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):

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

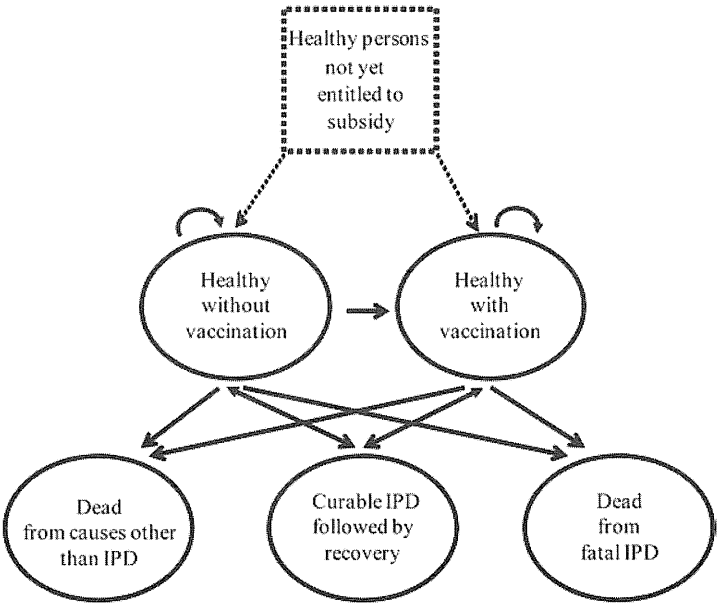

Figure 1. Markov model.

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.

Design of program		Base-case analysis			Probabilistic sensitivity analysis		
Starting age criterion	Level of co-payment (¥)	Incremental cost (¥)	Incremental effect (YOLS)	ICER (¥/YOLS)	Incremental cost Median (2.5^{th} & 97.5^{th} percentile) (¥)	Incremental effect Median (2.5^{th} & 97.5^{th} percentile) (YOLS)	ICER Median (2.5^{th} & 97.5^{th} 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.

Non-commercial use only

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-

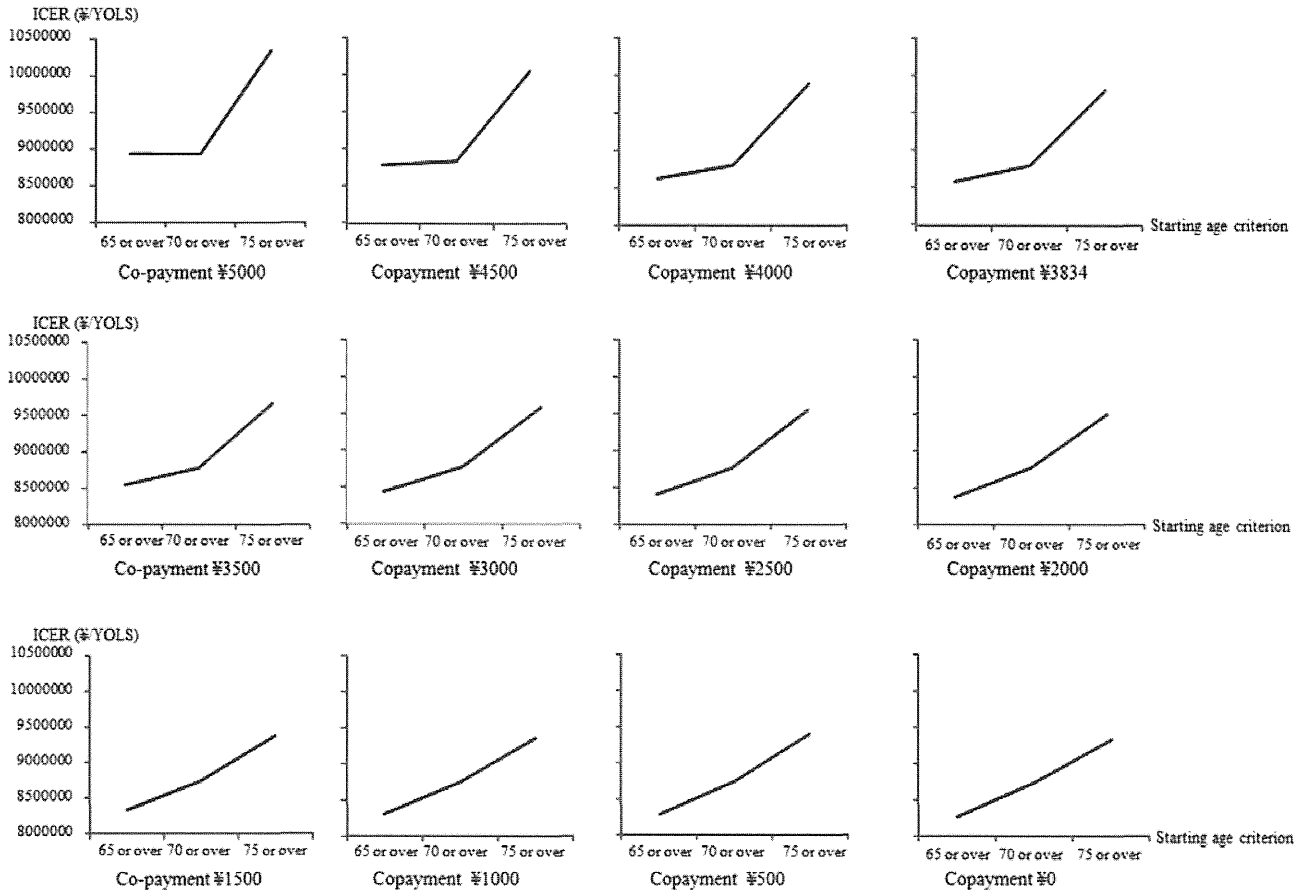

Figure 2. Incremental cost-effectiveness ratios (ICERs) of different age criteria in different co-payment level. Within a co-payment level, the ICER of program targeting age 75 or over is always the highest, while of program targeting age 65 or over is always the lowest.

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-

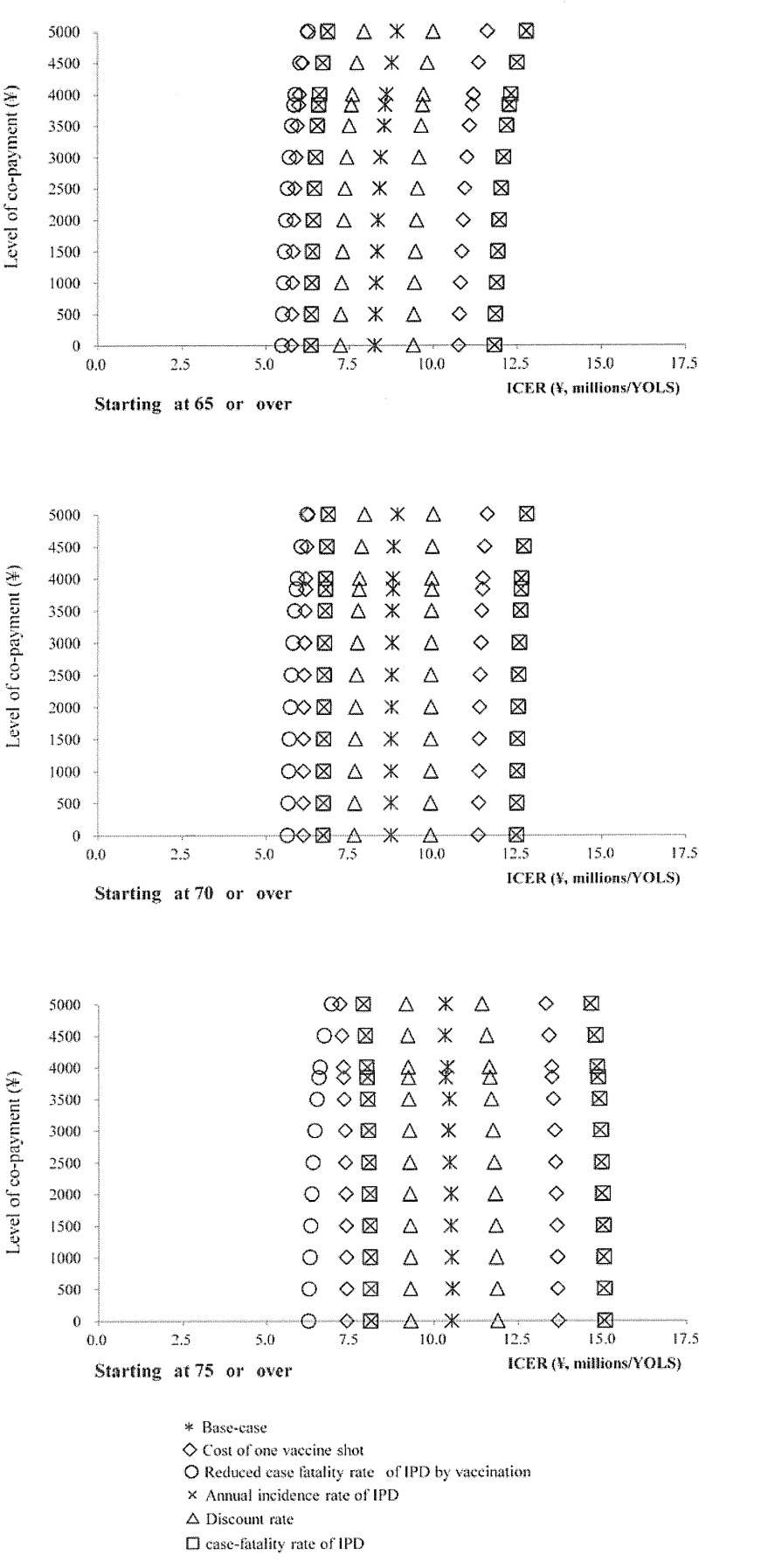

Figure 3. Results of one-way sensitivity analyses.

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*.

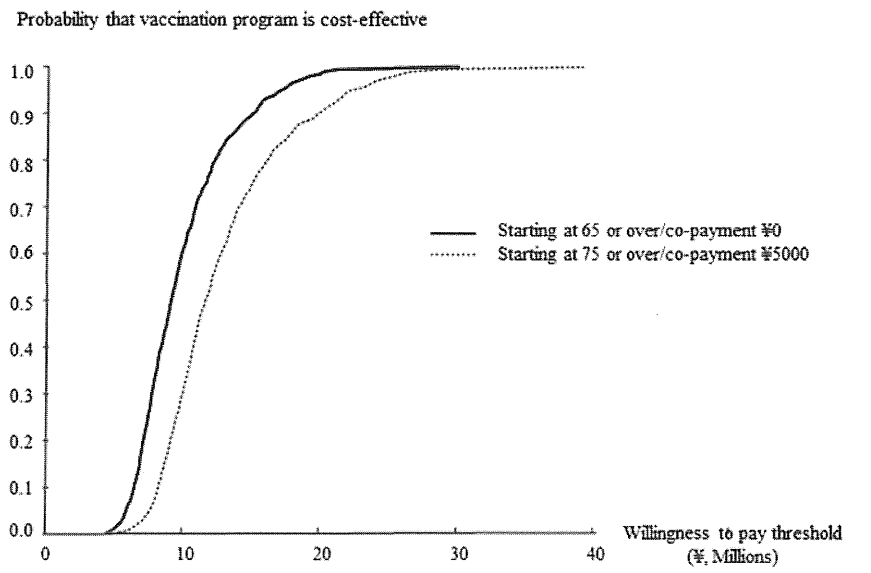

Figure 4. Cost-effectiveness acceptability curves.

References

1. Centers for Disease Control and Prevention. Influenza and pneumococcal vaccination coverage among persons aged ≥65 years - United States, 2004-2005. MMWR Morb Mortal Wkly Rep 2006;55: 1065-8.
2. U.S. Department of Health and Human Services. Healthy People 2010: Understanding and improving health. 2nd ed. Washington DC: US Government Printing Office; 2000.
3. Squires SG, Pelletier L. Publicly-funded influenza and pneumococcal immunization programs in Canada: a progress report. Can Commun Dis Rep 2000;26:141-8.
4. Department of Health and Health Protection Agency. Annual pneumococcal polysaccharide vaccine uptake report in 65 years old and over for England June 2008. London: Department of Health; 2008.
5. National Health and Medical Research Council. The Australian immunization handbook. 9th ed. Canberra: Australian Government Publishing Services; 2008.
6. Pebody RG, Leino T, Nohynek H, et al. Pneumococcal vaccination policy in Europe. Euro Surveill 2005;10:174-8.
7. Samson SI, Mégard Y. Overview of vaccination policies for the elderly in Western European countries. Aging Clin Exp Res 2009;21:210-5.
8. Shapiro ED, Berg AT, Austraian R, et al. The protective efficacy of polyvalent pneumococcal polysaccharide vaccine. N Engl J Med 1991;325:1453-8.
9. Moberley SA, Holden J, Tatham DP, Andrews RM. Vaccines for preventing pneumococcal infection in adults. Cochrane Database Syst Rev 2008;23:CD000422.
10. Fisman DN, Abrutyn E, Spaude KA, et al. Prior pneumococcal vaccination is associated with reduced death, complications, and length of stay among hospitalized adults with community-acquired pneumonia. Clin Infect Dis 2006;42:1093-101.
11. Johnstone J, Marrie TJ, Eurich DT, Majumdar SR. Effect of pneumococcal vaccination in hospitalized adults with community-acquired pneumonia. Arch Intern Med 2007;167:1938-43.
12. Ministry of Health, Labour and Welfare. Vital statistics of Japan 2006. Tokyo: Health and Welfare Statistics Association; 2008.
13. Ishida T, Hashimoto M, Arita M, et al. A 3-year prospective study of a urinary antigen-detection test for Streptococcus pneumoniae in a community-acquired pneumonia: utility and clinical impact on the reported etiology. J Infect Chemother 2004;10:359-63.
14. Hoshi SL, Kondo M, Okubo I. [Study on pricing and uptake rate of public funded pneumococcal vaccination for the elderly in Japan]. Nippon Koshu Eisei Zasshi 2008;55Suppl10:233. [Article in Japanese].
15. Preventive Vaccination Law, Supplementary Provisions, Extract. Pub. L. No. 116, Article 2 (November 7, 2001).
16. Committee to Study Priorities for Vaccine Development, Division of Health Promotion and Disease Prevention, Institute of Medicine. Vaccine for the 21st century: a tool for decision making. Washington DC: National Academy Press; 2000.
17. Shiroiwa T, Sung YK, Fukuda T, et al. International survey on willingness-to-pay (WTP) for one additional QALY gained: what is the threshold of cost effectiveness? Health Econ 2010;19:422-37.
18. Gold MR, Siegel JE, Russell LB, Weinstein MC. Cost-effectiveness in health and medicine. New York: Oxford University Press; 1996.
19. Fine MJ, Smith MA, Carson CA, et al. Efficacy of pneumococcal vaccination in adults. A meta-analysis of randomized controlled trials. Arch Intern Med 1994;154: 2666-77.
20. Ministry of Health, Labour and Welfare. The 20th Life Tables. Tokyo: Health and Welfare Statistics Association; 2007.
21. Ministery of Internal Affairs and Communications. Statistical observations of shi, ku, machi, mura. Tokyo: Statistics

Bureau; 2007.
22. Oishi K. [Recent pneumonia. Pneumococcal pneumonia and the countermeasure]. Japanese Journal of Clinical and Experimental Medicine 2005;82:1983-6. [Article in Japanese].
23. Fujiki R, Kawayama T, Ueyama T, et al. The risk factors for mortality of community-acquired pneumonia in Japan. J Infect Chemother 2007;13:157-65.
24. Sakaguti C, Ishida T, Arita M, et al. [The analysis of community-acquired pneumonia cases which presented bacteremia]. Annals of Kurashiki Central Hospital 2007;69:37-42 [Article in Japanese].
25. Chiba N, Morozumi M, Sunaoshi K, Takahashi S, Takano M, Komori T, et al. Serotype and antibiotic resistance of isolates from patients with invasive pneumococcal disease in Japan. Epidemiol Infect 2009;19:1-8.
26. Ministry of Health, Labour and Welfare. Survey of medical care activities in public health insurance 2007. Tokyo: Health and Welfare Statistics Association; 2009.
27. Oishi K, Yoshimine H, Watanabe H, et al. Drug-resistant genes and serotypes of pneumococcal strains of community-acquired pneumonia among adults in Japan. Respirology 2006; 11:429-36.
28. Mykietiuk A, Carratalà J, Domínguez A, et al. Effect of prior pneumococcal vaccination on clinical outcome of hospitalized adults with community-acquired pneumococcal pneumonia. Eur J Clin Microbiol Infect Dis 2006;25:457-62.
29. Christenson B, Hedlund J, Lundbergh P, Ortqvist A. Additive preventive effect of influenza and pneumococcal vaccines in elderly persons. Eur Respir J 2004;23:363-8.
30. Sisk JE, Moskowitz AJ, Whang W, et al. Cost-effectiveness of vaccination against pneumococcal bacteremia among elderly people. JAMA 1997;278:1333-9. Erratum in: JAMA 2000; 283:341.
31. Ament A, Baltussen R, Duru G, et al. Cost-effectiveness of pneumococcal vaccination of older people: a study in 5 Western European countries. Clin Infect Dis 2000; 31:444-50.
32. Evers SM, Ament AJ, Colombo GL, et al. Cost-effectiveness of pneumococcal vaccination for prevention of invasive pneumococcal disease in the elderly: an update for 10 Western European countries. Eur J Clin Microbiol Infect Dis 2007;26:531-40.
33. Postma MJ, Heijnen ML, Jager JC. Cost-effectiveness analysis of pneumococcal vaccination for elderly individuals in The Netherlands. Pharmacoeconomics 2001; 19:215-22.
34. Melegaro A, Edmunds WJ. The 23-valent pneumococcal polysaccharide vaccine. Part II. A cost-effectiveness analysis for invasive disease in the elderly in England and Wales. Eur J Epidemiol 2004;19:365-75.
35. Mangtani P, Roberts JA, Hall AJ, Cutts FT. An economic analysis of a pneumococcal vaccine programme in people aged over 64 years in a developed country setting. Int J Epidemiol 2005;34:565-74.

Vaccine 30 (2012) 3320–3328

Contents lists available at SciVerse ScienceDirect

Vaccine

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

Economic evaluation of vaccination programme of 7-valent pneumococcal conjugate vaccine to the birth cohort in Japan

Shu-ling Hoshi*, Masahide Kondo, Ichiro Okubo

Department of Health Care Policy and Management, Graduate School of Comprehensive Human Sciences, University of Tsukuba, 1-1-1, Tennoudai, Tsukuba, Ibaraki 3058577, Japan

ARTICLE INFO

Article history:
Received 7 October 2011
Received in revised form 13 February 2012
Accepted 13 February 2012
Available online 3 March 2012

Keywords:
Pneumococcal conjugate vaccine
Vaccination programme
Cost-effectiveness analysis
Budget impact analysis

ABSTRACT

Aiming to introduce 7-valent pneumococcal conjugate vaccine (PVC-7) into routine vaccination schedule, the government of Japan gives a temporary budget to encourage municipalities in launching public vaccination programme which started on November 26, 2010 and ends on March 31, 2012. This study aims to appraise the 'value for money' of PCV-7 vaccination programme from the societal perspective and the budget impact from the perspective of municipalities, which is responsible for providing routine vaccination.

We conducted a cost-effectiveness analysis with Markov modelling and calculated incremental cost-effectiveness ratio (ICER) value of launching such programme with two levels of co-payment, ¥1000 (US$13) or ¥0, and two scenarios of the uptake of vaccine (vaccinated-alone or co-vaccinated with other vaccines).

We found that when vaccinated-alone, ICERs in QALY were ¥7,441,000 (US$93,013) or ¥9,065,000 (US$113,313), and when co-vaccinated ¥7,441,000 (US$93,013) or ¥5,489,000 (US$68,613), without or with productivity loss, respectively, regardless of co-payment level of the programme. Co-vaccinated programmes had lower ICER than vaccinated-alone programmes due to the savings in productivity loss. By adopting WHO's classification that an intervention is 'cost-effective' if ICER (in QALY) is between 1 and 3 times of GDP as a criterion, PCV-7 vaccination programme in Japan is concluded as "cost-effective" from the perspective of society.

The introduction of either no co-payment or ¥1000 (US$13) co-payment vaccination programme appears to be not budget saving for the first 6 years, whereas the level of budget impact are less than ¥11,000,000 (US$137,500) or ¥8,500,000 (US$106,250), respectively, for a municipality with 1000 birth cohort in the 1st year and 2nd to 5th year birth cohort proportional to the birth cohort population of estimated future population.

© 2012 Elsevier Ltd. All rights reserved.

1. Introduction

7-Valent pneumococcal conjugate vaccine (PCV-7) has been licensed in approximately 90 out of 193 WHO member states, and 26 countries have introduced it into their national childhood vaccination programmes by August 2008 [1]. Out of these 26 countries, 24 countries are high-income countries [1]. These programmes are underpinned by evidence that the use of PCV-7 is effective in reducing disease caused by bacterium *Streptococcus pneumoniae* (pneumococcus) among infants and young children [2–7].

In Japan, PCV-7 was approved on October 26, 2009. Aiming to introduce PCV-7 into routine vaccination schedule, the government disbursed a temporary budget to encourage municipalities in launching a public vaccination programme which started on November 26, 2010, and ends on March 31, 2012. The costs for vaccination are shared between the central government and municipalities during this period. And after this period, PCV-7 is expected to be integrated into the routine vaccination schedule, and costs will be shared among the central government, prefectures and municipalities, while a municipality may ask the vaccinees to bear partial cost [8]. It is said that there are five hurdles to overcome in the diffusion process of new health intervention: quality, safety, efficacy, cost-effectiveness and affordability [9]. This study aims to appraise the latter two of launching a routine vaccination programme of PCV-7 in Japan, which are: cost-effectiveness from the societal perspective and affordability, i.e., budget impact from the perspective of a municipality, which is responsible for providing the routine vaccination [8]. The results should have implications for policy makers of Japan as well as in other developed countries in launching PCV-7 vaccination programmes.

* Corresponding author. Tel.: +81 29 853 3255; fax: +81 29 853 3255.
E-mail addresses: hoshi@hcs.tsukuba.ac.jp, shulingst@hotmail.com (S.-l. Hoshi).

0264-410X/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
doi:10.1016/j.vaccine.2012.02.033

2. Method

We conducted a cost-effectiveness analysis with Markov modelling from the societal perspective. In defining vaccination programmes and constructing the model, we conducted a deliberate literature survey to find out the available evidence. We did not exclude reports from overseas in case of lack of evidences from Japan. The PubMed database and Igaku Chuo Zasshi, a Japanese database, were accessed with combinations of relevant terms. Igaku Chuo Zasshi (Japana Centra Revuo Medicina) is a Japanese medical bibliographic database which contains 7.5 million citations originated in Japan and it comprehensively covers the articles published in Japanese-language medical journals.

2.1. Programmes

We defined four vaccination programmes with same vaccination schedule, which is a three dose primary series over 6 months followed by a fourth dose in the second year: two levels of co-payment, i.e., none or ¥1000 per shot (US$13; US$1 = ¥80, based on the average exchange rate of 2011 instead of purchasing power parity); and two scenarios of the uptake of PCV-7, i.e., vaccinated-alone or co-vaccinated (simultaneously inoculated with other vaccines). Combinations of these produced four different designs of vaccination programmes. These programmes were compared with no programme scenario, respectively. Two different levels of co-payment were set because: being responsible for routine vaccinations, each municipality decides the amount of co-payment for one shot in Japan [8], and during the year of 2010, seven out of all 1737 municipalities had set a co-payment between ¥300 (US$4) and ¥1000 (US$13) for one shot of vaccine in their routine vaccination schedule, while the rest provided programmes without co-payment [10]. Two scenarios were set because Ministry of Health, Labour and Welfare encourages vaccine given alone [11], while Japan Paediatric Society suggests co-vaccinated with other vaccines [12].

The average vaccine uptake rates for no co-payment programmes, 80%, was the rate of measles and rubella vaccination programme during 2009 [13]. We adopted this rate because the vaccination schedules of these are similar to that of PCV-7. For the uptake rate for ¥1000 (US$13) co-payment programme, 65% was estimated based on willingness to pay for the uptake of *Haemophilus influenza* type b (Hib) vaccine [14]. Hib vaccine, like PCV-7, is yet to be on the list of routine vaccination in Japan, but its widespread use is far more than PCV-7, and the related studies are much more available. The rate for no programme scenario was assumed at 0%.

We then considered about the municipality's decision in launching a 5-year programme with these design options. The period of 5 years was assumed for reconsideration or redesigning of the programme, as it is often employed in organising public health programmes in Japan [8]. The birth cohorts used in the model are from Population estimates of Japan [15]. Incremental cost-effectiveness ratios (ICERs) were calculated to determine the efficiency of the resource use:

$$\mathrm{ICER} = \frac{\mathrm{Cost}_{\mathrm{with\_programme}} - \mathrm{Cost}_{\mathrm{without\_programme}}}{\mathrm{Effect}_{\mathrm{with\_programme}} - \mathrm{Effect}_{\mathrm{without\_programme}}}$$

2.2. Markov model

A Markov model of courses followed by the birth cohort under consideration was constructed based on epidemiological data, vaccine effectiveness and models from previous studies. Six mutually exclusive health states were modelled (Fig. 1): (1) healthy, (2) bacteraemia (including sepsis) due to pneumococcus, (3) meningitis due to pneumococcus, (4) acute otitis media (AOM; including simple and complex) due to vaccine serotype pneumococcus, (5) all-cause hospitalised pneumonia, (6) dead from or other than the related diseases in the model. A certain portion of patients developing meningitis had hearing impairment or neurological sequelae (hydrocephalus 12.7%, mental retardation 21.6%, spasticity 18.1% and epilepsia 31.9%) [16]. Adverse effects associated with vaccination were not considered based on reports from Ministry of Health, Labour and Welfare [17] and other studies [18,19].

A Markov cycle for each stage was set at 1 year. Time frame is 5 years after the entering of a birth cohort because the diseases caused by S. pneumococcus decrease significantly among children aged 5 and over [20]. Life expectancy for survived patient with neurological sequelae, 53.9 years, is based on a report by Zhou et al. [21] and adjusted with Japanese average life expectancy. Those without sequelae are assumed to have a life expectancy of Japanese population [22].

We did not consider herd immunity in our base-case analysis, while we conducted scenario sensitivity analyses by assuming herd

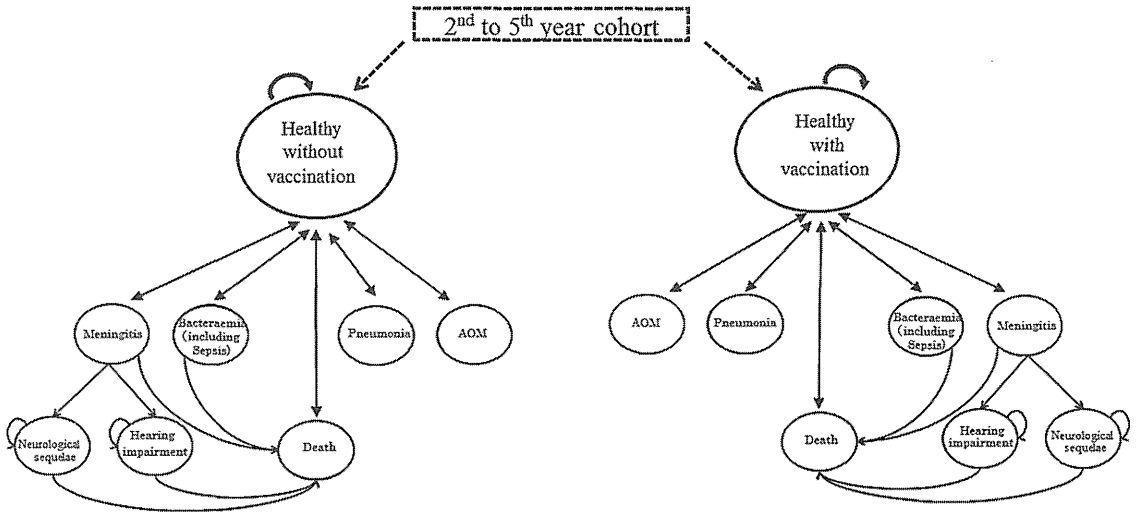

Fig. 1. Markov model "Healthy", means being without the diseases defined by the model under consideration. The dotted square indicates new birth cohort which falls into programmes during the 2nd to 5th year after the start of the vaccination programme. Transitions between each health state are indicated with arrows.

immunity in children aged under 5 years old which was observed in European countries and in the United States. The herd effect to non-vaccinees older than 5 years old was not considered in the sensitivity analyses, because of the discrepancies on reports from previous studies [23–27].

2.3. Outcomes estimation

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

2.3.1. Annual incidence rate and case fatality rate

Since there was no straightforward report on the annual incidence rates of relevant diseases in children younger than 5 years old without vaccination, we adopted or estimated these from the literature or published data. Variables on model are shown in Table 1. Incidence rates of meningitis were from Kamiya et al. [28]; of bacteraemia were from Sakata et al. [20]; of AOM were computed by the AOM episode by child [29], multiplied by the "proportion of clinically diagnosed AOM episodes due to pneumococcus" [30], and the "proportion of pneumococcal AOM due to vaccine serotype" [31]; of all-causes hospitalised pneumonia were estimated by using patient survey [32] and population estimation [15].

Proportions of meningitis that results in hearing impairment and in neurological sequelae as well as case fatality rates of bacteraemia were from Iwata et al. [16]. Case fatality rate of hospitalised pneumonia was estimated from patient survey [32] and vital statistics [33]. Deaths from causes other than IPD were also adopted from the vital statistics [33].

2.4. Vaccine effectiveness

Vaccine effectiveness shown in Table 1 was derived from the studies of overseas, because there was no available data from Japan. Its effectiveness in reducing all pneumococcus serotypes meningitis or bacteraemia, were from Ray et al. [27]. In reducing serotype AOM, and in reducing all-cause hospitalised pneumonia were both based on Cochrane review [34]. According to the epidemiological surveillance conducted by Chiba et al., serotypes of the PCV-7 vaccine cover 75.4% of strains isolated from children with IPD, which is similar to that of the U.S. before their introduction of PCV-7 [35]. Therefore, equivalent effectiveness is expectable. Nevertheless, we will conduct sensitivity analyses to cope with the uncertainties that come with this variable.

2.5. Costing

From the societal perspective, costing should cover the opportunity costs borne by various economic entities in the society [36]. In the context of this study, the amount of direct payments costs borne by municipal authorities, vaccinees, patients and social insurers were considered, while indirect costs of vaccination programme were not included, because it is assumed that the programme is built within the public health services infrastructure. Therefore, costs of vaccination, treatment costs of IPD and non-IPD cases, and costs associated to care-giver's lost productivity, such as accompanying a child for vaccination, for medical treatment, or to take care of a child with sequelae, were counted. Productivity loss due to mortality or morbidity were not included, as including these into cost-effectiveness analysis may be argued as double counting while survived cases were incorporated in the utility weights and disease duration in calculating QALYs [36]. All the variables used on the model were based on the literature.

2.5.1. Direct medical costs

The vaccination cost per shot was assumed at ¥10,000 (US$125) [10]. Treatment costs per episode of survived/fatal bacteraemia case were ¥419,153/¥1,032,126 (US$5239/US$12,902) and ¥392,802/¥1,010,205 (US$4910/US$12,628); of survived/fatal meningitis case were ¥852,642/¥1,470,421 (US$10,658/US$18,380) and ¥843,867/¥1,510,669 (US$10,548/US$18,883), for 0 to <3 and 3 to <5 years old, respectively, according to Iwata et al. [16]. Long-term treatment costs for an individual with hearing impairment were ¥79,422 (US$993) and ¥78,057 (US$976) per year; and suffering from neurological sequelae were ¥420,464 (US$5256) and ¥380,671 (US$4758) per year, for 0 to <3 and 3 to <5 years old, respectively, according to Iwata et al. [16]. Treatment costs per episode of pneumonia caused by S. pneumoniae were ¥221,133 (US$2764) for 0 to <3 years old and ¥164,916 (US$2061) for 3 to <5 years old, according to Ishiwada et al. [37]. Treatment costs per episode of AOM were ¥31,990 (US$400), ¥35,313 (US$441), ¥61,927 (US$774), ¥43,659 (US$546), ¥44,359 (US$554) for 0 to <1, 1 to <2, 2 to <3, 3 to <4, 4 to <5 years old, respectively. These were the weighted average of both simple and complex cases reported by Yamanaka et al. [29]. All these costs are shown in Table 1.

2.5.2. Productivity loss by care-giver

Under the context of this study, productivity loss per disease episode or per shot is valued as a product of care-giver's absent working hours from paid employment and an average hourly wage, ¥1328 (US$17), of Japanese women labourers [38]. Productivity loss of a care-giver to accompany a child for one uptake of vaccine was assumed as a half of a day (4 h) in vaccinated-alone scenario and a quarter of a day (2 h) in co-vaccinated scenario. As to the productivity loss per disease episode, the frequency of outpatient visits and the number of hospitalisation days of a meningitis episode were 8.1 visits/22.7 days and 7.8 visits/21.1 days; of a bacteraemia episode were 2.9 visits/11.5 days and 2.8 visits/10.5 days [16]; of a pneumonia episode were 2.7 visits/6.8 days and 2.8 visits/4.9 days, for 0 to <3 and 3 to <5 years old, respectively [37]. We assumed 4 absent working hours for one outpatient visit and 8 absent working hours for one hospitalised day. The average absent working hours of an AOM episode, 33.6 h, 27.7 h, 50.3 h, 43.1 h, 39.4 h for 0 to <1, 1 to <2, 2 to <3, 3 to <4, 4 to <5 years old, respectively, were derived from Yamanaka et al. [29], which were the weighted average of simple and complex AOM. We assumed that the absent working hours of a care-giver to take care of one child with neurological sequelae or hearing impairment is 8 h per day until the child is admitted to special support education system, which is at age 6 in Japan.

2.6. Discounting

Costs and outcomes were discounted at a rate of 3% [36].

3. Sensitivity analyses

We performed one-way sensitivity analyses to appraise the stability of ICERs against assumptions made in our economic model, and to explore the impact of each variable relative to each other. Except for vaccination cost per shot, which was changed to ¥11,000 (US$138) and ¥9000 (US$113) [10], and utility weights for quality of life adjustments, which were changed by ±20%, transition probability and other assumed values were changed by ±50% of base-case. In scenario sensitivity analysis, the herd effects to a non-vaccinee under 5 years old against diseases were the same as the vaccinated under no co-payment programme (assumed at 80% vaccine uptake rate), based on the report from the United States [27]. The herd effects under ¥1000 (US$13) co-payment programme (assumed at

Table 1
Variables on model.

Variable		Reference
Vaccine uptake rate		
No co-payment programme	80%	[13]
¥1000 co-payment programme	65%	[14]
Population of birth cohort entering the model		
1st year	801,000	[15]
2nd year	775,000	[15]
3rd year	752,000	[15]
4th year	730,000	[15]
5th year	715,000	[15]

Variable	Age groups					References
	0 to <1	1 to <2	2 to <3	3 to <4	4 to <5	
Annual incidence rates per 100,000 population						
Invasive pneumococcal disease cases: meningitis	7.10	1.60	0.30	0.30	0.00	[28]
Invasive pneumococcal disease cases: bacteraemia	43.70	79.10	22.90	3.80	7.50	[20]
Clinically diagnosed AOM episodes	103,100	113,881	67,160	52,589	40,371	[29]
All-causes hospitalised pneumonia	2037	2037	2037	2037	2037	[15,32]
Proportion of clinically diagnosed AOM episodes due to pneumococcus %	34.1	34.1	34.1	34.1	34.1	[30]
Proportion of AOM due to vaccine serotype %	68.2	68.2	68.2	48.5	48.5	[31]
Proportion of meningitis that results to hearing impairment %	1.28	1.28	1.28	0.83	0.83	[16]
Proportion of meningitis that results to neurological sequelae %	6.02	6.02	6.02	3.87	3.87	[16]
Case fatality rate %						
Bacteraemia	0.90	0.90	0.90	0.50	0.50	[16]
Meningitis	4.00	4.00	4.00	2.20	2.20	[16]
Hospitalised pneumonia	0.11	0.11	0.11	0.11	0.11	[32,33]
Vaccine effectiveness %						
In reducing serotypes meningitis or bacteraemia	72.3	75.1	73.4	60.9	58.5	[27]
In reducing serotypes AOM	59.0	59.0	59.0	59.0	59.0	[34]
In reducing all-cause hospitalised radiograph-confirmed pneumonia	27.0	27.0	27.0	27.0	27.0	[34]

Variable		References
Life expectancy for individual with neurological sequelae	53.9	[21,22]
Life expectancy of Japanese population at age 5	74.9 for male; 80.8 for female	[22]
Utility weight		
Healthy	1.0	[23]
Hearing impairment	0.90	[23]
Neurological sequelae	0.57	[23]
Curable bacteraemia	0.9921	[23]
Curable meningitis	0.9768	[23]
Curable pneumonia	0.9940	[23]
AOM	0.9950	[23]
Death	0	[23]

Variable	Age groups					References
	0 to <1	1 to <2	2 to <3	3 to <4	4 to <5	
Cost per vaccination	¥10,000					[10]
Treatment cost						
Bacteraemia episode, survive	¥419,153	¥419,153	¥419,153	¥392,802	¥392,802	[16]
Bacteraemia episode, death	¥1,032,126	¥1,032,126	¥1,032,126	¥1,010,205	¥1,010,205	[16]
Meningitis episode, survive	¥852,642	¥852,642	¥852,642	¥843,867	¥843,867	[16]
Meningitis episode, death	¥1,470,421	¥1,470,421	¥1,479,196	¥1,510,669	¥1,510,669	[16]
Pneumonia episode, survive	¥221,133	¥221,133	¥221,133	¥164,916	¥164,916	[37]
AOM episode	¥31,990	¥35,313	¥61,927	¥43,659	¥44,359	[29]
Hearing impairment	¥79,422	¥79,422	¥79,422	¥78,057	¥78,057	[16]
Neurological sequelae	¥420,464	¥420,464	¥420,464	¥380,671	¥380,671	[16]

Variables related to care-giver's productivity loss

Variable	Age groups					
Frequency of outpatient visits/number of hospitalisation days	0 to <1	1 to <2	2 to <3	3 to <4	4 to <5	
Bacteraemia episode	2.9 visits/11.5 days			2.8 visits/10.5 days		[16]
Meningitis episode	8.1 visits/22.7 days			7.8 visits/21.1 days		[16]
Pneumonia episode	2.7 visits/6.8 days			2.8 visits/4.9 days		[37]
Hearing impairment Neurological sequelae	8 h per day until the child is admitted to special support education system	Assumed				
Absent working hours per AOM episode (h)	33.6	27.7	50.3	43.1	39.4	[29]
Average hourly wage of Japanese women labourers	¥1328					[38]

65% vaccine uptake rate), were estimated based on indirect protection obtained by Hib vaccination in Finland [39], because there was no straightforward study that reports the extent of herd immunity of PCV-7 at 65% vaccine uptake rate. The herd effect was then estimated as a reduction of transition probabilities of bacteraemia and meningitis: 64.9%, 35.9%, 19.4%, 8.9%, 26.8%; of hospitalised pneumonia: 0.0%, 13.1%, 15.3%, 19.2%, 21.3%; of serotype AOM 25.3%, 29.7%, 31.5%, 34.7%, 36.4%; for 1st to 5th year, respectively. Both one-way and scenario sensitivity analyses were performed on base-case in QALY.

4. Results

4.1. Results of cost-effectiveness analyses

In our base-case analysis, the estimated cases averted by the start of the no co-payment vaccination programmes (with 80% vaccine uptake rate) for a 100,000 birth cohort followed for five years are as follows: 5.5 cases of meningitis, 91.4 cases of bacteraemia, 2194.2 cases of hospitalised pneumonia, 38,364.1 cases of AOM, and 3.3 cases of death due to either meningitis, bacteraemia or pneumonia. Under the ¥1000 (US$13) co-payment vaccination programmes (with 65% vaccine uptake rate), our analysis yielded the following results: 4.5 of meningitis, 74.3 of bacteraemia, 1782.8 of hospitalised pneumonia, 31,170.8 of AOM, and 2.7 cases of death due to either meningitis, bacteraemia or pneumonia.

Table 2 shows the results of each programme. Estimated average incremental effects per child were 0.0017 QALY or 0.0021 QALY for ¥1000 (US$13) co-payment programme or no co-payment programme, respectively. ¥1000 (US$13) co-payment or no co-payment programme reduced disease treatment costs, and care-giver's productivity loss due to disease treatment. However, these costs reduced did not offset the vaccination cost and productivity loss due to vaccination, which means that the vaccination programmes turned out to be 'gain more but cost more'.

Estimated ICERs were ¥7,441,000 (US$93,013) per QALY regardless of level of co-payment or vaccination scenario when productivity loss was not included; ¥9,065,000 (US$113,313) per QALY for vaccinated-alone scenario and ¥5,489,000 (US$68,613) per QALY for co-vaccinated scenario, regardless of level of co-payment but when productivity is included. ICERs of scenarios were larger when productivity loss included than when not included. When productivity loss was included, ICERs were smaller in co-vaccinated scenario compared to vaccinated-alone scenario.

4.2. Stability of ICER

Fig. 2a and b shows the top 22 variables that produced the large variations in ICER (in QALY, with productivity loss included) for vaccinated-alone or co-vaccinated scenario, respectively. In vaccinated-alone scenario, the largest change is seen in "vaccine effectiveness in reducing vaccine serotype AOM: aged 1–2", while in co-vaccinated scenario, it is "care-giver's productivity loss: to uptake vaccine". Variables that relate to AOM or hospitalised pneumonia tended to show larger impact to ICER compared to other variables.

Table 3 shows the results of programmes per person when herd immunity is assumed among children under 5 years old. All the estimated ICERs became smaller compared to those estimated in base-case analysis.

5. Budget impact analysis

Budget impact analysis was conducted to estimate its impact on public health care expenditure of a municipality. We set first year cohort population at 1000; and 2nd to 5th year cohort proportional to this birth cohort population. The estimation of annual incremental cost per person was then implemented in our economic model, whereas costs to sectors other than municipality and productivity loss were left uncounted. In Japan, the costs of routine vaccination schedule are evenly shared among the central government, prefectures and municipalities, while a municipality may ask the vaccinee to bear partial cost [8]. Therefore, the vaccine cost borne by municipality is ¥3333 (US$42) under no co-payment

Table 2
Results of base-case cost-effectiveness analyses.

Programme	Cost (¥) per child			
	Vaccine cost	Diseases treatment costs	Productivity loss (uptake vaccine)	Productivity loss (disease treatment)
No programme	0	43,855	0	36,502
Vaccine-alone (¥1000 co-payment)	22,974	33,577	12,204	27,069
Co-vaccinated (¥1000 co-payment)	22,974	33,577	6102	27,069
Vaccine-alone (no co-payment)	28,276	31,205	15,020	24,892
Co-vaccinated (no co-payment)	28,276	31,205	7510	24,892

Programme	Effect per child			
	QALY	Incremental QALY	YOLS	Incremental YOLS
No programme	30.7164	–	30.7203	–
Vaccine-alone (¥1000 co-payment)	30.7181	0.0017	30.7210	0.0007
Co-vaccinated (¥1000 co-payment)	30.7181	0.0017	30.7210	0.0007
Vaccine-alone (no co-payment)	30.7185	0.0021	30.7211	0.0009
Co-vaccinated (no co-payment)	30.7185	0.0021	30.7211	0.0009

Programme	ICER			
	Cost/QALY without productivity loss	Cost/QALY with productivity loss	Cost/YOLS without productivity loss	Cost/YOLS with productivity loss
No programme	–	–	–	–
Vaccine-alone (¥1000 co-payment)	7,441,000	9,065,000	18,066,000	22,009,000
Co-vaccinated (¥1000 co-payment)	7,441,000	5,489,000	18,066,000	13,326,000
Vaccine-alone (no co-payment)	7,441,000	9,065,000	18,066,000	22,009,000
Co-vaccinated (no co-payment)	7,441,000	5,489,000	18,066,000	13,326,000

Note: Some minor discrepancies due to rounding.

Table 3
Scenario sensitivity analysis: assumed there is herd effect to non-vaccinee.

Programme	Cost (¥) per child			
	Vaccine cost	Diseases treatment costs	Productivity loss (uptake vaccine)	Productivity loss (disease treatment)
No programme	0	43,855	0	36,502
Vaccine-alone (¥1000 co-payment)	22,974	29,218	12,204	22,944
Co-vaccinated (¥1000 co-payment)	22,974	29,218	6102	22,944
Vaccine-alone (no co-payment)	28,276	28,042	15,020	21,990
Co-vaccinated (no co-payment)	28,276	28,042	7510	21,990

Programme	Effect per child			
	QALY	Incremental QALY	YOLS	Incremental YOLS
No programme	30.7164	–	30.7203	–
Vaccine-alone (¥1000 co-payment)	30.7188	0.0024	30.7213	0.0010
Co-vaccinated (¥1000 co-payment)	30.7188	0.0024	30.7213	0.0010
Vaccine-alone (no co-payment)	30.7190	0.0026	30.7213	0.0011
Co-vaccinated (no co-payment)	30.7190	0.0026	30.7213	0.0011

Programme	ICER			
	Cost/QALY without productivity loss	Cost/QALY with productivity loss	Cost/YOLS without productivity loss	Cost/YOLS with productivity loss
No programme	–	–	–	–
Vaccine-alone (¥1000 co-payment)	3,424,000	2,868,000	8,323,000	6,972,000
Co-vaccinated (¥1000 co-payment)	3,424,000	362,000	8,323,000	881,000
Vaccine-alone (no co-payment)	47,848,000	4,942,000	11,445,000	11,912,000
Co-vaccinated (no co-payment)	47,848,000	2,081,000	11,445,000	5,016,000

Note: Some minor discrepancies due to rounding.

programme and ¥2333 (US$29) under ¥1000 (US$13) co-payment programme. As to the treatment costs of the disease, every child has a public medical insurance in Japan depending on the parent's occupation, such as the Employees' Health Insurance or the National Health Insurance run by municipalities. Here, since we are estimating the budget impact from the perspective of a municipality, we will consider the treatment costs of children who are covered by the National Health Insurance only. The treatment costs of disease is then computed as 18.8% times 12.5% times (1–20%), where 18.8% is the percentage of children who are covered by insurance run by municipality [40], i.e., National Health Insurance, 12.5% is the percentage medical expensive borne by municipality (the rest is borne by government and prefecture), 20% is standard co-payment for health care for children.

Fig. 3a and b shows the results. The largest impact was seen in the 2nd year, while the maximum savings of costs for disease treatment appeared in the 5th year, regardless of vaccination scenario or payment levels. In total, under no co-payment vaccination programme, the impacts on public health care expenditure of a municipality were ¥8,016,174 (US$100,202), ¥10,209,664 (US$127,621), ¥9,980,146 (US$124,752), ¥9,649,886 (US$120,624), ¥9,399,006 (US$117,488), ¥2,198,562 (US$27,482) for 1st to 6th year, respectively, and for the 7th year, though very small, it showed the expected benefit of the programme, i.e., net savings of costs for disease treatment. Similarly, under ¥1000 co-payment programme, they were ¥6,513,141 (US$81,414), ¥8,414,924 (US$105,187), ¥8,108,869 (US$101,361), ¥7,840,516 (US$98,006), ¥7,636,692 (US$95,459), ¥1,786,332 (US$22,329) for the 1st to 6th year, respectively.

6. Discussion

We conducted cost-effectiveness analyses of PCV-7 routine vaccination programme to the birth cohort in Japan with two different levels of co-payment, ¥1000 (US$13) or ¥0, and two different scenarios of vaccination, vaccinated-alone or co-vaccinated, with or without productivity loss. When vaccinated-alone, ICERs in QALY were ¥7,441,000 (US$93,013) or ¥9,065,000 (US$113,313), when co-vaccinated, ¥7,441,000 (US$93,013) or ¥5,489,000 (US$68,613), without or with productivity loss, respectively, regardless of co-payment level. Co-vaccinated scenarios have lower ICER than vaccinated-alone scenarios due to the savings in productivity loss, which is as assumed. A willingness-to-pay threshold, ¥5,000,000 (US$62,500) per QALY gained, has been suggested for healthcare intervention [41], while there is no established threshold for judging cost-effectiveness of public health programmes in Japan. Therefore, we adopted WHO's criterion: an intervention is 'cost-effective' if ICER (in QALY) is between 1 and 3 times of GDP (=¥11,000,000 or US$137,500 in Japan) [42], and concluded that PCV-7 vaccination programme in Japan would be "cost-effective". These conclusions are considered robust based on the results from our sensitivity analyses: only seven resulted in exceeding ¥11,000,000 (US$137,500)/QALY and the largest is still less than ¥12,600,000 (US$157,500)/QALY.

Our budget impact analysis reveals that the introduction of PCV-7 in neither programme appears to be budget saving for the first six years, whereas the level of budget impact are less than ¥11,000,000 (US$137,500) for a municipality with 1000 birth cohort in the first year, and 2nd to 5th year birth cohort proportional to the birth cohort population of estimated future population.

Due to the variations of serotype coverage, circulating serotypes causing the disease, baseline incidence rates of diseases among children, cost of vaccination programme and health care systems, it is difficult to compare the results of economic evaluation among different countries. For example, in our study, the ICER increases when productivity loss is included than when not included in vaccinated-alone programmes, which contradicts to the results of previous studies [43]. Low incidence rates of the diseases used in the model are considered to cause this phenomenon. This stresses that due caution is needed when interpreting the results of cost-effectiveness analysis among different countries or different settings.

This study has limitations. First, clinical evidences which show the effectiveness of vaccination in reducing annual incidence rates

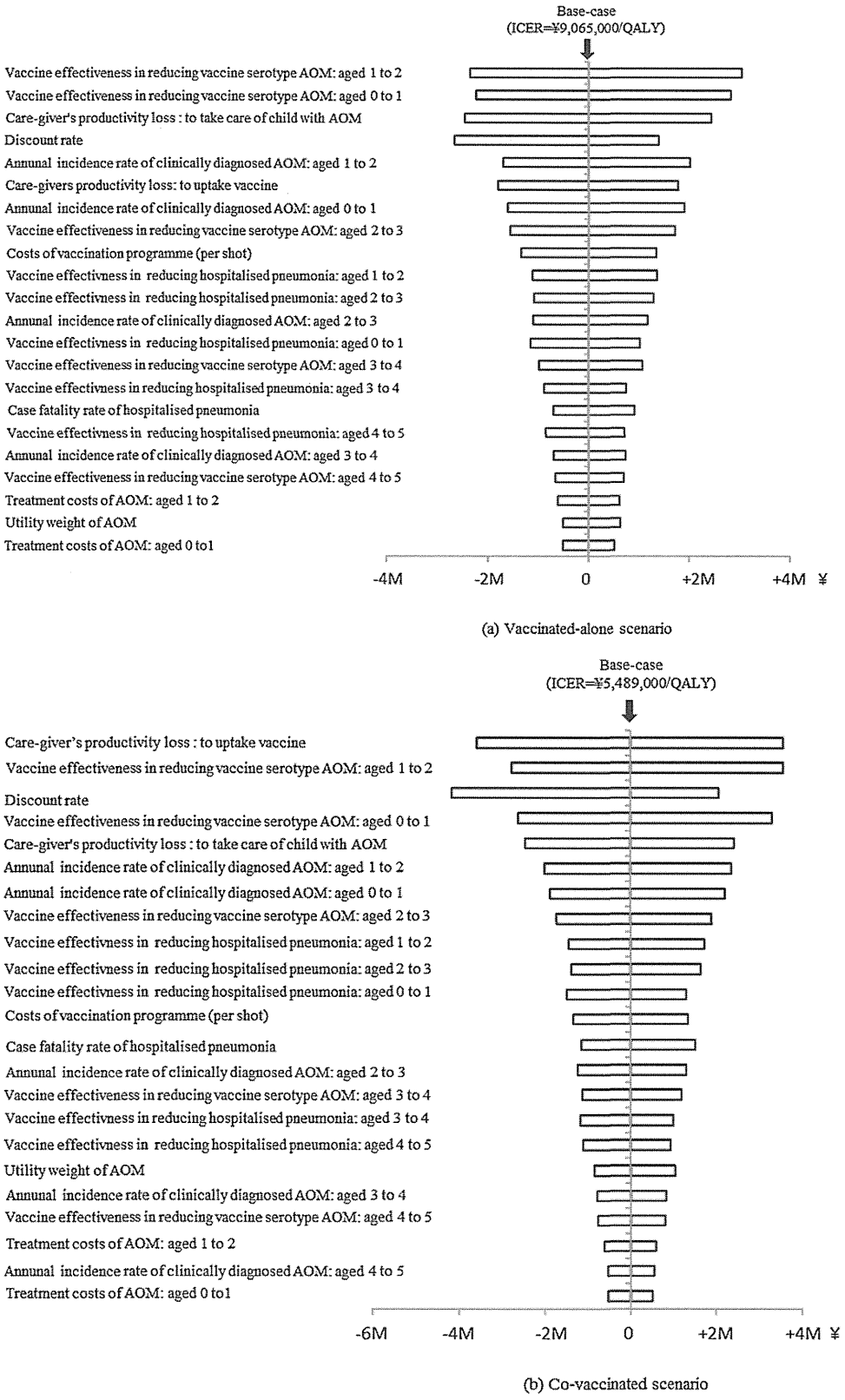

Fig. 2. One-way sensitivity analyses.

of the diseases in our model are adopted from studies carried out in other countries, since no similar study has been done in Japan. There should be differences in ethnicity as well as in the health system between those countries and Japan. Second, annual incidence rate of IPD used in this study is based on a 9-year observation studies done in only one prefecture because of the unavailability of national surveillance data, and such data would have bias. Third, we did not include the benefits of vaccination in preventing antibiotic resistance in our model. Including this benefit would bring more cost-effective results given that the serotypes identified as

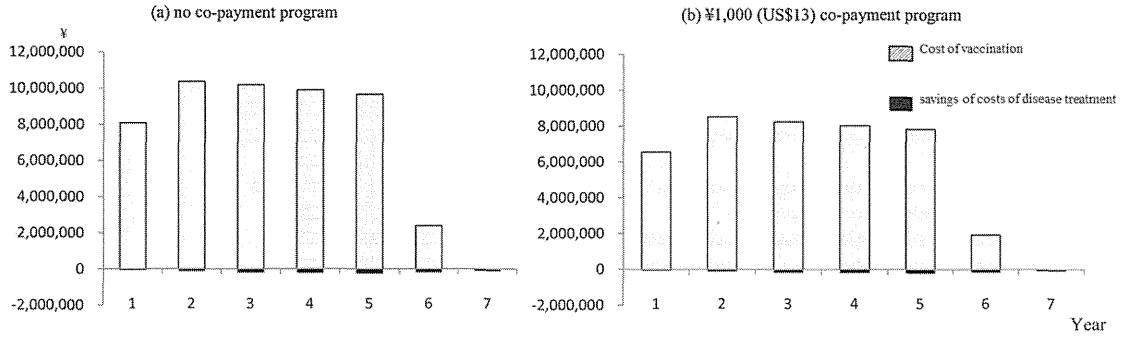

Fig. 3. Budget impact from 1st to 7th year on public health care expenditure of municipality of launching a routine PCV-7 vaccination programme. The first year cohort population is 1000; and 2nd to 5th year cohort proportional to birth cohort population.

penicillin resistant and covered by the PCV-7 is above 80% in Japan [31,35].

There are limitations mentioned as above, but our model deliberates the effect of subsidy policy on the uptake rate, which is unique in economic evaluation of PCV-7 in terms of context of choice under consideration. It provides insight and policy implications for health managers in charge of vaccination programmes, since it takes the choice they face into account. Before giving our conclusion, we must mention that from March 4 to April 1, 2011, the government had temporarily halted PCV-7 vaccination programme following the death cases reported after PCV-7 had been inoculated simultaneously with other vaccines. Based on the official comment from the government that 'there is no connection between the deaths and vaccination', we did not incorporate this event into our model. However, this is a matter of concern about its safety, and continued monitoring and attentive observation is essential.

7. Conclusion

When we adopt 3 times of GDP as a criterion, a routine vaccination programme of PCV-7 offered to the birth cohort in Japan is "cost-effective" from the societal perspective and the budget impact to municipality is under ¥11 million (US$137,500) per year. PCV-7 co-vaccinated with other vaccine list on the routine vaccination schedule will make the vaccination programme more cost-effective than vaccinated-alone.

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.

Contributors: 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 participated in the concept and design to the study, the interpretation of the data, and wrote the manuscript. Ichiro Okubo participated in the concept and design of the study, the interpretation of the data. *Conflict of interest statement*: None. *Funding*: None.

References

[1] Advisory Committee on Immunization Practices. Progress in introduction of pneumococcal conjugate vaccine-worldwide, 2000–2008. MMWR Recomm Rep 2008;57(42):1148–51.
[2] Claes C, Reinert RR, von der Schulenburg JM. Cost effectiveness analysis of heptavalent pneumococcal conjugate vaccine in Germany considering herd immunity effects. Eur J Health Econ 2009;10(1):25–38.
[3] Hubben GA, Bos JM, Glynn DM, van der Ende A, van Alphen L, Postma MJ. Enhanced decision support for policy makers using a web interface to health-economic models-illustrated with a cost-effectiveness analysis of nation-wide infant vaccination with the 7-valent pneumococcal conjugate vaccine in the Netherlands. Vaccine 2007;25(18):3669–78.
[4] McIntosh ED, Conway P, Willingham J, Hollingsworth R, Lloyd A. Pneumococcal pneumonia in the UK—how herd immunity affects the cost-effectiveness of 7-valent pneumococcal conjugate vaccine (PCV). Vaccine 2005;23(14):1739–45.
[5] Melegaro A, Edmunds WJ. Cost-effectiveness analysis of pneumococcal conjugate vaccination in England and Wales. Vaccine 2004;22(31–32):4203–14.
[6] Silfverdal SA, Berg S, Hemlin C, Jokinen I. The cost-burden of paediatric pneumococcal disease in Sweden and the potential cost-effectiveness of prevention using 7-valent pneumococcal vaccine. Vaccine 2009;27(10):1601–8.
[7] Tilson L, Usher C, Butler K, Fitzsimons J, O'Hare F, Cotter S, et al. Economic evaluation of a universal childhood pneumococcal conjugate vaccination strategy in Ireland. Value Health 2008;11(5):898–903.
[8] Preventive Vaccination Law, Supplementary Provisions, Extract, Pub. L. No. 116, Article 2; November 7, 2001.
[9] Trueman P, Drummond M, Hutton J. Developing guidance for budget impact analysis. Pharmacoeconomics 2001;19:609–21.
[10] Health Service Burea. Yobou sessyu ni kakawaru hiyou hutan genjyo ni tuite. Tokyo: Ministry of Health, Labour and Welfare; 2010 [in Japanese].
[11] Ministry of Health, Labour and Welfare. Shikyukeigan nado wakutin sessyukinkyu sokusin jigyou no jissi ni tsuite. Kenhatsu 1126 no. 10. Tokyo: Ministry of Health, Labour and Welfare; 2010 [in Japanese].
[12] Japan Pediatric Society. Nipon syonika gakai no yobousessyu no douji sessyu ni taisuru kangaekata; 28 April 2011 [in Japanese] http://www.jpeds.or.jp/pi-j.html.
[13] Ministry of Health, Labour and Welfare. Report on health center activities and health services for the aged 2008. Tokyo: Health and Welfare Statistics Association; 2010 [in Japanese].
[14] Iwashita Y, Takemura S. Factors associated with willingness to undergo vaccination against *Haemophilus influenzae* type B (Hib). Nippon Koshu Eisei Zasshi 2010;57(5):381–9 [in Japanese].
[15] Ministry of Internal Affairs and Communications. Population estimates of Japan. Tokyo: Statistics Bureau; 2002.
[16] Iwata S, Ishiwada N, Sakata H, Sakano T, Sato Y, Nakano T, et al. Burden of illness of bacterial meningitis and bacteremia caused by Streptococcus pneumonia in children. Jpn J Pediatr 2008;61:2206–20 [in Japanese].
[17] Ministry of Health Labour Welfare. Syoniyo haien kyukin wakutin, bihu wakutin no anzensei no hyouka kekka ni tuite; 2011. Press release, March 24, 2011 [in Japanese].
[18] Black S, Shinefield H, Fireman B, Lewis E, Ray P, Hansen JR, et al. Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children, Northern California Kaiser Permanente Vaccine Study Center Group. Pediatr Infect Dis J 2000;19(3):187–95.
[19] Kim NH, Lee J, Lee SJ, Lee H, Kim KH, Park SE, et al. Immunogenicity and safety of pneumococcal 7-valent conjugate vaccine [diphtheria CRM(197) protein conjugate; Prevenar] in Korean infants: differences that are found in Asian children. Vaccine 2007;5(45):7858–65.
[20] Sakata H, Shirai M, Kaijino M, Takase M, Okamoto T, Niura N, et al. Epidemiological study of bacterial meningitis in children in Kamikawa subprefecture in Hokkaido between 1988 and 2002. Acta Paediatr Jpn 2004;108:401–5 [in Japanese].
[21] Zhou F, Bisgard KM, Yusuf HR, Deuson RR, Bath SK, Murphy TV. Impact of universal *Haemophilus influenzae* type b vaccination starting at 2 months of age in the United States: an economic analysis. Pediatrics 2002;110(4):653–61.
[22] Ministry of Health, Labour and Welfare. The 20th life tables. Tokyo: Health and Welfare Statistics Association; 2007 [in Japanese].
[23] Rozenbaum MH, Sanders EA, van Hoek AJ, Jansen AG, van der Ende A, van den Dobbelsteen G, et al. Cost effectiveness of pneumococcal vaccination among Dutch infants: economic analysis of the seven valent pneumococcal conjugated vaccine and forecast for the 10 valent and 13 valent vaccines. BMJ 2010;340:c2509.

[24] Rodenburg GD, de Greeff SC, Jansen AG, de Melker HE, Schouls LM, Hak E, et al. Effects of pneumococcal conjugate vaccine 2 years after its introduction, the Netherlands. Emerg Infect Dis 2010;16(5):816–23.
[25] Lepoutre A, Varon E, Georges S, Gutmann L, Lévy-Bruhl D. Impact of infant pneumococcal vaccination on invasive pneumococcal diseases in France, 2001–2006. Euro Surveill 2008;13(August (35)).
[26] Munoz-Almagro C, Jordan I, Gene A, Latorre C, Garcia-Garcia JJ, Pallares R. Emergence of invasive pneumococcal disease caused bynonvaccine serotypes in the era of 7-valent conjugate vaccine. Clin infect Dis 2008;46:174–82.
[27] Ray GT, Pelton SI, Klugman KP, Strutton DR, Moore MR. Cost-effectiveness of pneumococcal conjugate vaccine: an update after 7 years of use in the United States. Vaccine 2009;27(47):6483–94.
[28] Kamiya H, Iwata S, Ishiwada N, Yamanaka M, Sugita R. Economic analysis of pneumococcal conjugate vaccination in Japan. Japanese Journal of Pediatrics 2008;61:2233–41 [in Japanese].
[29] Yamanaka N, Hotomi M, Sugita R. Cost-effectiveness of pneumococcal conjugate vaccine in Japan: Estimation on acute pneumococcal otitis media in children. Japanese Journal of Pediatrics 2008;61:2221–32 [in Japanese].
[30] Suzuki K, Kurono Y, Kobayashi T, Nishimura T, Baba S, Harabuchi Y, et al. The fourth nationwide survey of clinical isolates from patients with otolaryngological field infections. J Jpn Soc Infect Dis Otolaryngol 2008;26:15–26 [in Japanese].
[31] Hotomi M, Billal DS, Kamide Y, Kanesada K, Uno Y, Kudo F, et al. Serotype distribution and penicillin resistance of *Streptococcus pneumoniae* isolates from middle ear fluids of pediatric patients with acute otitis media in Japan. Clin Microbiol 2008;46:3808–10.
[32] Social Statistics Division, Statistics and Information Department, Minister's Secretariat, Ministry of Health, Welfare and Labour. Heisei 20 nen kanja chosa. Tokyo: Ministry of Health, Welfare and Labour; 2008 [in Japanese].
[33] Ministry of Health, Labour and Welfare. Vital statistics of Japan 2006. Tokyo: Health and Welfare Statistics Association; 2008 [in Japanese].
[34] Lucero MG, Dulalia VE, Nillos LT, Williams G, Parreño RAN, Nohynek H, et al. Pneumococcal conjugate vaccines for preventing vaccine-type invasive pneumococcal disease and X-ray defined pneumonia in children less than two years of age. Cochrane Database Syst Rev 2009;(4), doi:10.1002/14651858.CD004977.pub2. Art. No.: CD004977.
[35] Chiba N, Morizumi M, Sunaoshi K, Takahashi S, Sunakawa K, Ubukata K, et al. Serotype and antibiotic resistance of isolates from patients with invasive pneumococcal disease in Japan. Epidemiol Infect 2010;138:61–8.
[36] Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. Methods for economic evaluation of health care programmes. 3rd ed. Oxford: Oxford University Press; 2004.
[37] Ishiwada N, Iwata S, Sakata H, Sakano T, Sato Y, Nakano T, et al. Burden of illness of pneumonia caused by Streptococcus pneumoniae in children. Japanese Journal of Pediatrics 2008;61:2194–204 [in Japanese].
[38] Ministry of Health Labour Welfare. Basic survey on wage structure 2009. Tokyo: Health and Welfare Statistics Association; 2010 [in Japanese].
[39] Leino T, Takala T, Auranen K, Mäkelä PH, Takala AK. Indirect protection obtained by *Haemophilus influenza* type b vaccination: analysis in a structured population model. Epidemiol Infect 2004;132:959–66.
[40] Ministry of Health, Labour and Welfare. Comprehensive survey of living conditions of the people on health and welfare 2009. Tokyo: Health and Welfare Statistics Association; 2010 [in Japanese].
[41] Shiroiwa T, Sung YK, Fukuda T, Lang HC, Bae SC, Tsutani K. International survey on willingness-to-pay (WTP) for one additional QALY gained: what is the threshold of cost effectiveness? Health Econ 2010;19(4):422–37.
[42] World Health Organization. WHO guide for standardization of economic evaluations of immunization programmes. WHO Document Production Services: Geneva, Switzerland; 2008.
[43] Isaacman DJ, Strutton DR, Kalpas EA, Horowicz-Mehler N, Stern LS, Casciano R, et al. The impact of indirect (herd) protection on the cost-effectiveness of pneumococcal conjugate vaccine. Clin Ther 2008;30(2):341–57.

PEDIATRICS INTERNATIONAL Official Journal of the Japan Pediatric Society

Pediatrics International (2012) **54**, 613–618 doi: 10.1111/j.1442-200X.2012.03645.x

Original Article

Pediatric hospitalizations with influenza A infection during the 2009–2010 pandemic in five hospitals in Japan

Masayuki Kobayashi,[1] Satoko Ohfuji,[1] Wakaba Fukushima,[1] Shiro Sugiura,[3] Urara Kohdera,[2] Yuhei Itoh,[4] Saburo Ide,[5] Keizou Ohbu[6] and Yoshio Hirota[1]

[1]*Department of Public Health, Graduate School of Medicine, Osaka City University,* [2]*Department of Pediatrics, Nakano Children's Hospital, Osaka,* [3]*Department of Pediatrics, Toyohashi Municipal Hospital, Toyohashi,* [4]*Department of Pediatrics and Child Health, Kurume University Medical Center,* [5]*Department of Nursing, St. Mary's College, and* [6]*Department of Pediatrics, St. Mary's Hospital, Kurume, Japan*

Abstract ***Background***: The aim of this study was to identify the clinical characteristics of hospitalized children with the 2009 pandemic influenza virus infection in Japan.

Methods: We retrospectively reviewed cases of hospitalized children younger than 16 years with laboratory-confirmed influenza A virus infection during the 2009–2010 pandemic season in five hospitals in Japan.

Results: A total of 515 cases were included in the analysis. The median age was 6.3 years (range 0–15), and 216 subjects (41.9%) had one or more underlying medical conditions. There were no fatalities, but 16 patients (3.1%) required intensive care. More than 93% of the subjects received neuraminidase inhibitors, and more than 87% received these medications within 48 h of the onset of symptoms. Approximately 80% of all subjects were admitted to hospital within 48 h of the onset of symptoms.

Conclusions: There were no fatalities, and the proportion of patients with serious illness was substantially lower than previously reported from other countries. Good access to medical services and proactive treatment may have contributed to the lower disease burden of the 2009 influenza pandemic on Japanese children.

Key words 2009 H1N1 influenza pandemic, Japan, neuraminidase inhibitors, pediatric hospitalization.

The 2009 H1N1 influenza pandemic caused substantial disease burden all over the world during the 2009–2010 influenza season. In Japan, 202 deaths due to the 2009 H1N1 viral infection were reported to the Ministry of Health, Labor and Welfare (MHLW) during that season (25 August 2010). On the other hand, deaths due to 2009 H1N1 infection in the same season were estimated as up to 12 469 cases in the USA.[1] The World Health Organization reported the estimated incidences of hospitalization and mortality due to the 2009–2010 H1N1 pandemic in several countries in both northern and southern hemispheres, using data available by November 2009.[2] In that report, the mortality rate (deaths per million population) in Japan was estimated to be 0.2, while those in other countries, including the USA, Canada, the UK, Mexico, South Africa, Argentina, Australia, Brazil, Chile, and New Zealand, ranged from 1.8 to 14.6. The incidence of hospitalization in Japan was also lower than in other countries. These findings suggest that the clinical characteristics of illness caused by the 2009 influenza pandemic in Japan were substantially different from those in other countries. To date, a number of hospitalized case series have been reported from many countries.[3–10] However, not enough information has been reported from Japan. As 45% of hospitalized cases with H1N1 infection were reported to have occurred in children aged under 18 years, we focused on pediatric cases and conducted this study for identifying the clinical characteristics of hospitalized children with the 2009 H1N1 pandemic influenza infection in Japan.[5]

Correspondence: Masayuki Kobayashi, MD, Department of Public Health, Graduate School of Medicine, Osaka City University, 1-4-3 Asahi-machi, Abeno-ku, Osaka 545-8585, Japan. Email: koba7masa@med.osaka-cu.ac.jp

Received 3 July 2011; revised 17 January 2012; accepted 21 March 2012.

Methods

We retrospectively reviewed cases of hospitalized children under 16 years of age with laboratory-confirmed influenza A virus infection admitted to one of five hospitals in Japan (one central hospital in Aichi, one university hospital and two central hospitals in Fukuoka, and one general pediatric hospital in Osaka). Participating hospitals were enlisted through the network of the Analytic Epidemiology Research Group for Respiratory Infectious Diseases organized by the MHLW, Japan, and not based on population. All patients admitted between 1 August 2009 and 31 March 2010 were included in the analyses. Influenza A virus infection was confirmed in the subjects by testing nasal or throat swabs with the rapid influenza antigen test (widely used in

© 2012 The Authors
Pediatrics International © 2012 Japan Pediatric Society

Japanese clinical settings) or reverse transcriptase-polymerase chain reaction (RT–PCR) at the hospitals or regional laboratories.

Data was abstracted from medical records by a participating pediatrician at each hospital, and by study nurses under the supervision of a participating pediatrician in one hospital, using a structured data collection form. We obtained information including demographic characteristics, underlying medical conditions, the primary cause of hospitalization, the duration of hospitalization, the time from the onset of symptoms to hospitalization, clinical diagnoses, the types of treatment (antiviral medications, antibiotics, systemic steroids, oxygen supplementation, admission to an intensive care unit [ICU] and mechanical ventilation), the time from the onset of symptoms to the administration of antiviral medications, and outcomes.

Each clinical diagnosis was based on the attending pediatrician's assessment and the following findings: pneumonia, consolidation on chest X-ray; asthma attack, wheezing and/or retraction; acute respiratory distress syndrome (ARDS), diffuse pulmonary edema on chest X-ray and severe hypoxemia (partial arterial pressure of oxygen /fractional concentration of oxygen in inspired air <300);[11] pneumothorax or mediastinal emphysema, radiographic evidence of free air; atypical behavior, behavior that suggested the presence of temporal hallucination (visual, auditory, etc), delirium and/or disorientation without long altered consciousness; and encephalopathy, altered consciousness lasting longer than 12–24 h.

We did not obtain informed consent from the subjects or their guardians because this study was a retrospective case series and no identifiable personal information of the study subjects was handled. This study was approved by the ethics committee of the Osaka City University Graduate School of Medicine.

Statistical analysis

Percentages for categorical variables, and medians and ranges for continuous variables were calculated. The χ^2-test and Wilcoxon rank sum test were used where appropriate.

Univariate and multivariate logistic regression models were used to identify factors associated with admission to an ICU. Only patients who had been admitted to one of three of the participating hospitals (one in Aichi and two in Fukuoka), which provided intensive care to at least one subject, were included in these regression analyses.

All reported *P*-values are two-sided, and a *P*-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using SAS software version 9.1 (SAS Institute Inc, Cary, NC, USA).

Results

Study population and clinical characteristics

A total of 515 patients were reported by the hospitals, and the case details of all patients were obtained. There was a peak of hospitalizations in November, and more than 80% of the subjects were hospitalized between October and December 2009 (Fig. 1a). Age distribution is shown in Figure 1b. The median age was 6.3 years (range, 0–15), and children aged 4–6 years

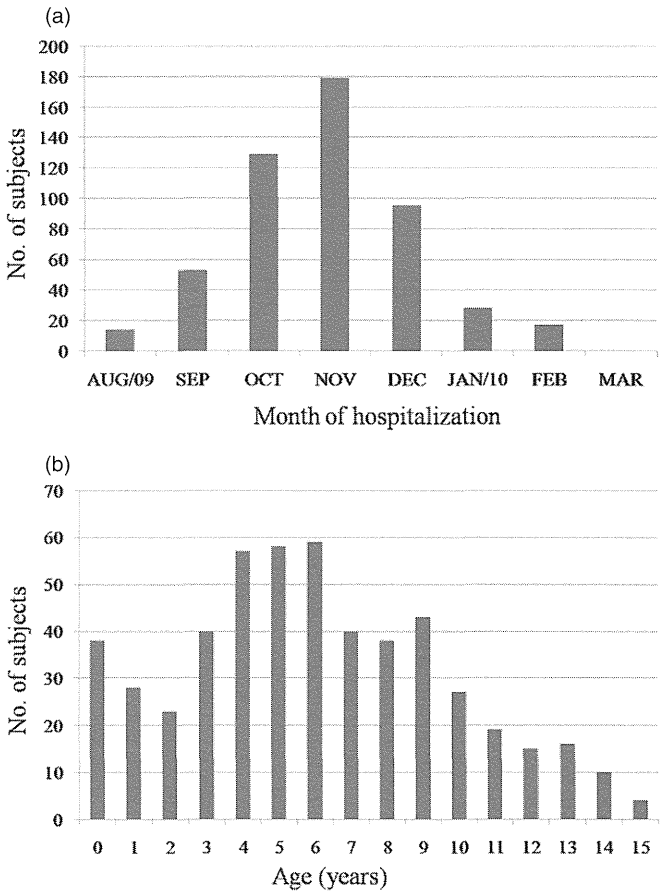

Fig. 1 Timing of hospitalizations and age distribution of subjects. (a) The number of hospitalizations is shown according to month. (b) Age distribution of the study subjects.

accounted for about one-third of our study subjects. Table 1 shows the background and clinical characteristics of the subjects. Approximately two-thirds of the subjects were male. Forty-two percent of the subjects had one or more underlying medical conditions. Asthma was the most frequently reported underlying condition (19.6%), followed by seizure and epilepsy (17.3%).

Approximately half of the subjects were hospitalized primarily due to respiratory complications, including pneumonia and asthma attack, and 28.0% primarily due to neurological complications, including seizure and atypical behavior. An additional 4.7% had both respiratory and neurological complications. The most frequent respiratory complication was pneumonia, followed by asthma attack. There was one patient with ARDS and six patients with pneumothorax or mediastinal emphysema. The most frequent neurological complication was seizure, and atypical behavior was almost as frequent as seizure. Four patients were diagnosed with encephalopathy.

Approximately 60% of the subjects were admitted to a hospital within 24 h of the onset of symptoms, and approximately 80% within 48 h.

Medical interventions and clinical course

Table 2 shows the types of treatment and outcomes. A total of 481 subjects (93.4%) received neuraminidase inhibitors. Oseltamivir

© 2012 The Authors
Pediatrics International © 2012 Japan Pediatric Society

Table 1 Background and clinical characteristics of subjects ($n = 515$)

	Number of subjects	
	n	(%)
Sex		
Male	331	(64.3)
Prefecture		
Aichi	70	(13.6)
Fukuoka	171	(33.2)
Osaka	274	(53.2)
Underlying medical condition†		
Any condition	216	(41.9)
Asthma	101	(19.6)
Chronic lung disease	1	(0.2)
Chronic heart disease	11	(2.1)
Chronic kidney disease	10	(1.9)
Seizure and epilepsy	89	(17.3)
Other neurological diseases	11	(2.1)
Hematologic disease	1	(0.2)
Metabolic disease	1	(0.2)
Malignant disease	1	(0.2)
Other diseases	25	(4.9)
Primary cause of admission		
Respiratory complications	251	(48.7)
Neurological complications	144	(28.0)
Both respiratory and neurological complications	24	(4.7)
Others‡	96	(18.6)
Diagnosis†		
Pneumonia	226	(43.9)
Asthma attack	98	(19.0)
Pneumothorax or mediastinal emphysema	6	(1.2)
Acute respiratory distress syndrome	1	(0.2)
Seizure	99	(19.2)
Atypical behavior	83	(16.1)
Encephalopathy	4	(0.8)
Dehydration	90	(17.5)
Time from onset of symptoms to admission		
<12 h	122	(23.7)
12 to <24 h	186	(36.1)
24 to <48 h	100	(19.4)
48 to <72 h	30	(5.8)
>72 h	77	(15.0)

†Underlying medial condition and diagnosis listed are not mutually exclusive. ‡Including high body temperature, dehydration, and anxiety of guardians.

was the antiviral medication of choice. Zanamivir was much less frequently prescribed than oseltamivir. Four patients received only *Maoto*, a traditional oriental medication (*Kampo* medication) that is reported to be effective against influenza illness in Japan, without either of the neuraminidase inhibitors. Of those who received neuraminidase inhibitors, 78.6% and 93.6% (respectively, 73.4% and 87.4% of all subjects) started the medication within 24 and 48 h of the onset of symptoms.

The median length of hospitalization was 6 (range, 1–77) days. Sixteen subjects (3.1% of all subjects) had been admitted to an ICU, and five (1.0%) required mechanical ventilation (Table 2). There was no fatality. One previously healthy female patient aged 6 years was reported to have had residual dysfunction, including paraplegia and vesicorectal disturbance. Thirteen patients were transferred to other hospitals, but no transfer due to the aggravation of illness was reported. The remaining 501 patients were discharged with complete recovery.

Risk factors for admission to an ICU

We divided subjects into two groups, Group A included 197 patients who were admitted to one of three of the participating hospitals (one in Aichi and two in Fukuoka) which provided intensive care to at least one patient, and Group B consisted of 318 patients who were admitted to one of the remaining two hospitals in which no patient was sent to the ICU (as described above, no patient in Group B was transferred to other hospitals because of the aggravation of illness). There were no significant differences in sex, time from onset to admission, proportion of subjects with any underlying medical condition, proportion of subjects who received neuraminidase inhibitors, and time from onset to the administration of neuraminidase inhibitors. However, there were statistically significant differences in age distribution (median 6.8 years in Group A, and 5.8 years in the Group B, $P \leq 0.001$), and proportion of subjects who received antibiotics (69.0% and 21.4%, respectively, $P \leq 0.001$) systemic steroids (47.7% and 10.5%, respectively, $P \leq 0.001$) or oxygen supplementation (61.4% and 19.5%, respectively, $P \leq 0.001$). Only the 197 subjects of Group A were included in regression analyses, as it was considered that the differences between the two groups could possibly affect the analyses. Among these subjects, 16 (8.1%) were admitted to an ICU, and five (2.5%) required mechanical ventilation. The median age of the ICU patients was 5.5 years, while the median age of the non-ICU patients was 7.0 years ($P = 0.382$). Eight of the 16 ICU patients (50.0%) and 67 of 181 non-ICU patients (37.0%) had one or more underlying medical conditions ($P = 0.314$).

The results indicated that underlying neurological medical conditions, including seizure and epilepsy, were a statistically significant independent risk factor (Table 3). Neither asthma nor

Table 2 Treatment and outcomes ($n = 515$)

	Number of subjects	
	n	(%)
Antiviral medications		
Oseltamivir	374	(72.6)
Zanamivir	80	(15.5)
Oseltamivir and zanamivir	27	(5.2)
Maoto†	4	(0.8)
None	30	(5.8)
Antibiotics	204	(39.6)
Systemic steroids	127	(24.7)
Oxygen supplementation	183	(35.5)
Admission to an intensive care unit	16	(3.1)
Mechanical ventilation	5	(1.0)
Outcome		
Recovered	501	(97.3)
Transferred‡	13	(2.5)
Residual dysfunction	1	(0.2)
Died	0	(0.0)

†A traditional oriental medication (*Kampo* medicine) with anti-influenza efficacy reported in Japan. ‡No subject was transferred to another hospital due to the aggravation of illness.

© 2012 The Authors
Pediatrics International © 2012 Japan Pediatric Society

Table 3 Risk factors for admission to an ICU (n = 197)

	ICU patients (n = 16)		Others (n = 181)		Univariate†			Multivariate†		
	n	(%)	n	(%)	OR	(95%CI)	P-value	OR	(95%CI)	P-value
Sex										
Male	12	(75.0)	117	(64.6)	1.00			1.00		
Female	4	(25.0)	64	(35.4)	0.61	(0.19–1.97)	0.307	0.67	(0.20–2.29)	0.526
Age (years)										
<3	4	(25.0)	22	(12.2)	1.00			1.00		
3–5	4	(25.0)	65	(35.9)	0.44	(0.10–1.92)	0.275	0.37	(0.08–1.79)	0.218
6–11	5	(31.3)	106	(58.6)	0.30	(0.08–1.22)	0.093	0.25	(0.06–1.15)	0.076
12-	3	(18.8)	22	(12.2)	0.92	(0.18–4.64)	0.916	0.79	(0.14–4.59)	0.794
Underlying medical condition										
Any	8	(50.0)	67	(37.0)	1.70	(0.61–4.74)	0.310			
Asthma	1	(6.3)	37	(20.4)	0.26	(0.03–2.03)	0.198	0.35	(0.04–2.90)	0.332
Neurological diseases‡	6	(37.5)	22	(12.2)	4.34	(1.44–13.12)	0.009	4.64	(1.41–15.29)	0.012
Other conditions	1	(6.3)	11	(6.1)	1.03	(0.12–8.53)	0.978	1.27	(0.14–11.33)	0.831
Neuraminidase inhibitors within 48 h	14	(87.5)	159	(87.8)	0.97	(0.21–4.55)	0.967	1.10	(0.20–6.20)	0.912

†Logistic regression model was used. ‡Including seizure and epilepsy. ICU, intensive care unit.

the administration of neuraminidase inhibitors within 48 h of the onset of symptoms was significantly associated with admission to an ICU.

Discussion

We have reported here a case series of influenza A virus infection confirmed by a rapid influenza antigen test or RT–PCR. Therefore, our subjects may include those hospitalized with influenza subtype viruses other than the 2009 A H1N1 pandemic influenza strain. However, according to the data from the National Institute of Infectious Diseases of Japan, almost all of the influenza A viruses detected in Japan during the study period were identified as the 2009 H1N1 pandemic influenza virus (18 November 2010). Thus, it was considered that our results reflect the disease burden caused by the 2009 influenza pandemic in Japan.

Our results have a number of similarities with previous reports from other countries on pediatric hospitalizations with the 2009 pandemic influenza virus infection. Most of these hospitalizations were due to respiratory complications and neurological complications. Encephalopathy was not common, even though this study was conducted in Japan where encephalopathy associated with seasonal influenza infection has been reported.[12,13] The age distribution of the study subjects was not substantially different from those of previous reports except for a report from Argentina.[3,4,14–17] Furthermore, the proportion of subjects with one or more underlying medical conditions was similar to some of the previous reports.[15–18] However, our results revealed some unique characteristics of pediatric hospitalizations in Japan as described below.

There was no fatality, although our sample size was not small compared to previous studies. In addition, the proportion of subjects who were admitted to an ICU or required mechanical ventilation was substantially smaller than in those studies. Only 16 of our subjects (3.1%) were admitted to an ICU, and five (1.0%) required mechanical ventilation (8.1% and 2.5%, respectively, among subjects from hospitals with at least one ICU patient). In contrast, Libster *et al.* reported that 19% of hospitalized children were admitted to an ICU, and 17% required mechanical ventilation in Argentina.[3] Corresponding proportions of 16.6% and 6.4% were reported from Canada, and 18.6% and 6% from Milwaukee, USA.[4,14] These differences in our results from other studies might be partially because of the flexibility of the pediatrician's judgment or the differences in the features of participating hospitals; however, in light of the reported low incidence of hospitalization and mortality rate with the 2009 H1N1 infection in Japan, our results sufficiently reflect the situation in Japan.[2]

The proportion of the subjects who received neuraminidase inhibitors was much higher than that in previous studies.[3,6,16] Much earlier administration of these medications was also a unique feature. More than 93% of our subjects received neuraminidase inhibitors, and more than 87% of all subjects were administered these medications within 48 h of the onset of symptoms. Furthermore, a considerable proportion of our subjects received these medications within 24 h. In contrast, Libster *et al.* reported that oseltamivir was administered within 48 h of the onset of symptoms in 12–13% of hospitalized children with 2009 pandemic influenza infection in Argentina.[3] Hackett *et al.* reported that oseltamivir was given to only 26 of 65 hospitalized children with 2009 pandemic influenza infection in Birmingham, UK.[16] Louie *et al.* reported that antiviral treatment was administered within 48 h of the symptom onset to 57% of non-fatal hospitalized pediatric cases in California, USA.[6] In addition, the timing of hospital admission in our study was much earlier than that in the previous reports. Approximately 60% of our subjects were admitted to hospital within 24 h of the symptom onset, and approximately 80% within 48 h. In contrast, the median time to consultation from the onset was 4 days in Argentina.[3] Louie *et al.* reported that the median time from the onset to hospitalization among all their subjects, adults included, was 2 days.[6] We speculate that these characteristics of our study subjects are because of Japan's national universal health insurance system. This insur-

© 2012 The Authors
Pediatrics International © 2012 Japan Pediatric Society