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Cost-effectiveness analyses of monovalent mumps vaccination programs for Japanese children

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ABSTRACT

Background: The most common preventative measure against mumps is vaccination with mumps vaccine. Over 122 countries have implemented mumps vaccine routine immunization programs, mostly via Measles-Mumps-Rubella (MMR) vaccine. In Japan, the unexpectedly high incidence of aseptic meningitis caused by mumps vaccine led to the discontinuation of the MMR national vaccination program in 1993, inadvertently resulting in the re-emergence of mumps. Plans of introducing monovalent mumps vaccine into routine vaccination schedule have become one of the emerging topics in health policy that has warranted the need in evaluating its value for money.
Methods: We conducted cost-effectiveness analyses with Markov model and calculated incremental cost-effectiveness ratios (ICERs) of two different vaccination programs (a single-dose program at one-year-old, a two-dose program with second dose uptakes at five) compared to status quo from both payers' and societal perspectives. Transition probabilities and utility weights in estimating quality-adjusted life-year (QALY), and disease treatment costs were either estimated or obtained from literature. Costs per vaccination were assumed at ¥6140 (US$58;1US$ = ¥106).
Results: Both programs reduce disease treatment costs compared to status quo, while the reduction cannot offset vaccination cost. ICER of either program is found to be under ¥5,000,000 (US$47,170)/QALY willingness-to-pay (WTP) threshold from either perspective. Results of probabilistic sensitivity analyses expressed by net monetary benefit indicated that at the WTP threshold, the acceptability is at 92.6% for two-dose vaccination program, 0% for single-dose vaccination program, and 7.4% for current no vaccination program. Two-dose program was optimal among the alternatives. One-way sensitivity analyses revealed that proportion of mumps-related hearing loss among mumps cases and vaccine effectiveness (VE) were key variables in changing the ICERs.
Conclusion: Routine vaccination program of single- and two-dose programs were cost-effective from both payers' and societal perspectives. Between the two, the two-dose vaccination program was observed to be more favorable.

1. Introduction

Mumps is a viral infection of humans, primarily affecting the salivary glands. Serious complications of mumps include meningitis, encephalitis, orchitis, and hearing loss [1,2]. While there is no specific therapy for mumps, several countries have rolled out live attenuated Measles-Mumps-Rubella (MMR) immunization, which has led to a dramatic reduction of mumps incidence [1,2]. The World Health Organization (WHO) has recommended the introduction of mumps vaccine in all national immunization programs. Since July 2018, two-dose schedules were implemented in more than 90 % of the 122 countries where mumps vaccine is part of the routine immunization schedule, with most of the countries utilizing the Jeryl-Lynn (JL) mumps strain containing measles-mumps-rubella (MMR) vaccines [1,3]. These introductions not only have had a profound effect on the population's health, but also freed several healthcare resources for other priorities in resource-constrained settings.

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In Japan, the unexpectedly high incidence of aseptic meningitis (from 1 case/403 vaccinations to 1 case/1375 vaccinations) caused by mumps vaccine (with Urabe Am9 strain) has led to the discontinuation of MMR vaccines in the national vaccination program since 1993 [3]. Since then, mumps is not among the target diseases for immunization in the Preventive Vaccination Act [3–5], which makes Japan the only developed country where mumps vaccine is voluntary. In other countries, on the other hand, aseptic meningitis after mumps vaccination has been reported at widely varying frequencies (for example from 1 case/400 vaccinations to 1 case/1,500,000 vaccinations). However, the difference in frequency of vaccine-associated aseptic meningitis is not only a reflection of differences in vaccine strains and their preparation, but also of variation in study design, diagnostic criteria, and clinical practice, unique to a country's setting [1].

Vaccine uptake rate in Japan has declined rather quickly relative to mumps' non-inclusion in the target disease for immunization, leading to its re-emergence [3,5]. In 2013, the Committee on Immunization and Vaccine, Health Science Council of the Ministry of Health, Labour and Welfare (MHLW) has asserted that safety should be settled first before including mumps vaccine into the routine immunization schedule. Thus, high priority was given to determining the safety of a new MMR vaccine, which contained the JL strain. However, until today, the new MMR vaccine has not yet been available.

Recent studies have shown that lowering the age of the first dose of mumps vaccine can reduce the incidence of vaccine-related aseptic meningitis [6]. This promising progress has subsequently led to the improved public's perception of the health concerns regarding the safety of domestic monovalent mumps. In 2018, the Expert Council on Promotion of Vaccination submitted a written request of putting mumps monovalent vaccine into routine vaccination schedule to the MHLW [7]; an emerging topic in the domestic health policy arena. Several municipalities have already started to subsidize the vaccination, prompting the need to evaluate its value for money. In particular, four studies have performed economic evaluations on the inclusion of monovalent mumps vaccine into the routine vaccination list [8–11]. However, in Japan, mumps is defined as a sentinel-reported disease, which has posed a challenge in obtaining key variables for economic evaluation, such as age-specific annual incidence rates and age-specific proportion of mumps-related complications among cases. These have been one of the few setbacks faced by previous studies, which has led them to estimate the annual incidence rates by using sentinel surveillance data and assuming a uniform value for the proportions of complications regardless of the patient's age. Recently published literature, which analyzed health insurance reimbursement data have reported the age- and sex-specific annual incidence rates of mumps, as well as the age- and sex-specific proportions of mumps-related complications among cases [12–13]. This now serves as an opportunity to perform an additional cost-effectiveness analysis taking into account the granular information. Against this backdrop, our study aims to conduct a cost-effectiveness analysis of the mumps monovalent vaccine immunization program, utilizing granular and up-to-date data, with the hope of providing updated and more precise information on the value for money of the aforementioned intervention (mumps monovalent vaccine immunization program) to the decision-makers.

2. Methods

2.1. Literature search

We searched various databases for parameters to be used in the economic modeling, which is discussed in full in the subsequent section. Studies pertaining to epidemiology and prognosis of mumps-relevant disease in Japan's setting were accessed from Medline database, Igaku Chuo Zasshi database (a Japanese medical bibliographic database which contains over 10 million citations originating from Japan), MHLW Grant System, and annual statistical reports published by the government. Due to insufficient pieces of evidence from Japan, overseas' reports from Medline, The Cochrane Database of Systematic Reviews, Health Technology Assessment database, and National Health Service, Economic Evaluation Database regarding vaccine effectiveness (VE) and utility weights to estimate quality-adjusted life-year (QALY) were used instead.

2.2. Models

We compared single-dose (vaccination at 1 year old) and two-dose routine mumps vaccination program (vaccination at 1 and 5 years old, recommended by Japan Pediatric Society [14]) with status quo (i.e., no vaccination program). The 1-year-old cohort in 2020 was the hypothetical target population. A decision tree with Markov model was used to estimate the incremental cost-effectiveness ratios (ICER) of the respective vaccination programs. Currently, there are two domestically available vaccines which are of the Hoshino and Torii strains. ICERs were estimated from both payers' (including government, municipalities, vaccinees, patients, and third-party payers) and societal perspectives. In payers' perspective, only direct medical costs were included, while in the societal perspective productivity loss of caregivers or of patients due to disease treatment were further included.

A Markov model of courses followed by the target cohort under consideration was constructed based on epidemiological data and VE (Fig. 1). Ten mutually exclusive health statuses were set based on studies, which reported mumps-related disease burden from 2005 to 2017, sourced out from health insurance reimbursement database [12–13]. In brief, these health statuses were: health, symptomatic infected without complications, symptomatically infected with complications (meningitis, encephalitis, hearing loss, orchitis, pancreatitis, and others), asymptomatically infected, and death. The vaccination branch was identical with the no-vaccination branch except that VE will be applied only to the vaccination branch. The Markov cycle for each stage was set at 1 year, with the model programmed to cease when the cohort's age reached 40. At the last cycle, those without sequelae were assumed to have an average life expectancy of the Japanese population at 40 years old [15], while those with neurological sequelae were assumed half of the average expectancy based on a study by Morrish et al., which reported that mortality rate of individuals with neurological sequelae at age 40 was twice of that in the matched population [16]. Outcomes in terms of QALY were estimated by assigning transition probabilities and utility weights from the literature to the Markov model. ICER, which was estimated as $(\text{cost}_{\text{vaccination program}} - \text{cost}_{\text{no vaccination program}})$ divided by $(\text{QALY}_{\text{vaccination program}} - \text{QALY}_{\text{no vaccination program}})$, was used to investigate whether the vaccination program yields sufficient value to justify its cost. The model was parameterized using TreeAge Pro software (version 2020; TreeAge, Inc, Williamstown, MA).

2.3. Outcomes estimation

2.3.1. Incidence of mumps, proportions of complications among cases and of adverse events

Age and sex-specific annual incidence rates of symptomatic mumps and proportions of mumps-related complications among cases were obtained from studies that analyzed the health insurance reimbursement data (from 2005 to 2017) [12–13]. Annual incidence rates of asymptomatic mumps were estimated based

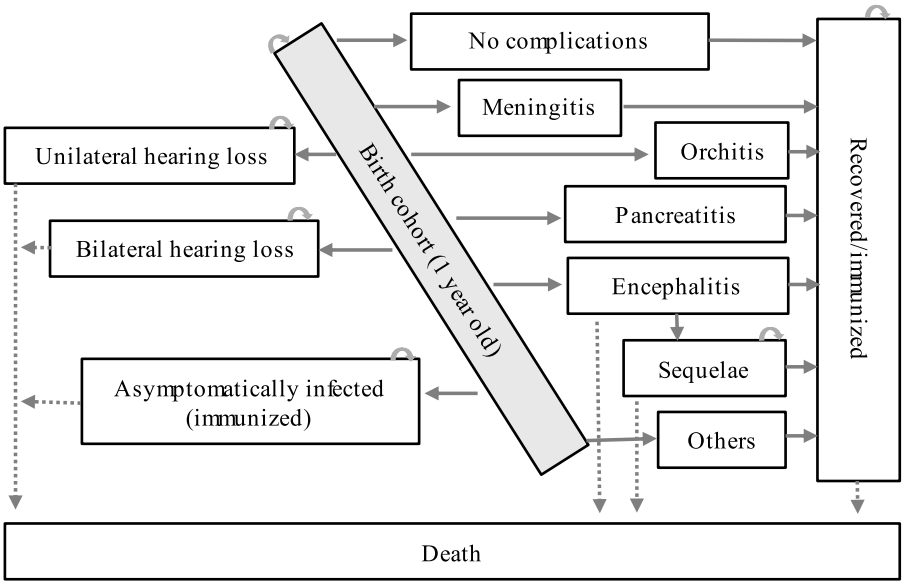


Fig. 1. Markov model. The Markov cycle for each stage was set at 1 year, with the model programmed to cease when the cohort's age reached 40.

on previous literatures [17,5]. We specifically utilized the following conditions: 1) "15 % to 24 % of infections were asymptomatic in pre-vaccine era" [17] and 2) "the younger the age, the higher is the proportion of subclinical to symptomatic infection" [5]. We assumed that the proportion to linearly decrease from 24 % for age 0–5 to 15 % for age 35–40. Estimates of adverse events (aseptic meningitis following mumps vaccination), 1.2 and 1.8 cases per 100,000 doses for 1st- and 2nd- dose, respectively, were from a study, which utilized the MHLW case data of adverse reactions [6]. All the parameters were shown in Table 1.

2.3.2. Prognoses of mumps and mumps related complications

Mumps without complications was managed on an outpatient basis with supportive care with analgesics and antipyretics as needed. Among mumps-related hearing loss cases, 4.5 % were bilateral hearing loss (BHL), while the remaining were unilateral hearing loss (UHL) [18]. Among BHL cases, 90 % had simultaneous bilateral cochlear implantation (CI) within one year after diagnosis, while others have sequential CI with a 1-year interval between 1st CI and 2nd CI. Due to the rapid expansion of bilateral CI surgery in Japan and the lack of sufficiently informative data about CI, the aforementioned variables were based on experts' opinions. Among UHL cases, 34.9 % received no treatment but were followed up, whereas others received steroids as either an outpatient procedure or those which requires hospitalization [18]. Vaccine-related aseptic meningitis and mumps-related meningitis were assumed to recover with no case of sequelae and of death [19–21]. Among mumps-related encephalitis cases, 21.6 % resulted in neurological sequelae and 1.9 % resulted in death based on a nationwide survey [22]. Annual mortality rates of individuals with neurological sequelae were assumed six times (<24 years old), four times (25–34 years old), and twice (35–40 years old), respectively, of those in the matched population mortality rates [16]. Due to the rarity of severe complications, mumps-related orchitis cases were assumed to have received outpatient treatment only [10,23]. Although mumps-related pancreatitis is usually mild with zero fatality rate, patients may still need to be admitted to the hospital to support bodily functions until the pancreas recovers [24–25]. Other complications were also assumed to recover from treatment with zero fatality rate. Deaths of causes other than mumps-related complication were from Vital Statistics [26].

2.4. Vaccine effectiveness

Since data regarding VE of domestic vaccines (Torii strain and Hoshino strain) are scarce, we assumed that VE in reducing infection is 72 % (95 % confidence interval: 38%–87%) after 1st-dose and 86 % (73 %–93 %) after the 2nd doses based on a report from the Cochrane Systematic Review [27]. Though the virus strains in the six cohort studies included in the Review were strains other than Torii and Hoshino, we assumed that there is no significant difference between different vaccines based on the results of a meta-analysis study by Schenk et al. [28]. In their study, the authors reported that except for the Rubini strain, there is no significant difference found among different mumps strains in reference to both immunogenicity and persistence. Data regarding the VE waning over time after vaccination have been scarce, thus, we adopted the waning rate of seroconversion reported by Schenk et al.'s meta-analysis as proxies. Specifically, we assumed that that the annual exponential waning rates after the first and second doses were at 0.039 (0.028-0.056) and 0.016 (0.008–0.031), respectively [28].

2.5. Utility weights

We couldn't identify any Japanese-specific studies which reported utility weights of mumps and of mumps-related complications, therefore, we adopted utility weights sourced out from literature. Utility weights for UHL/BHL individuals with/without CI were from Health Technology Assessment program reports (in the UK) [29]. They were 0.421 and 0.433 for BHL children and adults without CI, respectively. Utility gain for those with unilateral CI (versus no CI) were: 0.066, 0.212, 0.232, and 0.197, for children aged < 2, ≥2 < 4, ≥4 years old, and adults, respectively. Utility gain for those with bilateral CI (versus unilateral CI) was 0.03 for both children and adults. In sensitivity analysis, we used the data of primary economic evaluation from the Ontario Health Technology Assessment [30]: 0.585, 0.780, and 0.830 for children without CI, with unilateral CI, and with bilateral CI, respectively; 0.495,0.765, and 0.800 for adults, without CI, with unilateral CI, and with bilateral CI, respectively. As for the utility weight of UHL, previous studies used 0.9 as a utility weight [8–11], however, recent studies reported that if a person who is handicapped with BHL is assumed at 100 % utility, then that of UHL will be 50 % of

Table 1
Variables.

Variables					Reference
Aseptic meningitis following mumps vaccination per 100,000 doses		1st-dose: 1.2; 2nd-dose 1.8			[6]
Symptomatic mumps incidence rates per 100,000 population; age 0–5, 6–15, 16–25, 26–35, 36–40					
		Base-case	Lower limit of 95 %CI	Upper limit of 95 %CI	[12]
	Male	1649, 1231, 41, 57, 42	1622, 1214, 38, 54,39	1878, 1249, 44, 60, 44	
	Female	1449, 1138, 66, 92, 48	1423, 1121, 62, 87,45	1676, 1249,44, 60, 44	
Proportion of mump-related complications per1000 cases; age 0–5, 6–15, 16–25, 26–35, 36–40					
	Male	Base-case	Lower limit of 95 %CI	Upper limit of 95 %CI	
	Meningitis	4.6, 8.1, 10, 14.7, 12.3	3.6, 6.9, 4.0, 8.6, 6.4, 0	5.9, 9.5, 20.4, 23.5, 21.3	[12]
	Hearing loss	0.14, 1.16, 5.76, 6.06, 6.16	0.02, 0.73, 1.57, 2.44, 2.26	0.51, 1.75, 14.67, 12.44, 13.36	[13]
	Pancreatitis	0.4, 0.4, 2.8, 2.6, 2.0	0.2, 0.2, 0.3, 0.5 0.2	0.9, 0.8, 10.2, 7.5, 7.4	[12]
	Encephalitis	0.1, 0.3, 1.4, 1.7, 0	0, 0.1, 0, 0.2, 0	0.4, 0.7, 7.9, 6.2, 3.8	[12]
	Others	0.1, 0.3, 2.8, 3.4, 1.0	0, 0.1 0.3, 0.9, 0	0.5, 0.7, 0.2, 8.8, 5.7	[12]
	Orchitis	0.1, 1.7, 49.9, 86.4, 56.6	0, 1.2, 35.0, 70.8, 42.9	0.5, 2.4, 68.8, 104.0, 73.0	[12]
	Female	Base-case	Lower limit of 95 %CI	Upper limit of 95 %CI	[12]
	Meningitis	3.7, 4.3, 7.2, 7.2, 7.6	2.7, 3.4, 2.7, 3.3, 3.0	5.0, 5.4, 15.7, 13.6, 15.5	[12]
	Hearing loss	0.25, 1.62, 7.29, 11.21, 3.26	0.05, 1.07, 2.68, 6.14, 0.67	0.74, 2.36, 15.8, 18.74, 9.51	[13]
	Pancreatitis	0, 0.3, 1.2, 1.6, 3.2	0, 0.1, 0, 0.2, 0.7	0.3, 0.7, 6.7, 5.7, 9.4	[12]
	Encephalitis	0.3, 0.5, 0, 0, 0	0.1, 0.2, 0, 0, 0	0.9, 0.9, 4.4, 2.9, 4.0	[12]
	Others	0, 0.2, 1.2,,1.6, 2.2	0, 0.1, 0, 0.2, 0.3	0.3, 0.6, 6.7, 5.7, 7.8	[12]
Proportion of BHL among mumps-related hearing loss cases; %			4.5		[18]
Proportion of UHL among mumps-related hearing loss cases; %			95.5		[18]
Proportion of simultaneous bilateral CI among BHL cases; %			90		Experts' opinions[b]
Proportion of sequential CI among BHL cases; %			10		Experts' opinions[b]
Proportion of encephalitis cases resulted neurological sequelae (%)			21.6		[22]
Proportion of encephalitis cases resulted in death (%)			1.9		[22]
Annual mortality rate of individual with neurological sequelae			6, 4 or 2 × those of the matched population mortality rates[a]		[16]
Vaccine effectiveness in reducing infection after 1st dose/ 2nd dose					[27]
	1st dose		72 % (38–87)		[27]
	2nd dose		86 % (73–93)		
Waning of vaccine effectiveness					[28]
	Annual exponential waning rate after 1st dose		0.039 (0.028–0.056)		[28]
	Annual exponential waning rate after 2nd dose		0.016 (0.008–0.031)		
Utility weights for BHL without CI	age < 18 years old (y.o.)		0.421		[29]
	age ≥18 y.o.		0.433		[29]
Utility weight gain for 1-side CI (vs no CI)	age < 2 y.o.		+0.066		[29]
	age≥ 2 y.o. and < 5 y.o.		+0.212		[29]
	age≥ 5 y.0 and < 18 y.o.		+0.232		[29]
	age≥ 18 y.o.		+0.197		[29]
Utility weight gain for 2-side CI (vs 1-side CI)	all ages		+0.03		[29]
Utility weight for UHL		1–0.5 × (1-utility weight of BHL without CI)			[31–32]
Utility weights for other complications					
	Outpatient		0.99932	(0.95 × 5 + 365–5)/365	
	Meningitis and encephalitis	age < 6	0.99863	(0.9 × 5 + 365–5)/365	
		age≥6	0.99644	(0.9 × 13 + 365–13)/365	
	Pancreatitis (hospitalization)		0.99726	(0.9 × 10 + 365–10)/365	
	Orchitis (female only, outpatient treatment)		0.99808	(0.9 × 7 + 365–7)/365	
	Others (hospitalization)		0.99726	(0.9 × 10 + 365–10)/365	

Table 1 (*continued*)

Variables			Reference
Others		0.9	Assumed
Life expectancy of Japanese population at age 40/year (before discounting)	Male /Female	41.05/47.17	[14]
Costs per vaccination		¥6,140	[34]
Treatment costs per case			
Outpatient		¥10,187	[9]
Meningitis and encephalitis (Age < 15 year; ≥15 year)		¥116,494; ¥381,379	[34,35]
Pancreatitis (hospitalization)		¥289,751	[34,35]
Orchitis (male only, outpatient treatment)		¥29,017	[10]
Other complications		¥233,200	[10]
Sequential cochlear implantation		¥3,800,000/ each	[37]
Simultaneous cochlear implantation		¥6,600,000	[37]
Auditory-based habilitation/rehabilitation following cochlear implantation	age < 6 (1st year; 2nd ∼ year)	¥177,137; ¥69,116	[37]
	age ≥ 6(1st year; 2nd ∼ year)	¥163,437; ¥33,798	[37]
Long-term treatment cost for an individual suffering from neurological sequela per year		¥420,464	[37]
Duration of mumps or length of hospitalization for mumps-related complication treatment; days			
Outpatient		5	[8]
Meningitis/Encephalitis		9 (children); 8 (adults)	[19–20]
Cochlear implantation		10	[35–36]
Orchitis		7	[27]
Pancreatitis, Others		10	Assumed
Average hourly wage for Japanese workers		¥1,326	[39]

Abbreviations: BHL: bilateral hearing loss; UHL: unilateral hearing loss; CI: Cochlear implantation.
[a] 6 times (for individuals <24 years old.), 4 times (25–34 years old), and 2 times (35–40 years old.), respectively.
[b] Experts' opinions were used because bilateral CI surgery diffusion rapidly in Japan, and literature reviews were unable to provide up-to-date data.

BHL [31]. Based on this, we estimated these utilities as 1–0.5 * (1-utility of BHL without CI). Utilities for health statuses other than hearing loss are shown in Table 1.

2.6. Costing

Costing should cover the opportunity costs borne by various economic entities in society [32]. The amount of direct payment costs borne by municipal authorities, vaccinees, patients, and social insurers were considered, while indirect costs of vaccination programs were not included, because it is assumed that the program is built within the public health services infrastructure. Analysis conducted from payers' perspective considered the costs of vaccination and treatment costs of mumps-related disease. While the analysis conducted from a societal perspective also accounted for the costs associated with care-giver's/patient's lost productivity, such as accompanying a child for vaccination, for medical treatment, or to take care of a child with sequelae. Productivity loss due to mortality was not included, as including these into cost-effectiveness analysis may be argued as double counting, whereas survived cases were incorporated in the utility weights and disease duration in calculating QALYs [32]. All variables related to costs are shown in Table 1.

2.6.1. Direct medical costs

Vaccination cost per shot was assumed at ¥6,140 (US$58;1US$ = ¥106, 2020 average), which included the doctor's fee for medical advice, technical fee for administering the vaccine, etc. [33]. The treatment costs for mumps-related complications shown in Table 1 were from either published data, a previous study, or diagnosis procedure combination/per-diem Japanese payment system [10,34–35]. Costs related to CI were estimated from a report of the Association of Cochlear Implant Transmitted Audition (ACITA) [36]. Costs for sequential CI (including costs for surgery, device, and hospitalization) were ¥3,800,000 (US$35,849) for 1st- and 2nd- CI, respectively. Whereas, for simultaneous bilateral CI, it was at ¥6,600,000 (US$62,264). Auditory-based habilitation/rehabilitation costs after CI were ¥177,137 (US$1,671) (1st year after surgery) and ¥69,116 (US$652) (2nd year and after) for those age < 6 years, and were ¥163,437 (US$1,542) (1st year after surgery) and ¥33,798 (US$319) (2nd year after surgery) for those aged ≥6 years. Mumps without complications was assumed to only receive outpatient treatment which was at ¥10,187 (US$96) [9]. Long-term treatment cost for an individual suffering from neurological sequela was at ¥420,464 (US$3,967) per year [37].

2.6.2. Productivity loss

Productivity loss of a care-giver accompanying a child for vaccine uptake was not included, because the mumps vaccine was assumed to be simultaneously taken with any other vaccines already on the routine schedule. Productivity loss per disease episode was valued as a product of care-giver's or patient's absent working hours due to the mumps or related complications. The duration per case was assumed at 5 days for outpatient, 7 days for orchitis [23], 10 days for pancreatitis or cochlear implantation [35–36], and 9 days/8 days for child/adult meningitis as well as for encephalitis [20,21]. We assumed absent working hours per day at 8 h for both care-giver and for adult patients. As for the productivity loss of auditory-based habilitation/rehabilitation cases, we assumed that absent working hours of either care-giver or adult patient was at 8 h, because habilitation/rehabilitation can only be done at specific facilities, which took time for the commute. The average hourly wage for Japanese workers at ¥1,326 (US$13), was used in this study [38]. Care-giver's absent working hours of taking care of one child with neurological sequelae or hearing impairment was assumed to be 8 h per day until the child is admitted to the special support education system, which is at age 6 in Japan.

2.7. Discounting

Outcomes and costs were discounted at a rate of 3 % [32].

2.8. Sensitivity analyses

To appraise the ICERs' stability with the assumptions made in our economic model, and to explore the impact of each variable relative to each other, we performed one-way sensitivity and probabilistic sensitivity analyses (PSA), i.e., 1000 Monte Carlo simulations. Lower and upper limits were adopted from 95% confidence interval of the variables; if not available, ±50 % of base-case value for cost items, ±30 % for probabilities, and ±20 % for utility weights (while upper limit was set not higher than 1) were adopted. We used a triangular distribution for each variable.

3. Cost-effectiveness threshold and net monetary benefit (NMB)

Although the MHLW has not yet set a willingness-to-pay (WTP) threshold for judging the cost-effectiveness of public health programs in the country, the Central Social Insurance Medical council suggests ¥5,000,000 per QALY gain as a threshold for evaluating healthcare interventions from payers' perspective [39]. In this study, we also used net monetary benefits (NMB) to express cost-effectiveness. NMB is another way of presenting the results of cost-effectiveness, especially when multiple alternatives are compared [32]. It is a summary statistic that represents the value of an intervention in monetary terms when a WTP threshold for a unit of benefit (QALY in this study) is known. NMB was calculated as "(incremental benefit × threshold) – incremental cost". A positive incremental NMB indicates that the intervention was cost-effective compared with the alternative at the given WTP threshold. This means the cost to derive the benefit is less than the maximum amount that the decision-maker would be willing to pay for this benefit.

4. Results

4.1. Results of base-case analysis

In our base-case analysis, with a comparison to status quo, the estimated incremental effects were 79 QALYs and 213 QALYs per100,000 persons for single-dose and two-dose programs, respectively. Both single- and two-dose vaccination programs reduced disease treatment costs. However, these reduced costs did not offset vaccination cost, which means that both programs gained more QALYs but cost more. On the other hand, the two-dose programs yielded more QALYs but at a greater cost. Estimated ICERs of single-dose and two-dose programs were ¥3,899,544 (US $36,788) and ¥3,368,302 (US$31,776) per QALY gained respectively; from payers' perspective and were ¥1,236,081 (US $11,661) and ¥1,566,286 (US$14,776) from societal perspective. When comparing the two-dose program with single-dose program, the ICER was ¥3,058,104 (US$28,850) and ¥1,759,096 (US$16,595) per QALY gained from payers' and societal perspective, respectively (Table 2).

4.2. Results of one-way sensitivity analysis

One-way sensitivity analysis revealed that from payer's perspective, the comparisons between single-dose program to no program, two-dose program to no program, or two-dose program to single-dose vaccination program resulted to four consistent variables which made the changes of the ICER (from base-case) greater than ¥1,000,000 (US$9,434). These variables were: 1) VE in reducing infection after 1st-dose or 2nd -dose, 2) vaccination cost, 3) proportion of mump-related hearing loss among mumps cases, and 4) annual waning rate of 1st dose or 2nd-dose (Fig. 2). Largest ICER, ¥9,194,039 (US$86,736) per QALY gained, was observed in the lower limit of VE in reducing infection in the 1st dose (0.38 in sensitivity analysis vs 0.72 in base-case), when comparing single-dose vaccination program to no program (Fig. 2-a); ¥6,607,724 (US$62,337) and ¥6,397,912 (US$60,358) per QALY gained, in lower limit of proportions of mump-related hearing loss among mumps cases (about 1/7 and 1/5 of the base-case value for male and female individual age under 5 year-old), when comparing two-dose program to no program (Fig. 2-b) or two-dose program to single-dose program (Fig. 2-c), respectively.

4.3. Results of probabilistic sensitivity analysis (PSA)

In Fig. 3, we noted that when comparing both vaccination programs with current no vaccination program (Fig. 3-a), with 1,000 ICERs produced by Monte Carlo simulations, the probabilities that ICER is under ¥5,000,000 (US$47,170) per QALY gained was at 63.4 % and 88.4 % for single-dose and two-dose programs, respectively. Whereas, for under ¥10,000,000 (US$9,340) it was at 99.3 % and 99.8 % for single-dose and two-dose programs, respectively. When comparing the two-dose program with single-dose program (Fig. 3-b), the probability of ICER under ¥5,000,000 (US$47,170) per QALY was at 97.9 %, while it was 100 % for under ¥10,000,000 (US $94,340) per QALY gained.Fig.

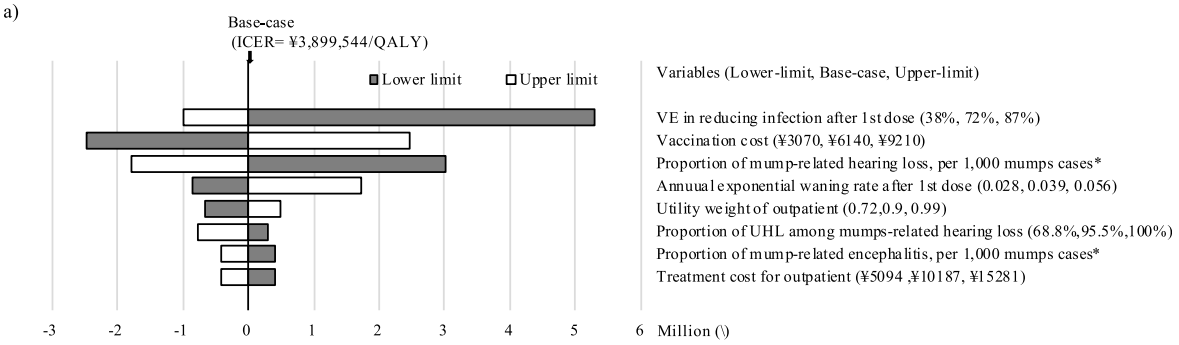
The cost-effectiveness acceptability curves (CEACs) derived from NMB (Fig. 4) showed that at any WTP threshold, the acceptability of single-dose program was always at zero percent, while the acceptability for two-dose program is at 56.2 % or 92.6 % with a WTP of ¥3,000,000 (US$28,302) or ¥5,000,000 (US$47,170) per QALY gained, respectively.

Table 2
Results of base-case analysis.

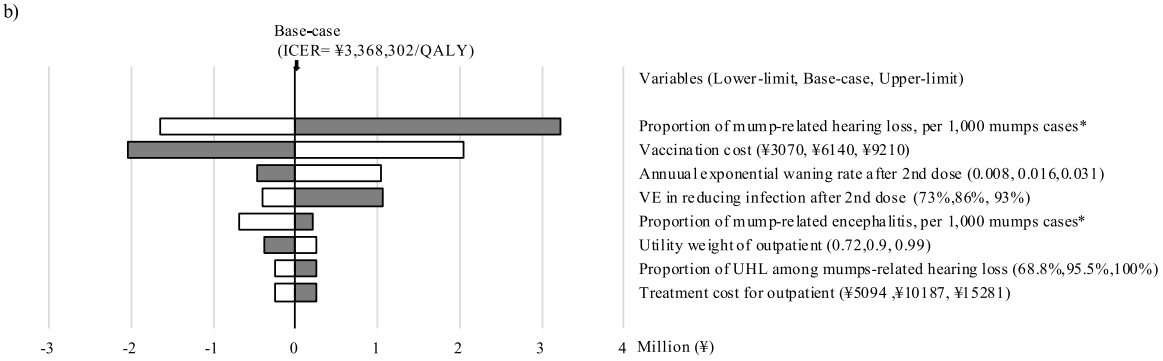
Strategy	Vaccination cost; ¥	Disease treatment cost; ¥	Productive loss; ¥	Total Cost; ¥ Payers' perspective	Societal perspective	Effectiveness (QALY)
	(1)	(2)	(3)	(4) = (1) + (2)	(5) = (1) + (2) + (3)	(6)
No program	2,149	2,588	6,484	4,737	11,221	31.27866265
Single-dose program	6,048	1,758	4,387	7,806	12,193	31.27944962
Two-dose program	10,891	1,036	2,637	11,928	14,564	31.28079739

ICER	Payers' perspective		Societal perspective	
	vs no program (¥/QALY)	vs Single-dose program (¥/QALY)	vs no program (¥/QALY)	vs Single-dose program (¥/QALY)
	$\Delta(4)/\Delta(6)$		$\Delta(5)/\Delta(6)$	
No program	–	–	–	–
Single-dose program	3,899,544	–	1,236,081	–
Two-dose program	3,368,302	3,058,104	1,566,286	1,759,096

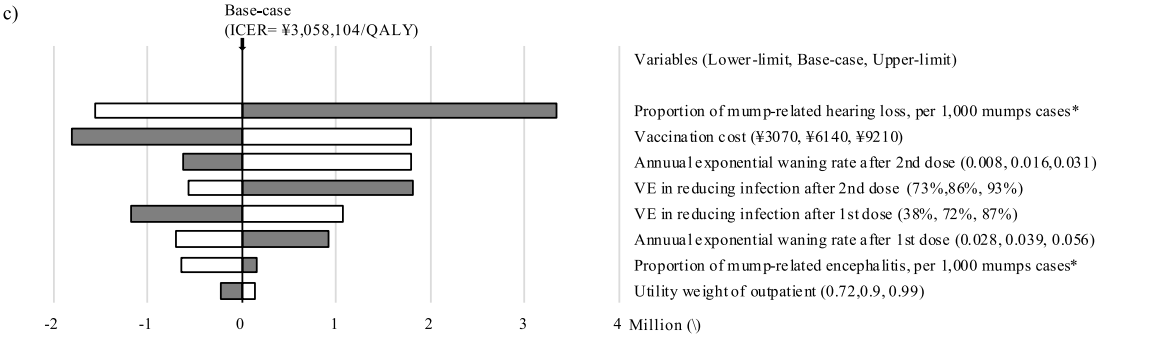
a)



b)



c)



d)

		Hearing loss			Encephalitis		
Age		Lower	Base-case	upper	Lower	Base-case	upper
Male	0-5	0.02	0.14	0.51	0	0.1	0.4
	6-15	0.73	1.16	1.75	0.1	0.3	0.7
	16-25	1.57	5.76	14.67	0	1.4	7.9
	26-35	2.44	6.06	12.44	0.2	1.7	6.2
	36-40	2.26	6.16	13.36	0	0	3.8
Female	0-5	0.05	0.25	0.74	0.1	0.3	0.9
	6-15	1.07	1.62	2.36	0.2	0.5	0.9
	16-25	2.68	7.29	15.8	0	0	4.4
	26-35	6.14	11.21	18.74	0	0	2.9
	36-40	0.67	3.26	9.51	0	0	4

Fig. 2. Results of one-way sensitivity analyses. (a) Single-dose program vs No program, (b) Two-dose program vs No program, (c) Two-dose program vs Single-dose program, (d) Lower and upper limits of variabes with "*" in figure (a), (b), and (c). VE: vaccine effectiveness. UHL: unilateral hearing loss.

5. Discussion

We conducted cost-effectiveness analyses on routine monovalent mumps vaccine immunization programs for a 1-year old cohort in Japan. In this study, the single-dose program was at 1 year old, while the two-dose program with second dose uptakes was at 5 years old. Analyses were done from both payer's perspectives (only direct medical costs were considered) and societal (productivity loss was further added). Both programs gained QALYs with more costs when compared with status quo (no vaccination program). ICER of either program was under ¥5,000,000 (US$47,170) per QALY from either perspective. Results of PSA using NMB indi-

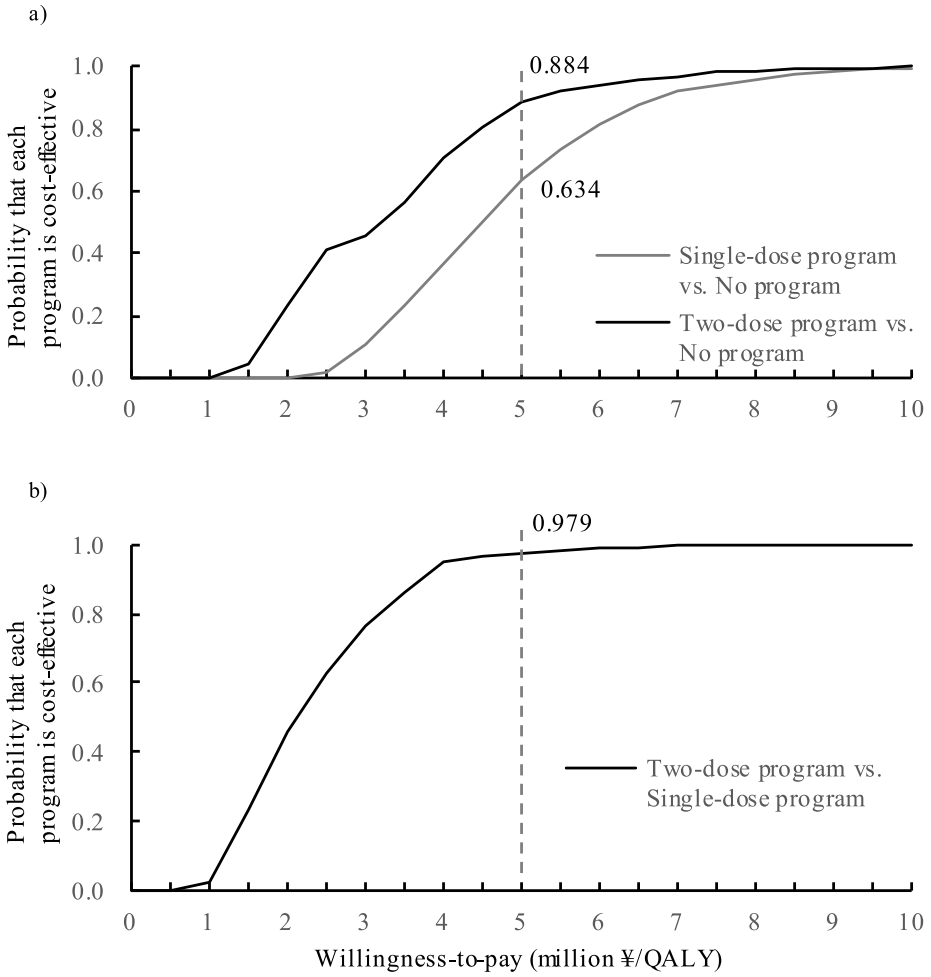


Fig. 3. Results of probabilistic sensitivity analyses: cost-effectiveness acceptability curve (CEAC). (a) Among 1,000 ICERs produced by Monte Carlo simulation, the probabilities that ICER is under ¥5,000,000 (US$47,170) per QALY gained was at 63.4% and 88.4%, respectively, for single-dose and two-dose programs, respectively. b) Among 1,000 ICERs produced by Monte Carlo simulation, the probabilities that ICER is under ¥5,000,000 (US$47,170) per QALY gained was at 97.9%.

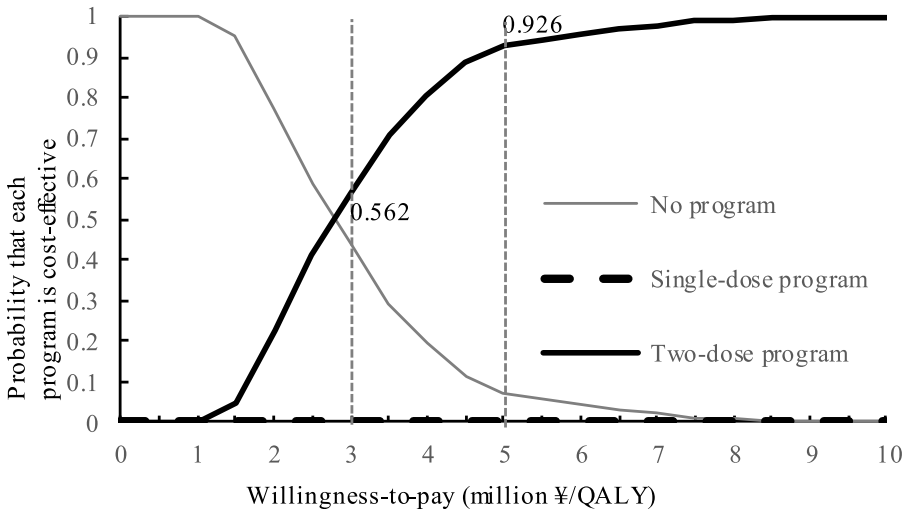


Fig. 4. Cost-effectiveness expressed by net monetary benefit (NMB). NMB was calculated as "(incremental benefit × threshold) – incremental cost". A positive incremental NMB indicates that the intervention was cost-effective compared with the alternative at the given WTP threshold. Which means the cost to derive the benefit is less than the maximum amount that the decision-maker would be willing to pay for this benefit. The acceptability for two-dose program is at 56.2 % or 92.6 % with a WTP of ¥3,000,000 (US$28,302) or ¥5,000,000 (US$47,170) per QALY gained, respectively.

cated that at the ¥5,000,000 per QALY WTP threshold, the 'acceptability is at 92.5 % for two-dose vaccination program, 0 % for single-dose vaccination program, and 7.4 % for current no vaccination program, while they are 99.8 %, 0 % and 0.2 %, respectively at ¥10,000,000 (US$94,340) per QALY. Two-dose program was optimal among the alternatives. One-way sensitivity analyses revealed that except vaccination costs, variables related to proportion of mumps-related hearing loss among mumps cases and VE were key variables in making the changes in the ICER greater than ¥1,000,000 (US$9,434). When comparing single-dose vaccination program to no program, the largest ICER was observed in the lower limit of VE in reducing infection in the 1st dose (¥9,194,039 or US $86,736 per QALY gained). On the other hand, when comparing the two-dose program to no program or two-dose program to single-dose program, the largest ICER was noted in the lower limit of proportions of mump-related hearing loss among mumps cases at ¥6,607,724 (US$62,337) and ¥6,397,912 (US$60,358) per QALY gained, respectively. By using ¥5,000,000 (US$47,170) per QALY gained as a WTP threshold [40], both programs in our model can be concluded as cost-effective, while the two-dose vaccination program was observed to be more favorable.

Studies from overseas reported that single- or two-dose mumps vaccination program as highly cost-beneficial, in which mumps vaccine was given through MMR [40–41]. However, we are not able to identify any cost-effectiveness studies of monovalent mumps vaccine immunization programs from overseas, except for the four previous studies conducted in Japan. We have thus narrowed down our comparisons to these four domestic studies. The first study published in 2007, reported an incremental benefit-cost-ratio (BCR) of 5.1 for single-dose mumps vaccination program from a societal perspective [8]. The second study in 2014, reported that the ICER of two-dose program (vaccination at 1- and 6-year old) was at ¥4,512,419 (US$42,570). Additionally, the same study noted that the single-dose program was cost-saving from the payers' perspective apart from a cost-saving for both two- and single-dose program from the societal perspective [9]. In 2017, the third study reported an incremental BCR of 6.84/5.97 for single-/two-dose program from societal/payers' perspective [10]. The fourth study (in 2018), which used a dynamic transmission model reported that over the 50-year period, reported that both single- and two-dose programs were predominated compared to status quo and two-dose program was more cost-effective than single-dose program [11]. The previous studies were able to make use of the available data to perform an economic evaluation, though potential improvements could have been done regarding the: assumption that 100 % of non-vaccinees will be infected [8], non-inclusion of asymptomatic patients [11], assumption that all susceptible individuals have contact with persons of all age groups at the same rate irrespective of their age [11], utilization of sentinel surveillance reports from 3,000 pediatric sites around the country to estimate the annual incidence rate and set the proportions of mumps-related complications uniform for all age [8–11], and adoption of utility weights of patients with hearing loss (UHL, BHL without CI, BHL with unilateral CI or bilateral CI) evaluated by generic questionnaires, such as SF-36 or EQ-5D, etc. [8–11]. In our study, on the other hand, annual incidence rates and proportions to mumps-related complications by age and by sex were adopted from studies that analyzed health insurance reimbursement data of 5,209,660 individuals aged 0–64 years from January 2005 to December 2017, which is considered to have less uncertainty than those estimated by previous studies. As to values of the utility weights of patients with hearing loss utilized in our study, they were adopted from studies that reported these values by using the Health Utilities Index Mark III (HUI-3) questionnaire instead of those derived from other generic questionnaires. Several studies have revealed that the inclusion of a question on hearing among other health attributes (such as pain and mobility) allows HUI-3 to be more responsive than other generic questionnaires in estimating utility related to hearing loss [42–43]. The National Institute for Health and Care Excellence (NICE) performed a systematic review to examine the appropriateness of three Generic preference-based measures (GPBMs) of health-related quality of life (EQ-5D, HUI-3, and SF-6D) for hearing loss and other three health conditions. They reported that HUI-3 was the most used measure in all the 18 studies found in the review [43].

Our study has several limitations. First, clinical evidence of the efficiency of vaccination in reducing annual incidence rates of mumps cases in the model was not derived from the Japanese domestic vaccine. Although the study has reported that there is no significant difference found among different mumps strains on immunogenicity and persistence, different vaccine effectiveness may exist in real-world because of ethnicity, the behavior of an individual, as well as in the healthcare system. Second, the annual mortality rates of individuals with neurological sequelae were not specific to Japan. Though its impact on the ICER, based on the sensitivity analysis, was only minimal. Third, we assumed that the mortality rate of individuals with hearing loss followed the age- and sex-specific mortality rate of the Japanese population. Several studies reported that survival time was significantly shorter in individuals who had troubles in hearing than those who had little/-moderate troubles or those who had good hearing [44]. If this were to be included, the results will turn out to be more favorable. Fourth, reversion surgery of CI (due to device failure, infection, etc.) was not considered. Its potential inclusion may make the results become more favorable. Fifth, the incidence rates of mumps and mumps-related complications were reported before the COVID-19 pandemic, how COVID-19 affects the subsequent mumps epidemic may be beyond the scope of this study.

Regardless of these limitations, we believed that our results, which were estimated by using the latest and with high statistically powered data, can provide newer and more reliable information about the value for money of mumps vaccine immunization program to decision-makers.

6. Conclusion

A routine vaccination program of single- and two-dose programs were considered to be cost-effective from both payers' and societal perspectives. Between the two, the two-dose vaccination program was observed to be more favourable.

Author's contributions

Shu-Ling Hoshi participated in the concept and design of the study, performed the literature searches, acquired the data, participated in the analysis, interpretation of the data, and wrote the manuscript. Masahide Kondo, Reiko Okubo, Keiji Tabuchi participated in the concept and design of the study, the interpretation of the data. Xerxes Seposo and Aiko Shono participated in explained the results and writing of the manuscript.

Data availability

Data will be made available on request.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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