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Economic evaluation of vaccination programme of mumps vaccine to the birth cohort in Japan

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ABSTRACT

The most common preventative measure against mumps is vaccination with mumps vaccine. In most parts of the world, mumps vaccine is routinely delivered through live attenuated Measles-Mumps-Rubella (MMR) vaccine. In Japan, receiving mumps vaccine is voluntary and vaccine uptake rate is less than 30%. The introduction of mumps vaccine into routine vaccination schedule has become one of the current topics in health policy and has raised the need to evaluate efficient ways in protecting children from mumps-related diseases in Japan.

We conducted a cost-effectiveness analysis with Markov model and calculated incremental cost effectiveness ratios (ICERs) of 11 different programmes; a single-dose programme at 12–16 months and 10 two-dose programmes with second dose uptakes at ages 2, 3, 4, 5, 6, 7, 8, 9, 10 and 11. Our base-case analyse set the cost per shot at ¥6951 (US$72; 1US$ = 96.8).

Results show that single-dose programme dominates status quo. On the other hand, ICERs of all 10 two-dose programmes are under ¥6,300,000 (US$65,082) per QALY from payer's perspective while it ranged from cost-saving to <¥7,000,000 (US$72,314) per QALY from societal perspective.

By adopting WHO's classification that an intervention is cost-effective if ICER (in QALY) is between one and three times of GDP as a criterion, either of the vaccination programme is concluded as cost-effective from payer's or societal perspectives. Likewise, to uptake second dose at 3–5 years old is more favourable than an uptake at any other age because of lower incremental cost-effectiveness ratios.

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. There is no specific therapy for mumps. In most countries, live attenuated Measles-Mumps-Rubella (MMR) immunisation is delivered against mumps which dropped the incidence of mumps dramatically [1,2]. By December 2005, two-dose schedules were implemented in more than 80% of 110 countries where mumps vaccine is on routine immunisation schedule [1].

In Japan a voluntary mumps vaccination begun in 1981. From 1989, MMR vaccination has been allowed as an alternative to monovalent mumps vaccine for routine immunisation. However, because of unexpected high incidence of aseptic meningitis caused by mumps vaccine (Urabe Am9 strain), MMR vaccination was discontinued in 1993. Since then, measles and rubella vaccines have been in routine vaccination schedule, while mumps monovalent vaccine has been optional as it was before 1989 [3]. Currently, two kinds of mumps vaccine are available in Japan, each containing different strains, namely, Torii and Hoshino [4]. Despite some municipalities giving subsidies to vaccinees to encourage the uptake of mumps vaccine, the estimated vaccine uptake rate is less than 30% [4]. Consequently, Japan has experienced annual outbreaks of mumps estimated from 430,000 to more than one million cases [5], and thus an increase in hearing loss caused by mumps was also observed [6]. The introduction of mumps vaccine into routine vaccination schedule has become one of the current topics in health policy [7] and has raised the need to evaluate efficient ways in protecting children from mumps-related diseases in Japan.

The efficiency of mumps vaccination has been reported overseas since 1970s. Either single-dose strategy or two-dose strategy was shown to be cost-beneficial [8–12]. In Japan, only one peer-reviewed article [13] reported a benefit-cost ratio of 5.1 for single-dose mumps vaccination programme from societal perspective

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with an unrealistic assumption of 100% non-vaccinee infection. The same study also assumed that there is no waning of vaccine-derived immunity, which contradicts the findings of several studies where waning of vaccine-derived immunity is observed [14–21].

This study aims to appraise the value for money of expanding the current voluntary mumps vaccination to routine single-dose or two-dose vaccination programmes, and also to explore the potential impacts of schedule changes, i.e., the appropriate age to uptake the second dose, because of the variety of ages being recommended to uptake the second dose among countries where two-dose MMR is recommended [22,23].

2. Method

We conducted a cost-effectiveness analysis with Markov modelling from both payer's and societal perspectives. In defining vaccination programmes and constructing the model, we conducted a literature survey to find out the available evidence. Studies pertaining to epidemiology and prognosis of mumps-relevant disease in Japan's setting were accessed from PubMed database, Igaku Chuo Zasshi database, MHLW (Ministry of Health, Labour and Welfare) Grant System, and annual statistic reports published by the government. Igaku Chuo Zasshi (Japana Centra Revuo Medicina) is a Japanese medical bibliographic database which contains 7.5 million citations originating in Japan, which comprehensively covers articles published in Japanese-language medical journals. Due to insufficient evidences from Japan, overseas' reports from PubMed, Medline, The Cochrane Database of Systematic Reviews, HTA (Health Technology Assessment database), and NHS EED (The NHS Economic Evaluation Database) regarding vaccine effectiveness, utility weight to estimate QALY and economic evaluation related to mumps vaccine were used instead.

2.1. Programmes

The 11 routine vaccination programmes were composed of one single-dose programme and 10 two-dose programmes. All programmes schedule the first dose at 12–18 months. Each of the 10 two-dose programmes will have the second dose at ages 2, 3, 4, 5, 6, 7, 8, 9, 10 and 11. All these programmes were compared to status quo. We also compared two-dose programmes with single-dose programme to explore the efficiency of the second dose. The vaccine uptake rates are assumed at 30% for status quo [4] and 76% for single-dose programme and for first dose of two-dose programme based on the willingness-to-pay reported by Muta et al. [24], and 72.7% (76% × 0.957) for second dose of two-dose programme; where 0.957 is the proportion of second dose to first dose of vaccine coverage of measles over the last 5 years in Japan [25]. Vaccination with MMR2 was not considered as an alternative because it is not yet approved in Japan [4,26].

2.2. Markov model

A Markov model of courses followed by the birth cohort under consideration was constructed based on epidemiological data, vaccine effectiveness and models from previous studies. Eleven mutually-exclusive health states were modelled (Fig. 1). A Markov cycle for each stage was set at 1 year with a cohort time frame of 40 years. After turning 40 years old, those without sequelae were assumed to have a life expectancy of Japanese population [27], while those with neurological sequelae will have an average life expectancy of 53.9 years old [28]. Natural infection is thought to confer lifelong protection [1]. Considering that all state transitions do not occur simultaneously at the end of each cycle, we implemented a half-cycle correction in estimating the incremental cost effectiveness ratios (ICERs) of the programmes. We did not consider herd immunity in our model because: (1) the reported basic reproduction number of mumps is largely varied from 4 to 12 [29,30], (2) even when the assumption of vaccine effectiveness is as high as 95% for two doses of vaccine, vaccine coverage of 78.9%, 87.7%, 92.1%, 94.7% are needed to reach herd immunity if the corresponding reproductive values were four, six, eight, and 10; respectively [17], and (3) the experience of unexpected high incidence of aseptic meningitis caused by mumps vaccine in MMR during 1989–1993 in Japan [3] became a barrier to raise vaccine coverage in reaching herd immunity [31].

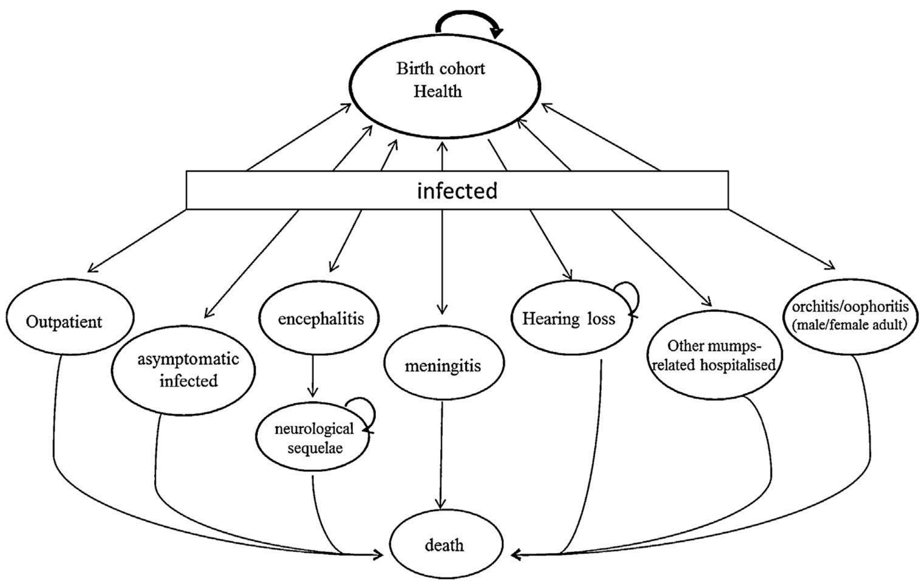

Fig. 1. Markov model. Eleven mutually-exclusive health states were modelled: health, asymptomatic infected, symptomatic infected (outpatient), hospitalised due to meningitis, encephalitis, neurological sequelae due to encephalitis, hearing loss, other mumps-related hospitalisation (including pancreatitis, myocarditis, severe mumps without complication), hospitalised due to orchitis/oophoritis (male/female adult patient only), and death of or other than the related diseases.

2.3. Outcomes estimation

Outcomes in terms of quality adjusted life year (QALY) were estimated by assigning transition probabilities and utility weights from literature to the Markov model.

Age-specific annual incidence rates of symptomatic mumps case were estimated by combining data from three reports: (1) a study grant funded by the Ministry of Health, Welfare and Labor, which estimated the nationwide mumps cases from 2000 through 2007 based on sentinel surveillance reports [5], (2) age distribution of mumps cases reported by Infectious Disease Surveillance Center [32], and (3) population data [33]. As to the incidence rates of asymptomatic mumps case, previous studies reported that approximately 15–40% of mumps infection is subclinical and the younger the age, the higher is the proportion of subclinical to symptomatic infection [1,34]. We assumed that the proportion is linearly decreased from 40% for those aged <2 to 15% for aged 20 to <40. These data are shown in Table 1.

Proportion of hearing loss among symptomatic mumps cases, 1 in 1000 cases, is from a prospective study which enrolled 7502 mumps patients from 40 institutes in Japan [35]. Proportion of meningitis, encephalitis, orchitis, oophoritis, and other mumps-related hospitalisation cases were estimated by using proportion of hearing loss and numbers of relevant disease cases reported by nationwide survey conducted from December 2011 to March 2012 [36]. Proportion that resulted in neurological sequelae among cases of encephalitis age <20 is from the same report [36]. Deaths of causes other than the above diseases were taken from the vital statistics [37]. All these data are shown in Table 2.

Table 1
Estimation of incidences of symptomatic and asymptomatic cases.

(1) Cases of symptomatic mumps estimated by Nagai et al. [5]

2000	1,170,000
2001	2,260,000
2002	1,089,000
2003	515,000
2004	821,000
2005	1,356,000
2006	1,186,000
2007	431,000

(2) Age distribution of symptomatic mumps cases reported by NIID [32]; %

Year	Age <2	Age 2 to <4	Age 4 to <6	Age 6 to <8	Age 8 to <10	Age 10 to <15	Age 15 to <20	Age 20 to <40
2000	5.0	22.3	36.2	20.7	8.1	5.4	0.5	1.8
2001	5.2	23.5	34.9	20.8	8.0	5.3	0.5	1.8
2002	5.1	23.0	34.9	20.3	8.7	5.7	0.6	1.7
2003	4.9	22.1	35.9	20.0	8.9	5.9	0.6	1.8
2004	5.1	24.0	36.4	19.8	7.9	4.7	0.5	1.7
2005	5.2	24.4	35.6	20.0	7.7	4.9	0.5	1.7
2006	5.0	22.6	35.0	20.3	9.1	5.7	0.5	1.8
2007	5.1	22.3	34.4	20.4	9.5	6.3	0.5	1.6

(3) Case of symptomatic mumps estimated from (1) and (2)

Year	Age <2	Age 2 to <4	Age 4 to <6	Age 6 to <8	Age 8 to <10	Age 10 to <15	Age 15 to <20	Age 20 to <40
2000	58,500	260,910	423,540	242,190	94,770	63,180	5,850	21,060
2001	117,520	531,100	788,740	470,080	180,800	119,780	11,300	40,680
2002	55,539	250,470	380,061	221,067	94,743	62,073	6,534	18,513
2003	25,235	113,815	184,885	103,000	45,835	30,385	3,090	9,270
2004	41,871	197,040	298,844	162,558	64,859	38,587	4,105	13,957
2005	70,512	330,864	482,736	271,200	104,412	66,444	6,780	23,052
2006	59,300	268,036	415,100	240,758	107,926	67,602	5,930	21,348
2007	21,981	96,113	148,264	87,924	40,945	27,153	2,155	6,896

(4) Populations [33]

Year	Age <2	Age 2 to <4	Age 4 to <6	Age 6 to <8	Age 8 to <10	Age 10 to <15	Age 15 to <20	Age 20 to <40
2000	2,342,000	2,385,000	2,393,000	2,401,000	2,425,000	6,559,000	7,502,000	35,172,000
2001	2,345,000	2,364,000	2,379,000	2,413,000	2,401,000	6,382,000	7,350,000	35,245,000
2002	2,339,000	2,338,000	2,390,000	2,391,000	2,400,000	6,245,000	7,194,000	35,195,000
2003	2,292,000	2,337,000	2,368,000	2,375,000	2,414,000	6,120,000	6,997,000	35,133,000
2004	2,241,000	2,328,000	2,335,000	2,382,000	2,388,000	6,060,000	6,762,000	34,960,000
2005	2,156,000	2,274,000	2,356,000	2,382,000	2,381,000	6,037,000	6,592,000	34,263,000
2006	2,138,000	2,213,000	2,320,000	2,366,000	2,390,000	6,008,000	6,424,000	34,243,000
2007	2,171,000	2,145,000	2,269,000	2,347,000	2,378,000	5,983,000	6,281,000	33,823,000

(5) Incidence of symptomatic mumps cases per 100,000 population (estimated from (3) and (4))

Aged	<2	2 to <4	4 to <6	6 to <8	8 to <10	10 to <15	15 to <20	20 to <40
	2499.2	11142.0	16598.5	9438.9	3829.0	962.1	83.0	55.7

(6) Incidence of asymptomatic mumps cases per 100,000 population*

Aged	<2	2 to <4	4 to <6	6 to <8	8 to <10	10 to <15	15 to <20	20 to <40
	1666.1	6384.8	8122.6	3909.1	1325.4	273.6	18.9	9.8

* The proportion of subclinical infection cases is assumed linearly decrease from 40% for age <2 to 15% for age 20 to <40 [1,34].

Table 2
Variables.

Variable	Base-case	Value applied on one-way sensitivity analyses		Reference
Vaccine uptake rate		Lower limit	Upper limit	
Status quo	30.0%	–	–	[4]
Single-dose programme	76.0%	–	–	[24]
Two-dose immunisation programme	1st dose: 76.0%	–	–	[24,25]
	2nd dose: 72.7%	–	–	
Annual incidence rates per 100,000 population				
Symptomatic mumps case	Shown on Table 1	−50%	+50%	See Table 1
Symptomatic mumps	Shown on Table 1	−50%	+50%	See Table 1
Proportion of revalent mumps diseases among symptomatic mumps cases				
Healing loss	0.10%	0.05%	0.15%	[35]
Meningitis	2.23%	1.12%	3.35%	[36]
Encephalitis	0.05%	0.02%	0.07%	[36]
Orchitis (male, ≥20 years old)	25.00%	12.50%	37.50%	[36]
Oophoritis (female, ≥20 years old)	5.00%	2.50%	7.50%	[36]
Other mumpus-related hospitalization	1.52%	0.76%	2.27%	[36]
Outpatient	66.11%	33.05%	99.16%	[36]
Proportion of encephalitis cases under 20 years old resulted in neurological sequelae	0.43%	0.21%	0.64%	[36]
Proportion of hearing loss cases resulted in bilateral hearing loss	2.00%	1.00%	3.00%	Assumed
Vaccine effectiveness in reducing symptomatic cases				
First-dose	69.6%	54.0%	87.0%	[14,17–20,38]
Second-dose	87.0%	69.6%	93.0%	[14,17–20,38]
Waning of vaccine-derived immunity	75% in 20 years	50% in 20 years	–	[15]
Life expectancy of Japanese population at age 40/year	41.05 male; 47.17 female			[27]
Life expectancy of neurological sequelae at age 40/year	13.9	–	–	[28]
Utility weight				[12,13,28]
Healthy,	1	–	–	
Hearing loss, unilateral	0.900	0.720	1	
Hearing loss, bilateral	0.800	0.640	0.900	
Neurological sequelae	0.570	0.456	0.684	
Curable encephalitis	0.977	0.781	1	
Curable meningitis	0.977	0.781	1	
Hospitalisation other than above diseases	0.990	0.792	–	
Death	0	–	–	
Cost				
Cost per shot	¥6972	¥3486	¥10,458	[40]
Treatment cost per case				
Meningitis/Encephalitis episode	¥852,642	¥426,321	¥1,278,963	[41]
Unilateral hearing loss	¥79,422	¥39,711	¥119,133	[42]
Bilateral hearing loss	¥4,000,000	¥2,000,000	¥6,000,000	[44]
Orchitis	¥171,732	¥85,866	¥257,598	[43]
Oophoritis	¥186,905	¥93,453	¥280,358	[43]
Hospitalised due to other than the above complications	¥233,200	¥116,600	¥349,800	[13]
Outpatient	¥10,477	¥5239	¥15,716	[13]
Neurological sequelae (long-term trearment cost per case per year)	¥420,464	¥210,232	¥630,696	[41]
Discount rate	3.0%	0%	5.0%	[39]
Variables related to care-giver's productivity loss				
Uptake vaccine	4 h, if uptake alone; zero, if co-vaccinated with other vaccine			
Meningitis/Encephalitis episode	22.7 days			[41]
Unilateral hearing impairment	8 h per day until the child is admitted to special support education system			
Bilateral hearing impairment				
Neurological sequelae				
Orchitis	4.9 days			[43]
Oophoritis	5.3 days			[43]
Other mumps-related hospitalisation	5 days			[13]
Outpatient	5 days (schooldays suspension)			[13]
Average hourly wage of Japanese women labourers	¥1328			[45]

Case-fatality rate of encephalitis.

2.4. Vaccine effectiveness and waning of vaccine-derived immunity

Due to low uptake of mumps vaccine, data regarding vaccine effectiveness or efficacy are scarce in Japan. After reviewing researches from overseas [14,17–20,38], we assumed that vaccine effectiveness in reducing infection is 69.6% for the first dose and 80% for the second dose. Kontio et al.'s [15] findings which regarded that waning of vaccine-derived immunity will decrease by 75% in 20 years was also used in the study, and from which we assumed the remaining 25% to last until the end of the model.

2.5. Costing

From societal perspective, costing should cover opportunity costs borne by various economic entities in society [39]. Therefore, costs of vaccination, treatment costs of mumps-related diseases, and costs associated to care-giver's productivity loss, were counted. Productivity loss due to mortality was not included because it can be argued as double counting, while survived cases were incorporated in utility weights and disease duration in calculating QALYs [39]. From the payer's perspective, care-giver's productivity loss was not included. All variables related to costs are shown in Table 2.

2.5.1. Direct medical costs

Vaccination cost per shot was assumed at ¥6951 (US$72; 1US$ = ¥96.8, average of 2013) [40], which was estimated as sum of the following: (1) doctor's fee for medical advice (¥3450, US$35.6), (2) technical fee for administering vaccine (¥330, US$30.4), (3) price of vaccine (¥2840, US$29.3) and (4) tax [40]. The doctor's fee and technical fee are from the National fee schedule, while the vaccine price comes from the average company prices of mumps vaccine in Japan. Vaccine price is more expensive than those of overseas' due to the vaccine protection and delivery system under strict governmental plan in Japan.

We used Iwata et al.'s treatment cost, ¥852,642 (US$8808) per episode of meningitis, and assumed it to hold through for encephalitis [41]. Likewise, we used Yamanaka et al.'s treatment cost ¥79,422 (US$821) per case of unilateral hearing loss [42]. Orchitis and oophoritis with rates ¥171,732 (US$1774) and ¥186,905 (US$1931) per case, respectively, were based from the Survey on Medical Benefits [43]. For bilateral hearing loss, it was at ¥4,000,000 (US$41,322) per case (including cost of cochlea implant) [44]. We used Sugawara et al.'s [13] treatment cost for cases other than the above diseases and per mumps outpatient at ¥233,000 (US$2407) and ¥10,477 (US$108); respectively. We used Iwata et al.'s [41] estimate for long-term treatment cost for an individual suffering from neurological sequelae at ¥400,000 (US$4132) per year.

2.5.2. Productivity loss

Productivity loss of a care-giver accompanying a child for vaccine uptake was estimated depending on how mumps vaccine was taken. If mumps vaccine was simultaneously taken with any other vaccines already on the routine schedule (i.e. co-vaccinated scenario), no productivity loss will occur. If it was taken alone (i.e. vaccine alone scenario), then productivity loss will be calculated by 4 h × wage of care-giver. Productivity loss per disease episode is valued as a product of care-giver's or patient's absent working hours from paid employment and an average hourly wage that depends on the age of the individual who suffers from the diseases. If the patients are less than 18 years old an average hourly wage of ¥1326 (US$14) for Japanese women workers will be used; otherwise, an age-specific average hourly wage will ensue [45]. For outpatients younger than 18 years old, five school days suspension was assumed. We assumed that a care-giver's absent working hours of taking care of one child with neurological sequelae or hearing impairment is 8 h per day until the child is admitted to special support education system, which is at age 6 in Japan.

2.6. Discounting

Costs and outcomes were discounted at a rate of 3% [39].

3. Sensitivity analyses

We performed one-way sensitivity analyses to appraise the stability of ICERs against assumptions made in our economic model, and to explore the impact of each variable relative to each other. The lower limits and upper limits used on sensitivity analyses are shown in Table 2.

4. Results

4.1. Results of cost-effectiveness analyses

In our base-case analysis, with a comparison to status quo, the estimated mumps cases averted per 100,000 population by the start of routine vaccination programmes followed for 40 years was at 15,206 cases for single-dose programme and from 16,169 cases (uptake second dose at age 11) to 24,734 cases (uptake second dose at age 3) for two-dose programmes.

Table 3 and Fig. 2 show the estimated incremental effects per child ranging from 0.00053 QALY to 0.00086 QALY. Among all the programmes, the two-dose programme with second dose uptake at 3 years old gained the most. All vaccination programmes reduced disease treatment costs. However, except single-dose programme, these reduced costs did not offset vaccination cost, which means the single-dose programme gained more QALY with less cost, while the two-dose programmes turned out to yield more QALY but cost more from payer's perspective. Estimated ICERs of two-dose programmes ranged from ¥2,977,695 (US$30,761) per QALY to ¥6,288,633 (US$64,965) per QALY. Among the two-dose programmes, the lowest ICER was recorded in the second dose uptake at age 4 followed by ages 3, 2, 5, 6, 7, 8, 9, 10, and 11.

In societal perspective, wherein a care-giver's productivity loss was included, the sum of reduced productivity loss due to disease and reduced disease treatment costs offset the sum of vaccination cost and productivity loss due to vaccine uptake, which means these programmes turned out to be cost-saving in single-dose programme and some of two-dose programmes, such as: uptake in alone/co-vaccinated scenario with second dose uptakes at ages 2, 3, 4, 5, 6, and 7. ICERs of programmes which did not turned out to be cost-saving ranged from ¥1,050,933 (US$10,857) per QALY to ¥6,926,263 (US$71,552) per QALY in alone/alone scenarios and ¥1,028,707 (US$10,627) per QALY to ¥1,801,783 (US$18,613) per QALY in alone/co-vaccinated scenarios.

When comparing two-dose programmes with the single-dose programme, ICERS per QALY from payer's perspective ranged from ¥7,997,190 (US$82,616) to ¥122,934,023 (US$1,269,980), while in societal perspective it ranged from ¥9,838,812 (US$101,641) to ¥212,586,977 (US$2,196,146) in alone/alone scenario and from cost-saving to ¥113,454,799 (US$1,172,054) in alone/co-vaccinated scenario.

4.2. Stability of ICER

Fig. 3 shows the top five variables that produced large ICER variations when compared with status quo from payer's perspective. Largest change was seen in costs per shot of vaccine in all programmes. When cost is decreased to half of its base-case, all programmes turned out to have negative ICERs, which means that the implementation of any of these programmes will result in gaining more QALYs with lesser cost. The next top four variables that produced large changes in ICER are any four of the six variables: treatment costs per meningitis case, proportion of meningitis among symptomatic mumps cases, incidence of symptomatic mumps cases, vaccine effectiveness of first dose, vaccine effectiveness of second dose, and utility weight of unilateral hearing loss, whose order are influenced by the programme and age. Among 726 ICERs estimated (66 changes in variables, 11 programmes), 22 ICERs from five variables in two-dose programmes were found to be larger than ¥10,000,000 (US$103,306) per QALY. These resulted because of the: (1) lower limit of incidence of symptomatic mumps cases, if second dose uptake is at age ≥6, (2) lower limit of vaccine effectiveness of the first-dose, if uptake is at age ≥8, (3) upper limit of costs per vaccine shot, if uptake is at ≥7, (4) proportion of meningitis among symptomatic mumps cases, if uptake is at ≥10, and (5)

Table 3
Results of base-case analysis from payer's perspective.

Per child						Cost(¥)/QALY	
Programme (age of 2nd dose)	Vaccine cost	Diseases treatment costs	Total costs	QALY	Incremental effects (QALY)	Compared with status quo	Compared with single-dose programme
Status quo	2085	14,422	16,507	30.77595	–	–	–
1-dose	5283	11,188	16,470	30.77648	0.00053	gained more, cost less	–
2-dose (at 2 yr)	10,191	9182	19,373	30.77680	0.00085	3,370,669	9,126,515
2-dose (at 3 yr)	10,048	9108	19,156	30.77681	0.00086	3,076,136	8,163,270
2-dose (at 4 yr)	9910	9144	19,053	30.77681	0.00085	2,977,695	7,997,190
2-dose (at 5 yr)	9774	9540	19,315	30.77674	0.00079	3,544,574	10,940,253
2-dose (at 6 yr)	9644	10,063	19,707	30.77666	0.00071	4,512,419	18,285,133
2-dose (at 7 yr)	9517	10,348	19,865	30.77661	0.00066	5,064,338	25,914,654
2-dose (at 8 yr)	9394	10,692	20,086	30.77656	0.00061	5,875,233	46,950,392
2-dose (at 9 yr)	9274	10,818	20,091	30.77654	0.00059	6,084,222	63,522,279
2-dose (at 10 yr)	9157	10,909	20,066	30.77652	0.00057	6,199,236	85,607,727
2-dose (at 11 yr)	9045	10,991	20,035	30.77651	0.00056	6,288,633	122,934,023

Results of base-case analysis from societal perspective by

						Cost(¥)/QALY			
	Productivity loss (uptake vaccine) by scenario of uptake 1st-/2nd-vaccine		Productivity loss (diseases treatment)	Total costs		Compared with status quo		Compared with single-dose programme	
	Alone/alone	Alone/co-vaccinated		Alone/alone	Alone/co-vaccinated	Alone/alone	Alone/co-vaccinated	Alone/alone	Alone/co-vaccinated
Status quo	1594	1594	20,772	38,873	38,873				
1-dose	4037	4037	16,086	36,593	36,593	gained more, cost less	gained more, cost less		
2-dose (at 2 yr)	7788	4037	13,191	40,352	36,601	1,740,071	gained more, cost less	11,819,023	23,460
2-dose (at 3 yr)	7679	4037	13,090	39,925	36,284	1,222,499	gained more, cost less	10,127,539	gained more, cost less
2-dose (at 4 yr)	7573	4037	13,145	39,771	36,236	1,050,933	gained more, cost less	9,838,812	gained more, cost less
2-dose (at 5 yr)	7470	4037	13,716	40,500	37,068	2,055,068	gained more, cost less	15,026,933	1,824,386
2-dose (at 6 yr)	7370	4037	14,469	41,546	38,213	3,769,764	gained more, cost less	27,978,257	9,149,198
2-dose (at 7 yr)	7273	4037	14,881	42,019	38,783	4,744,663	gained more, cost less	41,412,979	16,713,355
2-dose (at 8 yr)	7179	4037	15,377	42,641	39,499	6,186,973	1,028,707	78,535,788	37,738,593
2-dose (at 9 yr)	7087	4037	15,559	42,737	39,687	6,560,788	1,382,617	107,784,091	54,276,315
2-dose (at 10 yr)	6998	4037	15,691	42,755	39,794	6,764,205	1,605,623	146,715,293	76,214,681
2-dose (at 11 yr)	6912	4037	15,811	42,758	39,884	6,926,263	1,801,783	212,586,977	113,454,799

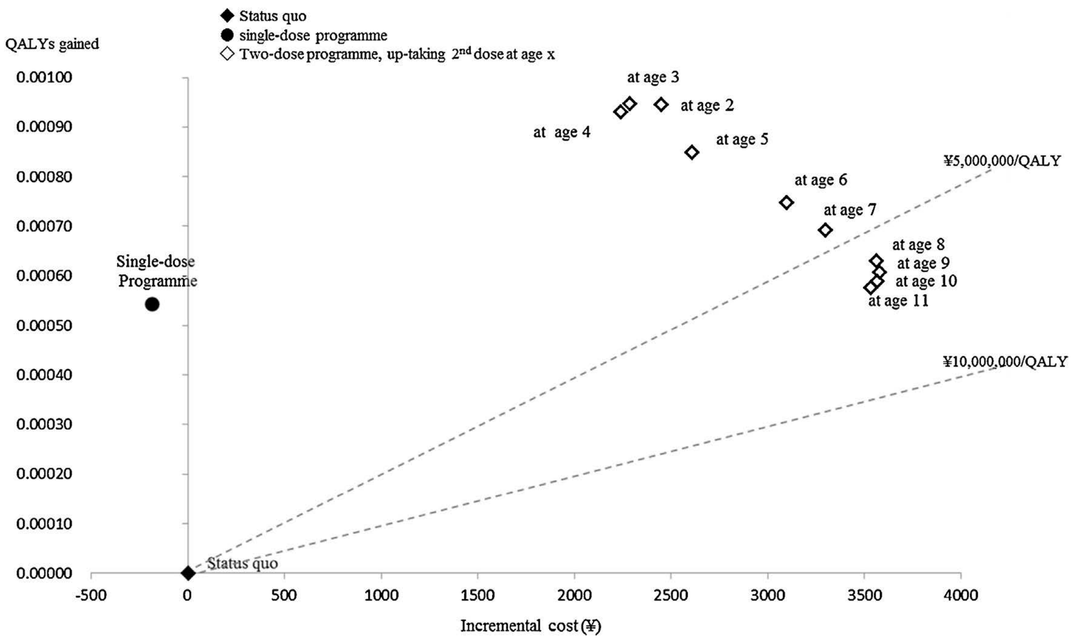

Fig. 2. Cost-effectiveness plane.

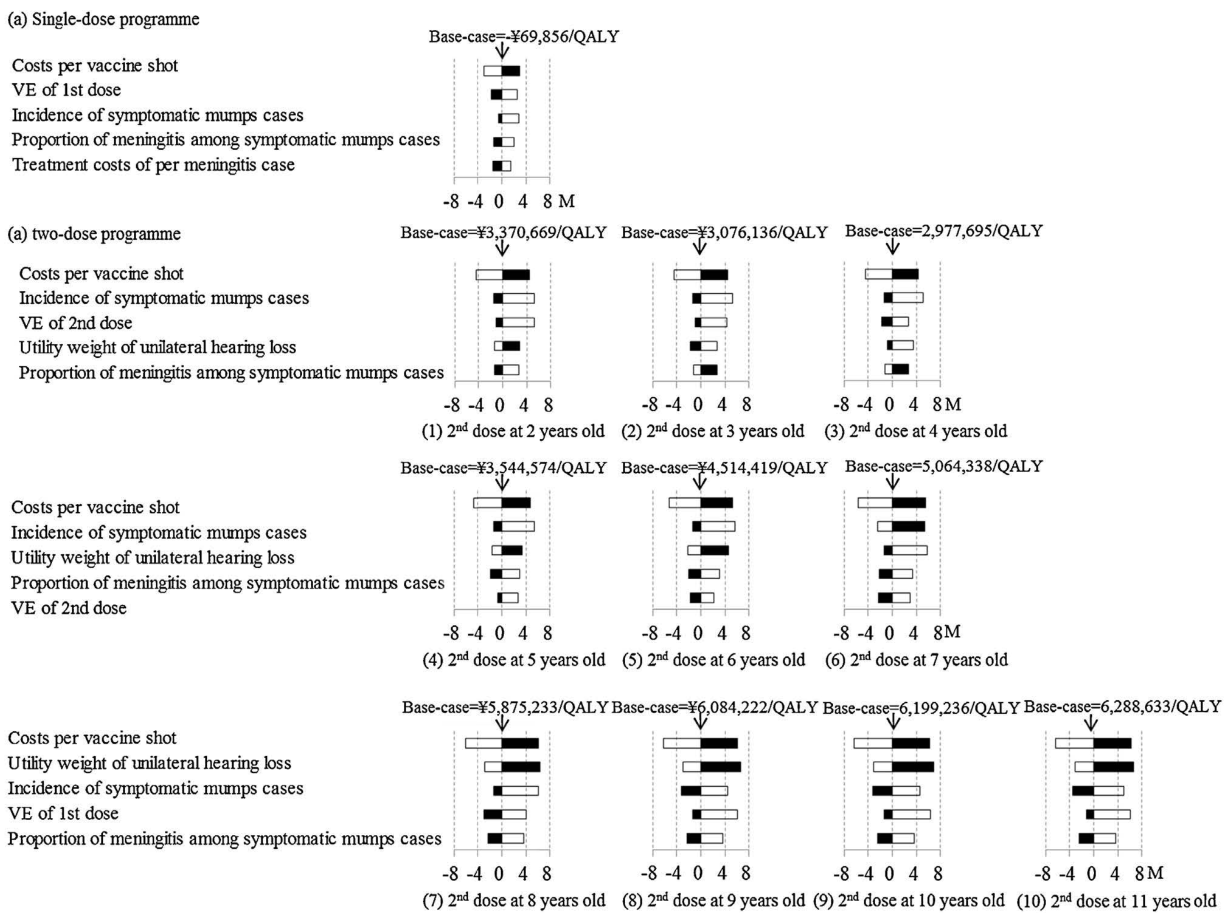

Fig. 3. Results of one-way sensitivity analysis. Variables were changed one at a time when performing one-way sensitivity analysis.

upper limit of utility weight of unilateral hearing loss, if uptake is at age ≥7.

5. Discussion

We conducted cost-effectiveness analyses on routine mumps vaccine immunisation programmes for the birth cohort in Japan. There were 11 different programmes, a single-dose programme at 12–16 months and 10 two-dose programmes with second dose uptakes at ages 2, 3, 4, 5, 6, 7, 8, 9, 10 and 11. Analyses were done from both societal (with productivity loss) and payer's perspectives (without productivity loss).

The single-dose programme gained more QALY with less cost when compared with status quo. ICERs of all 10 two-dose programmes are under ¥6,300,000 (US$65,083) per QALY from payer's perspective; while it ranged from cost-saving to <¥7,000,000 (US$72,314) per QALY from societal perspective. A willingness-to-pay threshold, ¥5,000,000 (US$51,653) per QALY gained, has been suggested for healthcare intervention [46], while WHO suggests three times of GDP (around ¥11,000,000 or US$113,636 in Japan) as a criterion to judge whether an immunisation programme is cost-effective or not [47]. By using the ¥10,000,000 (US$103,306) threshold, all programmes in our model can be concluded as cost-effective. Moreover, the single-dose programme is deemed to be cost-saving regardless of the perspective. Among the 10 two-dose programmes, second dose uptake at 3 or 4 years old has lower ICER than others, also these two programmes turned out to be cost-saving from societal perspective when vaccine uptake was done simultaneously with other vaccine. When compared with the single-dose programme, ICERs of additional second dose will be lower than ¥10,000,000 (US$103,306) per QALY if the second dose of the vaccine uptake is ≤4 years old from payer's perspective, at 4 years old from societal perspective in the vaccine alone scenario, and if ≤6 years old in co-vaccinated scenario. Comparing ICERs of the programmes with PCV-7, about ¥7,400,000 per QALY [27], which is now on the list of routine immunisation schedule in Japan, the two-dose mumps vaccination programme are considered to be more favourable. With these results, when routine mumps vaccination programme were to be implemented, two-dose programme with second dose schedule at 3–5 years old are favourable than schedules at higher ages.

Our conclusions are considered robust based on the results from our sensitivity analyses: only 22 out of 726 ICERs exceeded ¥10,000,000 per QALY and the largest ICER is less than ¥13,200,000 (US$136,363) per QALY. Also, five out of these 22 ICERs are from the upper limit at 150% base-case cost of cost per vaccine shot. Cost per shot rising to 150% from current costs is relatively low because of the strict vaccine protection and delivery system in Japan.

Studies from overseas reported that single- or two-dose mumps vaccination programmes as highly cost-beneficial, in which mumps vaccine was given through measles-mumps-rubella combination [8–12]. In Japan, only one peer-reviewed article reported an incremental benefit-cost ratio of 5.1 for single-dose mumps vaccination programme only from societal perspective and unrealistically assumed that 100% of non-vaccinees will be infected [13], which we consider as an over evaluation due to improbable assumptions. Though it is difficult to directly compare the results of economic evaluation among different countries or even within a country due to model and parameter variations, our analysis from societal perspective shows that single-dose and two-dose programmes with second dose uptake at 2–7 years old were cost-saving, which is consistent with the results of previous studies.

This study has limitations. First, clinical evidence of the efficiency of vaccination in reducing annual incidence rates of mumps cases in the model were adopted from studies carried out in other countries since no similar study has been done in Japan. There should be differences in vaccine strains, in ethnicity, as well as in healthcare system between those countries and Japan. Second, proportion of meningitis, encephalitis, orchitis, oophoritis, and other mumps-related hospitalisation cases among symptomatic mumps cases were indirectly estimated by using a nationwide survey jointly conducted by Japan Medical Association, Japan Pediatric Association, and Japan Pediatric Society [36] wherein the response rate of the survey is not high enough to ensure against bias. Third, though aseptic meningitis is a side effect of mumps vaccine, we did not include it in our model. A study, which enrolled 1051 children with mumps and 21,465 vaccine recipients by 143 paediatric primary care practitioners from 2000 to 2003, reported an incidence of aseptic meningitis at 1.24% in patients with symptomatic natural mumps infection and 0.05% in vaccine recipients [34]; hence, its inclusion would bring more favourable results to the vaccination programmes.

Regardless of these limitations, our model considers the potential impact of waning immunity and schedule changes, i.e. different ages of up-taking the second dose, which is unique in the economic evaluation of mumps vaccine in terms of context of choice under consideration.

6. Conclusion

A routine vaccination programme of single-dose is cost-saving from both payer's and societal perspectives. All two-dose programmes are considered cost-effective from both perspectives. Among them, second dose uptake at age 3, 4 and 5 are recommended because they are highly cost-effective from payer's perspective and will turn out to be cost-saving from societal perspective.

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 and interpretation of the data, and wrote the manuscript. Masahide Kondo and Ichiro Okubo participated in the concept and design of the study, the interpretation of the data.

Sponsors role

None.

Conflict of interest

None.

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