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ORIGINAL RESEARCH

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Pneumococcal conjugate vaccines reduce myringotomy with tympanostomy tube insertion in young children in Japan

Yui Ogawa MD[1] | Masaru Kunimoto MD, PhD[1,2] | Sachio Takeno MD, PhD[1] | Toru Sonoyama MD[1] | Takashi Ishino MD, PhD[1] | Takao Hamamoto MD, PhD[1] | Tsutomu Ueda MD, PhD[1]

[1]Department of Otorhinolaryngology, Head and Neck Surgery, Graduate School of Biomedical Sciences, Hiroshima University, Hiroshima City, Japan

[2]Kunimoto ENT Clinic, Hiroshima City, Hiroshima, Japan

Correspondence
Masaru Kunimoto, Department of Otorhinolaryngology, Head and Neck Surgery, Kasumi 1-2-3, Minami-ku, Hiroshima 734-8551, Japan.
Email: makunimoto@makunimoto-orl.com

Abstract

Objective: Pneumococcal conjugate vaccines (PCVs) have been reported to reduce the incidence of myringotomy with tympanostomy tube insertion (MTTI) in children. However, little information is available focusing specific ages. We examined the prophylactic efficacy of PCVs on the onset of complex otitis media (ComOM) that requires MTTI.

Method: From 2011, the public support for PCV7 started with the usual four-dose schedule and an emergency schedule for 2- to 4-year-old children in Japan. PCV7 was replaced with PCV13 in 2013. We reviewed the nationwide database obtained from the JMDC Claims Database (https://www.jmdc.co.jp/en/) to examine the MTTI incidence during the era before and after PCV introduction (from 2008 to 2010 and from 2011 to 2017, respectively). Subjects were analyzed by stratified age groups (from 0 to 8 years old) and in subdivided groups of 6 months (from 0 to 35 months old). We compared the MTTI incidence between the groups for each age as well as between those for each calendar year.

Results: A significant reduction in the MTTI incidence was detected in the 1-year-old children of the PCV era compared to those of the pre-PCV era. The reduction rates were more prominent in the 12–17 months group as compared to the 18–23 months group (PCV7 $p = .005$ and PCV13 $p = .011$, PCV7 $p = .014$ and PCV13 $p = .153$, respectively). The significant difference in the 1-year-old children continued in six of seven calendar years from 2011 to 2017, whereas no significant reduction was detected in children >3 years old.

Conclusions: The introduction of both PCV7 and PCV13 reduced MTTI incidences in children around 1 year old, and the effects were more prominent during the early half-periods. Our results support etiological evidence that pneumococcal infection in children aged 1 year and younger might play roles in the pathogenesis of ComOM that requires MTTI.

KEYWORDS
acute otitis media, myringotomy, otitis media with effusion, pneumococcal conjugate vaccine, tympanostomy tube

1 | INTRODUCTION

Myringotomy with tympanostomy tube insertion (MTTI) is a surgical procedure designed to treat the prolonged conductive hearing loss that occurs due to otitis media with effusion (OME). MTTI is also one of the methods used to reduce the recurrence of acute otitis media (AOM). Many studies have indicated that a bacterial ribonuclear acid is present in the middle ear effusions (MEFs) of OME patients.[1,2] In their 2016 systemic review, Ngo et al. reported that higher rates of bacterial components were detected in the MEF of patients with AOM, recurrent AOM (ROM), and OME by a combination of standard bacterial analyses and PCR methods.[3] Therefore, bacterial infection is speculated to play a role in the pathogenesis of OME.[4]

Streptococcus pneumoniae is one of the major causative microorganisms of AOM in children. The effectiveness of the heptavalent pneumococcal conjugate vaccine (PCV7) against AOM has been examined in respect to the total number of AOM episodes and the number of visits to healthcare facilities in pediatric patients. Meta-analyses indicated that PCV7 exerted preventive effects on pneumococcal AOM episodes and unidentified effects on AOM from all-causes.[5–7] With the use of databases across the total age groups, this vaccination was shown to reduce the rates of ROM and MTTI. Some studies further suggest prophylactic effects on the onset of ROM and the incidence of MTTI caused by complex otitis media (ComOM).[8–14] However, little information is available about specific age groups who would receive health benefit from the prevention of ComOM that requires MTTI.

We conducted the present study to investigate the etiological changes in the incidence of MTTI for pediatric ComOM in Japan after the introduction of PCV7 and PCV13 from the year of 2011 supported by a public health care program. For this purpose, we used the nationwide real-world database from multiple health insurance associations directed by the Ministry of Health and Welfare in Japan. The classification of otitis media (OM) was based on the International Classification of Diseases 10th Revision (ICD-10). The database was analyzed based on the groups of children stratified by age from 0 to 8 years old. We compared the MTTI incidence between the groups for each year of age as well as between those for each calendar year from 2008 to 2017. A subgroup analysis was conducted between the groups for every 6-month period from 0 to 35 months old. In Japan, mainly ear/nose/throat (ENT) specialists diagnose and manage OME cases on outpatient clinic base. We therefore consider that the ICD-10 classification of OM is reliable and tends to show a normalized distribution in terms of socioeconomic backgrounds.

2 | SUBJECTS AND METHODS

The study protocol was approved by the Ethics Committee at Hiroshima University (protocol No. E-953-1). PCV7 was launched and gained public funding in early 2011 of the Japanese market. In 2011 and 2012, the Japanese Government Policy on Emergency Vaccination (JGPonEV) encouraged three vaccinations of 7- to <12-month-old infants, two vaccinations of 12- to <24-month-old children, and a single vaccination of 24- to <60-month-old children. Typically, infants were vaccinated four times with PCV7: three doses before 12 months of age and one dose at 12–15 months of age as a booster dose. PCV7 was replaced with PCV13 in November 2013.

We used nationwide data collected from the JMDC Claims Database (https://www.jmdc.co.jp/en/) which is Japan's largest epidemiological receipt database. They accumulate health insurance receipts of insured individuals and their families those who were covered by the multiple health insurance associations. The maximum number of monthly enrollments for each age group in each calendar year served as the study population for the present analyses. The data of patients <15 years of age were used for this pediatric OM analysis. The following diagnoses in the ICD-10 were used to identify the targets for the OM analysis (Table 1): H65.2 (chronic serous OM), H65.3 (chronic mucoid OM), H65.4 (other chronic nonsuppurative OM), H65.9 (unspecified nonsuppurative OM), H66.0 (acute suppurative OM), H66.4 (suppurative OM, unspecified), and H66.9 (otitis media, unspecified). We consider that these disease categories include nearly 90% of the causative diseases for MTTI indications in the study.

Changes in the average rate of MTTI were analyzed for the 10-year period from 2008 to 2017. The period was subdivided into three eras based on the PCV introduction and types. They are called the pre-PCV era (2008–2010), the PCV7 era (2011–2013), and the PCV13 era (2014–2017). The comparison was made among the

TABLE 1 ICD-10 codes and corresponding diseases in this study

Codes of nonsuppurative otitis media	Codes of suppurative and unspecified otitis media
H65, Nonsuppurative otitis media	H66, Suppurative and unspecified otitis media
H65.1, Other acute nonsuppurative otitis media	H66.0, Acute suppurative otitis media
# H65.2, Chronic serous otitis media	H66.1, Chronic tubotympanic suppurative otitis media
# H65.3, Chronic mucoid otitis media	H66.2, Chronic atticoantral suppurative otitis media
# H65.4, Other chronic nonsuppurative otitis media	H66.3, Other chronic suppurative otitis media
# H65.9, Unspecified nonsuppurative otitis media	H66.4, Suppurative otitis media, unspecified
	H66.9, Otitis media, unspecified

Note: Codes with # were used as OME.
Abbreviations: ICD-10, International Classification of Diseases 10th Revision; OME, otitis media with effusion.

TABLE 2 The total number, population, and incidence of (MTTI) for each age from 2008 to 2017

Year	Age, years →	0	1	2	3	4	5	6	7	8
2008	No. VTI	9	46	23	21	22	24	12	5	4
	Population	6352	6619	6566	6237	6593	6477	6557	6489	6739
	Rate per 10,000	14	69	35	34	33	37	18	8	6
2009	No. VTI	15	64	25	16	18	32	25	16	10
	Population	8736	8889	9009	8851	8572	8917	8840	9013	8957
	Rate per 10,000	17	72	28	18	21	36	28	18	11
2010	No. VTI	39	125	50	38	47	51	31	27	10
	Population	15,379	15,521	15,209	15,101	14,734	14,153	14,789	14,624	14,772
	Rate per 10,000	25	81	33	25	32	36	21	18	7
Total of pre-PCV	No. VTI	63	235	98	75	87	107	68	48	24
	Population	30,467	31,029	30,784	30,189	29,899	29,547	30,186	30,126	30,468
	Rate per 10,000	21	76	32	25	29	36	23	16	8
2011	No. VTI	58	109	69	57	59	47	64	25	14
	Population	19,186	19,499	19,250	19,094	18,931	18,523	18,114	18,827	18,566
	Rate per 10,000	30	56	36	30	31	25	35	13	8
	CHISQ.TEST	0.0355*	0.0083**	0.4493	0.2946	0.6834	0.0407*	0.0091**	0.4591	0.8967
2012	No. VTI	50	154	81	60	70	59	54	33	26
	Population	24,699	25,056	25,133	24,583	24,600	24,252	23,970	23,416	24,305
	Rate per 10,000	20	61	32	24	28	24	23	14	11
	CHISQ.TEST	0.9107	0.0429*	0.9346	0.9184	0.8892	0.0134*	0.9998	0.5868	0.2775
2013	No. VTI	71	214	115	86	101	108	93	54	30
	Population	38,741	39,910	39,394	39,394	38,576	38,769	38,314	37,844	36,799
	Rate per 10,000	18	54	29	22	26	28	24	14	8
	CHISQ.TEST	0.4849	0.0002***	0.5277	0.4123	0.4695	0.0534	0.6394	0.5777	0.9001
Total of PCV7	No. VTI	179	477	265	203	230	214	211	112	70
	Population	82,626	84,465	83,777	83,071	82,107	81,544	80,398	80,087	79,670
	Rate per 10,000	22	56	32	24	28	26	26	14	9
	CHISQ.TEST	0.7503	0.0002***	0.9568	0.9027	0.7622	0.0062**	0.2723	0.4490	0.6439
2014	No. VTI	75	231	99	81	107	112	98	66	36
	Population	40,163	41,927	42,259	41,762	41,565	40,882	40,996	40,642	40,001
	Rate per 10,000	19	55	23	19	26	27	24	16	9
	CHISQ.TEST	0.5502	0.0005***	0.0305*	0.121	0.3951	0.0381*	0.7065	0.92	0.6127
2015	No. VTI	80	311	119	94	120	133	105	53	39
	Population	49,258	49,726	50,659	50,712	50,229	50,106	49,635	49,715	49,340
	Rate per 10,000	16	63	23	19	24	27	21	11	8
	CHISQ.TEST	0.1502	0.0261*	0.0251*	0.0574	0.1602	0.0162*	0.6859	0.0422*	0.9894
2016	No. VTI	93	355	110	134	149	177	117	72	36
	Population	49,877	52,285	51,353	52,309	52,349	52,007	51,990	51,578	51,639
	Rate per 10,000	19	68	21	26	28	34	23	14	7
	CHISQ.TEST	0.5255	0.1921	0.004**	0.8314	0.8699	0.6115	0.9947	0.4772	0.6427
2017	No. VTI	77	314	163	125	119	160	142	79	52
	Population	49,020	51,430	52,192	51,220	52,059	52,055	51,812	51,762	51,293
	Rate per 10,000	16	61	31	24	23	31	27	15	10
	CHISQ.TEST	0.1042	0.012*	0.8807	0.9027	0.0859	0.188	0.1823	0.814	0.3051
Total of PCV13	No. VTI	325	1211	491	434	495	582	462	270	163
	Population	188,318	195,368	196,463	196,003	196,202	195,050	194,433	193,697	192,273

(Continues)

TABLE 2 (Continued)

Year	Age, years →	0	1	2	3	4	5	6	7	8
	Rate per 10,000	17	62	25	22	25	30	24	14	8
	CHISQ.TEST	0.1881	0.0047**	0.0281*	0.3566	0.2187	0.0648	0.6809	0.3927	0.7367

Note: Populations are the maximum number of children who belonged to the JMDC Claims Database for each age group in each calendar year. *$p < .05$. **$p < .01$. ***$p < .001$ by χ^2-test.
Abbreviations: MTTI, myringotomy with tympanostomy tube insertion; PCV, pneumococcal conjugate vaccine.

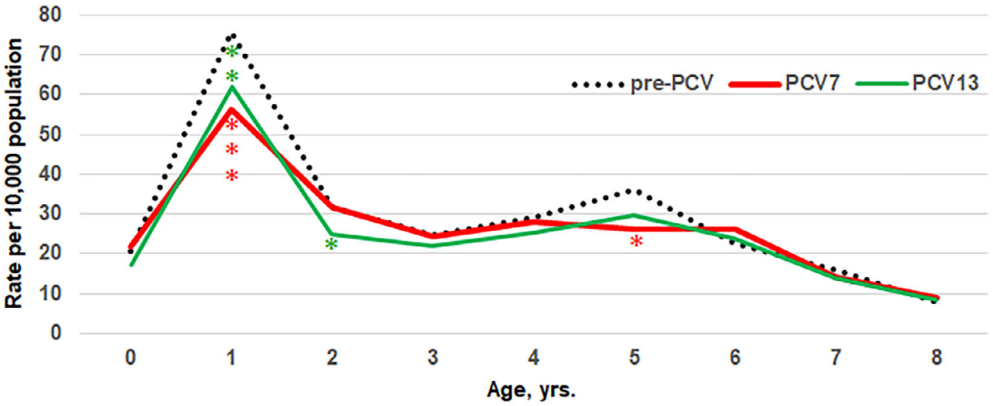


FIGURE 1 Changes in the myringotomy with tympanostomy tube insertion (MTTI) rate for each age group of children before and after the introduction of pneumococcal conjugate vaccines (PCVs). Pre-PCV: 2008–2010 ($n = 805$), PCV7: 2011–2013 ($n = 1089$), PCV13: 2014–2017 ($n = 5305$). *$p < .05$, **$p < .01$, ***$p < .001$ by χ^2-test

three era groups classified by year age (from 0 to 8 years old) and by 6-month age (from 0 to 35 months old). The distribution of the overall MTTI rates was calculated for each year age group, and the difference was compared between the pre-PCV era and the two PCV eras.

2.1 | Statistical analyses

We used the χ^2-test to examine differences in the MTTI incidences between the groups for era and for each age (years and months).

3 | RESULTS

To estimate the actual vaccination rate in children in Japan, we obtained the medical records from the Health Services and Welfare Division of Hiroshima City. The records indicated that the rate of PCV7 vaccination in infants born in Hiroshima City as of March 2012 was 100% based on the calculated number of vaccine lots and the targeted age population.[15] The average population of children from 0 to 14 years old in Japan during 2008–2017 was 17,963,400 (51% males, 49% females) according to the Ministry data. We used the data of the total of 4,593,845 cases among children of all ages on the JMDC Claims Database; the number of MTTIs in this population was 7600 (62% males, 38% females).

Table 2 shows summarized data of the number of cases, total population, incidence rates, and statistical results for each age group under 8 years old from 2008 to 2017. We found that approx. 90% of the MTTI cases were identified as derived from OME listed on ICD-10 codes (# in Table 1). The remaining 10% were suspected to be caused by ROM.

Figure 1 illustrates changes in the mean rates of MTTI for each year age in the pre-PCV era (2008–2010), the PCV7 era (2011–2013), and the PCV13 era (2014–2017). The mean rates of MTTI in 1-year-old children were significantly reduced in both the PCV7 and PCV13 eras compared to that in the pre-PCV era. The rates (per 10,000 age population) were 56 for PCV7, 62 for PCV13, and 76 for pre-PCV. As shown in Figure 2, the significant reduction of MTTI in the group of 1-year-old children continued in six of seven consecutive calendar years after the introduction of the PCV program from 2011; the exception was 2016. Partial reduction was observed in the groups of 2- and 5-year-old children. No significant reduction was observed in the groups of 0-, 3-, and 4-year-old children. This is in contrast with the fact that all of the enrolled children <5 years old had been vaccinated more than once due to the JGPonEV rescue program since 2011.

Because the mean MTTI rates in the group of 1-year-old children decreased significantly after the introduction of PCV, we conducted a subgroup analysis in a group of children <3 years old (Table 3). Figure 3 summarizes the changes in the mean MTTI rates subdivided into 6-month period in the three era groups. We observed that the decrease was significant especially in the 12- to 17-month-old group rather than in the 18- to 23-monthold group (PCV7 $p = .005$ and PCV13 $p = .011$ for the 12- to 17-month-old group; PCV7 $p = .014$ and PCV13 $p = .153$ for the 18- to 23-month-old group). These results suggest that the prophylactic effects appear more prominent during the early half periods of the one-year-old group.

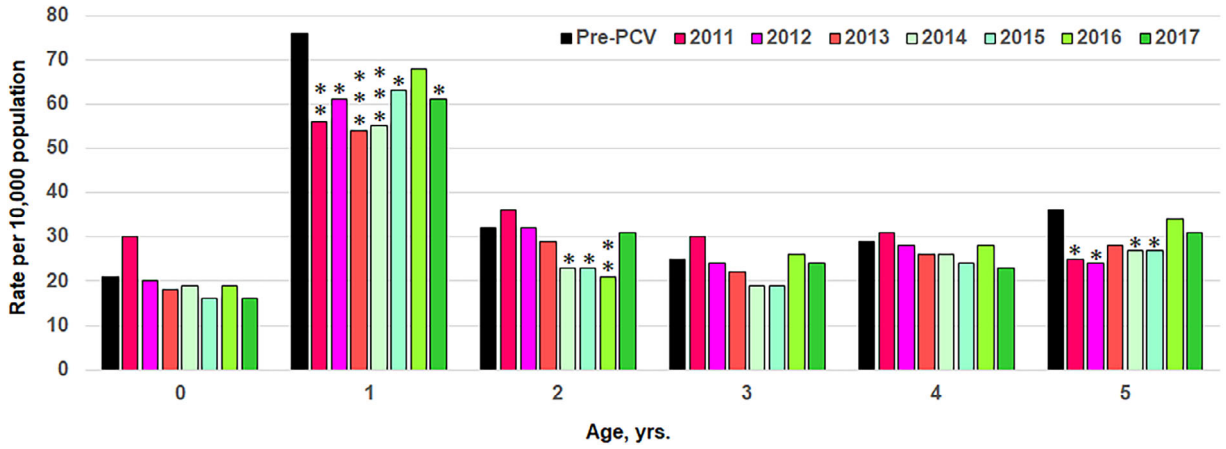


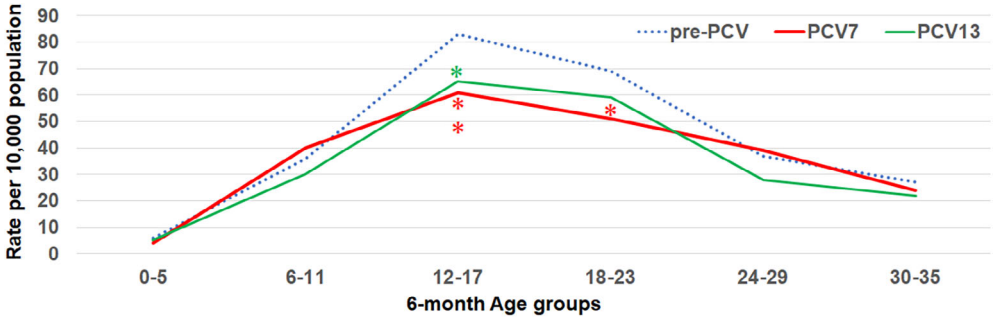
FIGURE 2 Comparison of the incidence of myringotomy with tympanostomy tube insertion (MTTI) for each age group after the pneumococcal conjugate vaccine (PCV) introduction. Pre-PCV: 2008–2010, PCV7: 2011–2013, PCV13: 2014–2017. *$p < .05$, **$p < .01$, ***$p < .001$ by χ^2-test

TABLE 3 The total number, population, and incidence of MTTI in the pre-PCV era, PCV7 era, and PCV13 era for 6-month age groups

Year	Age, months	0–5	6–11	12–17	18–23	24–29	30–35
Pre–PCV	No. VTI	9	54	131	104	58	40
	Population	15,556	14,911	15,854	15,175	15,731	15,053
	Rate per 10,000	6	36	83	69	37	27
PCV7	No. VTI	17	162	268	209	169	96
	Population	42,383	40,243	43,629	40,836	43,076	40,701
	Rate per 10,000	4	40	61	51	39	24
	CHISQ.TEST	n.a.	0.500	0.005**	0.014	0.682	0.526
PCV13	No. VTI	44	281	658	553	287	204
	Population	96,077	92,241	101,420	93,948	102,225	94,238
	Rate per 10,000	5	30	65	59	28	22
	CHISQ.TEST	n.a.	0.243	0.011	0.153	0.057	0.234

Note: Populations are the maximum number of children who belonged to the JMDC Claims Database for each age group in each calendar year. *$p < .05$. **$p < .01$ by χ^2-test. n.a.: not available.
Abbreviations: MTTI, myringotomy with tympanostomy tube insertion; PCV, pneumococcal conjugate vaccine.

FIGURE 3 Changes in the myringotomy with tympanostomy tube insertion (MTTI) incidence for each 6-month age group before and after the introduction of pneumococcal conjugate vaccines (PCVs). *$p < .05$, **$p < .01$ by χ^2-test



4 | DISCUSSION

OME is usually treated medically, and MTTI is indicated mainly for prolonged cases, although controversy remains regarding the indications. The incidence of MTTI thus reflects the rate of severe OME among children and pediatric ROM (which often accompanies uncontrollable repeated eustachian tube infection). Altogether, our findings indicate that the MTTI incidence can be employed as a useful marker that reflects the prevalence of severe ComOM. In this sense, etiological analyses using a large database require accurate diagnoses. In the study, we used the nationwide real-world database from multiple health insurance associations directed by the Ministry of Health and Welfare of Japan. The system maintains healthcare standards through the public health insurance coverage system.[16] We therefore consider that the dataset used herein is

unlikely to contain any bias in the distribution of patient demographics in respect to socioeconomic status, residence area, and income.

Prophylactic effects of PCV were examined in studies of the 10-valent pneumococcal non-typable Hemophilus influenzae protein D conjugate vaccine (PHiD-CV); most of the studies reported a reduction in the MTTI incidence by PHiD-CV.[17–19] Investigations conducted after the introduction of PCVs indicated that both PCV7[8–14,20] and the subsequent introduction of PCV13 continued to reduce the incidence of MTTI.[21–23] However, most of those etiological studies were conducted based on the use of the whole data with all age groups of children. There are few studies available for the specific age groups who would receive benefit for the prevention of ComOM that requires MTTI.

In 2016, Dagan et al. hypothesized that the prevention of early episodes of OM by pneumococcal vaccines might reduce the progression to complex diseases.[24] Their results suggest that PCVs are useful to reduce the frequency of severe ComOM. However, they did not discuss the specific ages at which PCVs may act most effectively or how long the vaccination effects will last. It is difficult to answer these questions with a prospective cohort study and multiple-center analysis, because the research entails high costs and requires a large pediatric population. Against this background, we used a nationwide real-world database in the present study because it has the advantages of providing a large population for each age during designated years with little bias based on the reliable health insurance records.

Jardine et al. noted that PCV7 administered on a three-dose schedule at 2, 4, and 6 months of age was routinely used in Australia without a booster shot, and they observed a significant effect on the total number of MTTIs.[13] They reported the adjusted incidence of MTTI in children was significantly reduced by 23, 16, and 6% for children aged <1, 1, and 2 years old, respectively. In contrast, the standard four-dose schedule in Japan includes a booster shot at 12–15 months of age. We found that the incidences of MTTI in 1-year-old significantly decreased by 26 and 18% in the PCV7 and PCV13 eras, respectively. These results might imply the augmented prophylactic effects of the last booster shots on the onset of severe ComOM that requires MTTI around this period.

Our present study contains three main findings. (1) A significant reduction of the MTTI incidence was detected among 1-year-old children after the introduction of PCVs (26% for PCV7 and 18% for PCV13, respectively). (2) No significant reduction was observed for infants (0-year-old) and 3- to 4-year-old children. (3) The results of the 6-month age-group analysis demonstrated that the prophylactic effects were more prominent during the early half of the first year of 1 year old, especially in the 12- to 17-month-old group. Taken together, these results suggest that the reduction in the MTTI incidence is not evenly distributed among all children, except for the group of 1-year-old children, who often suffer severe ComOM that requires MTTI.

Our results coincide with reports from randomized studies that estimated the vaccine effects for older children with ROM or OME who were vaccinated with PCV7 followed by a 23-valent pneumococcal polysaccharide vaccine (PPSV23)[25–27] Veenhoven et al. reported that combined vaccination did not affect the next occurrence of AOM and MTTI reduction in children >1 year old in Netherlands.[25] There was no protective effect of combined vaccination on AOM recurrences in older children aged 1–7 years in a study in Belgium.[26] Van Heerbeek et al. reported that a combined vaccination did not prevent the recurrence of OME among children aged 2–8 years old.[27] Considering the findings of these studies together with ours, it appears that the first vaccination for children >1 year old seems to have no ability to reduce the development of ROM or OME.

Few studies have compared the MTTI incidence before and after the introduction of PCV in different age groups of children. In the present study, the notable changes in the MTTI incidence mainly reflected the fact that >90% of the MTTIs were performed for children with severe OME based on the ICD-10 codes. In Japan, ENT specialists examine and treat most of patients with middle ear disease on an outpatient clinic basis. We speculate that the risk of MTTI patients being left off the database might be low enough to obtain reliable statistics in this study.

It remains to be determined whether the prevalence of MTTI derived from other causes including ROM shows the same tendency. Earlier studies including meta-analyses have shown that the effects of PCV7 on AOM remain unclear. The controversies include the vaccine's ability to reduce the incidence of AOM episodes and the frequency of emergency room visits for AOM.[5–7] Other studies have reported that PCVs reduce the incidence of MTTI caused by OME and recurrent OM. The Japanese guidelines for pediatric AOM recommend a myringotomy for moderate-grade cases with severe local findings, severe-grade cases, and treatment-resistant cases. The incidence of myringotomy thus reflects the prevalence of severe AOM in Japan.[28]

Sugino et al. reported that the rate of myringotomies performed for AOM in 1-year-old infants decreased significantly 2 years after the introduction of PCV7 compared to the rate before its introduction.[15] Our previous investigations also revealed a significant decline in the rate of myringotomies for AOM among 1- and 5-year-old children after the introduction of PCV7.[29] The present results together with those of the previous studies further indicate a close relationship between the pathogeneses of prolonged OME and ROM and eustachian tube dysfunction triggered by bacterial infection in children, especially those ≤1 year old. This may also explain the etiological findings that effects of PCVs do not manifest in children >2 years old.

5 | CONCLUSION

Our analysis of a nationwide database in Japan indicates that both the PCV7 and PCV13 inoculations reduced the incidence of MTTI for ComOM in younger children. The prophylactic effects were more prominent in the early half of the first year of age. Our results support etiological evidence that pneumococcal infection in children ≤1 year old might play roles in the pathogenesis of ComOM that requires MTTI.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

ORCID

Masaru Kunimoto https://orcid.org/0000-0002-1128-5449
Sachio Takeno https://orcid.org/0000-0002-9853-2501
Tsutomu Ueda https://orcid.org/0000-0001-9771-3880

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