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Annual trends in adverse events following mumps vaccination in Japan: A retrospective study

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ABSTRACT

Background: In Japan, a monovalent mumps vaccine is provided on a voluntary basis. Due to public concerns over post-vaccination aseptic meningitis, the vaccination coverage is not high enough. The present study investigated the incidence of adverse events, including aseptic meningitis, after Torii strain–derived mumps vaccination.

Methods: This retrospective, observational study used data collected by a vaccine manufacturer regarding adverse events following mumps vaccinations at medical institutions between 1992 and 2018. In addition, the number of Torii strain–derived mumps vaccines shipped each year was obtained. The incidence (per 100,000 doses) and 95% confidence intervals (CIs) were calculated for all adverse events and each adverse event, categorized as aseptic meningitis, encephalitis, mumps, mumps complications, and others.

Results: During the study period, 8,262,121 mumps vaccine doses were shipped, and 688 subjects reported adverse events. The incidence for all adverse events (per 100,000 doses) was 8.33, and the incidence was 4.19 for aseptic meningitis, 0.33 for encephalitis, 0.80 for mumps, 0.25 for mumps complications, and 3.78 for others. The incidence of aseptic meningitis (per 100,000 doses) was 7.90 (95% CI: 5.61–10.18) between 1998 and 2000 but declined by half, to 3.91 (2.46–5.36), between 2001 and 2003. The most recent incidence (per 100,000 doses) of aseptic meningitis, for the period 2016 to 2018, was 2.78 (1.94–3.62).

Conclusion: The incidence of post-vaccination aseptic meningitis has declined significantly since 2001, and the incidence has remained stable at fewer than 3 cases per 100,000 doses since 2010. Multiple factors might have contributed to the decline in aseptic meningitis incidence, including (i) lowered misclassification of aseptic meningitis resulting from echovirus infection; (ii) changes in the vaccine manufacturing process in 2000; and (iii) publication in 2008 of the recommendation for vaccination of children at 1 year of age.

1. Introduction

In Japan, a mumps vaccine using the Urabe Am9 strain (Biken) was first licensed in 1981 and had been used since that date. Subsequently, mumps vaccines containing other strains have also been approved. The Urabe strain-derived mumps vaccine was reported to have the highest effectiveness of the available mumps vaccines, and it was therefore used worldwide [1]. However, several studies suggested a relationship between the Urabe strain-derived mumps vaccine and the occurrence of aseptic meningitis [2–4]. Also in Japan, when routine immunization of children with a measles, mumps, and rubella (MMR) combined vaccine began in 1989, a number of cases of post-vaccination aseptic meningitis were reported, which caused considerable public concern [5–8]; thus,

Abbreviations: CI, confidence interval; MMR, measles, mumps, and rubella; NIID, National Institute of Infectious Diseases; PT, preferred term.

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use of the MMR vaccine was discontinued in 1993. Since that time, a monovalent mumps vaccine has been provided on a voluntary basis, and now two types of vaccines, made with the Hoshino strain and Torii strain, are available in Japan. The voluntary nature of the vaccination program is why coverage has remained at 30–50% [9,10] in Japan, considerably lower than in other countries, such as the US [11].

Due to the low vaccine coverage, many individuals remain susceptible to mumps in Japan. Mumps epidemics occur every 4–5 years in Japan [9], and complications (e.g., aseptic meningitis, deafness, orchitis) following natural mumps infection are public health concerns [9,12,13]. Reports have shown that the incidence of aseptic meningitis per 1000 mumps cases is 5.8, whereas the incidence rates of deafness and orchitis are 1.3 and 6.6, respectively [12,13]. Some of these cases could have been prevented if the individuals had been vaccinated. For example, in the US, which has an active vaccination program, the annual incidence of mumps has been reduced by more than 99%, and the incidence of mumps-related complications is lower among vaccinated subjects than unvaccinated subjects, even during outbreaks [14].

Because the mumps vaccine contains attenuated live virus, mumps-related complications can occur following vaccination; however, the post-vaccination incidence is thought to be much lower compared with post–natural infection [9]. Nevertheless, fear of complications among the public has hindered the vaccination program in Japan. Besides, a recent study demonstrated that the incidence of aseptic meningitis following vaccination using Hoshino strain (Kitasato Daiichi Sankyo) decreased from 10 cases per 100,000 doses in 1994–1998 to 5 cases per 100,000 doses in 2003–2009 and 2.5 cases per 100,000 doses since 2010 [15]. If another type of mumps vaccine, the Torii strain vaccine (Takeda Pharmaceutical), shows a similar decrease in the incidence of aseptic meningitis following vaccination, it could remove obstacles to recommending vaccination, and vaccine recipients could feel at ease receiving the vaccine.

The present study investigated annual trends in the incidence of adverse events, including aseptic meningitis, after mumps vaccination using the Torii strain between 1992 and 2018. In addition, background factors potentially associated with the annual trends (e.g., correlation with viral epidemics, changes in the manufacturing process, and changes in the recommended age for vaccination) were also considered.

2. Methods

2.1. Different mumps vaccine strains

To date, the following five mumps vaccine strains have been approved for administration to children in Japan: Urabe Am9 strain (Biken), NK M−46 strain (Chiba Serum Institute), Miyahara strain (Chem-Sero Therapeutic Research Institute), Hoshino (Kitasato Institute), and Torii strain (Takeda Pharmaceutical). All of these vaccine strains belong to clade B [16]. The last two vaccines are only available in Japan, and therefore this study focused on adverse events following the Torii strain-derived mumps vaccine.

2.2. Study design and database

This retrospective, observational study used data regarding post–mumps vaccination adverse events collected from medical institutions by a vaccine manufacturer. In Japan, the Law on Ensuring the Quality, Effectiveness and Safety of Pharmaceuticals and Medical Devices obligates vaccine manufacturers to report any adverse events following vaccinations to the Ministry of Health, Labor and Welfare. Therefore, vaccine manufacturers encourage physicians to report post-vaccination adverse events using anonymized patient data in order to fully account for adverse events. However, because it is not mandatory for physicians to report adverse events to manufacturers, medical representatives of the manufactures usually visit physicians and collect these data via personal interviews with physicians. In addition, the manufactures often obtain supplement information regarding post-vaccination adverse events with data retrieved from conference presentations and published literature. Manufacturers can thus construct a database of post-vaccination adverse events through these measures.

This study was conducted following the signing of a non-disclosure agreement between the vaccine manufacturer and the leader of researchers, after which the anonymized database was received from the manufacture.

2.3. Data collection

The database includes the following patient information: sex, age, vaccination date, concurrent medications, and detailed information regarding the adverse event(s) (i.e., the System Organ Classes and Preferred Terms (PTs) based on the Medical Dictionary for Drug Regulatory Activities, version 22.1, date of onset, severity, and overall judgement regarding causation between the mumps vaccine and the adverse events). The present study examined data reported between April 1992 and December 2018 (the study period).

To calculate the annual incidence of post-vaccination adverse events, the number of Torii strain–derived mumps vaccines shipped by year was also determined. Although we have no information as to how many doses of the mumps vaccine were actually administered, the vaccine is typically purchased on an as-needed basis in Japan; thus, it is likely that very few doses are discarded by medical institutions because they are not used. Therefore, in the present study, we assumed that all vaccines shipped during the study period were administered.

Background factors potentially associated with annual trends in adverse events were evaluated based on the following information: viral epidemics, such as enterovirus, coxsackievirus, and echovirus infections; changes in the manufacturing process of the mumps vaccine during the study period; and changes in the recommended age for vaccination during the study period. For viral epidemics involving enterovirus, coxsackievirus, and echovirus infections, data regarding the number of isolates of these viruses collected between January 1992 and December 2016 were gathered from the Infectious Agents Surveillance Report of the National Institute of Infectious Diseases (NIID) [17]. Information regarding whether there were any changes in the manufacturing processes of the vaccine during the study period was collected from the manufacturer. Changes in the recommended age for vaccination during the study period were determined by referring to the recommended immunization schedule in Japan [18].

2.4. Statistical analysis

For statistical analyses, the total number of adverse events and total number of cases involving reported adverse events were calculated. Reported adverse events were classified into five categories: mumps, aseptic meningitis, encephalitis, mumps complications other than aseptic meningitis or encephalitis, and others. PTs noted as mumps, parotitis, or parotid enlargement were classified as "mumps". PTs noted as aseptic meningitis, meningitis, viral meningitis, mumps meningitis, or viral meningoencephalitis were classified as "aseptic meningitis". PTs noted as encephalitis, viral encephalitis, encephalopathy, or cerebral edema were classified as "encephalitis". PTs noted as mumps orchitis, orchitis, testicular swelling, testicular pain, mumps deafness, hearing loss, or

acute pancreatitis were classified as "mumps complications other than aseptic meningitis or encephalitis". All other PTs were classified as "others".

The incidence (per 100,000 doses) and 95% confidence interval (CI) for all adverse events as well as the incidence (per 100,000 doses) and 95% CI for each adverse event classified into one of the five above-mentioned categories during the study period were calculated. Incidence (per 100,000 doses) was calculated as follows: number of reported cases/number of vaccines shipped × 100,000. The 95% CI was calculated as incidence ± 1.96 × standard error.

In addition, analyses were conducted for adverse events that (i) occurred within 28 days of vaccination, and (ii) were considered caused by the mumps vaccine based on the overall judgement on causation. Ultimately, the analyses in category (ii) were prioritized and shown in the results.

The relationship between the annual incidence of post-vaccination aseptic meningitis and the number of enterovirus, coxsackievirus, and echovirus isolates was examined by calculating Pearson's correlation coefficients and *P* values.

As the incidence of post-vaccination aseptic meningitis was very low, the incidence (with 95% CI) data were summarized for 3-year periods, and the period trends were then compared. For these comparisons, if the upper limit of 95% CI of the incidence for the current 3-year period was below the lower limit of 95% CI for the prior 3-year period, the incidence was defined as having declined significantly.

All tests were two-sided. All analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC, USA).

2.5. Ethical considerations

As the data used in the present study were retrospective and anonymized, it was not possible to provide a direct explanation of the study to participating subjects; therefore, informed consent was not necessary. The Ethical Guidelines for Medical and Health Research Involving Human Subjects [19] do not apply to research utilizing only already-established anonymized or de-identified information, as specified in Part 3, "Scope of Application" in Chapter 1. As the present study utilized only existing anonymized information, it would pose no risk or disadvantage to subjects. In addition, we disclosed the implementation of the present study. The study protocol was approved by the Ethics Committee of the Osaka City University Graduate School of Medicine (approval no. 4332; date of approval: May 21, 2019).

3. Results

A total of 8,262,121 doses of mumps vaccine were shipped between 1992 and 2018, and 1034 adverse events were reported by 688 vaccinated recipients (Table 1). The incidence (per 100,000 doses) was 8.33 for all adverse events, 0.80 for mumps, 4.19 for aseptic meningitis, 0.33 for encephalitis, 0.25 for mumps complications other than aseptic meningitis or encephalitis, and 3.78 for others. Aseptic meningitis accounted for approximately half of all adverse events. As for the subsequent process of AEs, 94% were reported to be recovered or improved. Among cases with aseptic meningitis, 98% were recovered or improved. Sequelae were reported from 10 cases including 5 encephalitis cases, one aseptic meningitis case, one deafness case, one acute disseminated encephalomyelitis case, one systemic rash and one cognitive dysfunction. One death was reported from encephalitis case who received mumps vaccine and pneumococcal conjugate vaccine at the same day. The incidence of AEs with sequelae or death was 0.13 per 100,000 doses.

Fig. 1 summarizes the incidence (per 100,000 doses) of each adverse event by year. The annual incidence of aseptic meningitis appeared to follow the trend for the annual incidence of all adverse events. The incidence of post-vaccination aseptic meningitis peaked in 1992 and 1997 and has been decreasing since 2000. There have been < 4 cases of post-vaccination aseptic meningitis per 100,000 doses since 2010.

Fig. 2 shows the relationship between the annual incidence of post-vaccination aseptic meningitis and the annual number of various viruses isolated. The correlation coefficients for the relationship between the annual number of enterovirus, coxsackievirus, and echovirus isolates and the annual incidence of post-vaccination aseptic meningitis were –0.17 (P = 0.41), –0.41 (P = 0.04), and 0.45 (P = 0.02), respectively. A significant positive correlation was observed between the annual number of echovirus isolates and the annual incidence of post-vaccination aseptic meningitis.

Table 2 shows the relationship between the incidence of post-vaccination aseptic meningitis for each 3-year period from 1992 to 2018 and background events. Although the incidence in the 1990 s was approximately 10 cases per 100,000 doses, it has declined continuously since 2001. The incidence (per 100,000 doses) of post-vaccination aseptic meningitis was 7.90 (95% CI: 5.61–10.18) between 1998 and 2000 but declined by half, to 3.91 (2.46–5.36), between 2001 and 2003. The most recent incidence (per 100,000 doses), for the period 2016 to 2018, was 2.78 (1.94–3.62). The upper limits of the 95% CI for the incidence (per 100,000 doses) since 2001 were lower than the lower limits of the 95% CI of the incidence (per 100,000 doses) prior to 2000, suggesting that events that occurred around 2000 contributed to the declining incidence of post-vaccination aseptic meningitis. With regard to background events, the incidence of echovirus infection has been very low since a large echovirus epidemic that occurred in 1998. Besides, in the manufacturing process of the mumps vaccine, the seed virus used when mumps vaccine was produced was passed through one generation in 2000. As for the recommended age for vaccination, various organizations and groups, such as the NIID and the Japan Pediatric Society, began to recommend vaccination of children at age 1 year in 2008. Perhaps due to these back-

Table 1
Incidence of adverse events following vaccination with Torii strain–derived mumps vaccine between 1992 and 2018.

	Reported number	Number of cases	Incidence (per 100,000 doses)	(95% confidence interval)
Number of vaccine doses shipped	8,262,121			
Total reported adverse events	1034	688	8.33	(7.71–8.95)
Mumps	66	66	0.80	(0.61–0.99)
Aseptic meningitis	346	346	4.19	(3.75–4.63)
Encephalitis	30	27	0.33	(0.20–0.45)
Mumps complications other than aseptic meningitis or encephalitis	22	21	0.25	(0.15–0.36)
Others	570	312	3.78	(3.36–4.20)

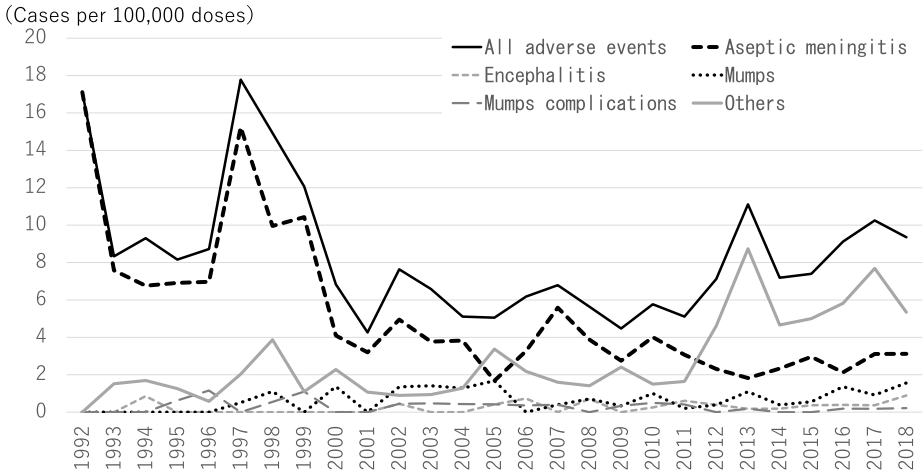

Fig. 1. Annual incidence of each adverse event (per 100,000 doses).

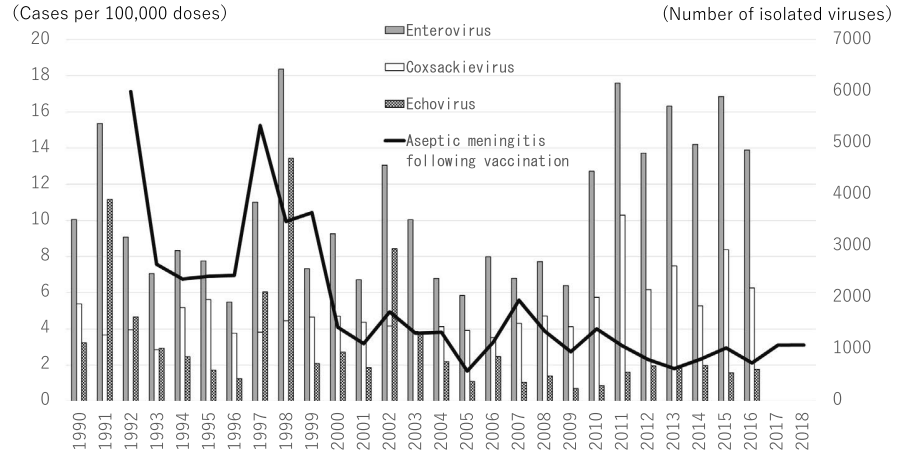

Fig. 2. Relationship between the incidence of post-vaccination aseptic meningitis and the annual number of specific viruses isolated in Japan.

ground events, the recent incidence of post-vaccination aseptic meningitis has remained stable at fewer than 3 cases per 100,000 doses.

4. Discussion

Vaccine safety is an important issue in carrying out a vaccination program. In Japan, the MMR vaccine using the Urabe Am9 mumps strain, AIK-C measles strain, and To-336 rubella strain was introduced as a routine vaccination program for children in 1989 [1]. However, post-vaccination aseptic meningitis was reported with a frequency of 0.16% [6], which caused considerable public concern. In 1991, the vaccination program switched to using MMR vaccines from each of three manufactures (i.e., the Biken vaccine included the Urabe strain, the Kitasato vaccine included the Hoshino strain, and the Takeda vaccine included the Torii strain of mumps). The frequency of aseptic meningitis after vaccination was 0.005% for the Biken vaccine [9], 0.03% for the Kitasato vaccine and 0.11% for the Takeda vaccine [6]. The frequency was not regarded as indicative of acceptable improvement, and thus the routine vaccination program was ended in 1993. These events may be one of the reasons that Japanese parents are reluctant to give their children a mumps vaccine. As the frequency of aseptic meningitis after vaccination with the Jeryl Lynn strain, which is the most widely used vaccine in other countries, is approximately 1 case per 1 million vaccinations [1,9], a new domestic MMR vaccine, if developed, is expected to have comparable safety, although it generally takes time to develop such a vaccine. While some hope to develop new domestic MMR vaccines, others have suggested that a vaccination program using currently available mumps vaccines should be introduced to reduce the number of people suffering from mumps disease burden as much as possible.

The results of this study revealed that the incidence of post-vaccination aseptic meningitis in persons vaccinated with the Torii strain has declined significantly since 2001, with the incidence remaining stable at fewer than 3 cases per 100,000 doses since 2010. The incidence trend is similar to that for the Hoshino strain-derived mumps vaccine [15]. Although the incidence of aseptic meningitis after natural infection is 5.8 per 1,000 mumps cases [12], the incidence of post-vaccination aseptic meningitis for both vaccine strains is considerably lower, at approximately 3 cases per 100,000 doses. The reason why the number of shipped vaccine doses increased after 2001 might have been related to the increased needs due to the mumps epidemic in 2001 and 2002 [9]. In addition to that, the coverage of the mumps vaccine is being increased year by year as awareness of mumps vaccine is being raised in Japan for a couple of decades. However, at the same time, there was no fact that special information about effec-

Table 2
Relationship between the incidence of aseptic meningitis every 3 years from 1992 to 2018 and background events.

Years	Events	Number of vaccine doses shipped	Reported cases of aseptic meningitis	Incidence (per 100,000 doses)	(95% confidence interval) [a]
1992–1994	1991 Echovirus epidemic 1993 Discontinuation of the measles, mumps, and rubella vaccine	338,020	33	9.76	(**6.43**–13.09)
1995–1997		528,269	53	10.03	(**7.33**–12.73)
1998–2000	1998 Echovirus epidemic 2000 Change in vaccine manufacturing process	582,568	46	7.90	(**5.61**–10.18)
2001–2003		716,556	28	3.91	(2.46–**5.36**)
2004–2006		747,767	22	2.94	(1.71–**4.17**)
2007–2009	2008 Publication of recommendation that children be vaccinated at age 1 year	824,981	33	4.00	(2.64–**5.37**)
2010–2012		1,408,185	43	3.05	(2.14–**3.97**)
2013–2015		1,604,590	38	2.37	(1.62–**3.12**)
2016–2018		1,511,185	42	2.78	(1.94–**3.62**)

[a] Bold figure indicates significant difference, compared the value of lower limit before 2000 with that of upper limit after 2001.

tiveness or safety of mumps vaccine was distributed in the public or medical staffs, and the AEs reporting system continued without any change. If aseptic meningitis was related to the vaccination, the number of reported post-vaccination aseptic meningitis would have been increased according to the increased doses, but such tendency was not observed. Although some cases may go unreported, it is reasonable to infer a downward trend, as the same reporting procedure has been used since 1992.

One background event that may have contributed to the decline in the incidence of post-vaccination aseptic meningitis is the low epidemic of echovirus since 1998. A moderate correlation (correlation coefficient of 0.45) was observed between the annual number of echovirus isolates and the annual incidence of post-vaccination aseptic meningitis; according to the coefficient of determination, 20% of post-vaccination aseptic meningitis cases can be explained by the echovirus epidemic. Echovirus epidemics occurred in 1991 and 1998, which coincided with periods of high post-vaccination aseptic meningitis incidence. Indeed, of the aseptic meningitis cases reported after vaccination, virologic testing of spinal fluid was done in only a few cases. Therefore, it is possible that cases of aseptic meningitis caused by echovirus infection may have been reported as post-vaccination aseptic meningitis as a result of misclassification. Echovirus is the most common causative virus of aseptic meningitis patients in general population in Japan [17]. Although the number of aseptic meningitis reported from sentinel institutions reached 2,985 cases (i.e., 6.31 per sentinel) in 2002, only small epidemics (i.e., less than 3.0 per sentinel) have been observed since then [20,21]. Because not only the number of aseptic meningitis but also the incidence of echovirus infections in general population has been very low in recent years, there is less impact due to misclassification, possibly contributing to the decline in the incidence of reported post-vaccination aseptic meningitis. To properly evaluate the safety of vaccination programs, it is important to implement accurate pathogenic diagnosis of post-vaccination aseptic meningitis cases.

As indicated above, the incidence of post-vaccination aseptic meningitis has declined significantly since 2001. This period coincides with the time that the seed virus used in production of the mumps vaccine was passed through one generation in the vaccine manufacturing process. Thus, the decline in this adverse effect following vaccination could be related to passage of the seed virus. However, some may raise concerns that a reduction in the incidence of adverse reactions to the vaccine due to passage of the seed virus could simultaneously be associated with a reduction in the immunogenicity and effectiveness of the vaccine. With regard to mumps, however, the epidemic has not increased even after 2001, compared with before [9]. The dominant circulating mumps virus in Japan had been in clade B before 1999 and thereafter was in clade G [22]. The clade of the vaccine strain thus differed from the circulating mumps virus after 2000, but vaccination conferred cross-immunity. Therefore, even if there was a simultaneous reduction in immunogenicity and effectiveness along with the decline in adverse reactions to the vaccine resulting from passage of the seed virus, it does not appear to have led to an increased incidence of mumps.

Another background event that may have affected the incidence of post-vaccination aseptic meningitis is the change in the recommended age for vaccination. Since 2008, vaccination has been recommended for children at age 1 year in Japan [18]. Previous reports have noted that there are fewer cases of post-vaccination aseptic meningitis among 1-year-olds compared with other age groups [23,24]. Although based on the data examined in this study, no further significant reductions in incidence after 2010 were observed; the incidence has remained stable at fewer than 3 cases per 100,000 doses since 2010.

This study did have some limitations, the most significant of which is that the investigation was based on information gathered from spontaneous reports. Spontaneous reports are extremely useful for detecting rare or serious adverse events; however, in the medical setting, only a fraction of cases with confirmed adverse events might be reported, and the proportion varies depending on various factors, which can lead to reporting bias. However, as mentioned earlier, the interpretation that the incidence of post-vaccination aseptic meningitis has declined since 2001 is reliable, as the same reporting procedure has been used since 1992. Second, the number of vaccinations in the present study was regarded as the same as the number of shipped mumps vaccines, as we have no information as to how many doses of the mumps vaccine were actually administered. If a large number of vaccines were discarded at the clinic, the incidence of adverse events might have been underestimated in the present study. However, the vaccine is typically purchased at each clinic on an as-needed basis in Japan, and thus, the number of discarded vaccines would likely be very small. The third limitation is that, although the present study considered the relationship with various viral epidemics as background events associated with the decline in the incidence of post-vaccination aseptic meningitis, the echovirus epidemic explains only 20% of aseptic meningitis cases; thus, the remainder may have been influenced by other factors. The effect of other factors such as changes in vaccine manufacturing processes and the recommended age for vaccination were also investigated; however, their associations with the decline in the incidence of aseptic meningitis may have been a coincidence in terms of timing. Furthermore, to what extent these events can explain the decline in incidence of aseptic menin-

gitis could not be clearly shown. In addition, other factors not investigated in the present study could have impacted the incidence of aseptic meningitis.

In conclusion, the incidence of post-vaccination aseptic meningitis has declined significantly since 2001, and the incidence has remained stable at fewer than 3 case per 100,000 doses since 2010. Multiple factors might have been contributed to the decline in post-vaccination aseptic meningitis incidence, including (i) lowered misclassification of aseptic meningitis resulting from echovirus infection; (ii) changes in the vaccine manufacturing process in 2000; and (iii) publication in 2008 of the recommendation for vaccination of children at 1 year of age.

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Declarations of interest

TN receives rewards such as lecture fees from Takeda Pharmaceutical Co., Ltd and Daiichi Sankyo Co., Ltd. All other authors declare they have no conflict of interest with respect to this research study and paper.

Authors' contributions

Ohfuji S designed the study, analyzed and interpreted the data, and wrote the initial draft of the manuscript. Nakano T assisted in preparation of the manuscript. All other authors contributed to data collection and interpretation and critically reviewed the manuscript. All authors approved the final version of the manuscript and agreed to be accountable for all aspects of the work and ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Yoshio Hirota reports financial support was provided by The Ministry of Health, Labor and Welfare, Japan. Takashi Nakano reports a relationship with Takeda Pharmaceutical Co Ltd that includes: speaking and lecture fees. Takashi Nakano reports a relationship with Daiichi Sankyo Co., Ltd that includes: speaking and lecture fees.

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