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Cost-effectiveness of Recombinant Zoster Vaccine (RZV) and Varicella Vaccine Live (VVL) against herpes zoster and post-herpetic neuralgia among adults aged 65 and over in Japan

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ABSTRACT

Background: The approval of the extended use of 1-dose varicella vaccine (VVL) in adults aged 50 and older against herpes zoster (HZ) in 2016 and the 2-dose recombinant zoster vaccine (RZV) in 2018 raised the need to evaluate the value for money between these two vaccines.
Methods: We conducted a cost-effectiveness analysis with Markov modelling to evaluate the efficiency of the immunisation programmes from payer's perspective. Eight strategies with different ages to receive VVL or RZV were set, namely: 65–84 year old (y.o.), 70–84 y.o., 75–84 y.o., and 80–84 y.o. VVL- or RZV-strategy. Incremental cost-effectiveness ratios (ICERs) compared with curative care scenario were calculated. The health statuses following the target cohort were as follows: acute HZ followed by recovery, post-herpetic neuralgia followed by recovery, post HZ/PHN, recurrence of HZ, and general death.
Results: At the vaccination cost ¥8000 (US$73) for 1-dose ZVL and ¥30,000 (US$273) for 2-dose RZV, ICERs ranged from ¥2,633,587/US$23,942 (age 80–84 y.o.) to ¥3,434,267 or US$31,221 (age 65–84 y.o.)/QALY gained for VVL-strategies; from ¥5,262,227 or US$47,838 (age 80–84 y.o.) to ¥6,278,557 or US$57,078/QALY gained (age 65–84 y.o.) for RZV-strategies. Cost-effectiveness acceptability curves derived from probabilistic sensitivity analyses showed that if the cost-effective threshold was at ¥3,000,000 or US$27,273/QALY, the acceptability was 90.7% and 8.8% for 65–84 VVL-strategy and 65–84 RZV-strategy, respectively; if at ¥5,000,000 or US$45,455/QALY, 56.2% and 43.8%, and if at ¥10,000,000 or US$90,909/QALY 11.9% and 88.1%, respectively.
Conclusion: Vaccinating individuals aged 65–84 y.o., 70–84 y.o., 75–84 y.o., 80–84 y.o. with VVL or RZV to prevent HZ-associated disease in Japan can be cost-effective from payer's perspective, with vaccination costs at ¥8,000 per shot for VVL, ¥30,000 for 2-dose RZV. While the results suggesting that only 65–84 VVL-strategy and 65–84 RZV strategy should be considered when introducing HZ immunisation programme. The optimal strategy varies depending on the willingness-to-pay threshold.

1. Introduction

Herpes zoster (HZ) results from the reactivation of varicella-zoster virus (VZV) in sensory ganglia after a long latency period following primary infection from varicella [1,2]. In high-income settings, age-adjusted HZ incidence in the total population ranged from 3.4 to 5.0 per 1000 person-years, with particularly higher incidence (8.0–11.0 per 1000 person-years) for those aged 65 and over [3]. Post-herpectic neuralgia (PHN) is the most common serious complication of HZ, which is characterised by persistent pain beyond the acute phase of vesicular rash [3]. Common treatment for HZ complications include antiviral chemotherapy, which shortens the length and severity of acute HZ, provided that the therapy must be started as soon as the rash appears [3]. Although healthcare in Japan is easily accessible, percentage of HZ patients visiting within the ideal period for antiviral chemotherapy, 0–2 days, is still low at 37% [4].

There are two kinds of HZ vaccine currently available in some countries for the immunisation of adults with HZ, who are aged 50 and over, namely single-dose Zoster Vaccine Live (ZVL, Zostavax®) and two-dose Recombinant Zoster Vaccine (RZV, Shingrix®).

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ZVL has been licensed for use among immunocompetent adults ≥50 years old (y.o.) since 2006 in over 60 countries [3]. On the other hand, RZV has been approved and used in the USA, Canada, and EU for HZ prevention in adults aged ≥50 y.o. from 2017 to 2018 [5].

In Japan, HZ incidence ranged from 3.0 to 8.0 per 1000 person-years, with particularly higher incidence (8.0 per 1000 person-years) for those 70 and over, according to a large-scale epidemiological study [6,7]. Though ZVL is not available, there are two kinds of vaccine available for the immunisation of HZ among adults aged 50 y.o. and over, namely: (1) 1-dose Varicella Vaccine Live (VVL), which has similar annual mean titer (42,000–67,000 plaque-forming unit (PFU) per dose) with ZVL [8] and has been approved in March 2016 for the extended use in adults aged 50 y.o. and over against HZ, and (2) 2-dose RZV, which was approved in March 2018. In Japan, Pharmaceuticals and Medical Devices Agency (PMDA) approves vaccines based on quality, safety and efficacy. There are two categories for approved vaccine immunisation, namely: routine immunisations and voluntary immunisations. Routine immunisations are defined by the Preventive Vaccination Law and scheduled in the National Immunisation Programme (NIP). These vaccinations included several childhood vaccinations and two vaccinations (seasonal influenza and pneumococcal diseases) for adults aged 65 and over. Childhood vaccinations are fully funded by public fund, while influenza and pneumococcal vaccinations are fully or partially funded depending on the municipalities, which are responsible for the implementation of the immunisation programme. Voluntary immunisations are not covered by the NIP, while individuals can uptake the vaccine with their own pocket money if only the vaccine is approved and is marketed. RZV utilisation was considered to be zero, since it was not included in the routine immunisation, given that the vaccine was just approved one years ago, and it is yet to be available in the market. On June 22, 2016, the Health Science Council in charge of Immunisation and Vaccine started to discuss issues related to VVL against HZ among elderly, on the premise of defining VVL into the routine immunisation [9]. This has raised the need to evaluate its value for money particularly taking into consideration the matters related to or arising from disease burden, effectiveness and safety of vaccine, and its cost-effectiveness. Based on the progress of these events, we have published a cost-effectiveness analysis in 2017, which estimated the value for money of VVL immunisation programme against HZ and PHN for adults aged 65 and over in Japan. We found that VVL immunisation programme is highly cost-effective compared to no immunisation programme, i.e., curative care scenario, (from ¥2,670,000 or US$24,273/QALY gained for adult age 65–84 to ¥3,650,000 or US$33,182/QALY for age 80–84) from payer's perspective (1US$ = ¥110, average of 2017) [10]. Amidst the increasing number of available HZ vaccines, a public immunisation programme (against HZ) is yet to be implemented. If ever the HZ immunisation programme were to be implemented, this raises the need to compare the value for money between the currently available vaccines (VVL and RZV).

Two cost-effectiveness studies from USA reported that RZV dominated ZVL from both payer's and societal perspectives [11,12]. The vaccination costs (including administration cost) of RZV/ZVL in these studies were at US$332/US$238.7 [11] and US$320/US$217 [12], respectively. In Japan, VVL vaccination cost ranges from ¥6,000 (US$55) to ¥10,000 (US$91), which is much lower than that of ZVL in previous studies, and may therefore provide varying yet insightful results if compared to that of other studies.

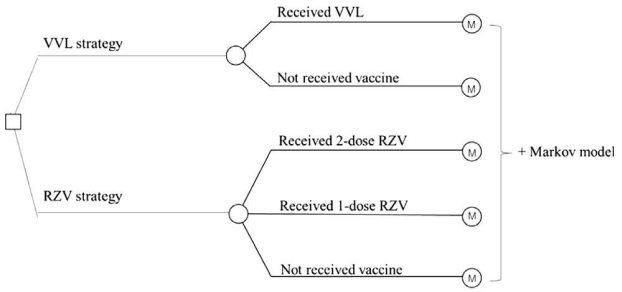
2. Method

We conducted a cost-effectiveness analysis with a decision tree and Markov modelling to evaluate the efficiency of 1-dose VVL immunisation programmes and 2-dose (administered 2–6 months apart) RZV immunisation programmes among Japanese elderly from payer's perspective, in which costs included both vaccination costs and disease treatment costs borne by all payers (including government, municipalities, vaccinees, patients and third-party payers), following the Research guidelines on the evaluation of the cost-effectiveness of vaccination in Japan [13,14]. Incremental cost-effectiveness ratios (ICERs) were calculated to determine resource use efficiency. In reference to the research guidelines on the evaluation of the cost-effectiveness of vaccination in Japan, the ICERs compared to curative care scenario (i.e., status quo in Japan) were reported as the base-case results. While ICERs compared to the next best alternative were also reported. The software used in this study was TreeAgePro 2018 [15]. In defining immunisation programmes and constructing the model, we conducted a literature survey to find out the best available evidence.

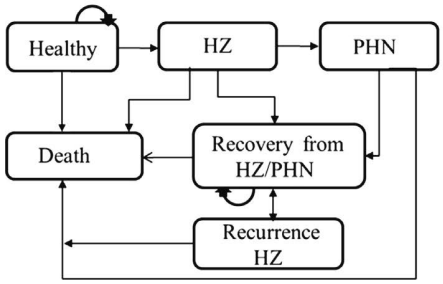
2.1. Programme and model

While both VVL and RZV were approved for adults aged 50 and over in Japan, we defined the study target population of the immunisation programmes to be evaluated as immunocompetent adults aged 65–84 [16]. We set the lower age of vaccination at 65 because: (1) in Japan, inoculated subjects' age of a routine immunisation programme was specified by a Cabinet Order; the target population of the currently being implemented immunisation programmes for adults (against seasonal influenza and pneumococcal disease) were those aged 65 and over, regardless that influenza vaccine and pneumococcal vaccination were also approved for adults under 65, and (2) the sub-committee, infections committee for national immunisation policy established by MHLW, is currently working on establishing the baseline data of herpes zoster of the "elderly" (defined to be aged 65 and over in Japan) [17,18]. We applied eight different preventive strategies with different ages to receive VVL or RZV, namely: 65–84 y.o. VVL- or RZV-strategy, 70–84 y.o. VVL- or RZV-strategy, 75–84 y.o. VVL- or RZV-strategy, and 80–84 y.o. VVL- or RZV-strategy. Because VVL and RZV were approved recently and since vaccination is voluntary, no data is available for the uptake rates. Instead, we adopted the vaccine uptake rate of the routine 23-valent pneumococcal polysaccharide vaccination in 2016, 40.8%, for the VVL-strategies and of the first dose of RZV-strategies [19]. As for the uptake rate of the second dose of RZV-strategies, we assumed it at 80% of 1st dose of RZV in base-case, in reference to those in previous cost-effectiveness studies [11,12,20]. Sensitivity analyses for the uptake rate were also performed.

The decision tree started from a decision node (Fig. 1a). For those under the VVL or RZV strategies, two/three kinds of decisions were considered for VVL/ZVL. For VVL strategies it is either they receive vaccine or not, while for ZVL strategies, decisions included: "to receive 1-dose", "to receive 2-dose", or "not to receive". The vaccinated and not vaccinated then followed the Markov model (Fig. 1b). Static Markov model with one-year cycle was updated from our previous study by including one time recurrence of HZ into the model based on recently published Miyazaki study by Shiraki et al. [6]. Six mutually exclusive health states considered, namely: healthy (being without the diseases defined by the model under consideration), HZ, PHN, recovery from HZ/PHN, recurrent HZ and death. Transitions between states were indicated with arrows. The model followed up the individuals in the cohort until they reach 100 y.o. Our model did not include, however, VZV-related complications (ophthalmic, neurological, or ocular) due to insufficient data in Japan. To accurately assess the value of an intervention, the benefits for the treated individual as well as for others must be considered, thus, a dynamic model should be considered initially. However, there were certain conditions which



(a) Decision tree model



(b) Markov Model

Fig. 1. Decision tree mocel (a) and Markov model (b). □: Decision node, ○: Chance node, M with circle: Markov node. Six mutually exclusive health states considered, namely: healthy (being without the diseases defined by the model under consideration), HZ, PHN, recovery from HZ/PHN recurrent HZ and death. Transitions between states were indicated with arrows. A Markov cycle for each stage was set at one year, the model continued until the surviving individual/s reached 100 y.o. Only one-time recurrence was assumed.

favoured more the use of a static Markov model, than of a dynamic model. In our case, these were due to: (1) 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], and (2) the groups we targeted were individuals aged ≥65, among them very few individual were susceptible to the transmission of varicella [21]. These conditions ignored the potential protective effect of vaccination for preventing varicella, both in the vaccinated individual as well as in the remainder of the community, which most of the previous studies did (Table S1, Supplementary 1), thus, we also used static Markov models to conduct the analysis.

2.2. Outcome estimation

Outcomes in terms of QALY were estimated by assigning transition

probabilities and utility weights from literature. There were four epidemiological studies [6,7,22,23], which reported age- and sex-specific HZ incidence rates in Japan (supplementary 2, Fig. S1). The incidence rates were from the Miyazaki study, which we also utilised in our previous study [10], but were updated by using the latest data (1996–2006 data [7] vs. 2009–2015 data [6]). The Miyazaki study was a large-scale epidemiological study, which included 36 dermatology clinics and the dermatology departments of seven flagship general hospitals belonging to the Miyazaki Dermatologist Society. Age- and sex-specific proportion of recurrence were also estimated from the latest Miyazaki study, while only one-time recurrence was assumed, based on the low proportion of patients experiencing three to four episodes (0.3%). Since data related to PHN was not available in the Miyazaki study, we used the proportion of PHN cases among HZ cases from the SHEZ study [22], which were at 19.4%, 12.5%, 34.8% for men and 10.8%, 24.7%, 32.0% for women aged 60–69, 70–79 and 80, respectively. SHEZ study was a prospective cohort study, which recruited participants aged ≥50 y.o. from 19,058 residents between Dec 2008 and Nov 2009. Rates of general death were from vital statistics [24].

Health-related quality of life utility weights of HZ and PHN were also updated from our previous study. They were calculated from the recent studies of Mizukami et al [25] and Kawashima et al [26]. The former was a prospective observational cohort study, which recruited 412 adult age ≥60 y.o. diagnosed with HZ and demonstrated the first EuroQol-5 Dimension (EQ-5D) utility scores in HZ with/without PHN by age group over time (from day 0 to day 360, Supplementary 3, Table S3-1) as well as the median duration and quartile (134 days, 185 days, and 274 days for Q1, median, and Q3, respectively) (Supplementary 3, Table S3-2) in Japan. The latter, which was the first randomized double-blind study in Japan to evaluate the efficacy and safety of amenamevir (for treatment of HZ), reported pain resolution duration as 5 days, 10 days, and 19 days for Q1, median, and Q3, respectively (Supplementary 3, Table S3-2). Using these EQ-5D scores and durations of pain release, we estimated the utility weights of HZ/PHN of each age group. Data and process to estimate the figures were shown in Table S3-3 (Supplementary 3).

2.3. Vaccine effectiveness (VE)

Although VVL was developed in Japan, not until October 2014 when the routine vaccination for children started, the vaccination has been used primarily for voluntary vaccination [8]. Most of the evidence related to the efficacy against varicella of Oka strain varicella vaccine for children were largely based on studies conducted in the United States, since they have adopted early the vaccine as part of the universal immunisation in 1996 [27]. Same situation happened with the evidence related to efficacy against HZ and PHN. An application, submitted on the pretense that overseas usage of drug and medical literature published both in Japan and other countries were sufficient to prove that the drug's safety and efficiency based on the common scientific knowledge within the medical and pharmacological communities, and does not require additional clinical studies to be conducted, either in whole or in part, was used to approve the extended use of VVL in adults ≥50 years old against HZ in Japan. We used instead the vaccine effectiveness (VE) of VVL in reducing HP/PHN incidence rates from overseas' studies on ZVL. Table S4 (Supplementary 4) indicated the similarities and differences between these two vaccines.

Since the first clinical trial, comparing RZV and ZVL directly, is expected to be completed on December 2019 [28], we decided to adopt the VEs from different studies which compared each vaccine with placebo, respectively. VEs of VVL for prevention of HZ were adopted from VEs of ZVL. In our study, they were 70.6%/64.5%/63.7% during the first year after vaccination for age 65–69/70–79/80+, waned to 48.8%/45.2%/41.8% during the second year after vaccination, then waned to zero until the 9th year in our study as shown in Table 1. These data were from a recently published long-term cohort study (5.8million person-years of follow-up, from 2007 to 2014) in USA by Baxter et al [29].

VEs of 2-dose/1-dose RZV, and waning duration (the duration that VE declines linearly from the initial VE to 0%) of 2-dose/1-dose RZV were based on the Advisory Committee on Immunization Practices (ACIP) presentation document on Oct. 25th, 2017 by Dr. Prosser [30]. In the document, VEs of initial year of 2-dose RZV's were cited from study of Lal et al. [31] (ZOE 50/70 study) and study of Cunningham et al. [32], which were two pivotal studies related to VEs of RZV. VEs of initial year of 1-dose RZV's, duration of 2-dose RZV was based from Cummingham et al. with an additional assumption; while waning duration of 1-dose RZV was thoroughly

Table 1
Variables.

Base case				One-way sensitivity analyses				PSA[b]	Reference
				Low		High			
Target Population of alternative strategies (×1000)									[16]
Age 65–84 strategy		29,389							
Age 70–84 strategy		19,115							
Age 75–84 strategy		11,707							
Age 80–84 strategy		5,181							
Male and female population in different age strata (×1000)									
Age	Male	Female							
65–59	4,971	5,303							
70–74	3,452	3,956							
75–79	2,906	3,620							
80–84	2,096	3,085							
Age-specific incidence rates of HZ (per 1000 persons)								ß	[6]
Age	Male	Female		Male	Female	Male	Female		
60–69	6.25	8.08		5.0	6.46	7.5	9.70	Male:(500; 80,000)[a] Female (690; 85,000)	
70–79	8.44	8.89		6.75	7.11	10.13	1.067	Male:(440; 58,000) Female (630; 76,000)	
80–89	8.45	8.30		6.76	6.64	10.14	9.96	Male:(250; 30,000) Female (420; 55,000)	
90+	6.78	6.51		5.42	5.21	8.14	7.81	Male:(20; 5000) Female (110; 17,000)	
Percentage of PHN cases among HZ cases								ß	[22]
Age	Male	Female		Male	Female	Male	Female		
60–69	19.4%	10.8%		15.5%	8.6%	23.3%	8.6%	Male: (7; 29)[a]; 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)	
Percentage of HZ recurrence; %									[6]
Age	Male	Female		Male	Female	Male	Female		
60–69	4.32	10.77		3.46	8.62	5.18	12.92		
70–79	6.87	9.56		5.50	7.65	8.24	11.47		
80–89	6.27	9.04		5.02	7.23	7.52	10.85		
90+	5.60	5.84		4.48	4.67	6.72	7.01		
General death (per 100,000 persons)									[24]
Age	Male	Female							
65	1315.6	538.8							
70	2111.2	896.4							
75	3354.6	1550.6							
80	6124.0	3114.3							
85	11144.9	6326.7							
90	18771.1	12624.0							
95	31750.7	23627.2							
100	44611.1	39319.3							
Vaccine effectiveness for VVL (%)									[29]
Base-case				Sensitivity analyses (Low, High)			Uniform		
Age	65–69	70–79	≥80	65–69	70–79	≥80	95(CI)		
Year 1	70.6	64.5	63.7	67.9, 73.2	60.5, 68.1	57.3, 69.1	95(CI)		
Year 2	44.8	45.2	41.8	44.5, 52.7	39.5, 50.3	31.9, 50.3	95(CI)		
Year 3	40.5	36.8	35.4	35.1, 45.5	29.9, 43.0	22.3, 46.3	95(CI)		
Year 4	40.5	44.2	34.7	33.8, 45.6	36.9, 50.7	18.8, 47.5	95(CI)		
Year 5	39.9	32.6	39.8	32.8, 46.2	23.6, 40.5	21.8, 53.7	95(CI)		
Year 6	34.3	29.1	35.8	25.3, 42.2	18.3, 38.4	12.0, 53.2	95(CI)		
Year 7	34.7	26.9	0	22.7, 44.7	12.3, 39.0	–	95(CI)		
Year 8	32.1	0	0	8.1, 49.9	–	–	95(CI)		
Year 9	0	0	0	–	–	–			
Vaccine effectiveness for 2-dose RZV (%)[b]							Uniform		[30–32]
		65–69	≥70	65–69	≥70				
Initial year		100	97.0	95.0, 1	92.0, 1				
Waning duration		19.4 years	18.8 years	10, 30	10, 30				
Vaccine effectiveness for 1-dose RZV (%)							Uniform		[30–32]
Initial year		90.0	69.0	0.85, 0.95	0.64, 0.74				
Waning duration		11.0 years	4.0 years	1, 17.5	1, 13.4				
Grade 3 solicited systemic events (myalgia, fatigue, headache, shivering, fever, and gastrointestinal symptoms)									[33]
VLV		2%							
RZV		10.8%							
Utility weights									
Age	HZ	PHN	HZ (Low)	HZ (High)	PHN (Low)	PHN (High)			[25,26]
65–69	0.99098	0.87983	0.95480	–	0.79000	0.89400			

(*continued on next page*)

Table 1 (*continued*)

Base case				One-way sensitivity analyses			PSA[b]	Reference
				Low		High		
70–79	0.98633	0.82631	0.95440	–	0.76000	0.84400		
80+	0.98363	0.76661	0.95440	–	0.76000	0.84400		
Costs per vaccination			VZV (1-dose ¥8000; RZV (2-doses) ¥30,000					Assumed
Treatment costs							Normal	[36]
Age	HZ	PHN	SD (HZ)	SD (PHN)				
65–69	36,615	123,988	35,418	147,992				
70–79	38,414	82,502	25,151	74,362				
80+	33,853	113,304	20,418	60,806				

[a] First and second values in parentheses correspond to α and ß in ß distribution, or α and λ in γ distribution.

[b] VE of year1 to year4 for age 70+ (both in base-case and in sensitivity analysis were based on study of ZOE-70 by Cunningham et al [32] except year3, which is estimated by 0.5 * (year2 + year4), in order to make VE to decrease yearly. Waning duration of 2-dose was 19.4 year (range 10–30)/18.8 year (range 10–30) for age 65–69/age 70+ (Cunningham et al 2016, assumption made by Prosser [30]. Waning duration of 1-dose was 11.0 year (range 1–17.5)/4.0 year (range 1–13.4) for age 65–69/age 70 +) [30].

based on assumption. We conservatively assumed no additional VE against PHN and burden of illness for both vaccines.

Serious adverse events (SAE) associated with vaccination were not considered because no serious adverse events related to both vaccination was found, while Grade 3 solicited systemic events (myalgia, fatigue, headache, shivering, fever, and gastrointestinal symptoms) were included in sensitivity analyses (10.8% for RZV vs. 2% for VVL [33].

2.4. Costing

In reference to the "Research guidelines on the evaluation of the cost-effectiveness of vaccination in Japan" [13,14], this study defined costs in terms of those (costs) borne by the government, municipalities, vaccinees, patients and third-party payers, while direct non-medical costs and productivity costs were not included. Direct non-medical costs related to the immunisation programme were not included because the vaccination programme was built within the public health services routine. Likewise, productivity costs were not included in accordance with the guidelines (only when the target population aged less than 65, will the productivity loss be incorporated). Amount of direct payments to healthcare providers by these entities was estimated as costs, whereby cost items were identified along the decision tree and Markov model. All cost data were shown in Table 1.

The vaccination costs (including vaccine price, doctor fee and technical fee) of 1-dose VVL, ¥8000 (US$73; US$1 = ¥110, average of 2017) (¥6,000–¥10,000), was based on an ad hoc internet survey from about 60 clinics. In Japan, regardless of voluntary or routine vaccination, only physicians can administer a vaccine, and the vaccination costs (including administration fee) for one shot is decided by the private or public facilities (clinics or hospitals). If the vaccination is defined as routine vaccination, then public subsidy (full or partial subsidy will depend on the municipality where the vaccinee inhabits) will pay directly to the private or public facilities and the facility will request the payment difference from the vaccinee. VVL is currently in the category of voluntary vaccination in Japan, therefore, the use of the vaccination costs at ¥8,000 or US$73, based on an ad hoc internet survey is considered to be sufficiently adequate. With reference to the CDC cost/private sector cost, US$ 102.19/US$140 per dose and average wholesale price, US$336 for 2-dose series [34,35], we assumed that the 2-dose RZV cost was at ¥300,000 or US$273. In Japan, in determining the vaccination costs for a newly vaccinated, costs in other high-income countries are usually used as a reference.

Disease treatment costs were updated from our previous study based on a recently published prospective physician practice-based cohort study, which reported age-specific treatment costs collected from 412 aged ≥60 y.o. patients diagnosed with herpes zoster: ¥33,853–¥38,414 (US$308–US$349) for HZ without PHN, ¥82,502–¥123,988 (US$750–US$1127) for HZ with PHN [36]. 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.

2.5. Discounting

Outcomes and costs were discounted at a rate of 3% [37].

2.6. 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). The probability density functions and the ranges for sensitivity analyses were shown in Table 1.

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

Although the MHLW of Japan has not yet set a willingness-to-pay (WTP) threshold for judging the cost-effectiveness of public health programmes in the country [38], local studies have initially begun citing the WTP threshold, at ¥5,000,000 (US$45,455) per QALYgained, from Shiroiwa et al. [39] to facilitate the analysis. 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 [37,40,41]. 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. 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 [41].

4. Results

Table 2(a) showed the expected costs per person and expected QALYs per person associated with curative care scenario and eight preventive alternatives. We have observed that compared to curative care scenario, all eight preventive strategies reduced disease treatment costs, however, these reduced costs did not offset vacci-

Table 2
Result of cost-effectiveness analysis.

(a). Costs, effectiveness, incremental costs, incremental effectiveness, and incremental cost-effectiveness ratio (compared to curative care scenario) in Japanese context

Scenario/ Strategies	Vaccination costs (¥)	Disease treatment costs (¥)	Total costs (¥)	Effectiveness (QALY)	Incremental costs (¥)	Incremental effectiveness (QALY)	Incremental cost-effectiveness ratio (¥/QALY)	NMB at certain WTP threshold (¥/QALY) 5,000,000	10,000,000
Curative care scenario	0	6,520	6,520	11.81693378	–	–	–	–	–
VVL 80–84	782	6,343	7,125	11.81716358	605	0.000230	2,633,587	544	1,693
VVL 75–84	2,071	6,035	8,106	11.81748032	1,586	0.000547	2,902,059	1,147	3,879
VVL 70–84	2,250	5,992	8,242	11.8175153	1,722	0.000582	2,961,041	1,186	4,093
VVL 65–84	3,200	5,750	8,950	11.81764131	2,430	0.000708	3,434,267	1,108	4,645
RZV 80–84	2,640	6,189	8,826	11.81737193	2,306	0.000438	5,262,227	−115	2,076
RZV 75–84	6,991	5,589	12,580	11.81802341	6,060	0.001090	5,561,451	−612	4,836
RZV 70–84	7,592	5,503	13,096	11.81810179	6,575	0.001168	5,629,590	−735	5,105
RZV 65–84	10,800	5,004	15,804	11.81841243	9,284	0.001479	6,278,557	−1,891	5,503

(b). Costs, effectiveness, incremental costs, incremental effectiveness, and incremental cost-effectiveness ratios (compared with the next best alternative)

Scenario/Strategies	Total costs (¥)	Incremental cost (¥)	Effectiveness (QALY)	Incremental effectiveness (QALY)		ICER (excluding dominated)
Curative care scenario	6,520	–	11.81693	–		–
VZV 80–84	7,125	605	11.81716	0.00023		2,633,587
VZV 75–84	8,106	981	11.81748	0.00032		3,096,832
VZV 70–84	8,242	136	11.81752	0.00003		3,882,797
RZV 80–84	8,826		11.81737		abs. dominated	–
VZV 65–84	8,950	708	11.81764	0.00013		4,540,425
RZV 75–84	12,580		11.81802		ext. dominated	–
RZV 70–84	13,096		11.81810		ext. dominated	–
RZV 65–84	15,804	6,854	11.81841	0.00077		8,888,295

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life years; NMB: net monetary benefits; WTP: willingness-to-pay.

nation costs, which means all the strategies gained more QALYs but cost more. Incremental costs per person ranged from ¥605–¥2430 or US$76–US$22 for VVL-strategies; from ¥2306–¥9284 or US$21–US$84 for RZV-strategies. Incremental effectiveness per person ranged from 0.000230 to 0.000708 QALYs for VVL-strategies; from 0.000438 to 0.001479 QALYs for RZV-strategies. Both incremental costs and incremental effectiveness increased with increasing target age in both VZV- and RZV-strategies. ICERs of strategies using the same vaccine were nearly similar, such as ¥2,633,587 or US $23,942 (age 80–84 y.o.) – ¥3,434,267 or US$31,221 (age 65–84 y.o.) per QALY gained for VVL-strategies; ¥5,262,227 or US $47,838 (age80-84 y.o.) – ¥6,278,557 or US$57,078 (age 65–84 y. o.) per QALY gained for RZV-strategies. VVL-strategy gained less QALY and cost less than their corresponding RZV-strategy, the ICER of VVL-strategy was around half of their corresponding RZV-strategy. Table 2(b) showed ICERs compared to the next best alternative. Among all the eight vaccination strategies, three RZV-strategies, namely 70–84 RZV-strategy, 75–84 RZV-strategy and 80–84 RZV-strategy, were dominated (absolute or extended, as shown in Table 2(b) and Fig. 2). The NMBs on Table 2(a) showed that all the strategies have positive values if the cost-effectiveness threshold was at ¥10,000,000 or US$90,909/QALY, with 65–84 RZV-strategy having the highest NMB. On the other hand, when WTP threshold was at ¥5,000,000 or US45,455/QALY, all four RZV strategies have negative values.

One-way sensitivity analyses showed that among four VVL-strategies, costs of vaccination, utility weight (HZ without PHN, only for 65–84 strategy), VE of VVL (only for 80–84 strategy) were variables which made the ICERs to change over ±¥1,000,000 or US $9,091 per QALY from the base-case ICERs. While among four RZV-strategies, vaccination cost, waning duration of 2-dose RZV and utility weight (HZ with/without PHN), made the ICERs change over ±¥1,000,000 or US$9,091 per QALY from the base-case ICERs. Other variables have less impact to the ICERs (Fig. 3).

The cost-effectiveness acceptability curves (CEACs) derived from PSA (Fig. 4) showed that if the cost-effective threshold was at ¥2,000,000 or US$18,182/QALY, the acceptability for 65–84 VVL-strategy was 97.1% (ie., the uncertainty for 65–84 VVL-strategy not to be accepted was only 2.9%), 0.24% for 70–84 VVL-strategy, 0.5% for 80–84 VVL-strategy. Whereas, if the threshold increased to ¥3,000,000 or US$27,273/QALY, the acceptability for 65–84 VVL-strategy decreased to 90.7% and 65–84 RZV-strategy increased from 0% to 8.8%. If the threshold increased to ¥5,000,000 or US$45,455/QALY, the acceptability for 65–84 VVL-strategy further decreased to 56.2% and 65–84 RZV-strategy increased to 43.8%. While if the threshold increased to ¥10,000,000 or US$90,909/QALY, the acceptability for 65–84 VVL-strategy decreased to 11.9% while for 65–84 RZV-strategy increase to 88.1%. For the other 6 strategies (70–84 y.o., 75–84 y.o., 80–84 y. o. VVL- or RZV-strategy) the acceptability were either 0% or less than 0.1%.

5. Discussion

With the approval of RZV in March 2018, two kinds of vaccines, against HZ (VVL and RZV) became available for adults aged 50 and over in Japan, which has raised the need to compare the value for money of immunisation programmes using VVL and RZV. We conducted cost-effectiveness analyses using age and sex-specific- incidence rates, VEs, utility weights, and disease treatment costs to estimate ICERs of four VVL-immunisation programmes and four RZV-immunisation programmes targeting different age stratum: 65–84 y.o, 70–84 y.o., 75–84 y.o., and 80–84 y.o. All the strategies were compared to curative care scenario (i.e., status quo). Results showed that, at the vaccination cost of ¥8,000 (US$73) for 1-dose VVL and ¥30,000 (US$273) for 2-dose RZV, all the fourVVL strategies' ICERs were less than, while all the four RZV strategies' ICERs were higher than, the frequently cited WTP threshold of ¥5,000,000 or US$45,455 per QALY gained [39]. On the other hand, cost-effectiveness results using NMB varied depending on the WTP threshold being utilised. At ¥5,000,000 or US$45,455/QALY, four VVL-strategies were considered to be cost-effective. All eight strategies were cost-effective at WTP threshold of ¥10,000,000 or US$90,909/QALY. The 70–84 and 65–84 VVL-strategy (at WTP threshold of ¥5,000,000 or US$45,455/QALY) and the 70–84 and

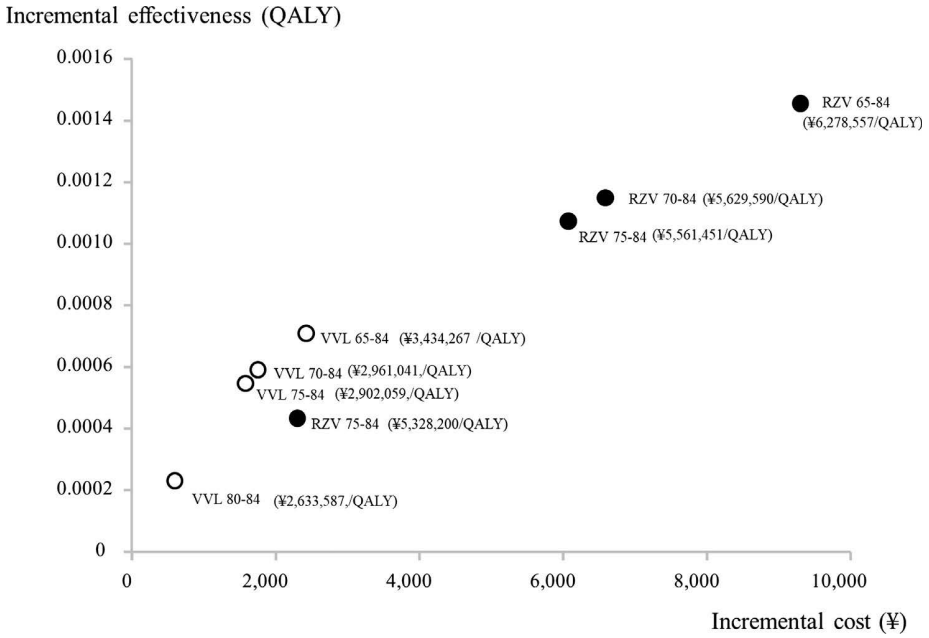


Fig. 2. Results of base-case analyses. Among strategies which used same vaccine (VVL or RZV), ICERs are very similar.

65–84 RZV-strategy (at WTP threshold of ¥10,000,000 or US $90,909/QALY) were considered to be optimal alternatives, since they have higher NMBs in the respective WTP threshold groups. One-way sensitivity analyses revealed that for VVL-strategy, vaccination costs, utility weight (HZ without PHN, only for 65–84 strategy), VE of VVL (only for 80–84 strategy) were the variables which made the ICERs increase or decrease over ¥1,000,000 or US$9,091 per QALY from base-case ICER, while for RZV-strategy, vaccination cost, RZV waning duration, and the utility weight (HZ with/without PHN) made the ICER increase or decrease over ¥1,000,000 or US $9,091 per QALY from the base-case ICER. CEACs derived from PSA showed that among the eight strategies, only 65–84 y.o. VVL-strategy and 65–84 y.o. RZV-strategy should be considered when introducing HZ immunisation programme, the other six strategies should be excluded because their acceptabilities were either 0% or less than 0.1%. The acceptability of 65–84 VVL-strategy reached 97.1% at ¥2,000,000 or US$18,182/QALY WTP threshold, decreased to 56.2% at ¥5,000,000 or US$45,455/QALY, further decreased to11.9% at ¥10,000,000 or US$90,909/QALY. On the other hand, the acceptability of 65–84 RZV-strategy increased from 0% at ¥2,000,000 or US$18,182/QALY to 43.8% at ¥5,000,000 or US$45,455/QALY and to 88.1% at ¥10,000,000 or US$90,909/QALY. This means that the optimal strategy change between these two strategies depend on the WTP threshold.

Since our study is the first study which estimated the value for money of VVL-immunisation programme and RZV-immunisation programme against HZ in Japan's healthcare setting, no comparison can be done within same healthcare setting. A study which evaluated the potential public health impact but not cost-effectiveness of HZ vaccination (VVL vs. RZV) among adults conducted by Watanabe et al [20], reported that RZV demonstrated a superior public health impact compared with VVL. Though our study presented the same results (RZV-strategy gained more QALYs than VVL-strategy), there are apparent differences between our study and that of Watanabe et al's study. Firstly, the incidence rates in Watanabe et al.'s were from the SHEZ study [22], while our data were adopted from the Miyazaki study [6]. As we have mentioned in Section 2, there are four epidemiological studies which reported age- and sex-specific HZ incidence rates in Japan, namely SHEZ study [22], Kushiro Study [23] and two Miyazaki studies (1997–2006 study and 2009–2015 study) [6,7] (supplementary 2, Fig. S1). Among them, SHEZ study reported the highest HZ incidence rates. The population, ageing rates, demographic composition of adult ≥65, and number of medical facilities of the site where the SHEZ study was conducted were significantly different to that of Miyazaki studies (supplementary 2, Table S2). Secondly, study of Watanabe et al. adopted lower vaccine waning rates than our study. Thirdly, the Markov model of Watanabe et al's study included ocular, neurologic and cutaneous complications, while we only used a simple model without including these complications.

We were able to identify two previously published studies which compared RZV- and ZVL- (similar to VVL in our study) vaccination programmes, namely; by Le et al. [11] and by Curran et al. [12], both from USA. Markov Model and data used in these two studies are not completely the same, therefore caution is warranted when comparing these two studies. We found that though both studies reported that RZV-programme dominated (gained more QALYs with less costs) ZVL-programme for adults aged ≥60 y.o., however, the ICERs (compared to no programme, including indirect costs) in the two studies were significantly different. Firstly, the ratio of ICER (vaccination adult aged ≥60) of ZVL to that of RZV in Curran et al. was 10.1:1, while in Le et al. were at 2.2:1 (vaccination at age 60), 1.7:1 (at age 70), 1.9:1 (at age 80). Secondly, Curran et al. reported lower ICERs of RZV-strategies and higher ICERs of ZVL-strategy than those reported by Le et al. In Curran et al, ICERs of RZV-programmes were about 0.5 time of those in Le et al., while ICERs of ZVL-programmes were around 1.5 time of those in Le et al. Higher HZ incidence rates, higher RZV's VEs, lower RZV's VE waning rates, higher RZV's second dose uptake rate, and lower RZV's vaccination costs were considered to contribute to the lower ICERs of RZV-programme in Curran et al. Curran et al. was an industry-funded study, while Le et al. reported no conflict of interest. Our study showed that, in Japan ICERs of VVL-programmes were lower than RZV-programmes, which is inconsistent with the results of the above mentioned two studies. Reasons for the inconsistency may be due to (1) the low vaccination costs of VVL (US$73) compared to ZVL (US$217 or US$239) in previous

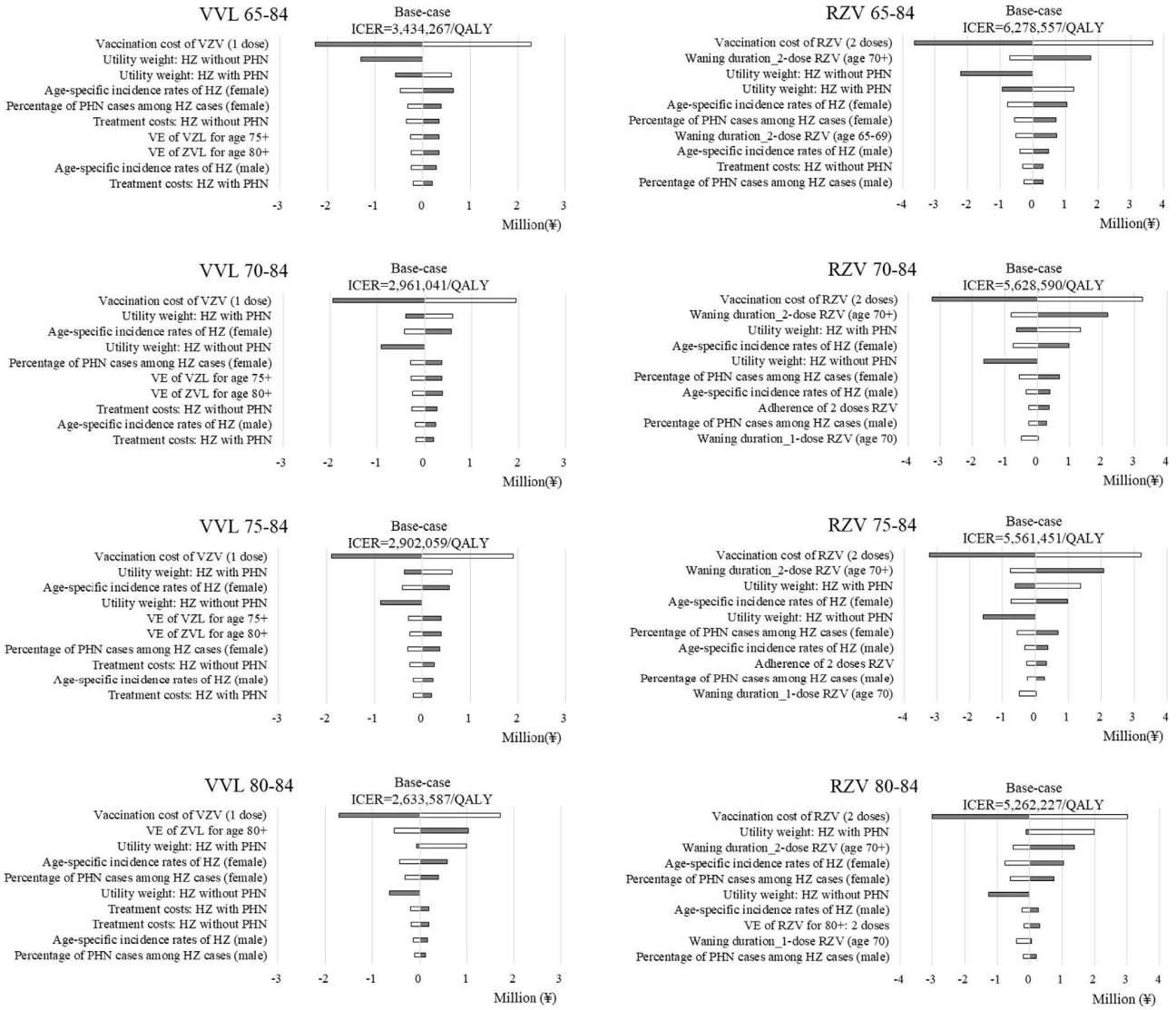


Fig. 3. Results of one-way sensitivity analyses. One-way sensitivity analyses were performed by varying one input at a time while holding others constant at their base-case estimates.

studies, and (2) the higher VEs of VVL in our study than in previous studies, especially VEs of the first 3 years after vaccination. Curran et al. and Le et al. adopted VEs of VZL from the initial RCT, while our study utilised VEs from a recently published large-scale cohort study presented by Baxter et al [29]. Baxter et al. reported higher VEs of time since vaccination and age at vaccination than those reported in previous studies. Baxter et al. highlighted that their overall VE estimate (49.1%) was consistent with the 51.3% VE estimate from the initial report on the pivotal trial [42], the 48.7% estimate based on longer follow-up from the trial [43], the 55% estimate from the initial report on the Kaiser Permanente Southern California population [44], and the 51% estimate from longer follow-up on the same population [45]. The 2-dose VEs of RZV in our study were not all that different from those in the two previous studies, while the 1-dose VEs of RZV in our study were more conservative than those in the two previous studies. VEs of both 2-dose and 1-dose RZV in our study were based on the ACIP presentation document by Prosser [30]

This study also updated our previous study, which evaluated the value for money of VVL immunisation programmes for adult aged ≥65 [10]. Regardless of the adoption of higher utility weights, the ICERs in the current study were slightly lower than those in our previous study. This was due to the higher incidence rates, the lower vaccination costs, the inclusion of one HZ recurrence into the model, and the adoption of VEs from Baxter et al. [29].

Our study faced certain limitations, such as: (1) in the absence of long-term effectiveness data, we modeled RZV effectiveness, in adults aged 65–69 years or ≥70 years, in such a way that it would wane to zero by 19 years following vaccination based on the rate of waning observed during the first four years of clinical trials as well as expert opinion, (2) Markov model used in the study is simple compared to previous studies from overseas. 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 due to the insufficient of data. Exclusion of these aspects of HZ infection could underestimate health benefits of all the strategies, (3) our incidence rates of HZ were from the Miyazaki study, the authors discussed that a proportion of participants with HZ likely received prompt antiviral therapy in Japan, which may have reduced the rate of complications and hospitalisation, (4) adverse

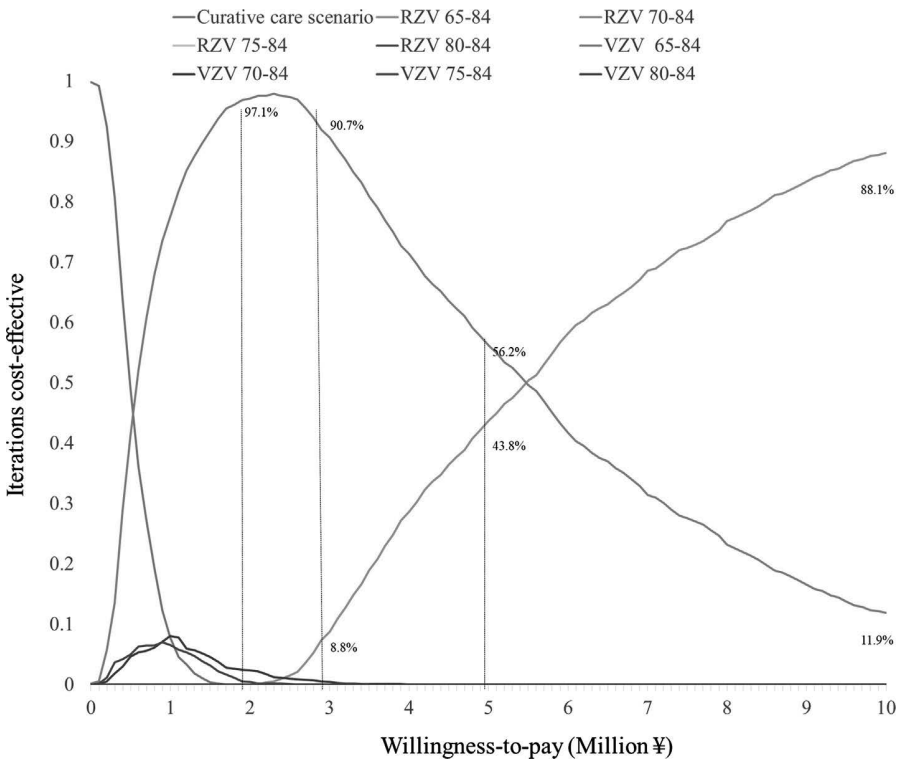


Fig. 4. Probabilistic sensitivity analyses (PSA). In PSA, all the inputs simultaneously varied according to pre-specified distributions of 1000 iterations. Acceptability curves indicate that at ¥2,000,000 (US$ 18,182)/QALY WTP threshold, the acceptability is at 97.1% for 65–84 VVL-strategy and 0% for 65–84 RZV-strategy. For ¥3,000,000 (US $27,273)/QALY, 65–84 VVL-strategy acceptability is at 90.7%, while 8.8% for 65–84 RZV-strategy. On the other hand, at ¥5,000,000 (US$45,455)/QALY, 65–84 VVL-strategy acceptability is at 56.2% and 43.8% for 65–84 RZV-strategy. While at 10,000,000/per QALY, 65–84 VVL-strategy is at 11.9% and 88.1% for RZV-strategy.

reaction was not incorporated into the model, while one-way sensitivity analysis has shown that the impact of Grade 3 reaction was small because it only lasts for 1–3 days, and (5) 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]. On the other hand, some recent studies reported that there is no conclusive evidence in whether varicella vaccination programmes have been associated with an HZ incidence increase [46]. While the influence of the childhood varicella vaccination in our results remains to be unknown, we believe that the incorporation of robust, locally-published epidemiologic data, utility weights 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.

6. Conclusion

From our analyses, we found that vaccinating individuals aged 65–84 y.o., 70–84 y.o., 75–84 y.o., 80–84 y.o. with VVL or RZV to prevent HZ-associated disease in Japan can be cost-effective from payer's perspective, with vaccination costs at ¥8,000 (US$73) per shot for VVL, ¥30,000 (US$280) for 2-dose RZV, while the results of PSA suggest that only 65–84 VVL-strategy and 65–84 RZV strategy should be considered when introducing HZ immunisation programme. The optimal strategy varies depending on the WTP threshold. When the WTP threshold ≥¥5,000,000 or US$45,455/QALY, RZV-strategy is preferred, whereas, when WTP <¥5,000,000 or US$45,455, VVL-strategy is preferred. Our results are partially consistent with the results of two previous cost-effectiveness studies and recommendation of CDC, which preferred RZV than ZVL (VVL in Japan). The main factor affecting these results is the cost of VVL in Japan, which is much lower than cost of VZL in USA. Further analysis is warranted when costs per shot of RZV become apparent as well as when long-term VEs of RZV is reported, because waning duration of RZV is a key variable which has a large impact in the results.

Sponsors role

None.

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. Xerxes Seposo participated in the writing of the manuscript. Aiko Shono participated in collecting data. Ichiro Okubo and Masahide Kondo participated in the concept and design of the study, and in the interpretation of the data.

Declaration of Competing Interest

None.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.05.006.

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