Cost-effective policy option in launching a community-based pneumococcal vaccination program among the elderly in Japan

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Abstract

In Japan, some municipalities introduced a publicly funded pneumococcal vaccination program for the elderly. The expansion of such program has become one of the current topics in the health policy arena. We aim to appraise the *value for money* of expanding such programs, or starting one in a municipality without a program. We conducted a cost-effectiveness analysis with Markov modelling and calculated incremental cost-effectiveness ratio value of starting such a program with 36 different design options, 3 minimum age criteria for the entitlement to the subsidy and 12 levels of co-payment. We found that the introduction of vaccination programs costs more and gains more regardless of targeting ages and co-payment levels. Estimated incremental cost-effectiveness ratios range from ¥ 8,263,340 per year-of-life-saved (targeting age 65 or over, setting co-payment level at ¥ 0) to ¥ 10,351,324 per year-of-life-saved (targeting age 75 or over, setting co-payment level at ¥ 5000). According to cost-effectiveness acceptability curves, the probability that a vaccination program is less than ¥ 10,000,000 (US $ 1=¥ 100) per life-year gained ranges from 28.5% to 57.5%. By adopting the threshold of the Committee to Study Priority for Vaccine Development in the US, US $ 100,000 per quality adjusted life year gain, all the programs are almost certainly judged *cost-effective* as vaccination strategies.

Introduction

Several developed countries have implemented national pneumococcal vaccination programs for the elderly in order to prevent invasive pneumococcal disease (IPD) caused by *Streptococcus pneumoniae* (*S. pneumoniae*).[1-7] These programs are underpinned by evidence that the 23-valent pneumococcal polysaccharide vaccine (PPV) is effective in reducing the incidence of IPD among the elderly by 50% to 70%.[8-9] Recently, it has been reported to be also effective in reducing mortality from severe community acquired pneumonia (CAP) that requires hospitalisation.[10-11]

In Japan, despite of the fact that pneumonia has been the fourth leading cause of death among the elderly aged 65 or over since 1975,[12] and *S. pneumoniae* being the most common etiologic agent of CAP which accounts for 38.7% of such cases,[13] a national pneumococcal vaccination program is yet to be set. The use of 23-valent PPV has been approved since 1988, but decisions to receive vaccination is left at the discretion of the aged person under current national vaccination framework. In 2001, however, a small town started a pneumococcal vaccination program for the elderly, under which aged inhabitants received a subsidy for a shot of PPV. Subsequently, several municipalities introduced similar programs, and by 2007, they amounted to 63 out of all 1821 municipalities.[14] The expansion of such publicly funded programs has become one of the current topics in the health policy arena.

This study aims to appraise the *value for money* of expanding such programs, or launching one in a municipality where there is no program yet, in Japan. The results should have implications for policy makers of Japan as well as for other developed countries in starting or redesigning PPV vaccination programs.

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Materials and Methods

We conduct a cost-effectiveness analysis with Markov modelling, based on the findings of our complete count survey on the practice of municipality-organised PPV vaccination programs, which results have been published elsewhere,[14] and the literature from the societal perspective.

Program and decision

Our survey of 63 municipalities with PPV vaccination programs revealed that there are two key options in organising a publicly funded PPV vaccination program:[14] an age criterion for the entitlement to the subsidy, and the level of subsidy. We set three minimum age criteria according to the three major variations observed in the currently running programs: person aged 65 or over, 70 or over, and 75 or over. Since the averages of total cost and co-payment of one shot were ¥ 7100 and ¥ 3834 (US $ 1=¥ 100), respectively, we set twelve levels of co-payment: from ¥ 0 to ¥ 5000 in increment of ¥ 500 and ¥ 3834. The difference between ¥ 7100 and each level of co-payment is the amount of subsidy for one shot. Combinations of these options produce 36 different designs of vaccination programs.

We consider about the municipality's decision in launching a five year publicly funded PPV vaccination program with these design options. This period of five years is assumed for reconsideration or redesigning of the program, as it is often employed in organising public health programs in Japan such as national influenza vaccination program for the elderly.[15] Thirty-six incremental cost-effectiveness ratios (ICERs) are calculated to determine the efficiency of the resource use accompanying each design.

$$ICER = \frac{Cost_{with\_program} - Cost_{without\_program}}{Effect_{with\_program} - Effect_{without\_program}}$$

The threshold of the Committee to Study Priorities for Vaccine Development in the US,[16] US $ 100,000 (¥ 10,000,000) per quality adjusted life year gain (QALY). We adopted this threshold because there is no established willingness to pay threshold for judging cost-effectiveness of public health programs in Japan, while Shiroiwa *et al.* (2009) suggests ¥ 5,000,000 per QALY gained for innovative clinical intervention,[17] which is quite similar to the one recommended in the US.: US $ 50,000 (¥ 5,000,000) per QALY gained.[18]

Markov model

A Markov model of courses followed by an aged person under consideration is shown in

Figure 1. Five health states are modelled after an entitlement to the subsidy: i) healthy without vaccination, ii) healthy with vaccination, iii) dead from causes other than IPD, iv) curable IPD followed by recovery, and v) dead from fatal IPD. Adverse effects that may be encountered by vaccination are not considered in our model based on a meta-analysis by Fine *et al.* (1994).[19] *Healthy*, in this context, means being without the disease under consideration, that is, IPD. The dotted square indicates a person who is not yet entitled to the subsidy in order to illustrate how they fall into programs. Transitions between health states are indicated with arrows. When a program is launched, entitled persons are assumed to make a decision whether to receive a shot within three years. After the second year of the program, new eligible persons are also assumed to decide whether to receive a shot within three years. Revaccination is not considered here since it is currently not approved in Japan.

A Markov cycle for each stage is set at 1 year. Time horizon is five years after the last shot, which is in accordance with the duration of vaccine effectiveness,[8] and survived persons are assumed to have life expectancy of Japanese population by age.[20]

Outcomes estimation

Outcomes in terms of QALYs, is recommended for economic evaluation of health care.[18] QALYs are calculated as the sum of the adjusted life-years experienced by a patient, where the adjustment is made by multiplying time by weights linked to the changing health state of the patient. However, because the utility weight for the disease under consideration, *i.e.*, IPD, is not available in Japan, outcomes in terms of years of life saved (YOLSs) are applied instead of QALYs. YOLSs are estimated by assigning transition probabilities from our survey and the literature to the Markov model.

To cope with the problem that we take US $ 100,000 (¥ 10,000,000) per QALY gain,[16] as the threshold to judge cost-effectiveness of programs with ICERs defined as *cost per YOLS*, we will conduct sensitivity analyses by adopting utility weight to *curable IPD followed by recovery* from previous studies of developed countries to estimate QALY-based ICERs and to see how they differ from their correspondent YOLS-based ICERs.

Uptake rates of vaccination

Transition probabilities to healthy states are calculated from the observed uptake rates of vaccination in our complete count survey on the practice of municipality-organized PPV vaccination programs from 2001 to 2007, of which results has been published elsewhere.[14]

$$U=-0.00009P+0.05207T+0.47787$$

where U is a cumulative uptake rate, P is a level of co-payment (¥), and T is the year after the start of the program (1, 2, 3 for first, second, third year, respectively) Although we consider that this is the best available evidence, its representativeness of 1821 municipalities needs to be scrutinized. The 63 municipalities with program have smaller population than the 1758 municipalities without program on average with statistical significance: 42,904 and 70,195, respectively. However, no statistically significant differences are found in major socioeconomic indices published by the government between municipalities with and without program,[21] such as the percentage of aged population, 25.6% and 25.0%; or taxable income per person, ¥ 1,207,915 and ¥ 1,140,472. Municipalities' fiscal health is also comparable in terms of financial capability index, which suggest better when larger, 0.544 and 0.508, respectively. The reason why the 63 municipalities operated the program is unknown except the case of the first town where a key physician's advocacy succeeded in starting the program. The story was covered by national media, which was believed to encourage the following municipalities. Smaller municipalities might be more responsive in this case. In this study, we assume that there is no systematic difference between municipalities with and without program, and cope with accompanying uncertainty in our sensitivity analysis. Transition probabilities are calibrated so that the model estimation of probabilities of remaining at *healthy with vaccination* in one Markov cycle corresponds to the cumulative uptake rates from 1st to 3rd year with an assumption that the law of diminishing marginal returns is good after the 4th year. Age distribution of population is considered in this calibrating process. And persons aged 85 or over are assumed not to receive any shot, since physicians are expected to explain the ineffectiveness of vaccine at such age. Table 1 shows the probabilities to *healthy with vaccination* after entitlement to the subsidy by the year, the level of co-payment, and the age group.

New eligible persons who do not receive any shot flow into *healthy without vaccination*, of which transition probability is calculated as:

$$P_{HV-}=1 - P_{HV+}$$

where PH_{V-} is a transition probability from *healthy person not yet entitled to subsidy* to *healthy without vaccination*, and P_{HV+} is a transition probability from *healthy person not yet entitled to subsidy to healthy with vaccination*.

We also assume that no one receives a shot without the program.

Annual incidence rate and case fatality rate of invasive pneumococcal disease

Transition probabilities from a health state, *healthy without vaccination*, to disease states, *curable IPD followed by recovery or dead from fatal IPD*, are calculated from incidence rates and case fatality rate of IPD. Since there is no straightforward report on the annual incidence rate of IPD for aged persons without vaccination, we take an approach used by Oishi.[22] Oishi uses an equation to estimate an annual incidence rate of community acquired *S. pneumoniae* pneumonia (SPP):

$$I_{SPP}=S_{SPP/CAP}\times M_P/A_{SPP}$$

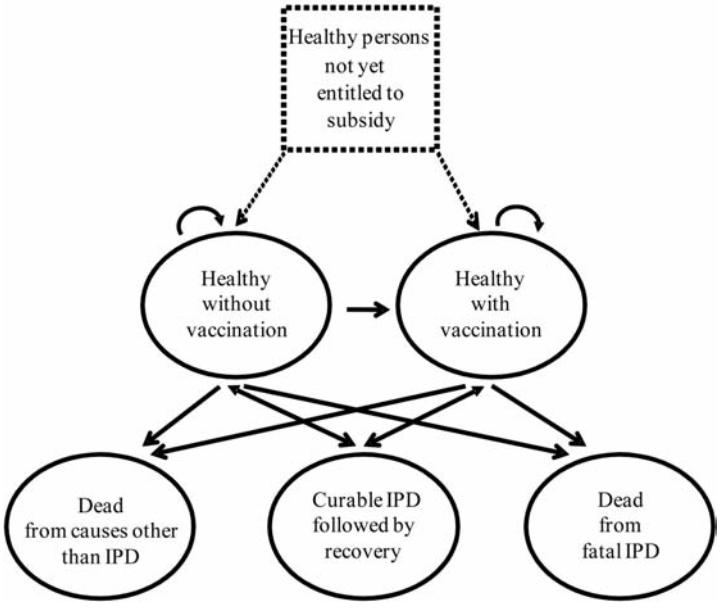

Figure 1. Markov model.

where I_{SPP} is an annual incidence rate of community acquired SPP, $S_{SPP/CAP}$ is a proportion of SPP among CAP, MP is an annual mortality rate of pneumonia, and ASPP is a case fatality rate of CAP. In order to estimate an annual incidence rate of IPD, we modified the equation as below:

$$I_{IPD}=S_{IPD/SPP}\times I_{SPP}$$

where I_{IPD} is an annual incidence of IPD, $S_{IPD/SPP}$ is a proportion of IPD among community acquired SPP, and I_{SPP} is an annual incidence rate of community acquired SPP.

Transition probabilities are calculated as below, since we set one cycle of Markov model at one year:

$$P_{cIPD}=I_{IPD}\times(1 - A_{IPD})$$
$$P_{fIPD}=I_{IPD}\times A_{IPD}$$

where P_{cIPD} is a transition probability from *healthy without vaccination* to *curable IPD followed by recovery*, A_{IPD} is a case fatality rate of IPD, and P_{fIPD} is a transition probability from *healthy without vaccination* to *dead from fatal IPD*. Table 1 shows annual incidence rates and case fatality rate of IPD by the age group. Incidence rates are calculated from $S_{SPP/CAP}$ of 0.387 adopted from Ishida *et al.* (2004),[13] and MP of 42.9 per 100,000 population for age 65-69, 100.1 for age 70-74, 247.6 for age 75-79, 565.5 for age 80-84, 1216.3 for age 85-89 are adopted from the Vital Statistics 2006.[12] And ASPP of 0.0300 for age 65-69, 0.0870 for age 70-79, 0.1890 for age 80-89 are adopted from Fujiki *et al.* (2007).[22] And SIPD/SPP of 0.0263 is adopted from Oishi (2005).[23] AIPD of 0.175 for age 65-89 is adopted from Sakaguti *et al.* (2007).[24]

Vaccine effectiveness

Transition probabilities from a healthy state, *healthy with vaccination*, to disease states, *curable IPD followed by recovery or dead from fatal IPD*, are calculated by adding vaccine effectiveness to the annual incidence rates and case fatality rates of IPD. As shown in Table 1, the vaccine effectiveness of 23-valent serotypes only is taken into account, of which share in SPP is 85.4%.[25] The effectiveness in reducing the incidence rate of vaccination group is adopted from Shapiro *et al.* (1991),[8] while its effectiveness in reducing case fatality rate is assumed 0% because of insufficient evidence.

Outcomes are discounted at a rate of 3%.[18]

Costing

From the societal perspective, costing should cover opportunity costs borne by various economic entities in the society. In the context of this study, costs borne by municipal authorities, vaccinees, patients and social insurers are considered, since the former two are direct payers to vaccination programs, the latter two are major payers to health care providers under Japan's social health insurance system. The amount of direct payments by these entities are estimated as cost, while indirect costs of vaccination program are not included, because it is assumed that the program is built within the public health services infrastructure.

Therefore, as shown in Table 1, costs of vaccine shots and treatment costs of IPD cases are counted. One vaccine shot is assumed to cost ¥ 7100 according to our survey.[14] And treatment costs of IPD cases are estimated as the product of daily cost multiplied by the average length of hospital stay, depending on severity. The daily cost of treatment is assumed at ¥ 26,300 regardless of the severity, which is estimated from Survey of Medical Care Activities in Public Health Insurance 2007.[26] The average length of hospital stay for curative IPD patients without vaccination is assumed at 29 days.[22,27] With vaccination, it is assumed to shorten the stay up to 27 days,[28,29] while fatal IPD patients are assumed to stay longer, of which days are set at 38.[23]

Costs are also discounted at a rate of 3%.[18]

Sensitivity analysis

In order to appraise the stability of ICERs against assumptions made in our economic model, one-way sensitivity analyses are performed. Transition probabilities and other assumed values are changed by ±30% except

Table 1. Assumptions used in Markov Model.

Assumption					Range tested in sensitivity analysis	Source
Uptake rates of vaccination					±50%	estimated
Aged		65-69	70-74	75-79	80-84	
1st year after the entitlement:						
Level of co-payment(¥)	5000	0.0965	0.0852	0.0685	0.0476	
	4500	0.1514	0.1337	0.1075	0.0747	
	4000	0.2064	0.1823	0.1465	0.1018	
	3834	0.2257	0.1985	0.1595	0.1108	
	3500	0.2610	0.2308	0.1855	0.1289	
	3000	0.3163	0.2794	0.2245	0.1560	
	2500	0.3712	0.3279	0.2635	0.1831	
	2000	0.4262	0.3764	0.3025	0.2102	
	1500	0.4824	0.4261	0.3424	0.2379	
	1000	0.5373	0.4746	0.3814	0.2650	
	500	0.5923	0.5231	0.4204	0.2921	
	0	0.6472	0.5717	0.4595	0.3192	
2nd and 3rd year after the entitlement:		0.0635	0.0561	0.0451	0.0313	
Annual incidence rate of IPD (per 100,000 population)					±30%	12,13,22-24
Aged	65-69		14.6			
	70-74		11.7			
	75-79		29.0			
	80-84		30.5			
	85+		65.5			
Case fatality rate of IPD (%)			17.5		±30%	23
Share of 23-valent serotypes among SPP (%)			85.4		±30%	25
Reduction of incidence rate of IPD by vaccination (%)					±30%	4
0 to 2 years after vaccination	Aged	65-74	80.0			
		75-84	67.0			
3 to 5 years after vaccination	Aged	65-74	71.0			
		75-84	0.0			
Reduced case fatality rate of IPD by vaccination (%)			0		30%	
Cost of one vaccine shot (¥)			7100		±30%	14
Daily cost of treating IPD in hospital (¥)			26300		±30%	26
Average length of hospital stay for treating IPD (day)					±30%	
Curative patient without vaccination			29		±30%	22,27
Curative patients with vaccination			27		±30%	28,29
Fatal patients			38		±30%	23
Discount rate (%)			3		0-5	18

IPD, invasive pneumococcal disease; SPP, *S. pneumoniae* pneumonia.

for the reduction of case fatality rate of IPD, which is changed from 0% at base-case value to 30%, the discount rate, which is changed from 0% to 5% and the vaccine uptake rates, which is changed by ±50%. To estimate QALY-based ICERs, a utility weight is needed for each health state in the model. It is 0 for *dead from fatal IPD* or *dead from causes other than IPD*, 1 for *healthy with or without vaccination*. As to the utility weight for *curable IPD followed by recovery*, an upper value of 0.416 and a lower value of 0.276 are given; these weights are derived from overseas.[30]

We also conduct a thousand times Monte Carlo simulation, *i.e.*, probabilistic sensitivity analysis, for which probabilities and values are assumed to have equilateral triangle distribution corresponding to the range tested in one way sensitivity analyses except for the reduction of case fatality rate of IPD. Uniform distribution is assumed for this variable. The discount rate is fixed at 3% for the simulation.

Results

Cost, effectiveness, and cost-effectiveness

Table 2 shows the results of base-case analyses: incremental costs and effects per entitled person, and ICERs. Regardless of design options, vaccination programs turn out to be *cost more and gain more*.

Estimated incremental costs range from ¥ 880 (targeting age 75 or over, setting co-payment level at ¥ 5000) to ¥ 4016 (targeting age 65 or over, setting co-payment level at ¥ 0). Within an age criterion, the incremental cost increases as level of co-payment decreases. Within a co-payment level, it decreases as minimum age for entitlement rises.

Estimated incremental effects range from 0.000085 YOLS (targeting age 75 or over, setting co-payment level at ¥ 5000) to 0.000486 YOLS (targeting age 65 or over, setting co-payment level at ¥ 0). Within an age criterion, the incremental effect increases as level of co-payment decreases. Within a co-payment level, it decreases as minimum age for entitlement rises. These changes are similar to those of the incremental cost.

Estimated ICERs range from ¥ 8,263,340 per YOLS (targeting age 65 or over, setting co-payment level at ¥ 0) to ¥ 10,351,324 per YOLS (targeting age 75 or over, setting co-payment level at ¥ 5000). Within an age criterion, the

Table 2. Results of base-case analyses and probabilistic sensitivity analyses.

Base-case analysis					Probabilistic sensitivity analysis		
Design of program		Incremental	Incremental	ICER	Incremental cost	Incremental effect	ICER
Starting age criterion	Level of co-payment (¥)	cost (¥)	effect (YOLS)	(¥/YOLS)	Median (2.5th & 97.5th percentile) (¥)	Median (2.5th & 97.5th percentile) (YOLS)	Median (2.5th & 97.5th percentile) (¥/YOLS)
65 or over	5,000	1,153	0.000129	8,939,167	1,153 (1,073 1,240)	0.000113 (0.000054 0.000179)	10,194,988 (6,445,197 21,053,583)
	4,500	1,439	0.000164	8,772,008	1,436 (1,319 1,557)	0.000143 (0.000069 0.000234)	9,966,445 (6,224,964 20,521,936)
	4,000	1724	0.000200	8,622,232	1,727 (1,573 1,885)	0.000176 (0.000086 0.000283)	9,803,375 (6,107,055 20,118,847)
	3,834	1,820	0.000212	8,583,128	1,827 (1,662 1,981)	0.000186 (0.000088 0.000302)	9,727,650 (6,059,930 20,167,216)
	3,500	2,010	0.000235	8,552,780	2,012 (1,830 2,206)	0.000207 (0.000101 0.000338)	9,697,618 (6,006,235 20,069,491)
	3,000	2,296	0.000272	8,440,222	2,293 (2,083 2,520)	0.000238 (0.000114 0.000386)	9,540,752 (5,951,179 20,099,468)
	2,500	2,581	0.000307	8,407,808	2,634 (2,351 2,943)	0.000272 (0.000130 0.000454)	9,508,217 (5,875,590 19,732,139)
	2,000	2,867	0.000343	8,358,171	2,868 (2,581 3,173)	0.000301 (0.000140 0.000498)	9,490,380 (5,817,545 19,703,319)
	1,500	3,159	0.000390	8,335,308	3,161 (2,855 3,487)	0.000330 (0.000156 0.000553)	9,423,560 (5,772,498 19,744,840)
	1,000	3,445	0.000415	8,300,093	3,443 (3,095 3,830)	0.000364 (0.000175 0.000606)	9,427,261 (5,787,497 19,588,476)
	500	3,730	0.000450	8,289,568	3,696 (3,336 4,066)	0.000390 (0.000189 0.000648)	9,375,082 (5,747,809 19,532,787)
	0	4,016	0.000486	8,263,340	4,045 (3,592 4,508)	0.000432 (0.000208 0.000729)	9,360,463 (5,759,372 19,393,821)
70 or over	5,000	1,037	0.000115	8,993,989	1,036 (947 1,124)	0.000101 (0.000047 0.000167)	10,234,768 (6,417,673 21,439,203)
	4,500	1,297	0.000147	8,825,805	1,296 (1,170 1,415)	0.000127 (0.000060 0.000215)	10,100,076 (6,267,151 21,025,524)
	4,000	1,558	0.000177	8,805,077	1,556 (1,407 1,714)	0.000154 (0.000075 0.000258)	10,041,179 (6,176,812 20,756,401)
	3,834	1,645	0.000187	8,799,360	1,647 (1,486 1,814)	0.000120 (0.000054 0.000210)	10,019,638 (6,154,428 20,760,099)
	3,500	1,819	0.000207	8,789,059	1,820 (1,629 2,022)	0.0002182 (0.000088 0.000300)	9,988,249(6,051,849 20,680,023)
	3,000	2,080	0.000237	8,778,230	2,076 (1,844 2,318)	0.000207 (0.000098 0.000346)	9,911,594 (6,046,978 20,573,618)
	2,500	2,341	0.000267	8,768,828	2,350 (2,071 2,931)	0.000232 (0.000110 0.000405)	9,925,364 (6,010,787 20,667,929)
	2,000	2,602	0.000297	8,761,326	2,593 (2,271 2,931)	0.000263 (0.000121 0.000439)	9,901,056 (5,988,711 20,424,498)
	1,500	2,869	0.000328	8,747,397	2,861 (2,532 3,223)	0.000289 (0.000137 0.000494)	9,892,812 (5,992,454 20,429,732)
	1,000	3,130	0.000358	8,742,968	3,132 (2,731 3,520)	0.000315 (0.000151 0.000532)	9,861,061 (5,972,243 20,514,660)
	500	3,391	0.000388	8,739,225	3,402 (2,980 3,794)	0.000345 (0.000161 0.000593)	9,843,159 (5,957,934 20,518,403)
	0	3,652	0.000418	8,737,196	3,689 (3,254 4,146)	0.000372 (0.000177 0.000636)	9,874,788 (5,975,140 20,458,112)
75 or over	5,000	880	0.000085	10,351,324	880 (787 975)	0.000074 (0.000035 0.000125)	1182352,4 (7,220,106 25,566,542)
	4,500	1,106	0.000107	10,325,728	1,105 (979 1,231)	0.000093 (0.000043 0.000158)	11,794,288 (7,071,444 25,135,714)
	4,000	1,333	0.000130	10,257,719	1,328 (1,173 1,494)	0.000113 (0.000052 0.000197)	11,716,606 (7,019,632 25,182,811)
	3,834	1,408	0.000138	10,207,070	1,414 (1,236 1,582)	0.000120 (0.000054 0.000210)	11,658,753 (7,015,036 25,140,066)
	3,500	1,559	0.000153	10,203,240	1,551 (1,363 1,755)	0.000132 (0.000060 0.000227)	11,654,379 (6,916,317 25,089,420)
	3,000	1,785	0.000175	10,200,203	1,781 (1,537 2,015)	0.000151 (0.000069 0.000261)	11,650,910 (6,894,781 25,459,106)
	2,500	2,012	0.000197	10,193,217	2,014 (1,768 2,272)	0.000170 (0.000076 0.00293)	11,642,930 (6,854,948 25,602,773)
	2,000	2,238	0.000220	10,173,329	2,233 (1,906 2,538)	0.000189 (0.000982 0.000332)	11,620,213 (6,786,061 25,893,212)
	1,500	2,469	0.000243	10,165,744	2,475 (2,120 2,809)	0.000209 (0.000094 0.000375)	11,611,550 (6,858,602 25,886,456)
	1,000	2,696	0.000265	10,161,638	2,692 (2,319 3,108)	0.000231 (0.000104 0.000409)	11,606,860 (6,785,388 25,932,094)
	500	2,922	0.000287	10,181,254	2,930 (2,478 3,339)	0.000250 (0.000111 0.000435)	11,629,266 (6,784,388 26,287,972)
	0	3,149	0.000310	10,168,741	3,212 (2,712 3,754)	0.000173 (0.000118 0.000493)	11,614,973 (6,789,881 26,324,523)

ICER, incremental cost-effectiveness ratio; YOLS, years of life saved.

ICERs decrease as co-payment level decreases. Within a co-payment level, the ICER of program targeting age 75 or over is always the highest, while of program targeting age 65 or over is always the lowest. Figure 2 shows the ICERs of choosing differing age criteria for different co-payment level.

One-way sensitivity analyses

Figure 3 shows the results of one-way sensitivity analyses. All 1764 results (49 changes of variables, 3 age criteria and 12 levels of co-payment) are plotted in addition to base-case values. Our model is found sensitive to the changes of annual incidence rate of IPD, case fatality rate of IPD, cost of one vaccine shot, and discount rate. Lowering case fatality rate or annual incidence rate of IPD by 30% increases ICERs by 42% to 43%, while raising them by 30% decreases it by 23% to 24%. Raising the cost of a vaccine shot by 30% increases ICERs by 29% to 30%, while reducing it by 30% decreases ICERs by 30%. No discounting decreases ICERs by 77% to 83%, while raising the discount rate to 5% increases ICERs by 19% to 27%. QALY-based ICERs were consistently smaller than their correspondent YOLS-based ICERs, regardless of age criterion, level of co-payment. The difference between QALY-based ICERs and their correspondent YOLS-based ICERs are less than ¥ 35,000 when 0.276 was assigned as utility weight to *curable IPD followed by recovery*, are less than ¥ 18,000 when 0.412 was assigned.

Probabilistic sensitivity analyses and cost-effectiveness acceptability curves

Table 2 shows the results of probabilistic sensitivity analyses as well: median incremental costs and effects, and median ICERs with 2.5th and 97.5th percentile. Median incremental costs are similar to the corresponding incremental costs in base-case analysis, while median incremental effects are 12% to 15% less than the corresponding incremental effects. Consequently, median ICERs increase by 12% to 15% from the base-case values.

Figure 4 presents two cost-effectiveness acceptability curves (CEACs): one for targeting age 65 or over, setting co-payment level at ¥ 0, and another for targeting age 75 or over, setting co-payment level at ¥ 5000. CEACs for the other 34 options have similar sigmoid curves, which would be drawn in between the presented two curves, although they are not presented here for the sake of simplicity. Within an age criterion, the lower the co-payment level, CEAC shifts to the more left. Within a co-payment level, it shifts toward right as the raise of minimum age for entitlement. If we take a willingness to pay threshold of one-year life gained at ¥ 5 million, the probabilities that a vaccine program is cost-effective ranges from 0 to 0.5%; 28.5% to 57.5% at ¥ 10 million; 72.5% to 88.5% at ¥ 15 million; and from 89.5% to 97.5% at ¥ 20 million.

Discussion and Conclusions

We conduct a cost-effectiveness analysis of starting a publicly funded PPV program among the elderly in a municipality in Japan with 36 different design options: 3 minimum age criteria for the entitlement to the subsidy and 12 levels of co-payment. The minimum age crite-

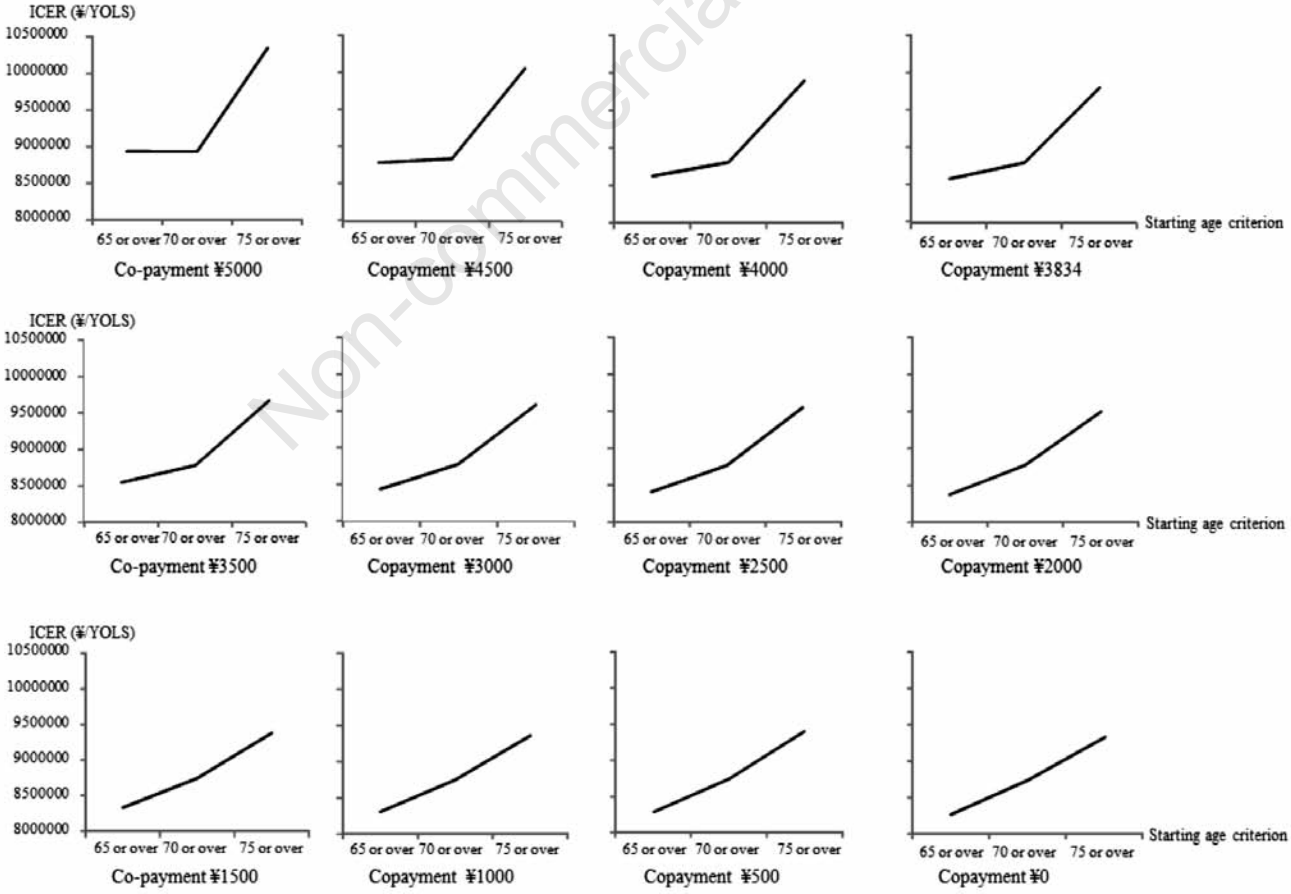

Figure 2. Incremental cost-effectiveness ratios (ICERs) of different age criteria in different co-payment level. Within a co-payment level, the ICER of program targeting age 75 or over is always the highest, while of program targeting age 65 or over is always the lowest.

ria considered are: 65 or over, 70 or over and 75 or over. The levels of co-payment are from ¥ 0 to ¥ 5000 in increment of ¥ 500 and ¥ 3834, which is an average of levels set for those already running programs.

Our base-case analyses indicate that the introduction of vaccination programs costs more and gains more regardless of targeting ages and co-payment levels. Estimated ICERs range from ¥ 8,263,340 per YOLS to ¥1 0,351,324 per YOLS.

The results of sensitivity analyses show that QALY-based ICER was smaller than YOLS-based ICER in any scenario. Therefore, willingness to pay for per QALY is a rather conservative threshold to determining the cost-effectiveness of the vaccination program presented in YOLS; thus, the use of the threshold of the Committee to Study Priority for Vaccine Development in the US, US $ 100,000 per QALY gain should be acceptable.[16] Applying this threshold to our results, all the programs are almost certainly judged *cost-effective* as vaccination strategies.

Our CEACs show that the probability of vaccine program to be cost-effective is ranging from 28.5% to 57.5% at ¥ 10,000,000 per life-year gained. Therefore, we consider that the *value for money* of starting a vaccination program under consideration is socially acceptable in Japan from the viewpoint of health economics.

Among 36 design options, the lower the minimum age for entitlement and level of co-payment tend to produce the more favourable ICERs; hence targeting age 65 or over, and setting co-payment level at ¥ 0 is the most efficient design according to our results.

These conclusions are considered robust based on the results of our sensitivity analyses and probabilistic sensitivity analyses. Among the results of one-way sensitivity analyses, ICERs which exceed ¥ 10,000,000 per life-year gained more than ¥ 2,000,000 are limited to the changes of case fatality rate, annual incidence rate of IPD or cost of one vaccine shot.

There are several reports of cost-effectiveness analyses from overseas regarding PPV vaccination,[30-35] while due caution is needed to discuss such models built under different health systems. An economic model from the US suggests a shot of PPV cost-saving,[30] and other models from Western European countries suggest cost-effective.[31-34] However, these models assume the unrealistic 100% uptake rates. Another model from UK also assumes the 100% uptake rate of PPV from those vaccinated for influenza when considering a joint vaccination program, concluding it cost-effective.[35] Our model deliberates the effect of subsidy policy on the uptake rate, which is different from those previous models in terms of the context of choice under consideration, and therefore offers more policy implications for health managers in charge of vaccination pro-

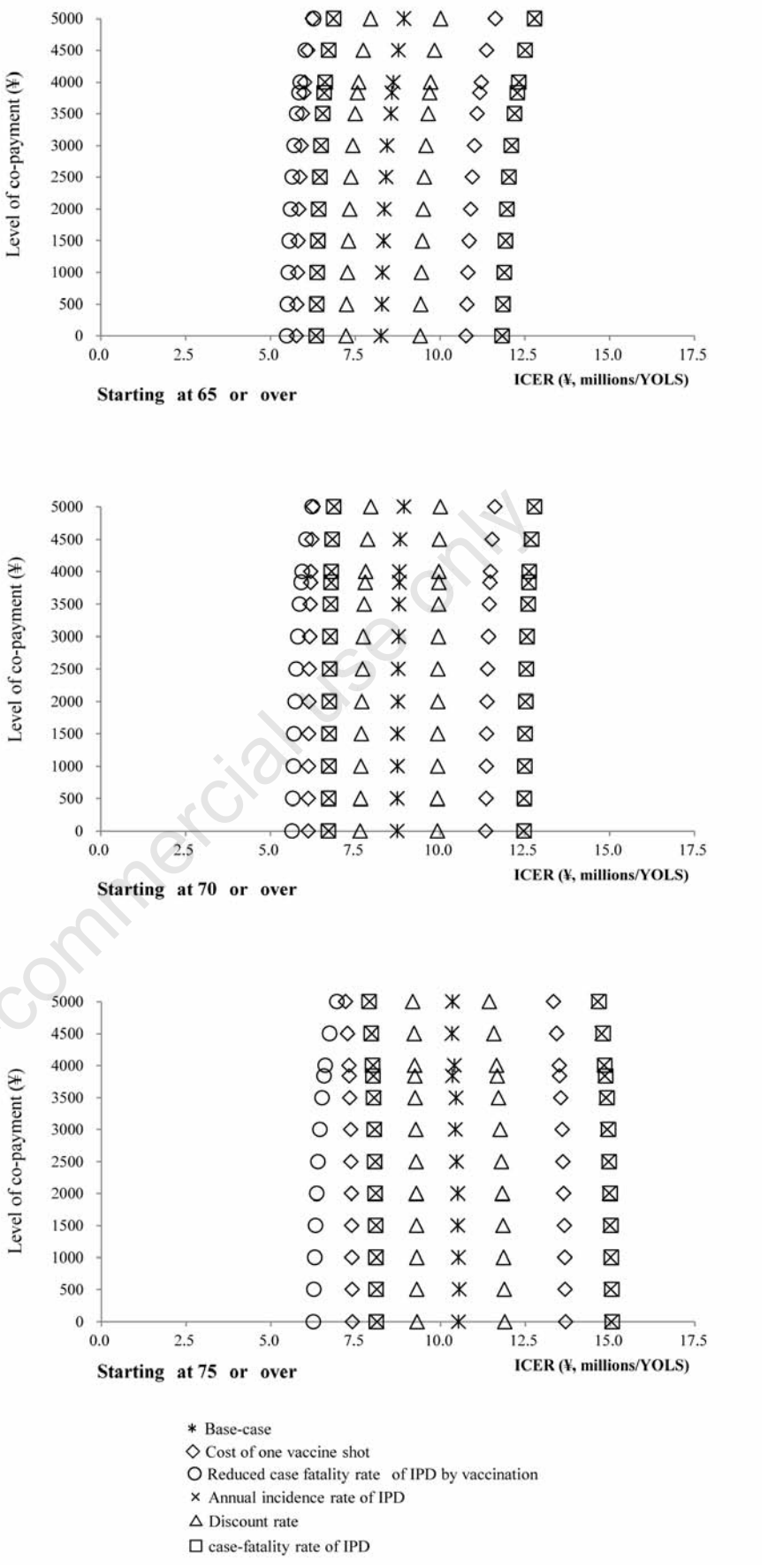

Figure 3. Results of one-way sensitivity analyses.

grams, since it takes account of the choice they face. However, they will not be able to make any decision depending solely on the economic evidence of efficiency under strict budget constraints. The most efficient design is to set the minimum age for entitlement at 65 or over with no co-payment, which brings the highest uptake and coverage as well as the largest total amount of subsidy. Our study implies a trade-off between efficiency and budget impact across different designs of vaccination programs. A further budget impact analysis is awaited for well-informed policy making by health managers.

This study has its own limitations. First of all, clinical evidences that vaccination is effective in reducing annual incidence rate is adopted from studies carried out in the US, since no similar study has been done in Japan.[8] There should be differences in ethnicity as well as in the health system between the US and Japan. Other significant figures in estimating outcomes, annual incidence rate and case fatality rate of IPD, are indirectly calculated from case fatality rate of CAP,[23] proportion of SPP among CAP,[13] and proportion of IPD among community acquired SPP.[22] Although these are based on studies done in Japan, such calculation would have bias. In costing, the daily cost of treating IPD is extrapolated from that of treating pneumonia, whereas there is no ground for assuming that these are the same. We, however, believe that our modelling exercise is one with best available knowledge for the purpose of this study, and that our sensitivity analyses mitigate these limitations.

In conclusion, launching a community-based pneumococcal vaccination program among the elderly is most likely to have the *value for money* in Japan. And the lower the minimum age for entitlement and level of co-payment, the more the *value for money*.

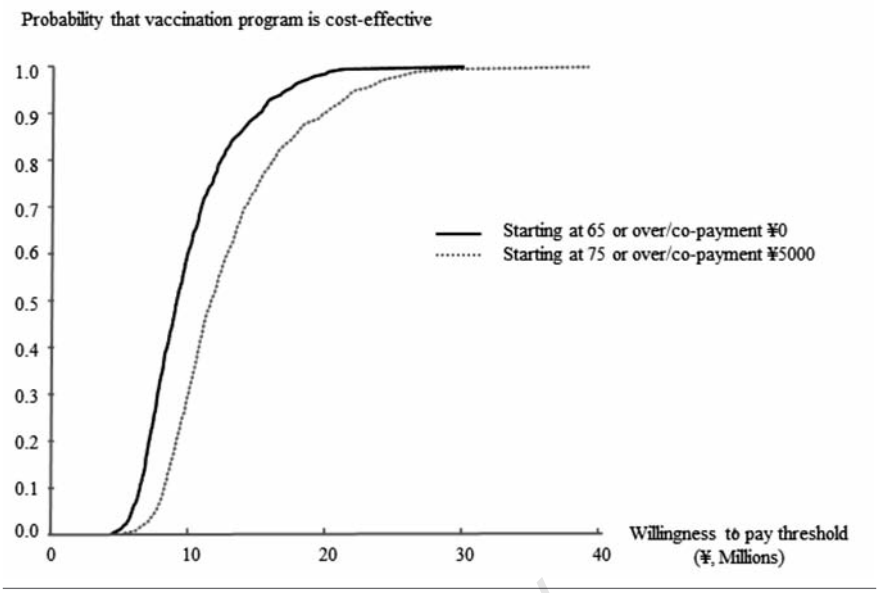

Figure 4. Cost-effectiveness acceptability curves.

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