OME	OME	137	18.2 (12.2–25.7)	302	24.5 (19.8–29.8)	318	11.9 (8.6–16.0)	327	17.4 (13.5–22.0)	1.44 (0.88–2.41)	0.61 (0.35–1.05)	0.94 (0.57–1.59)
	OME with VT pneumococcus carriage	134*	3.0 (0.8–7.5)	301*	1.7 (0.5–3.8)	313*	0.0 (0.0–1.2)**	321*	1.2 (0.3–3.2)	0.54 (0.15–2.03)	0.05 (0.00–0.44)	0.41 (0.10–1.61)
	OME with non-VT pneumococcus carriage	134*	5.2 (2.1–10.5)	301*	15.3 (11.4–19.9)	313*	5.1 (2.9–8.2)	321*	7.5 (4.8–10.9)	3.09 (1.47–7.45)	0.94 (0.40–2.43)	1.40 (0.63–3.49)
	OME with no pneumococcus carriage	137	9.5 (5.1–15.7)	302	7.3 (4.6–10.8)	318	6.3 (3.9–9.5)	327	8.9 (6.0–12.5)	0.74 (0.37–1.54)	0.63 (0.31–1.33)	0.91 (0.47–1.85)
Carriage	VT pneumococcus carriage	134*	16.4 (10.6–23.8)	301*	8.0 (5.2–11.7)	313*	6.1 (3.7–9.3)	321*	4.7 (2.6–7.6)	0.44 (0.24–0.82)	0.33 (0.17–0.63)	0.25 (0.13–0.50)
	non-VT pneumococcus carriage	134*	23.9 (16.9–32.0)	301*	34.2 (28.9–39.9)	313*	32.9 (27.7–38.4)	321*	34.0 (28.8–39.4)	1.64 (1.05–2.63)	1.55 (0.99–2.48)	1.63 (1.04–2.59)
	no pneumococcus carriage	137	58.4 (49.7–66.7)	302	57.6 (51.8–63.3)	318	60.1 (54.4–65.5)	327	60.2 (54.7–65.6)	0.97 (0.64–1.46)	1.07 (0.71–1.61)	1.08 (0.72–1.62)

OME; otitis media with effusion, VT pneumococcus carriage; pneumococcus carriage with at least one of serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F, non-VT pneumococcus carriage; pneumococcus carriage with serotypes other than 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F.
Prevalence; the proportion of children who had each outcome such as OME or carriage to those who were examined for OME and pneumococcus carriage in each age group, each year.
*Number of participants excluding those where a pneumococcal serotype could not be determined.
**One-sided, 97.5% confidence interval.

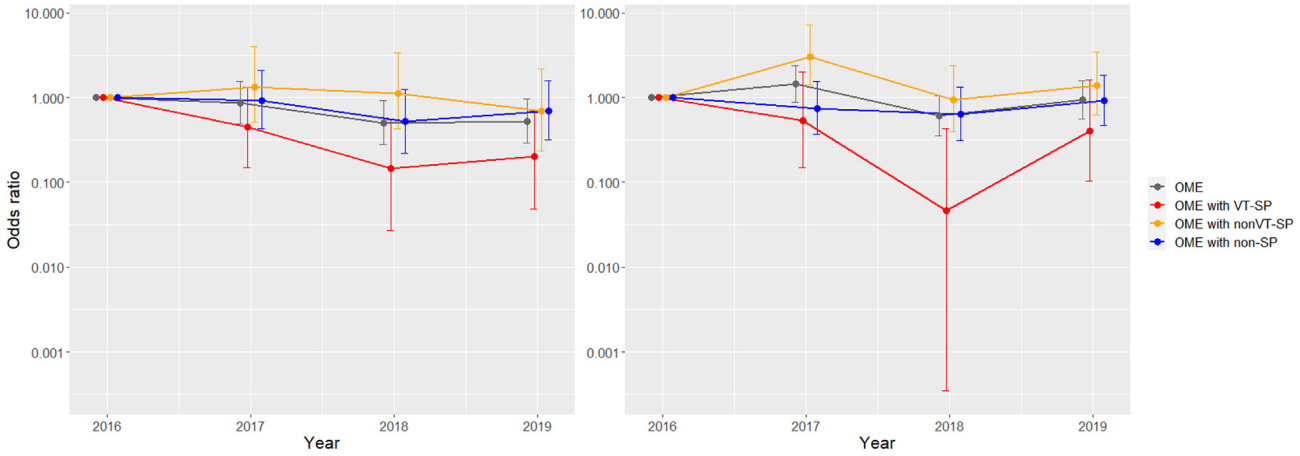

Fig. 2. Odds ratios (95% Confidence Intervals) for OME, OME with VT pneumococcal carriage in the nasopharynx, with non-VT pneumococcal carriage, and with no pneumococcal carriage in 2017, 2018 and 2019 compared to those in 2016 by age groups, presented on a log scale (left: <12 months, right: 12–23 months).

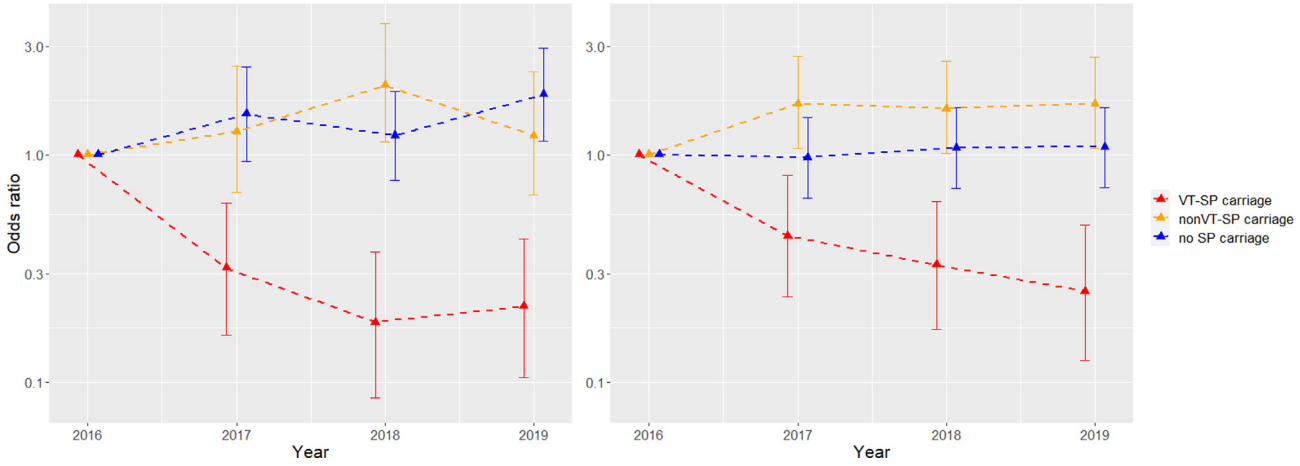

Fig. 3. Odds ratios (95% Confidence Intervals) for VT pneumococcal carriage in the nasopharynx, non-VT pneumococcal carriage, and no pneumococcal carriage in 2017, 2018 and 2019 compared to those in 2016 by age groups, presented on a log scale (left: <12 months, right: 12–23 months). OME; otitis media with effusion, VT; vaccine type including serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F.

a low effect of PCV in populations at very high risk of pneumococcal infection and concluded that a further study is necessary to document longer-term vaccine effectiveness. The poor effect of PCV introduction on all-cause OME in our study is comparable with these previous studies, although we detected the preventive effect in young children aged <12 months which was different from the report of the Finnish study. It might depend on the difference in pre-PCV VT pneumococcal carriage in this age group between in Nha Trang (18% in this study) and in Finland (12% [23]), which should be related to a proportion of pneumococcal OME in all-cause OME. Also, the indirect effect of PCV induced by the catch-up campaign in this study might contribute to reducing the OME prevalence in infants.

Pre-PCV pneumococcal carriage 28.5% and 41.6% in <12 and 12–23 month-olds, respectively, in this study are lower than those in the Gambia [24] (85.8%, 6–12 month-olds), Kilifi, Kenya [25] (74.4%, <5 years), Mozambique [26] (79.1%, HIV-uninfected aged <60 months), Nigeria [27] (71.0%, <5 years), and Cambodia [28] (68.0%, <5 years) and comparable with in Lao PDR [18] (14.3% in 5–8 weeks and 55.8% in 12–23 months) and Fiji [29] (23.6% in 5–8 weeks and 35.2% in 12–23 months). It might be because the study site, Nha Trang, is an urbanized place with good hygiene. A higher effect of PCV on reducing OME prevalence might be expected in countries with higher carriage rate before PCV introduction.

This study did not examine bacteriology in middle ear effusion, however, we used OME with pneumococcal carriage as a proxy of OME caused or triggered by pneumococcal infection or colonisation and the results of this study can be discussed comparing with studies of otitis media with pneumococcus cultured in the middle ear fluid. A prospective population-based study in Israel investigated the incidence of otitis media episodes clinically resulting in middle ear fluid culture, throughout pre-PCV, PCV7, and 13-valent PCV (PCV13) era [30]. Otitis media caused by PCV13 serotype-pneumococcus decreased significantly during PCV7-PCV13 period and those caused by non-PCV13 serotypes and culture-negative episodes increased significantly in PCV7 and then decreased in PCV13 period. The decreased PCV13-type pneumococcal otitis media in Israel, the relative risk reduction of pneumococcal AOM in the randomised controlled trials discussed in the Cochrane review [7], and the reduction of OME with VT pneumococcal carriage in this study concordantly suggested that PCV effectively reduces the development of AOM and OME following AOM caused by/associated with VT pneumococcus.

Dagan *et al.* [31] proposed that pneumococcus may be part of a disease progression in the pathogenesis of otitis media; infections

of the middle ear with a VT pneumococcus result in damage that promotes subsequent infections with other otopathogens, such as non-typeable *Haemophilus influenzae* (NTHi), non-VT pneumococcus, and *Moraxella catarrhalis*, leading to the formation of biofilms and more complex disease episodes, including chronic OME. OME defined in this study includes both chronic OME and transient middle ear effusion after AOM and it could reflect some stage of the disease continuum of otitis media in this theory. Therefore, change in the prevalence of OME with non-VT pneumococcal carriage in the 12–23 month-olds in this study might be supported by this theory. The 12–23 month-olds in 2017 were already born when PCV was introduced and not targeted for the routine vaccination but the catch-up campaign. Therefore, they might not be protected from the initial exposure by VT pneumococcus due to delayed timing of the initial dose of PCV which was given in February 2017 when they were 4–15 months old. While, the 12–23 month-olds in 2018–2019 might be protected from the initial VT pneumococcus exposure by the routine vaccination and PCV indirect (herd) effect possibly higher than in 2017, and had a lower prevalence of OME with non-VT pneumococcal carriage compared with that in 2017, despite a higher prevalence of non-VT pneumococcal carriage due to serotype replacement. So, the prevalence of OME may reduce also among the 12–23 months in later years if we continue the routine vaccination in this setting. Similar phenomena, increased and later decreased episodes of otitis media associated with non-VT pneumococcus, was observed in the aforementioned Israeli study [30] and in a randomised study in the Netherlands [32], although the change in Israel was seen in approximately ten years' span and that in Nha Trang was only in three years. It might be because the Nha Trang PCV trial achieved a high level of direct and indirect vaccine-induced immunity in the community quickly, with a catch-up campaign for children aged <37 months and high vaccine coverage, while the Israeli PCV7 introduction was nationwide with a catch-up for children <2 years and gradually increasing vaccine coverage. Other studies targeted children with a history of recurrent otitis media [33] or with documented persistent bilateral OME treated with tympanostomy tubes [34] to follow them up to see the effect of pneumococcal vaccine on recurrence of OME. These studies found no preventive effect of pneumococcal vaccine on subsequent OME development and might suggest a poor effect of PCV in children with established middle ear damage and biofilm formation. Additionally, differences in levels of immunity against VT-pneumococcus by different number doses of PCVs and different duration since the last vaccination [35,36] and difference in the distribution of pathogenic bacteria and viruses causing AOM or respiratory infection [37] could influence on the difference in the effect of PCV on the OME prevalence between <12 month and 12–23 month-olds although we do not have enough information in this study to discuss them further.

This study has some limitations. First, fewer communes were included in 2016 than 2017–2019 by practical consideration. Nevertheless, the sensitivity analysis focusing on the area included in the 2016 survey showed similar results to the main analysis and does not alter our conclusions. Second, we did not use tympanometry although it could have improved diagnostic accuracy for OME in this study as a guideline emphasised [1]. While, the guideline states that it should be used when the diagnosis is uncertain after performing pneumatic otoscopy. So we believe that our way of using pneumatic otoscopy, a tool with high diagnostic sensitivity and specificity [38], with three doctors' review could provide acceptably accurate diagnosis. Also, objectivity and inter-observer variability in diagnosis sometimes are problems in studies of OME. We recorded videos of pneumatic otoscopy and the three otolaryngologists assessed them independently. The inter-observer agreement among the three otolaryngologists was high. Therefore, we believe the evaluation was objective although we recognised there was no blinding for the probability of vaccination in the participants and it could cause a bias in diagnosis. Third, the study did not include the control arm (the communes with no PCV intervention in the main trial, not included to this study). The change in the OME prevalence over time might not be caused only by PCV introduction. However, there was no significant change in VT and non-VT pneumococcal carriage in the control arm from 2016 to 2019, observed in the main PCV trial (unpublished data). Fourth, this study did not test other respiratory viruses such as rhinovirus, Respiratory Syncytial virus, and influenza virus and bacteria such as *Haemophilus influenzae* and *Moraxeralla catarrhalis*, in the nasopharyngeal swab samples. The results could be confounded by the presence of other viruses or bacteria if it had changed over time and there was interference with pneumococcus. *Haemophilus influenzae* type-b vaccine (Hib) and measles containing vaccine (MCV), possibly influencing the prevalence of OME, were already introduced to the national immunization programme in Vietnam, in 2010 and in 1980′s, respectively. Vietnam has kept the Hib3 and MCV2 vaccination coverage mostly more than 90% since 2014 [39]. NTHi has been discussed as a major pathogen of middle ear diseases after PCV introduction. Studies are conflicting on whether pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV) provides protection against NTHi carriage or disease [12,14,40]. The effect of PHiD-CV (PCV10) on OME associated with NTHi might influence the results of this study. In addition, we did not quantify bacterial load of pneumococcus. Quantitative information of pneumococcus might support our assumption that OME with pneumococcal carriage is a proxy of OME caused in association with pneumococcal infection or colonisation if there is a load-dependent association between pneumococcal carriage and OME. However, there are no studies of the association to date and further studies are necessary for that.

In summary, the introduction of PCV10 was associated with a reduction in the prevalence of OME in the <12 month-old children. The effect was different in children aged 12–23 months, especially for OME associated with non-VT pneumococcal carriage, which increased and subsequently returned to the baseline level which could be explained by protection from VT pneumococcus in infancy. Additional cross-sectional surveys to see a longer term effect of PCV introduction on the OME prevalence in this community and also a longitudinal study following-up children from early infancy to see causal associations between pneumococcal or other virus or bacteria detection in the nasopharynx and OME development are required for further discussion.

4.1. Data sharing

The individual data of this study is a part of a large database of an ongoing PCV reduced dosing schedule trial which will be available after completion of the trial. So please contact the PI and we will consider the data sharing based on the purpose of the request.

CRediT authorship contribution statement

Michiko Toizumi: Conceptualization, Methodology, Investigation, Formal analysis, Writing – original draft. **Chisei Satoh:** Conceptualization, Methodology, Investigation, Writing – original draft. **Billy J. Quilty:** Formal analysis, Writing – review & editing. **Hien Anh Thi Nguyen:** Resources, Investigation, Data curation, Writing – review & editing. **Lina Madaniyazi:** Formal analysis, Writing – review & editing. **Lien Thuy Le:** Resources, Investigation, Data curation, Writing – review & editing. **Chris Fook Sheng Ng:** Formal analysis, Writing – review & editing. **Minoru Hara:** Conceptualization, Methodology, Investigation, Writing – review & edit-

ing. **Chihiro Iwasaki:** Resources, Investigation, Data curation, Writing – review & editing. **Mizuki Takegata:** Resources, Investigation, Data curation, Writing – review & editing. **Noriko Kitamura:** Resources, Investigation, Data curation, Writing – review & editing. **Monica Larissa Nation:** Resources, Investigation, Data curation, Writing – review & editing. **Catherine Satzke:** Resources, Investigation, Data curation, Writing – review & editing. **Yoshihiko Kumai:** Supervision, Writing – review & editing. **Hung Thai Do:** Resources, Investigation, Data curation, Writing – review & editing. **Minh Xuan Bui:** Resources, Investigation, Data curation, Writing – review & editing. **Kim Mulholland:** . **Stefan Flasche:** Formal analysis, Writing – review & editing. **Duc Anh Dang:** Resources, Data curation, Supervision, Project administration, Writing – review & editing. **Kenichi Kaneko:** Conceptualization, Methodology, Investigation, Supervision, Writing – review & editing, Funding acquisition. **Lay-Myint Yoshida:** Conceptualization, Methodology, Investigation, Supervision, Project administration, Writing – review & editing, Funding acquisition.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [Catherine Satzke and Kim Mulholland are investigators on a Merck Investigator Studies Program grant funded by MSD on pneumococcal serotype epidemiology in children with empyema and a clinical research collaboration on PCV vaccination in Mongolia funded by Pfizer. Both projects are unrelated to the current study].

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2022.07.047.

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