

〈Original Article〉**Age-specific incidence of aseptic meningitis following mumps vaccination from 2013–2016: estimation based on the number of reported adverse reactions to immunization in Japan****Hideaki Kumihashi^{1,*}, Munehide Kano^{1,*} and Satoko Ohfuji²**¹ Global Vaccine Business Unit, Takeda Pharmaceutical Company Limited, 2-1-1 Nihonbashi-Honcho, Chuo-ku, Tokyo 103-8668, Japan² Department of Public Health, Osaka City University Faculty of Medicine, 1-4-3 Asahimachi, Abeno-ku, Osaka 545-8585, Japan

(Received for publication September 26, 2018)

First-dose mumps vaccination at a younger age may be associated with a lower risk of vaccine-associated aseptic meningitis. However, to date, there are no estimates of the age-specific incidence of aseptic meningitis caused by the Torii strain-derived mumps vaccine. We investigated post-vaccination aseptic meningitis incidence in Japan using case data from the Ministry of Health, Labour and Welfare regarding adverse reactions following the Torii strain-derived mumps vaccine. The number of age-specific vaccine administrations was estimated from an Internet survey dataset and the number of vaccine shipments. Using these numbers, we estimated the age-specific post-vaccination aseptic meningitis incidence. Between April 1, 2013, and April 30, 2016, the incidence among first-dose vaccinations was 3.5 cases and the incidence among 1-year-old recipients was 1.3 cases (per 100,000 doses). Compared with the incidence at 1 year, significantly higher rates were observed at ages 2–6, 7–12, and ≥ 13 years. Our results suggest that vaccination with the Torii strain-derived mumps vaccine at age 1 carries a lower risk of aseptic meningitis compared with administration of this vaccine at older ages.

Introduction

Mumps, also known as epidemic parotitis, is a systemic infection caused by the mumps virus, which is a single-stranded, negative-sense RNA virus belonging to the *Rubulavirus* genus

*Corresponding author: Tel: +81-3-3278-3624, Fax: +81-3-3278-2502, E-mail: munehide.kano@takeda.com

of the Paramyxovirus family. The prognosis is generally good, but some cases complicate meningitis (frequency, <1–17%), encephalitis (frequency, <1–2%), mumps deafness (frequency, <1–7%)¹⁾. The incidence of mumps infection is estimated to have been 1.356 million in the peak year (2005) and 0.431 million in the bottom year (2007)²⁾. As mumps can be prevented by vaccination, routine immunization is performed in the majority of developed countries, which has resulted in fewer mumps epidemics in recent years³⁾.

The measles, mumps, and rubella (MMR) vaccine was introduced in Japan as a routine immunization in April 1989. However, aseptic meningitis following vaccination became a problem with social implications, leading to the discontinuation of MMR vaccination in April 1993. The incidence (0.05%)⁴⁾ was higher compared with the incidence ($\leq 0.001\%$) of aseptic meningitis following the Jeryl-Lynn strain-derived vaccine, which is used in many countries⁵⁾. Three types of mumps vaccines (Hoshino, Miyahara, and Torii strain) were used as voluntary vaccination thereafter, but the incidences of aseptic meningitis were 0.04%, 0.03%, and 0.06%, respectively⁶⁾. Although these incidences seemed to be substantially lower than the incidence following natural infection with mumps virus (1.24%)⁶⁾, mumps vaccination remains voluntary. Two types of mumps vaccine (Hoshino and Torii strain) are currently available, and the vaccination rate is 30%–40%, which has resulted in periodic epidemics every four or five years including the latest outbreak in 2015–2016⁷⁾.

The immunization schedule for mumps vaccine in Japan differs from that in other countries. Based on the package insert, the target age for vaccination is 1 year or older and the number of vaccinations is basically one, although some pediatricians give the second dose to preschool children. A recent study suggested that receiving the first mumps vaccine dose at a younger age reduces the risk of vaccine-associated aseptic meningitis⁸⁾. However, age-specific aseptic meningitis incidence caused by the Torii strain-derived mumps vaccine has not been estimated.

Here, we investigated age-specific incidence of post-vaccinal aseptic meningitis with Torii strain-derived mumps vaccine, which is produced by Takeda Pharmaceutical Company Limited. We used data on post-vaccination aseptic meningitis cases from The Adverse Reaction Review Committee, which is part of the Health Science Council in the Ministry of Health, Labour and Welfare (hereafter referred to as the Committee on Adverse Reactions)^{9–15)}. The number of age-specific vaccinations was estimated from an Internet survey dataset and the number of vaccine shipments.

Materials and Methods

Number of aseptic meningitis cases by age following vaccination with the Torii strain

The number of post-vaccination aseptic meningitis cases by age was based on reports submitted to the Committee on Adverse Reactions concerning adverse reactions to the Torii strain-

derived mumps vaccine. This study reviewed data collected over 37 months from April 1, 2013, when the first meeting of the Committee on Adverse Reactions was held, to April 30, 2016. During this period, the safety of the mumps vaccine was evaluated at the third (September, 2013)⁹⁾, eighth (February, 2014)¹⁰⁾, eleventh (October, 2014)¹¹⁾, thirteenth (January, 2015)¹²⁾, sixteenth (November, 2015)¹³⁾, eighteenth (April, 2016)¹⁴⁾, and twentieth (July, 2016)¹⁵⁾ meetings of the Committee on Adverse Reactions. Using the data on adverse reactions reported at these seven meetings, cases with any of the following adverse reaction terms were analyzed in this study: “aseptic meningitis,” “mumps meningitis,” “viral meningitis,” and “meningitis.” Information about the age of the subjects and the vaccine manufacturer in these cases was also collected.

Number of Torii strain-derived vaccine doses administered by age

The number of Torii strain-derived vaccine doses administered by age was estimated by multiplying the number of vaccine shipments by the age fraction of vaccine recipients. The number of vaccine shipments was regarded as the shipping quantity over the 37 months from April 1, 2013, to April 30, 2016, as reported by Takeda Pharmaceutical Company Limited to the Committee on Adverse Reactions. Because the mumps vaccine is purchased as needed, the number of doses that is likely to be discarded as unused in medical institutions is expected to be very low. Therefore, in this study, we assumed that all products shipped during the study period were administered.

To collect information on the age fraction of mumps vaccine recipients, an online survey was administered to pediatricians by Macromill Carenet, Inc., a contractor of Takeda Pharmaceutical Company Limited, from July 6–12, 2016. A request for participation in the survey was made to 5,350 pediatricians who were registered in a respondent panel of Macromill Carenet, Inc. The group of contacted pediatricians was selected in a manner aimed at ensuring that there was no bias in prefectures or in regions with local government vaccination funding (categorized by entire funding, partial funding, or no funding), with a target sample size of 50 responders each from regions with entire funding, partial funding, and no funding.

In this Internet survey, the surveyed pediatricians were asked to provide the following information: age and affiliation (clinic or other) of the pediatrician; public funding (entire funding, partial funding, or no funding) for mumps vaccination in the region where the pediatrician's facility is located; and the number of mumps vaccine doses administered (by age and by the first or second dose) in the past 3 months. This information was used to calculate the age fractions of vaccine recipients at the facilities where each pediatrician worked. When estimating the age fraction of vaccine recipients in Japan, we considered the possibility that the age distribution might differ depending on local public funding, so we also calculated the weighted-average of the age fraction with respect to local public funding. This integrated information about the funding of childhood vaccination in Japan (as of May 27, 2016)¹⁶⁾ was provided by the incorporated non-

profit organization “KNOW-VPD! Protect our Children”. For example, the vaccination fraction at 1 year of age in Japan was calculated as: vaccination fraction at 1 year of age according to pediatrician responses from the regions with entire funding \times proportion of local governments that entirely fund vaccination in Japan (9.8%) + vaccination fraction at 1 year of age according to pediatrician responses from the regions with partial funding \times proportion of local governments that partially fund vaccination in Japan (24.4%) + vaccination fraction at 1 year of age according to pediatrician responses from the regions with no funding \times proportion of local governments that do not fund vaccination in Japan (65.8%). A similar formula was used to estimate the vaccination fraction in each age group.

Age-specific incidence of post-vaccination aseptic meningitis

To calculate the age-specific incidence of post-vaccination aseptic meningitis (per 100,000 doses), the number of aseptic meningitis cases by age was divided by the number of doses administered by age and then multiplied by 100,000. Differences in the incidence of aseptic meningitis by age were tested for significance using a Fisher’s exact test. A two-sided significance level of 0.05 was used. All statistical analyses were performed using SAS version 9.3 software (SAS Institute Inc., Cary, NC, USA).

Results

Number of aseptic meningitis cases following vaccination with the Torii strain

During the period from April 1, 2013, to April 30, 2016, 46 cases of aseptic meningitis after vaccination with the Torii strain were reported. Of these, 44 cases were included in this study after excluding the following two cases: one case that reported vaccination with another manufacturer’s vaccine and one case that was the result of double reporting. The number of cases by age was 11 at age 1, 12 at age 2–6, 8 at age 7–12, 10 at ≥ 13 years of age, and 3 at an unknown age. The number of days from vaccination to onset was 3 to 34 days.

Number of Torii strain-derived vaccine doses administered by age

During the period from April 1, 2013, to April 30, 2016, the total number of Torii strain-derived vaccine shipments was 1,697,529. The results of the Internet survey conducted to investigate the age fraction of vaccine recipients are shown in Tables 1 and 2. The age distribution of survey participants did not differ from that of pediatricians working at medical facilities according to the “Current State of Physicians, Dentists and Pharmacists in 2014”¹⁷⁾ ($p=0.54$, Chi-squared test; Table 1). Additionally, no significant differences were observed in the proportions of affiliated medical institutions (Clinic versus Others) between participating pediatricians and overall pediatricians ($p=0.07$, Chi-squared test). There were similar numbers of pediatricians from

Table 1. Characteristics of the physicians who participated in the Internet survey

Characteristic	Category	Pediatricians participating in the Internet survey (N=154)		Pediatricians working at medical facilities (N=16,758)		<i>p</i> -value
		n	%	n	%	
Age (years)	20–29	1	0.6%	910	5.4%	0.54
	30–39	37	24.0%	4,305	25.7%	
	40–49	44	28.6%	3,510	20.9%	
	50–59	46	29.9%	3,680	22.0%	
	60–69	25	16.2%	2,937	17.5%	
	≥70	1	0.6%	1,416	8.4%	
Affiliation	Clinic	50	32.5%	6,650	39.7%	0.07
	Others	104	68.5%	10,108	60.3%	
Public funding by local government in the region where the facility is located	Entire funding	42	27.3%	N.D.	N.D.	Not determined
	Partial funding	54	35.1%	N.D.	N.D.	
	No funding	58	37.7%	N.D.	N.D.	

N.D.: No Data.

each region, which indicates that regions with different levels of public funding were equally represented (Table 1).

At the facilities where the survey participants worked, the first dose of the mumps vaccine was administered to 3,465 individuals, of whom 68.9% were age 1 (Table 2). The number of vaccine recipients tended to decrease with increasing age. The second dose was administered to 1,146 individuals, which is 33.1% of the number of first-dose administrations. The age distribution of vaccine recipients was investigated according to the public funding status in the region where the survey participants worked (Table 2). In regions with entire funding, the fraction of vaccine recipients at age 1 was as low as 37.2%, compared with 64.5% in regions with partial funding and 56.2% in regions with no funding, suggesting that the age distribution of vaccine recipients differs significantly depending on local public funding ($p < 0.05$). Considering the proportion of public funding for mumps vaccination in each region of Japan, the age fraction of mumps vaccine recipients in Japan was estimated to be 56.4%, 39.7%, 3.3%, and 0.8% at 1, 2–6, 7–12, and ≥13 year(s) of age, respectively (Table 2, overall, weighted-average of age fraction).

Based on these weighted-average of age fractions, the number of Torii strain-derived vaccine doses administered in Japan by age was estimated to be 957,406 at age 1, 673,919 at age 2–6, 56,018 at age 7–12, and 13,580 at ≥13 years of age.

Table 2. Age distribution of vaccine recipients by dose and public funding

Public funding	Dose timing	Number of doses administered Age fraction	Age (years)				Total	
			1	2–6	7–12	≥13		
Overall	First	Number of doses	2,387	1,007	53	18	3,465	
		Age fraction	68.9%	29.1%	1.5%	0.5%	100%	
		Weighted-average of age fraction	68.4%	28.7%	2.3%	0.6%	100%	
	Second	Number of doses	143	940	46	17	1,146	
		Age fraction	12.5%	82.0%	4.0%	1.5%	100%	
		Weighted-average of age fraction	14.4%	77.2%	6.9%	1.7%	100%	
	Total	Number of doses	2,530	1,947	99	35	4,611	
		Age fraction	54.9%	42.2%	2.1%	0.8%	100%	
		Weighted-average of age fraction	56.4%	39.6%	3.3%	0.8%	100%	
	Entire funding	First	Number of doses	378	330	0	1	709
			Age fraction	53.3%	46.5%	0.0%	0.1%	100%
		Second	Number of doses	32	354	2	4	392
Age fraction			8.2%	90.3%	0.5%	1.0%	100%	
Total		Number of doses	410	684	2	5	1,101	
		Age fraction	37.2%	62.1%	0.2%	0.5%	100%	
Partial funding	First	Number of doses	1,098	278	8	8	1,392	
		Age fraction	78.9%	20.0%	0.6%	0.6%	100%	
	Second	Number of doses	57	325	11	7	400	
		Age fraction	14.3%	81.3%	2.8%	1.8%	100%	
	Total	Number of doses	1,155	603	19	15	1,792	
		Age fraction	64.5%	33.6%	1.1%	0.8%	100%	
No funding	First	Number of doses	911	399	45	9	1,364	
		Age fraction	66.8%	29.3%	3.3%	0.7%	100%	
	Second	Number of doses	54	261	33	6	354	
		Age fraction	15.3%	73.7%	9.3%	1.7%	100%	
	Total	Number of doses	965	660	78	15	1,718	
		Age fraction	56.2%	38.4%	4.5%	0.9%	100%	

Weighted-average of age fraction: age fraction taking into account the proportion of public funding for the mumps vaccination.

Age-specific incidence of aseptic meningitis following vaccination with the Torii strain

The incidence of post-vaccination aseptic meningitis after the first dose in all age groups combined was calculated by dividing the number of aseptic meningitis cases during the study pe-

Table 3. Age-specific incidence of aseptic meningitis following vaccination with the Torii strain

		Age (years)					Total
		1	2–6	7–12	≥13	Unknown	
Aseptic meningitis incidence estimated from the number of administered first doses	Number of aseptic meningitis cases	11	12	8	10	3	44
	Weighted-average of age fraction of vaccine recipients	68.4%	28.8%	2.3%	0.6%	-	100%
	Estimated number of administered doses	872,532	367,383	29,340	7,654	-	1,275,632
	Age-specific incidence (per 100,000 doses)	1.3	3.3	27.3	130.7	N.D.	3.5
Aseptic meningitis incidence estimated from the total number of administered doses	Number of aseptic meningitis cases	11	12	8	10	3	44
	Weighted-average of age fraction of vaccine recipients	56.4%	39.7%	3.3%	0.8%	-	100%
	Estimated number of administered doses	957,406	673,918	56,018	13,580	-	1,697,529
	Age-specific incidence (per 100,000 doses)	1.2	1.8	14.3	73.6	N.D.	2.6

N.D.: not determined.

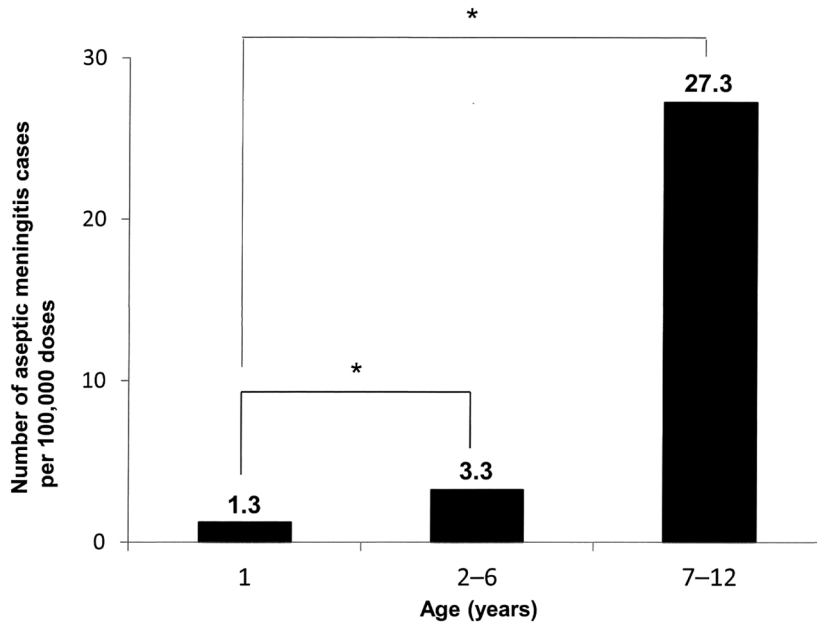
riod (44 cases) by the estimated number of vaccine shipments as the first dose, yielding 3.5 per 100,000 doses (Table 3).

The age-specific incidence (per 100,000 doses) from the number of administered first doses was estimated to be 1.3, 3.3, 27.3, and 131 at 1, 2–6, 7–12, and ≥13 years of age, respectively. Compared with the estimated incidence at age 1, significantly higher incidences by Fischer's exact test were observed at 2–6, 7–12, and ≥13 years of age (Table 3 and Fig. 1).

If post-vaccination aseptic meningitis is assumed to have occurred after the second dose as well as after the first, the post-vaccination aseptic meningitis incidence for all age groups would be 2.6 per 100,000 doses, based on the number of first doses (Table 3). When this incidence (per 100,000 doses) from the total number of administered doses is broken down by age, the rates are 1.2, 1.8, 14.3, and 73.6 at 1, 2–6, 7–12, and ≥13 years, respectively. Compared with the estimated incidence at age 1, significantly higher incidences by Fischer's exact test were observed at 7–12, and ≥13 years of age (Table 3 and Fig. 2).

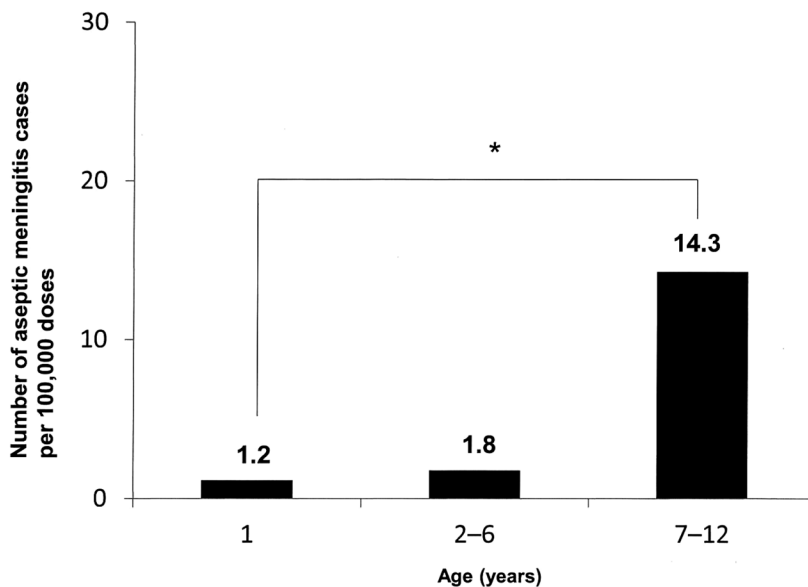
Discussion

Based on reports that the incidence of adverse reactions following MMR vaccination was lower among children receiving the second doses than among those receiving the first dose¹⁸⁾, and considering that complications from subsequent viral infection were reported to be less likely

Fig. 1. Aseptic meningitis incidence estimated from the number of administered first doses

The number of aseptic meningitis cases per 100,000 doses for each age group is shown, as calculated from the number of administered first doses. The data of ≥ 13 years of age was excluded in the figure due to the limited dose number administered to the age. The exact value for each group is listed in parentheses above the corresponding bar.

* $P < 0.05$

Fig. 2. Aseptic meningitis incidence estimated from the total number of administered doses

The number of aseptic meningitis cases per 100,000 doses for each age group is shown, as estimated from the combined number of first and second doses. The data of ≥ 13 years of age was excluded in the figure due to the limited dose number administered to the age. The exact value for each group is listed in parentheses above the corresponding bar.

* $P < 0.05$

after previous infection with or vaccination for mumps¹⁹⁾, aseptic meningitis incidence is assumed to have occurred following the first dose and, thus, was estimated from the number of administered first doses. This resulted in an incidence estimate for age 1 (1.3 per 100,000 doses) that was significantly lower than the incidences at ages 2–6, 7–12, and ≥ 13 years.

If mumps vaccination at age 1 were to be incorporated into the routine immunization program and the vaccination coverage reached to that of measles-rubella vaccination (MR vaccination) (96.2%)²⁰⁾, which is currently a routine immunization, we estimate that post-vaccination aseptic meningitis might occur in 13 per million children who are vaccinated at age 1. Notably, this incidence is approximately 1,000–4,000 times lower than that of aseptic meningitis following natural infection with mumps virus (1,6). However, if the mumps vaccination were recommended to older children, many more aseptic meningitis cases would be expected. Therefore, mumps vaccination should be incorporated into the routine immunization program and the administration of mumps vaccine at age 1 should be promoted to reduce the risk of post-vaccination aseptic meningitis.

The age dependence of aseptic meningitis following mumps vaccination observed in the present study is consistent with the results from a prospective cohort study by Muta *et al.*⁸⁾. Their study in Japan of 21,465 recipients of a domestically produced vaccine (Torii, Hoshino, or Miyahara strain) reported that the incidence of aseptic meningitis was 17.8 per 100,000 vaccine recipients who were < 3 years of age and 78.1 per 100,000 vaccine recipients who were ≥ 3 years of age, with a significant difference observed between the two age groups ($p=0.04$)⁸⁾. However, that study found that the overall incidence of aseptic meningitis following vaccination with a domestic Japanese strain was as high as 46.5 per 100,000 vaccine recipients⁸⁾, which is more than 10 times higher than that calculated in our study (2.6–3.5 per 100,000 doses). This difference may be attributed to the different survey methods used by these studies; our study included nationwide information, but the case detection was based on passive surveillance, while their prospective cohort study involved only limited medical institutions, but the case detection was based on active surveillance. In addition, the calculation of vaccine administration by the number of vaccine shipments may contribute to these differences.

Our study has some limitations. First, the age fraction of vaccine recipients was estimated based on information from an Internet survey. Although such a survey is easy to conduct and can be completed quickly, it may include selection bias caused by the computer literacy of solicited participants as well as information bias from the risk of fraud, such as the provision of false answers or replies by someone other than the intended participant. In addition, since the Internet survey targeted pediatricians, the estimated number of vaccine recipients ≥ 13 years of age might be obscure, which might bring about the higher incidence of this age group than the actual rate, because most of medical attendance after 15 years of age in Japan is managed by physicians in internal medicine and vaccination for preventing hospital infection including educational facilities are also excluded in the survey. Second, since we could not distinguish whether the reported

aseptic meningitis occurred after the first dose or the second dose, precise dose-based risk assessment is not possible. Third, the term of incidence may be inappropriate in this study, since it was calculated with the numerator being spontaneously reported cases (including cases for which virological diagnosis may not have been made) and as the denominator the quantity of vaccines shipped, which was assumed to be the number of vaccine recipients. Fourth, the coverage of local public funding was 37% (644/1,718) of whole local governments¹⁶⁾. This low coverage of local funding might be a reason of the difficulty to show the relationship between the local funding and the vaccination age. However, some misclassification, if any, would be non-differential, and thus does not materially affect the validity of the study results.

The Jeryl Lynn strain-derived vaccine and its derivative, the RIT-4385 strain-derived vaccine, are considered to be quite safe¹⁾. Besides, the mumps virus is classified into 12 genotypes from A to N, which are known to serologically differ from one another²¹⁾. The Jeryl Lynn and RIT-4385 strains belong to genotype A, the Japanese domestic strains including the Torii strain belong to genotype B, and the Japanese domestic epidemic strains belong to genotype G²²⁾. Previous reports indicate that while human serum antibodies induced by genotype B vaccines neutralize genotype G viruses as potently as genotype B viruses, hyperimmune rabbit serum antibodies induced by genotype A vaccines have slightly less potent neutralization activity against genotype G viruses²³⁾. Therefore, it may be important to retain mumps vaccines other than the Jeryl Lynn strain as options in anticipation of future mutations in the epidemic strains. Keeping in mind that complications of natural mumps infection still occur in Japan and that developing a mumps vaccine with further enhanced safety and efficacy may have its own set of challenges, it is important to actively recommend the currently available mumps vaccines as the immediate available measure to maximize a reduction in the disease burden.

Our results suggest that vaccination with the Torii strain-derived mumps vaccine at age 1 has a lower risk of aseptic meningitis compared with administration of this vaccine at higher ages. Although there were some limitations in the present study, together with the fact that the highest prevalence of mumps occurs at age 2–5, this finding suggests that the incorporation of the mumps vaccine into the routine immunization program of children would ideally target children at age 1.

Acknowledgment

We would like to thank the incorporated non-profit organization KNOW-VPD! Protect our Children for providing information about the public funding of mumps vaccination in Japan.

Conflict of Interest

Hideaki Kumihashi and Munehide Kano are employees of Takeda Pharmaceutical Company Limited.

References

- 1) Rubin SA, Plotkin SA: Mumps vaccine. In: Plotkin SA, Orenstein WA, Offit PA, editors. *Vaccines*. 6th Edition. Philadelphia: Saunders; 2012. p. 419–46.
- 2) National Institute of Infectious Diseases and Tuberculosis and Infectious Diseases Control Division, Ministry of Health, Labour and Welfare: The topic of this month: mumps (infectious parotitis) in Japan, as of July 2013. *Infectious Agents Surveillance Report* 2013; 34: 219–20. Available at <https://www.niid.go.jp/niid/images/iasr/34/402/tpc402.pdf> Accessed February 16, 2018.
- 3) Galazka AM, Robertson SE, Kraigher A: Mumps and mumps vaccine: a global review. *Bull World Health Organ*. 1999; 77: 3–14.
- 4) Kimura M, Kuno-Sakai H, Yamazaki S, *et al.*: Adverse reactions to MMR vaccines in Japan. The official report on nationwide postmarketing prospective study on standard strains MMR and each of three makers MMR vaccines. *Rinsho To Uirusu*. 1995; 23: 314–40. Japanese.
- 5) World Health Organization: Information sheet. Observed rate of vaccine reactions—measles, mumps, and rubella vaccines, May 2014. Available at http://www.who.int/vaccine_safety/initiative/tools/MMR_vaccine_rates_information_sheet.pdf Accessed February 16, 2018.
- 6) Nagai T, Okafuji T, Miyazaki C, *et al.*: A comparative study of the incidence of aseptic meningitis in symptomatic natural mumps patients and monovalent mumps vaccine recipients in Japan. *Vaccine*. 2007; 25: 2742–7.
- 7) National Institute of Infectious Diseases, Japan: Mumps (infectious parotitis) in Japan, as of September 2016. *Infectious Agents Surveillance Report (IASR)*. Available at <https://www.niid.go.jp/niid/ja/mumps-m/mumps-iasrtpc/6822-440t.html> Accessed August 16, 2018.
- 8) Muta H, Nagai T, Ito Y, *et al.*: Effect of age on the incidence of aseptic meningitis following immunization with monovalent mumps vaccine. *Vaccine*. 2015; 33: 6049–53.
- 9) Document distributed at the 3rd meeting of The Adverse Reaction Review Committee of Immunization Vaccination, Health Science Council of Ministry of Health, Labour and Welfare; September 12, 2013. Japanese.
- 10) Document distributed at the 8th meeting of The Adverse Reaction Review Committee of Immunization Vaccination, Health Science Council of Ministry of Health, Labour and Welfare; February 26, 2016. Japanese.
- 11) Document distributed at the 11th meeting of The Adverse Reaction Review Committee of Immunization Vaccination, Health Science Council of Ministry of Health, Labour and Welfare; October 29, 2014. Japanese.
- 12) Document distributed at the 13th meeting of The Adverse Reaction Review Committee of Immunization Vaccination, Health Science Council of Ministry of Health, Labour and Welfare; January 20, 2015. Japanese.
- 13) Document distributed at the 16th meeting of The Adverse Reaction Review Committee of Immunization Vaccination, Health Science Council of Ministry of Health, Labour and Welfare; November 27, 2015. Japanese.
- 14) Document distributed at the 18th meeting of The Adverse Reaction Review Committee of Immunization Vaccination, Health Science Council of Ministry of Health, Labour and Welfare; April 12, 2016. Japanese.
- 15) Document 1 distributed at the 20th meeting of The Adverse Reaction Review Committee of Immunization Vaccination, Health Science Council of Ministry of Health, Labour and Welfare; July

- 8, 2016. Japanese.
- 16) Incorporated non-profit organization KNOW-VPD! Protect our Children: Information on funding of childhood vaccination. As of May 27, 2016 (<http://www.know-vpd.jp/>) Accessed May 27, 2016. Japanese.
 - 17) Health Statistics Office, Vital, Health and Social Statistics Division, Statistics and Information Department, Minister's Secretariat, Ministry of Health, Labour and Welfare: 2014 Briefing of Survey of Physicians, Dentists and Pharmacists; December 17, 2015. Japanese.
 - 18) Patja A, Davidkin I, Kurki T, *et al.*: Serious adverse events after measles-mumps-rubella vaccination during a fourteen-year prospective follow-up. *Pediatr Infect Dis J.* 2000; 19: 1127–34.
 - 19) Yung CF, Andrews N, Bukasa A, *et al.*: Mumps complications and effects of mumps vaccination. England and Wales, 2002–2006. *Emerg Infect Dis.* 2011; 17: 661–7.
 - 20) Website of the Ministry of Health, Labour and Welfare: Final evaluation of measles-rubella vaccination in fiscal year 2015 (April 1, 2015 to March 31, 2016). (<http://www.nih.go.jp/niid/ja/id/545-disease-based/alphabet/aids/idsc/6790-01-2015.html>) As of March 31, 2016, Accessed 1 December 2016. Japanese.
 - 21) Jin L, Örvell C, Myers R, *et al.*: Genomic diversity of mumps virus and global distribution of the 12 genotypes. *Rev Med Virol.* 2015; 25: 85–101.
 - 22) Kidokoro M, Takeda M: New classification criteria for mumps virus and mumps epidemics in Japan. *IASR.* 2013; 34: 224–5.
 - 23) Inou Y, Nakayama T, Yoshida N, *et al.*: Molecular epidemiology of mumps virus in Japan and proposal of two new genotypes. *J Med Virol.* 2004; 73: 97–104.