Vaccine 35 (2017) 3264–3271

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Cost-effectiveness of varicella vaccine against herpes zoster and post-herpetic neuralgia for elderly in Japan

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ARTICLE INFO

Article history:
Received 12 October 2016
Received in revised form 18 April 2017
Accepted 19 April 2017
Available online 4 May 2017

Keywords:
Cost-effectiveness
Economic evaluation
Herpes zoster
Varicella vaccine
Vaccination
Quality-adjusted life year

ABSTRACT

Background: The extended use of varicella vaccine in adults aged 50 and older against herpes zoster (HZ) was recently approved in Japan, which has raised the need to evaluate its value for money.
Methods: We conducted a cost-effectiveness analysis with Markov modelling to evaluate the efficiency of varicella vaccine immunisation programme for the elderly in Japan. Four strategies with different ages to receive a shot of vaccine were set, namely: (1) 65–84, (2) 70–84, (3) 75–84 and (4) 80–84 years old (y.o.). Incremental cost-effectiveness ratios (ICERs) compared with no programme from societal perspective were calculated. The health statuses following the target cohort are as follows: without any HZ-related disease, acute HZ followed by recovery, post-herpetic neuralgia (PHN) followed by recovery, post HZ/PHN, and general death. The transition probabilities, utility weights to estimate quality-adjusted life year (QALY) and disease treatment costs were either calculated or cited from literature. Costs of per course of vaccination were assumed at ¥10,000 (US$91). The model with one-year cycle runs until the surviving individual reached 100 y.o.
Results: ICERs ranged from ¥2,812,000/US$25,680 to ¥3,644,000/US$33,279 per QALY gained, with 65–84 y.o. strategy having the lowest ICER and 80–84 y.o. strategy the highest. None of the alternatives was strongly dominated by the other, while 80–84 y.o. and 70–84 y.o. strategy were extendedly dominated by 65–84 y.o. strategy. Probabilistic sensitivity analyses showed that the probabilities that ICER is under ¥5,000,000/US$45,662 per QALY gained was at 100% for 65–84 y.o., 70–84 y.o., 75–84 y.o. strategy, respectively, and at 98.4% for 80–84 y.o. strategy.
Conclusion: We found that vaccinating individuals aged 65–84, 70–84, 75–84, and 80–84 with varicella vaccine to prevent HZ-associated disease in Japan can be cost-effective from societal perspective, with 65–84 y.o. strategy as the optimal alternative. Results are supported by one-way sensitivity analyses and probabilistic sensitivity analyses.

1. Introduction

Herpes zoster (HZ) results from reactivation of the varicella-zoster virus (VZV) in sensory ganglia after a long latency period following primary infection from varicella [1,2]. Epidemiological data of reports from high-income settings noted that age-adjusted HZ incidence in the total population ranging from 3.4 to 5.0 per 1000 person-years, while for those aged over 65 are from 8.0 to 11.0 per 1000 person-years [3]. The most common serious complication of HZ is post-herpetic neuralgia (PHN), i.e., persistent pain beyond the acute phase of vesicular rash [3]. Antiviral therapy can shorten the length and severity of acute HZ, but therapy must be started as soon as the rash appears [3]. In Japan, there are two large-scale epidemiological studies, which reported age-specific HZ incidence rates, namely: Miyazaki study and Shozu Herpes Zoster (SHEZ) study [4,5]. The former reported an HZ incidence rate of 7.48 per 1000 person-year for adult aged 50 and over, while the latter at 5.3–8.2. Although healthcare in Japan is easily accessible, percentage of HZ patients visiting within the ideal period for antiviral chemotherapy, day 0–2, is still low at 37% [6].

A single dose, high-potency, live-attenuated Oka VZV vaccine against HZ (Zostavax®) has been licensed for use among immunocompetent adults ≥50 years old [3], and has been used in over 60 countries for individuals ≥50 years old. The vaccine is formulated with a minimal potency of 194,000 plaque-forming units (PFU) and administered as a single 0.65 ml subcutaneous injection [7]. Cost-effectiveness studies from high-income countries found HZ vaccination to be less than US$50,000 per quality-adjusted life year (QALY) in 12 out of 15 studies, when the vaccine is given to those

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http://dx.doi.org/10.1016/j.vaccine.2017.04.046
0264-410X/

60–79 years old, and in 5 out of 5 studies when given to ≥65 years old [8].

Zostavax® is not available in Japan, while a Japan-approved Oka varicella vaccine with similar annual mean titer at 42,000–67,000 PFU per dose exists [9] (Table S1). In March 2016, the Ministry of Health, Labour and Welfare (MHLW) approved the extended use of varicella vaccine in adults aged 50 and older against HZ. On June 22, 2016, the Health Science Council in charge of Immunisation and Vaccine added varicella vaccine against HZ as one of the topics for discussion in one of their recent conferences [10], which has raised the need to evaluate its value for money. This study aimed to appraise the value for money of giving varicella vaccine to the Japanese elderly, likewise, also explored the appropriate age for vaccine uptake due to varying incidence of HZ, PHN, and vaccine efficacy.

2. Method

We conducted a cost-effectiveness analysis with Markov modelling to evaluate the efficiency of varicella vaccine immunisation programmes among Japanese elderly from a societal perspective. Incremental cost-effectiveness ratios (ICERs) were calculated to determine resource use efficiency. The software used in this study is TreeAgePro 2016 [11].

In defining immunisation programmes and constructing the model, we conducted a literature survey to find out the best available evidence (Table S2).

2.1. Programme and model

The target population of the immunisation programmes to be evaluated were those aged 65–84 in 2016 [12]. We set four different strategies with different ages to receive a vaccine shot, namely: (1) 65–84 years old (y.o.), (2) 70–84 y.o., (3) 75–84 y.o., and (4) 80–84 y.o. We set the upper age at 84 and the lower age at 65 due to the uncertainty of long-term vaccine efficacy of patients under 65 as well as beyond 85 years old. Since the coverage rate of seasonal influenza vaccine in 2014 was 50.6% [13], we expect that varicella vaccine coverage for HZ among elderly to be lower, hence, we assumed the vaccine uptake rates to be at 40% for all four strategies.

A static Markov model of courses followed by the cohort under consideration was constructed based on epidemiological data, vaccine effectiveness and models from previous studies [14–34]. Five mutually-exclusive health states were modelled: health (without any HZ-related diseases), acute HZ followed by recovery, PHN followed by recovery, post HZ/PHN, and general death (Fig. 1). Our model did not include VZV-related complications (ophthalmic, neurological, or ocular) due to insufficient data in Japan. A Markov cycle for each stage was set at one year, the model continued until the surviving individual/s reached 100 y.o. Adverse effects associated with vaccination were not considered in our model based on systematic reviews [35]. Death directly from HZ/PHN was omitted because the occurrence is rare in Japan.

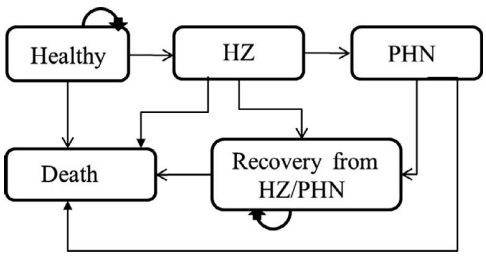

Fig. 1. Markov model.

2.2. Outcomes estimation

Outcomes in terms of QALY were estimated by assigning transition probabilities and utility weights from literature with incidence rates taken from the relevant Japanese studies; Miyazaki study and SHEZ [4,5]. Miyazaki study, a retrospective study conducted from 1997 to 2006 in Miyazaki Prefecture, reported the HZ incidence at 6.36, 8.08, 7.8, and 6.39 per 1000 person-year for persons aged 60–69, 70–79, 80–89, and 90 and over, respectively. While, SHEZ, a prospective cohort study, which recruited participants aged ≥50 from 19,058 residents between 12, 2008 and 11, 2009, reported higher HZ incidence than Miyazaki study, at 6.5 11.3, 10.8 per 1000 persons for men, 12.4, 14.1 13.6 per 1000 persons for women. In our model, HZ incidence was conservatively adopted from Miyazaki study, while proportion of PHN cases among HZ cases, namely 19.4%, 12.5%, 34.8% for men and 10.8%, 24.7%, 32.0% for women for person age 60–69, 70–79 and ≥80, respectively, were from SHEZ, because data related to PHN is not available in the Miyazaki study. Rates of general death are from vital statistics [36].

2.3. Vaccine effectiveness

The approval of extended use of varicella vaccine in adults ≥50 years old against HZ in Japan was through an application based on public knowledge. This type of application is submitted on the pretense that overseas usage of drug and medical literature published both in Japan and other countries are sufficient to prove that the drug's safety and efficiency is public knowledge within the medical and pharmacological community, and does not require additional clinical studies be conducted, either in whole or in part. Therefore, we used the vaccine effectiveness (VE) of varicella vaccine in reducing HP/PHN incidence rates from overseas' studies on Zostavax®.

Even though the Shingles Prevention Study, Short-Term Persistence Sub-study and Long-Term Persistence Sub-study (LTPS), have continuously reported VE by year after vaccination [37–39], these studies were not able to demonstrate how VE changed with chronological age (age at start of each year since vaccination) and duration after vaccination. We believe that the duration of protection and chronological age are important factors in evaluating HZ vaccination strategy cost-effectiveness, hence, we adopted the VE of model 3 from Li et al.'s study [40]. We further conservatively assumed that the vaccine will decrease HZ incidence and PHN proportion per HZ case, with no direct effects on PHN decrease. Age-specific VE data are shown in Table 1 and Fig. S1.

2.4. Utility weights

Since no study has reported the utility weights or health-related quality-of-life of HZ/PHN in Japan, we estimated these data based on two studies. Drolet et al. reported mean ED-5D score of HZ in different follow-up points after onset of rash as: 0.52 (0 day), 0.68 (30 days ~ 180 days) for patients 61–70 years old; 0.63 (0 days), 0.61 (30 days), 0.63 (90 days), 0.65 (180 days) for patients over 70 years old [41]. They also reported that "the score remained stable after 90 days (with a change of 0.2 points observed per week)". We therefore estimated the utility weights at 0.73 for 210 days and at 0.81 for 270 days and after. These figures were then weighted by the proportion of local patients with pain by month reported by Imafuku et al., which were 73.3%, 12.4%, 5.1%, 2.5%, 1.3%, 0.9% for month 0 to month 6, respectively [42]. These calculations were used to estimate average HZ QALY at 0.9548 for individuals age 60–69 and 0.9544 for those ≥70 years old, while, PHN utility weights, 0.79 (60–69 years old) and 0.76 (≥70 years old), were the averages of month 0 to month 12.

Table 1
Variables.

Base case					One-way sensitivity analyses[a]				PAS[b]	Reference
					Lower		Upper			
Target Population of alternative strategies (×1000)										[12]
Age 65–69 strategy	28,090									
Age 70–74 strategy	18,990									
Age 75–79 strategy	11,099									
Age 80–84 strategy	4854									
Male and female population in different age strata (×1000)										
Age	Male	Female								
65–59	4391	4715								
70–74	3673	4218								
75–79	2758	3487								
80–84	1938	2916								
Age-specific incidence rates of HZ (per 1000 persons)									β	[4]
Age	Male	Female			Male	Female	Male	Female		
60–69	6.36	7.78			5.09	6.22	6.50	12.40	Male:(4217; 62, 456)[c] Female (5, 854; 72, 473)	
70–79	8.08	8.25			6.46	6.60	11.30	14.10	Male:(3, 749; 44, 887) Female (5, 378; 62, 426)	
80+	7.80	7.13			6.24	5.70	10.80	13.60	Male:(1, 244; 15, 200) Female (2, 269; 32, 010)	
Percentage of PHN cases among HZ cases									β	[5]
Age	Male	Female			Male	Female	Male	Female		
60–69	19.4%	10.8%			15.5%	8.6%	23.3%	8.6%	Male: (7; 29); Female (8; 66)	
70–79	12.5%	24.7%			10.0%	19.8%	15.0%	19.8%	Male: (6; 42); Female (20; 61)	
80+	34.8%	32.0%			27.8%	25.6%	41.8%	25.6%	Male: (8; 15);Female (16; 34)	
General death (per 100,000 persons)										[36]
Age	Male	Female								
65	1,345.2	554.0								
70	2,104.0	890.2								
75	3,591.8	1,655.3								
80	6,481.9	3,272.5								
85	11,388.1	6,546.8								
90	18,861.4	12,874.9								
95	30,679.0	22,524.6								
100	42,375.0	39,256.9								
Vaccine effectiveness (%)[d]										[37–40]
	Age 65	Age 70	Age 75	Age 80					Uniform	
Year 1	66.0	58.9	52.3	45.7		(95 CI 60, 70)[e]			(95 CI 60, 70)[e]	
Year 2	64.2	57.2	50.8	44.4		[e]			[e]	
Year 3	61.9	55.2	49.0	42.8		[e]			[e]	
Year 4	59.6	53.1	47.2	41.3		[e]			[e]	
Year 5	57.3	51.1	45.4	39.7		[e]			[e]	
Year 6	55.0	49.0	43.6	38.1		[e]			[e]	
Year 7	51.9	46.3	41.1	35.9		[e]			[e]	
Year 8	48.8	43.5	38.6	33.8		[e]			[e]	
Year 9	45.7	40.7	36.2	31.6		[e]			[e]	
Year 10	42.5	37.9	33.7	29.5		[e]			[e]	
Year 11	39.4	35.1	31.2	27.3		[e]			[e]	
Utility weights										[41–42]
Age	HZ	PHN			HZ	PHN	HZ	PHN		
65–69	0.9548	0.7900			0.9518	0.7610	0.9698	0.8800		
70+	0.9544	0.7600			0.9514	0.7320	0.9693	0.8461		
Cost per vaccine shot					¥10,000					Assumed
Treatment costs[f]									γ	
HZ			¥15,000	¥7500	¥22,500				(1, 1/15,000)	[43]
PHN			¥200,000	¥100,000	¥300,00				(1, 1/200,000)	[43]

[a] Upper limits for incidence rates were from SHEZ, while lower limits were assumed to be 80% of the base-case data, with costs/utility weights assumed to be +50%/+20% for upper limits and −50%/−20% for lower limits.
[b] For PSA, β distribution is used for HZ incidence rates and PHN proportion among HZ; γ distributions were assumed for costs. For utility weights/VE, though β/lognormal distribution is more favourable, however, since there is no information about the probability density function, we used a uniform distribution instead.
[c] First and second values in parentheses correspond to α and β in β distribution, or α and λ in γ distribution.
[d] Also shown in Fig. S1.
[e] The 95% CI was first given to vaccine at age 65 (year 1) based on study of Li et al. [47], which was considered as the reference. CI for remaining age groups or remaining years after vaccination were determined by multiplying relative likelihood ratios among these ages and the reference age by the aforementioned reference.
[f] Treatment costs including consultation fee, prescription fee, Pharmaceutical management fee, dispensing fee (total of these 4 items were was estimated around ¥1720 (US$15.7) per visit), and drug fee (about ¥3200 per week). We assumed that a PHN patient sees a doctor once every two weeks.

2.5. Costing

To estimate the opportunity cost of resource use from societal perspective, we aggregated the direct medical costs borne by the government, vaccinees, patients and third party payers. Non-direct medical costs related to the immunisation programme, such as new staff, new cold chain were not included, because the vaccination programme was built within the public health services

routine; amount of direct payments to healthcare providers by these entities were estimated as costs, whereby cost items were identified along the decision tree and Markov model. We used the literature along with some assumptions to estimate the necessary data. Productivity cost and direct non-medical cost related to morbidity and immunisation were not incorporated, following the recommendation of the MHLW Vaccine Committee.

One vaccine shot is assumed to be ¥10,000 (US$91; US $1 = ¥109.5, average of 2016 January to August), which is the sum of vaccine price, doctor fee and technical fee per shot. Average treatment cost of per HZ case (¥15,000/US$14) and per PHN case (¥200,000/US$1826) were from Ikeda et al. [43]. We incorporated the costs reported before 2016 with no adjustment because the variation of consumer price index of services related to medical care was less than 0.1% during these 10 years. On the other hand, sensitivity analyses were conducted on cost-related data.

2.6. Discounting

Outcomes and costs were discounted at a rate of 3% [44].

2.7. 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 analyses, four sets of 1000 Monte Carlo simulations, i.e., probabilistic sensitivity analyses (PSA), and a threshold analysis on vaccination costs.

Table 2
Results of base-case analyses.

Strategies	Vaccination Cost (¥/person)	Treatment Costs ¥/person)	Total Costs (¥/person)	Effectiveness (QALY/person)	ICER (¥/QALY)[a]	
					Compared to no programme	Compared to next lowest cost alternative[b]
No programme	0	5581	5581	12.96049	–	–
Age 80–84	691	5477	6168	12.96065	3,643,599	3,643,599
Age 75–84	1580	5324	6904	12.96090	3,227,530	2,958,506
Age 70–84	2704	5109	7813	12.96127	2,883,491	2,495,974
Age 65–84	4000	4879	8879	12.96166	2,811,688	2,672,401

[a] ICERs, incremental cost-effectiveness ratios; QALY, quality-adjusted life years.
[b] When compared to next lowest cost alternative, we have observed that ICER of moving from 80–84 y.o. strategy to 75–84 y.o. strategy (¥2,959,000/US$27,023 per QALY) was higher than moving from 75–84 y.o. to 70–84 y.o. strategy (¥2,496,000/US$22,795 per QALY), which means that moving from 75–84 y.o. to 70–84 y.o. strategy offers greater health improvements at lower ICER. Thus, 75–84 y.o. strategy was ruled out as an alternative that will never be chosen because it was extendedly dominated by 80–84 y.o. strategy. After the second and third rounds of comparison using the next lowest cost procedure, 80–84 y.o. and 70–84 y.o. strategies were observed to be extendedly dominated by 65–84 y.o. strategy, which resulted to 65–84 y.o. strategy being the most cost-effective strategy.

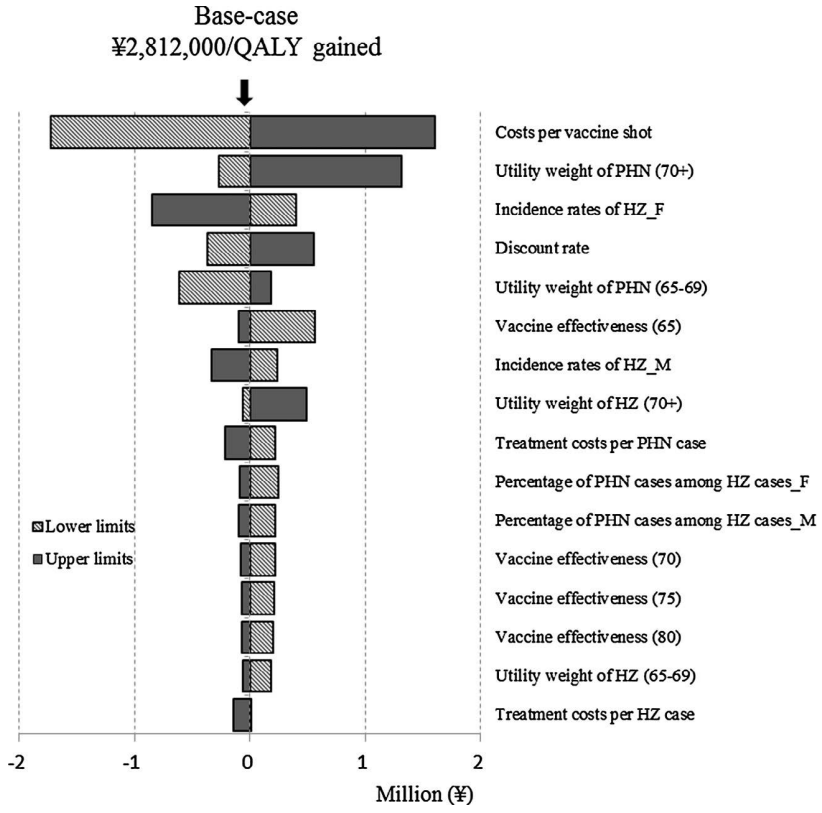

Fig. 2. Results of one-way sensitivity analyses (only 65–84 strategy vs. no immunisation programme was shown because others were in same pattern). One-way sensitivity analyses were performed by varying one input at a time while holding others constant at their base-case estimates.

The probability density functions and the ranges for sensitivity analyses are shown in Table 1.

3. Model validation

We validated our model by summing the annual cases of HA and PHN in the vaccinated and non-vaccinated groups, and then calculated the vaccine efficacy for time periods corresponding to the vaccine effectiveness used.

4. Cost-effectiveness threshold

Although MHLW has not yet set a willingness-to-pay threshold for judging the cost-effectiveness of public health programmes in the country [45], local studies have initially begun citing the willingness-to-pay threshold (at ¥5,000,000 (US$45,662) per QALY gained) from Shiroiwa et al. [46] to facilitate the analysis. There are also other existing thresholds being used by other studies, namely, the "favourable" level set by the Committee to Study Priority for Vaccine Development in the United States at US$ 10,000–100,000 per QALY [47], and WHO's suggested "cost-effective" criterion at 1 to 3 times of GDP [48].

5. Results

5.1. Results of base-case analyses

Table 2 reports the expected costs per person and expected QALYs per person associated with no immunisation programme and four alternatives. We have observed that compared to the lowest cost alternative, i.e., no immunisation programme, all four strategies reduced disease treatment costs, however, these reduced costs did not offset vaccination costs, which means it gained more QALYs but cost more. Incremental costs per person ranged from ¥587/US$5 (80–84 y.o. strategy) to ¥3298/US$30 (65–84 y.o. strategy), while incremental effect ranged from 0.000161 QALYs (80–84 y.o. strategy) to 0.001173 QALYs (65–84 y.o. strategy) per person. Both incremental costs and incremental effectiveness decreased with increasing age to uptake of vaccine. ICERs of all four strategies ranged from ¥2,812,000/US$25,680 to ¥3,644,000/US$33,279 per QALY gained, with 65–84 y.o. strategy having the lowest ICER, followed by 70–84 y.o., 75–84 y.o. and 80–84 y.o. strategies. None of the alternatives was strongly dominated by the other. If 65–84 y.o. strategy was to be adopted, at the 40% vaccine uptake rate, the total vaccine cost will be around ¥112.4 billion, while it will save ¥19.7 billion treatment costs and 32,957 QALYs, compared to current no immunisation programme.

5.2. Results of sensitivity analyses

One-way sensitivity analyses (Fig. 2) showed that, 65–84 y.o. strategy was always identified as the most cost-effective strategy among the four strategies. 80–84, 75–85 and 70–85 y.o. strategies were always extendedly dominated by other strategies, except for two variables, which are the HZ utility weight upper limit (=1) and VE lower limit on reducing HZ. The variables which changed the ICER more than ¥1,000,000/US$9132 per QALY gained, but did not make the ICER larger than ¥5,000,000/US$45,662 per QALY gained were: (1) cost per shot, and (2) PHN utility weight upper limit for ≥70 years old patient. Threshold analysis on cost per shot showed that the cost-saving cut-off point for immunisation programmes is at ¥1900/US$17. Table 3 and Fig. 3 shows the results of PSA of four alternative strategies compared to no programme.

Table 3
Results of probabilistic sensitivity analyses: incremental cost, incremental effectiveness, and ICER.

	Age 65–84 vs. no programme			Age 70–84 vs. no programme			Age 75–84 vs. no programme			Age 80–84 vs. no programme		
	Incr cost[a] (¥/person)	Incr eff[b] (QALY/person)	ICER (¥/QALY)	Incr cost (¥/person)	Incr eff (QALY/person)	ICER (¥/QALY)	Incr cost (¥/person)	Incr eff (QALY/person)	ICER (¥/QALY)	Incr cost (¥/person)	Incr eff (QALY/person)	ICER (¥/QALY)
Mean	1465	0.002017	769,229	959	0.00129	797,014	582	0.000682	929,623	238	0.00024	1,141,461
SD	2146	0.000440	1,162,922	1508	0.000303	1,300,682	874	0.000173	1,458,147	420	0.000079	2,149,605
Min	−9318	0.000918	−6,596,896	−6960	0.000550	−7,919,961	−4153	0.000277	−9,054,196	−2915	0.000067	−15,352,438
2.5%	−4171	0.001198	−2,075,02	−3024	0.000740	−2,577,404	−1826	0.000364	−2,962,891	−957	0.000104	−4,163,032
Median	2048	0.001995	1,003,758	1400	0.001279	1,062,361	848	0.000677	1,202,124	375	0.000242	1,445,776
97.5%	3746	0.002876	2,398,460	2533	0.001894	2,597,915	1479	0.001008	3,050,488	649	0.000396	4,510,405
Max	3936	0.003222	3,554,482	2660	0.002123	4,013,632	1555	0.001196	4,581,682	679	0.000474	8,737,822

[a] Incr cost: incremental cost.
[b] Incr eff: incremental effectiveness.

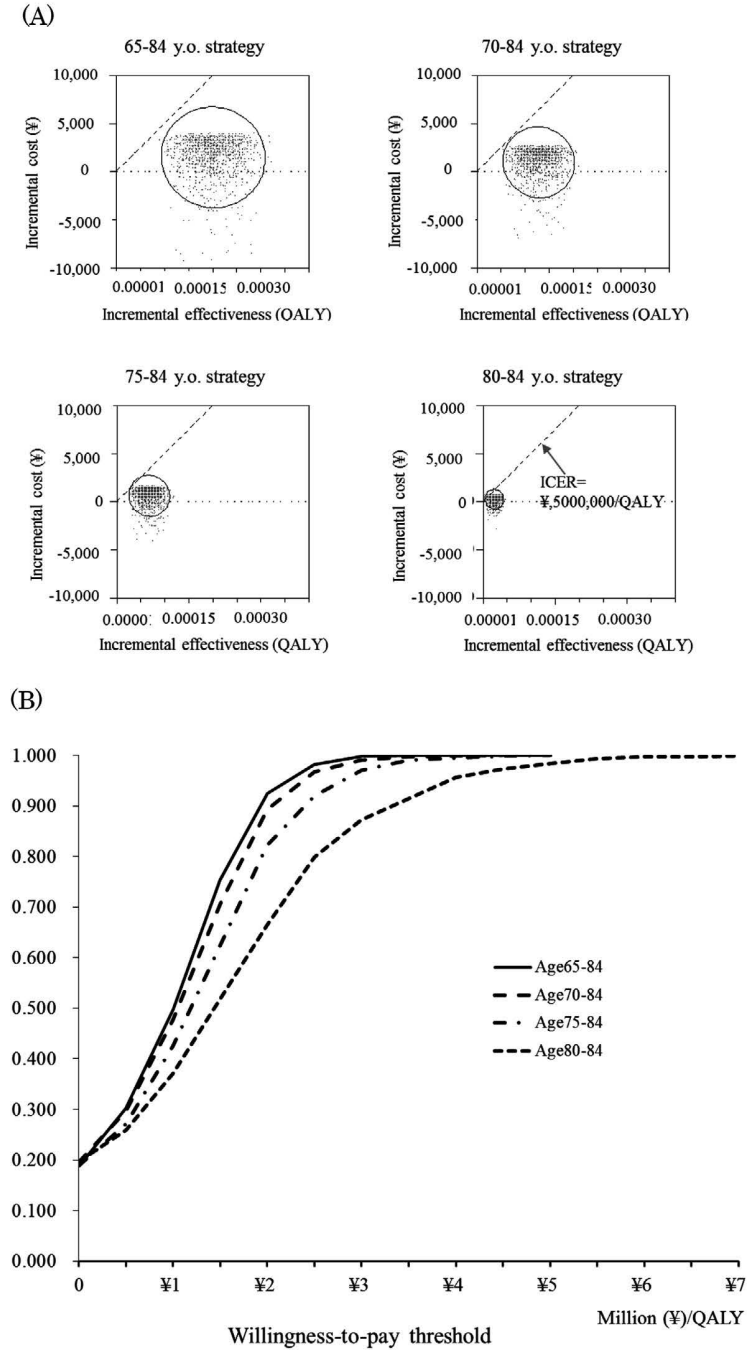

Fig. 3. Results of probabilistic sensitivity analyses (vs. no immunisation programme). PSA simultaneously varied all the inputs according to pre-specified distributions in 1000 iterations. (A) Scatterplots of incremental cost and incremental effectiveness per person on cost-effectiveness plane. Each dot represents the incremental costs and incremental effects per person obtained from one simulation following the random draw of model parameters from their respective distributions. (B) Acceptability curves. The probabilities that ICER is under ¥5,000,000 (US$45,662) per QALY gained was at 100% for 65–84 y.o. strategy, 70–84 y.o. strategy, 75–84 y.o. strategy, respectively, and at 98.4% for aged 80–84 y.o. strategy. The probability that the simulation resulted in cost less and gained more QALY was around 20% for all the four strategies.

6. Discussion

This is the first study which evaluated the value for money of giving varicella vaccine to the elderly in preventing HZ-associated diseases, and has also explored the appropriate age to uptake the vaccine in Japan. We set four strategies with different ages to receive the vaccine, which were 65–84, 70–84, 75–84 and 80–84 y.o. Results showed that all strategies were likely to provide public health benefits in Japan and ICERs were estimated to be lower than the cost-effective threshold, at ¥5,000,000/US$4 5,662 per QALY gained. We have also determined that the 65–84 strategy is the most cost-effective among the four. Sensitivity analyses confirmed the robustness of our findings, wherein vaccinated strategies always had an ICER less than ¥5,000,000/US$45,662 per QALY within the plausible range of model inputs. PSA showed that the probabilities that ICER is under ¥5,000,000/US$45,662 per QALY gained were at 100% for 65–84 y.o., 70–84 y.o., 75–84 y.o. strategy, respectively, and at 98.4% for 80–84 y.o. strategy.

We were able to identify 21 previously-published studies from developed countries: five from United States, three from United Kingdom, two from Canada, Belgium, Netherlands, France, Germany, respectively, and one from Switzerland, Spain, and Italy, respectively [14–34]. Although there were 5 studies which included the VZV-related complications in the models, the remaining 16 out of the 21 reviewed studies used a simplified model, in which we have opted to follow. When comparing our age-specific HZ incidence rates to those of the 21 studies, we found that the variables in our model are below the average (Fig. S2). While, percentages of PHN cases among HZ cases compared with those of the previous studies, are almost at the same level of the average of the previous studies, except for those aged greater than 80 (Fig. S3). All the previous studies except one study from Germany [22] assumed that VEs were not age-specific, lifelong or would remain stable for 10 years before decreasing annually by certain percentages. These assumptions seem unrealistic after the LTPS was published. Even with lower values of incidence of HN, percentage of PHN, and lower VEs, our study revealed that immunisation elderly aged 65 and over is cost-effective, which is consistent with those of previous studies. This may be due to the low vaccination cost in Japan. The vaccination cost for one shot (including vaccine price, doctor fee and technical fee) in our study is conservatively assumed at ¥10,000 (US$91), which is the highest cost from the internet survey. Previous studies set vaccine cost per shot at US$123-US$250, which is 140–270% of the cost in our study. The low vaccination cost may be due to the low price of live-attenuated Oka varicella vaccine, which was developed in Japan in 1947 and has been in supply from 1976.

We believe that the study's strengths are primarily due to the (1) usage of a Japanese data source with HZ incidence rates coming from a large-scale epidemiological study, the Miyazaki study, and (2) incorporation of VE waning assumption with age and time since vaccination. However, our study faced certain limitations, such as: (1) Markov model used in the study is simple compared to previous studies. For example, we did not model the reduction in HZ pain in patients who have HZ despite vaccination, nor did we incorporate ophthalmic zoster cases. Exclusion of these aspects of HZ infection could underestimate health benefits, while accounting these as part of prevention could lead to cost-savings for HZ vaccination, (2) due to the absence of Japanese disease-specific utilities, data were estimated by using a combination of overseas' data and Japanese data, with moderate impact on results using the combined data, (3) average duration of PHN which can persist for 12 months, may represent an overestimation for younger patients and underestimation for older patients, (4) we defined PHN as a persistent pain for 90 days after zoster onset, however, this is still subject to validation since there are different definitions of PHN, and can pose a difficulty when comparing our study with previous ones, and (5) since Japan started to give childhood varicella vaccination programme from October 2014, it has been hypothesised that varicella vaccine introduction might increase HZ incidence in the population because of VZV reduction circulating in the community, which can result to a decrease in the opportunity for boosting immunity against VZV [2]. In recent studies, they have reported that there is no conclusive evidence in whether varicella vaccination programmes have been associated with an HZ incidence increase [49]. Thus, we cannot incorporate the influence of childhood varicella vaccination programme into our model. Nevertheless, we believe that the incorporation of robust, locally-published epidemiologic data and costs, may have reduced this uncertainty to a certain level. We acknowledge that the study is limited to the Japanese setting. Nevertheless, we believe that the results of this study are fundamental components for policy-relevant strategies.

7. Conclusion

From our analyses, we found out that vaccinating individuals aged 65–84, 70–84, 75–84, 80–84 with local varicella vaccine to prevent HZ-associated disease in Japan can be cost-effective from societal perspective, with 65–84 strategy as the optimal alternative. The results are supported by one-way sensitivity analyses and by PSA. Aside from the cost per vaccination, we have observed that PHN utility weight for $\geq$70 years old has considerably influenced the result. A further budget impact analysis is needed for a well-informed policymaking.

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, and in the interpretation of the data.

Conflict of interest

None.

Sponsors role

None.

Acknowledgements

This study was supported by a research grant for Research on Emerging and Re-emerging Infectious Diseases, Health and Labour Sciences Research Grants from the Ministry of Health, Labour and Welfare, Japan. The authors declare no conflict of interest associated with this manuscript. We would also like to acknowledge the help of Dr. Xerxes Seposo regarding the language check of this manuscript.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2017.04.046.

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