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Influence of pneumococcal conjugate vaccines on acute otitis media in Japan

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ABSTRACT

Objective: This study investigated: (i) changes in the incidence of acute otitis media (AOM) following introduction of public funding for free inoculation with 7- and 13-valent pneumococcal conjugate vaccines (PCV7 and PCV13, respectively) and (ii) changes in the rate of myringotomies for AOM (MyfA) in children 1 year following the publication of the first edition of the clinical practice guidelines for the diagnosis and management of AOM in children in Japan.
Methods: PCV7 was launched on the Japanese market in 2010 and gained public funding in 2011. PCV7 was replaced with PCV13 in November 2013. Using the Japan Medical Data Center Claims Database, an 11-year study conducted between January 2005 and December 2015 investigated the decline in the incidence of visits to medical institutions (VtMI) due to all-cause AOM in children <15 years. The rate of MyfA from January 2007 to December 2015was also investigated and changes before and after introduction of public funding for PCV7 (pfPCV7) and PCV13 (pfPCV13) for children were examined. Statistical data for the age group between 10 years and <15 years served as the control. An analysis was conducted to examine changes for each age group, from infants that had received PCVs to children <5 years. Statistical analysis was performed using the chi-square test and Ryan's multiple comparison tests. Ryan's multiple comparison tests were applied at a 5% level of significance. Due to significant changes in the guidelines on the indications for myringotomy introduced in 2013, statistical analysis of the rate of MyfA was limited to the pre- and post-PCV7 period.
Results: After introduction of pfPCV7 and pfPCV13, no significant suppression of the incidence of VtMI was observed in any age group. There was a gradual decline in the rate of MyfA after 2011. Compared to the control group, significant differences in all age groups from infants to children <5 years were observed ($p < 0.009$, chi-square test). Within 2 years after the introduction of PCV7, a significant decline in the rate of MyfA was observed in 1- and 5-year-olds using Ryan's multiple comparison tests at a 5% level of significance.
Conclusion: The preventative effect of PCVs on AOM was not established in this study. There was, however, a significant decline in the rate of MyfA among 1- and 5-year-olds. Taking into consideration past studies, PCV7 may play a role in preventing the aggravation of AOM in 1-year-olds. When evaluating the effectiveness of PCVs, measures to evaluate severity may be as important as evaluating disease prevention.

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1. Introduction

Acute otitis media (AOM) is a common upper respiratory tract infection in children. *Streptococcus pneumoniae* is one of the major bacterial pathogens that cause AOM. The effect of the heptavalent pneumococcal conjugate vaccine (PCV7) on AOM is evaluated through: (i) literature reviews of analyses that look at the incidence of AOM-related visits to medical institutions (VtMI) and (ii) systemic literature reviews of questionnaire surveys. At present, the effect of PCV7 on preventing VtMI is considered to be marginal or modest [1,2]. According to a cohort study conducted by Hasegawa et al., PCV7 was shown to have an inhibitory effect on the incidence of AOM in Japan [3]. Conversely, an analysis using the Japan Medical Data Center (JMDC) Claims Database conducted by Yamanaka demonstrated that the number of AOM patients did not change significantly after the introduction of PCV7 [4].

Concerning the effect of 13-valent PCV (PCV13) on preventing VtMI, Marom et al. reported that there was a significant reduction in otitis media (OM) visits by children <2 years, which coincided with the advent of PCV13 [5].

The Japan Otological Society, the Japan Society for Pediatric Otorhinolaryngology, and the Japan Society for Infectious Diseases in Otolaryngology released the first edition of clinical practice guidelines for the diagnosis and management of AOM in children in Japan (JGfCA) [6] in 2006, with revisions published in 2009 and 2013 [7]. The JGfCA guidelines provide criteria for evaluating the degree of AOM and very detailed therapeutic methods using an algorithm based on subsequent severity classification. The first and second guidelines recommend myringotomy for AOM accompanied by severe otoscopic findings and for treatment-resistant cases. Myringotomy is performed after eligibility for the procedure is determined using a surgical microscope or magnifying otoscope. For this reason, changes in the incidence of myringotomies for AOM (MyfA) performed in Japan are thought to reflect changes in the incidence of AOM with severe middle ear inflammation. Sugino et al. reported that the rate of MyfA in 1-year-old decreased significantly in the first 2 years after the introduction of public funding for PCV7 compared to all years before introduction [8].

This study investigated changes in the incidence of VtMI and the rate of MyfA among children following the introduction of public funding for free inoculation with PCV7 and PCV13.

2. Methods

This study was approved by the Ethics Committee at Hiroshima University, Hiroshima, Japan (protocol # E-953).

In February 2010, PCV7 was launched on the Japanese market as a vaccination paid out of pocket. Public funding for PCV7 (PfPCV7) was initiated in 2011. 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. In 2011 and 2012, due to the government policy on emergency vaccination promotion, unvaccinated 7- to <12-month-old infants were vaccinated three times, 12- to <24-month-old children were vaccinated twice, and 24- to <60-month-old children were vaccinated once (Provisional Special Fund for the Urgent Promotion of Vaccination). PCV7 was replaced with PCV13 in November 2013.

This study investigated changes in the incidence of AOM-related pediatric VtMI between January 2005 and December 2015 and changes in the rate of MyfA starting in 2007, 1 year after the publication of JGfCA (2006), with a focus on infants and children <15 years. The investigation used data collected from the JMDC Claims Database. The JMDC Claims Database compiles information from approximately 310,000 to 2.69 million individuals that are covered by multiple health insurance associations (insured individuals and their families) belonging to the JMDC. As the study population, the number of annual and monthly enrollments, as well as their age groups, was examined. The maximum number of monthly enrollments for each age group in each fiscal year served as the study population for the analysis. Data for patients <15 years were used in the pediatric AOM analysis. The International Classification of Diseases 10th Revision with the following diagnoses were used to identify the targets for AOM analysis. In Japan, the Standard Disease-Code is used to classify and code diseases, which is based on the International Classification of Diseases 10th revision. The Standard Disease Name is the smallest unit recorded for an electronic medical record, which is managed by MEDIS-DC (https://www.medis.or.jp/) in Japan. In this study, the following diagnoses were used to identify targets for AOM analysis: H66.0 (acute suppurative otitis media), H66.4 (suppurative otitis media, unspecified), and some units under H66.9. H66.9 includes chronic otitis media, acute otitis media, otitis media, simple otitis media, traumatic otitis media, traumatic perforative otitis media, hemorrhagic otitis media, recurrent otitis media, hydrotympanum, postoperative otitis media, postoperative chronic otitis media, neonatal otitis media, perforative otitis media, old otitis media, facial palsy due to otitis media and late effects of chronic otitis media, exacerbation after surgery for chronic otitis media, chronic perforative otitis media, chronic otitis media acute exacerbation. In this study, only data of acute otitis media, recurrent otitis media, neonatal otitis media, perforative otitis media, simple otitis media, and otitis media from H66.9 were used as AOM data of H66.9.

The incidence of VtMI was analyzed using the monthly enrollment for each age group in that fiscal year within the study population. Myringotomy patients presenting both AOM and otitis media with effusion (OME) were included in the MyfA count; however, patients presenting with only OME were excluded from the count. As changes observed in children between 10 and <15 years were not associated with PCV immunization, their data were included in the analysis as the control.

For statistical analysis, the chi-square test was performed to determine whether differences existed in the incidence of VtMI and MyfA rate of each year in each age group. If significant differences were observed, Ryan's multiple comparison tests were applied to determine which pair of years was significantly different at a 5% level of significance.

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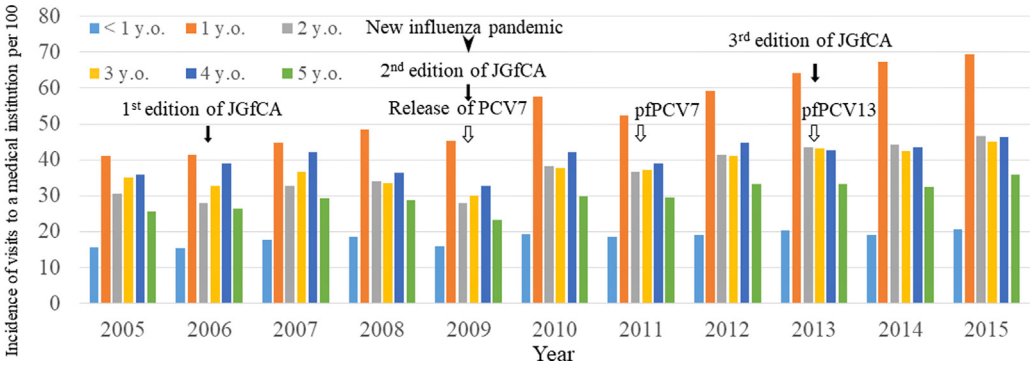

Fig. 1. Incidence of visits to medical institutions for acute otitis media in children ≤5 years. JGfCA, clinical practice guidelines for the diagnosis and management of AOM in children in Japan; PCV, pneumococcal conjugate vaccine; pfPCV, introduction of public funding for PCV; y.o., year old.

3. Results

In the age group comparison, the incidence of VtMI was highest in 1-year-olds followed by 2- to 4-year-olds. The incidence of VtMI tended to decline gradually as age increased. Compared to the 6 years prior to the introduction of pfPCV7, there were no age groups <5 years that demonstrated a decline in the incidence of VtMI in any fiscal year in the 2 years post-pfPCV7 (Fig. 1). Compared to all fiscal years prior to the introduction of PCV7/PCV13, there were no age groups in any fiscal year that demonstrated a decline in the incidence of VtMI in the 3 years post-PCV13 (Fig. 1).

The rate of MyfA tended to decline gradually after 2011 (Fig. 2). According to chi-square analysis, in 2011 (when pfPC7 was introduced) and 2012, significant changes were observed across all age groups from infants to 5-year-olds as well as in children aged 10 to <15 years ($p < 0.009$). At a 5% level of significance, a decline was also observed according to Ryan's multiple comparison test results for 1- and 5-year-olds (Table 1). However, according to Ryan's multiple comparison analysis, the rate of MyfA in 2007 was not significantly higher than those in 2008 and 2010 in <1-, 1-, 2-, and 5-year-olds. Additionally, the rate of MyfA in 2008 was not significantly higher than that in 2010 in <1-, 2-, 4-, and 5-year-olds. These results show that the incidence of MyfA had not significantly decreased in the pre-PVC era. Compared to pre-PCV introduction years, in 2011, increases were observed among <1-year-old infants and 7-, 9-, and 14-year-olds. Moreover, compared to the pre-PCV introduction years, in 2012, increases were observed among 7-, 11-, 13-, and 14-year-olds. The rate of MyfA tended to gradually decline further after 2013.

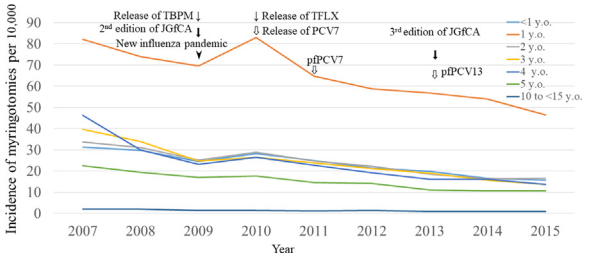

Fig. 2. Incidence of myringotomies for acute otitis media in children ≤5 years and 10 to <15 years. PCV7 was first introduced in February 2010. Public funding for PCV7 and PCV13 was approved in January 2011 and November 2013, respectively. Tebipenem (TBPM) was released in August 2009 and tosufloxacin (TFLX) was released in January 2010. JGfCA, clinical practice guidelines for the diagnosis and management of AOM in children in Japan; PCV, pneumococcal conjugate vaccine; pfPCV, introduction of public funding for PCV; y.o., year old.

4. Discussion

When the incidences of VtMI post-pfPCV7 and pfPCV13 were compared with the incidences of VtMI 6 years prior to PCV introduction, there were no age groups <5 years that showed a significant decline in the incidence of VtMI after the introduction of PCVs. Furthermore, there were some age groups that demonstrated an increase, although the reasons remain unknown.

Changes in the rate of MyfA based on JGfCA 2006 and 2009 [6] were also investigated. To our knowledge, no other studies in Japan have utilized large datasets to analyze the detailed post-pfPCV trends by age group. A decrease in the rates of MyfA was observed across all age groups post-pfPCV7 from 2011. Two years, in particular, showed significant declines in the rates for 1- and 5-year-olds. Using the JGfCA 2006 and 2009 guidelines, the clinical symptoms of AOM and eardrum findings were individually scored, and the severity was

Table 1
Ryan's multiple comparison analysis of myringotomies performed before and after introduction of publicly funded PCV7 at a 5% level of significance (*).

Age (year)	Year	2007	2008	2009	2010	2011	2012
<1	2011	*	*			–	*
	2012	*	*	*	*	*	–
1	2011	*	*	*	*	–	*
	2012	*	*	*	*	*	–
2	2011	*	*	*		–	*
	2012	*	*	*	*	*	–
3	2011	*	*	*		–	*
	2012	*	*	*	*	*	–
4	2011	*	*	*		–	*
	2012	*	*	*	*	*	–
5	2011	*	*	*	*	–	
	2012	*	*	*	*		–
10 to <15	2011	*	*			–	
	2012	*	*				–

diagnosed based on the total score. The 2006 and 2009 JGfCA guidelines recommended MyfA and high-dose amoxicillin, clavulanic acid/amoxicillin or high-dose cefditoren pivoxil therapy for moderate and severe cases that present with acute inflammation of the middle ear cavity. If the response was poor, intravenous ceftriaxone and ampicillin therapy were recommended. In the 2013 JGfCA guidelines, the use of tosufloxacin and tebipenem were added and the indications for MyfA were also modified. A previous study conducted in Japan also used MyfA as a parameter for treating AOM that presented severe inflammation of the middle ear cavity [4,8]. To understand the causes of declining MyfA rates, one must address not only pfPCV but also issues pertaining to (i) upper respiratory viruses in Japan such as changes in influenza, (ii) sales and usage data of new antimicrobials, and (iii) changes in the motivation of surgical practitioners.

According to the data from the National Institute of Infectious Diseases, Japan, there were no specific epidemics or downward trends related to influenza in 2011 and 2012 in Japan.

Yamanaka studied changes in the rate of MyfA between 2007 and 2013 for the following age groups: <2 years, between 2 years and ≤7 years, and between 7 years and ≤15 years. This study revealed that the decline in the rate of MyfA was associated with the increased usage of new antimicrobials on the market, which was reported to have a more significant effect than the effect of pfPCV7 [4]. Thus, it is difficult to deny the effect of these new antimicrobials. As such, physicians may have hesitated to perform surgeries on many borderline cases if effective, new antimicrobials were available. Sugino et al. conducted a multi-center analysis of changes for each age group that is eligible to receive pfPCV7 and found PCV7 had a significant role in decreasing MyfA rates of 1-year-olds, because no rapid increase in the usage of new antimicrobial in Hiroshima Prefecture was identifiable immediately after January 2011, decreases in myringotomies among <1-year-old infants were not justified according to use of tosufloxacin, and the number of MyfA has remained unchanged in ≥5-year-old children and adults, who can be treated with other strong new antimicrobials. Thus, these issues suggested that the decline in MyfA rate is not solely associated with the use of new antimicrobials [8]. Our findings, which used large datasets, seemed to also suggest that the preventive effect of PCVs on 1-year-old children may not be to inhibit the incidence of AOM but to protect against disease aggravation.

Next, we examined the effects of MyfA on changes in the motivation of surgical practitioners. Compared to the pre-PCV introduction period, an increase was observed in children <1year-old infants and 7-, 9-, and 14-year-olds in 2011 and 7-, 11-, 13-, and 14-year-olds in 2012. Therefore, it is difficult to solely attribute the significant decline in MyfA rates in 1-year-olds to the lack of motivation of practitioners. However, the decline in MyfA rates after 2013 may be largely related to significant changes in the mind of practitioners associated with the modification adopted by the revised 2013 JGfCA guidelines.

It is well known that 1 year after the introduction of PCV7 there was a significant decline in invasive pneumococcal disease among infants and 1-year-olds [9]. Our study poses very interesting results compared to these findings.

Numerous studies have evaluated PCV7 by investigating AOM episodes and the number of VtMI. These studies concluded that the preventive effect of PCV7 against AOM was very modest. In contrast, our study proposes the hypothesis that PCV7 use in 1-year-olds may contribute to the decreased incidence of severe middle ear inflammation of AOM. When evaluating the effectiveness of PCV, measures to evaluate severity may be as important as evaluating disease prevention.

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