Cost-effectiveness Analysis of Influenza and Pneumococcal Vaccinations among Elderly People in Japan

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During the periods of seasonal flu in 2003 and 2004, it was found that about 45 percent of elderly people in Japan had been inoculated with influenza vaccines. Comparatively, however, the proportion of inoculation with pneumococcal vaccine was only 0.1 percent.　Taking into account such incongruent proportions, this study assesses health and economic benefits of vaccination strategies for both influenza and pneumonia particularly for the elderly population in Japan.　To accomplish this objective, a cost-effectiveness analysis was conducted with the use of the Monte Carlo simulation based on the data from medical literature as well as from the public organizations, wherein three strategic patterns were delineated and compared (i) no vaccination (ii) influenza vaccine only, and (iii) combined influenza with pneumococcal vaccines.　The cost for one year of life saved by each strategy was compared with the scenario of no vaccinations.　It was found that for 100,000 elderly people over 65 years of age in Japan, the cost-effectiveness ratio of influenza-only vaccination was 516,332 Japanese yen per one year of life saved, while the combined vaccinations of influenza with pneumococcal was 459,874 Japanese yen for the same benefit.　The incremental cost-effectiveness ratio of the strategies (iii) versus (ii) was 426,698 Japanese yen per one year of life saved for 100,000 people.　Consequently it was indicated that the combined vaccinations would be more cost-effective than the vaccination for influenza only.

INTRODUCTION

Viral and bacterial diseases have tormented the humankind since the time immemorial. Some of such maladies are emerging or reemerging in recent years.　Still others have been in continuous existence, haunting the host population. Despite fluctuations, influenza and pneumonia have agonized and even killed people from time to time.　In 1918, for instance, influenza and pneumonia pandemic caused 25 million deaths worldwide.　In Japan, on the other hand, pneumonia (and bronchitis) caused 136,524 deaths in 1947, with the death rate of 174.8 per 100,000 people.　They were, in effect, the second leading causes of death in the country at the time (22).

Even today, pneumonia and influenza are two of the common causes of mortality, morbidity, and economic loss among the elderly in Japan.　During the rampancy of

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influenza in 1999, about 90 percent or 1,039 cases, of the total of 1,154 influenza-related mortalities including that from pneumonia, were among elderly people (35).   It is momentous to realize that about 24 or 25 percent of the elderly who get infected with influenza subsequently develop a complication with pneumonia (20).   In other words, infection with influenza makes an elderly person more vulnerable to pneumonia infection.   However, Fedson reported the relative importance of pneumococcal pneumonia among all pneumonia patients, stating that the proportions of admissions for community-acquired pneumonia are 30 to 50 percent (11).   Data from the Ministry of Health, Labour, and Welfare (Vital Statistics of Japan) indicate that, even in 2003, pneumonia was the fourth leading cause of deaths and the number of deaths resultant of pneumonia among the elderly reached as high as 90,757.   This latter figure constituted about 95.6 percent of all deaths from pneumonia inclusive of all age-specific subpopulation groups, and 9.3 percent of deaths from all causes throughout the year.   This constituted about 11 percent of the total mortality from all causes among the elderly. Seen from an epidemiological perspective, it is mainly the elderly people who are at risk.

Influenza and pneumonia pose medical as well as social problems in Japan, which is one of the countries that have a high demographic representation of the aged population.   At the current rate, as this demographic tendency progresses, the problems with influenza and pneumonia among the elderly will get even more difficult to deal with in the future, unless more efficient strategy for prevention is implemented.

Generally, in Japan, the economic benefit, from a societal perspective, not to mention the clinical effectiveness of influenza vaccine particularly for the elderly population, is better recognized and accepted than that of pneumonia.   Since November 2001, part of the cost for inoculating the elderly with influenza vaccine has been shared and is assisted by the Ministry of Health, Labour, and Welfare. In addition, it is noteworthy that the proportion of inoculation with influenza vaccines keeps rising in the country.   For example, the Infectious Disease Surveillance Center reports that the 27 percent of the elderly were vaccinated for influenza during its season in 2001-2002.   In the following two-year period, however, the figure rose up to 35 percent.   Moreover, it reached 45 percent in 2003 and 2004 (17).   Nevertheless, the proportion of inoculation with pneumococcal vaccine, in contrast, remains low.   It was only 0.1 percent.   In contrast, according to the data from the Centers for Disease Control (CDC) in the United States, the proportion of inoculation with pneumococcal vaccine in the USA was 45 percent (5).

A vaccine activates the immune system for a specific disease through introduction of an antigen to the body.   Preventive effects of vaccines against some viral diseases, such as smallpox, measles, mumps, rubella, and chickenpox, are without any doubt substantial.   As for influenza vaccines, previous studies also clearly indicate a firm effectiveness of the vaccines in reducing not only the number of deaths, but also the period of hospitalization (1)(2)(10)(27).   For instance, as part of preventive efforts, many studies find influenza vaccination among elderly people valuable as well as cost-effective.   Gross et al., in their meta-analysis, found that influenza vaccination is an indispensable part of caring for people over 65 years of age (14).

However, there have been controversies regarding the cost-effectiveness of pneumococcal vaccines (9)(11).   Jonkers and Boersma from Netherlands stated that there was adequate evidence suggesting the potency of pneumococcal vaccines against invasive infections (19), although, in their study, the question as to the combined effects of influenza and pneumococcal vaccines remained unanswered.   Moreover, in 2004, Christenson et al., in their large cohort studies (N=258,754), found that utilization of influenza and

pneumococcal vaccines jointly among the elderly population had additive preventive effect in reducing hospital admissions for influenza and pneumonia (7).   However, these vaccines are not without side effects, at least for some people.   The possible side effects of influenza vaccination include soreness, fever, aches, and, in rare cases, severe allergic reactions and paralytic illness (Guillain-Barre Syndrome).   As for pneumococcal vaccines, only mild side effects, if any, have been reported: e.g., redness or pain.   In short, severe side effects from both of these vaccines have rarely been reported.   Moreover, influenza and pneumococcal vaccinations can safely be administered simultaneously (16).

MATERIALS AND METHODS

Given the above circumstances surrounding influenza, pneumonia, and their vaccinations in Japan particularly for the elderly, we applied a set of data from a cohort study in Sweden(7), and conducted a cost-effectiveness analysis.

Cost-effectiveness Analysis (CEA): background and definition

A cost-effectiveness analysis refers to a method of analysis for evaluating the balance between cost and clinical benefit in order to accomplish the effective use of resources to be consumed in health care.   Preconditioning the difference in clinical efficacy, it assesses the difference in cost.   If no difference in clinical benefit is observed between two groups, cost minimization analysis (CMA) is conducted in terms of finance.   Generally speaking, however, a new technology is usually more expensive than a conventional one, whereas more benefit is obtained for health.   Society often faces a dilemma whether we can afford the incremental cost to obtain the incremental benefit.   The CEA, not CMA, is a quantitative solution to illuminate how much the new technology is affordable for the society.   Therefore, the CEA is an international standard for evaluating a healthcare program in societal perspective.

In this study, since the cohort study with reliable evidence from Sweden, which had confirmed the presence of difference in effectiveness, was made available, a CEA was performed in spite of the insufficient availability of data in Japan. The first reason why we take such a bridging study is that we assume the validity of an equivalent extent may be expected in Japan as well as Sweden, even though questions on the difference caused by ethnic factors remain to be answered in the future.   Secondly, although we are of the opinion that population-based epidemiologic studies are of tremendous importance and should be prioritized, we are not at the position that one should wait for sufficiently reliable epidemiologic data from own country, and that cost-effectiveness analysis should not be conducted unless such data are available, because of the limited availability of reliable data in Japan.   Such a position to wait dose not necessarily come to the benefit in public health, because epidemiologic data alone are not sufficient to influence decision-makers who seek the evidence of socio-economic justification. The third, in order to surmount the uncertainties with regard to insufficient data in Japan, we can adopt the method of Monte Carlo simulation, in which random variables under uncertainly can be fitted in the model in scientific and quantitative manners.

Modeling and Parameters

In order to estimate the social costs and benefits, we envisaged three vaccination strategies for 100,000 elderly persons: (i) no vaccination, (ii) influenza vaccine only, and (iii) influenza and pneumococcal vaccines combined.   Based on the real situation, it is likely that a patient who receives a pneumoccocal vaccine has already been vaccinated with influenza vaccine.   In line with this fact, pneumococcal-vaccine-only approach is not included in this study.

In Fig.1, a decision tree delineating the above-mentioned three scenarios with regard to the vaccinations was developed to visually display the structure of paths involved.   In this study, the diagnoses of influenza and pneumonia, respectively, were made according to the end-point diagnoses before being administered to a hospital (at the second depth of the decision tree in Fig.1).   For instance, if a person gets infected with influenza at first and then successively pneumonia, the latter diagnosis, i.e., pneumonia, is assigned to the end-point diagnosis.   In other words, only one end-point diagnosis was made for cases involving multiple episodes or both of the diseases.   Consequently, the notation with "pneumonia" in Fig.1 includes different kinds of pneumonia such as pneumococcal pneumonia, pneumonia induced by influenza, and pneumonia caused by miscellaneous etiology.

The following formulas materializing two concepts, a ratio and an incremental ratio, were employed to evaluate the cost-effectiveness of vaccination:

a) Cost-effectiveness ratio (CER) (a comparison with non-vaccinated strategy)

$$CER_{vaccinated} = \frac{C_{vaccinated} - C_{non}}{YOLS_{vaccinated}} \qquad (A),$$

In the context of this study, CER is the amount of Japanese yen, which is required to obtain a unit of health effect, which, in this case, is one year of life saved (YOLS).

b) Incremental cost-effectiveness ratio (ICER) (a comparison of influenza-vaccination-only with the combined approach of both influenza and pneumococcal vaccines)

$$ICER_{combined} = \frac{C_{combined} - C_{influenza}}{YOLS_{combined} - YOLS_{influenza}} \qquad (B).$$

ICER is the ratio of cost difference between two vaccination strategies to the difference in effectiveness, i.e., YOLS, in the given strategies.

The "C" denotes the total costs of the strategies.   The total cost can be summarized formulaically as follows:

Total cost = vaccination cost + not inpatient cost   + inpatient cost + medical treatment cost till death + cost from loss of productivity

Health outcomes of effectiveness are measured by years of life saved, which refers to the total number of life years gained through avoidance of deaths, which, in turn, resulted from receiving vaccinations.   It is formulated as follows:

YOLS = the number of death avoidances by vaccination $\times$ life expectancy of people over 65 years of age

In the above-mentioned three scenarios (i), (ii), and (iii), it is important to note that if the formula (A) is used to estimate the first scenario (i), both the numerator and the denominator would be equal to zero, thereby making it impossible to have a CER.   Hence, the formula (A) is applied to calculate the CERs of the scenarios (ii) and (iii): the former is to evaluate the influenza-vaccine-only approach and the latter for the combined approach of influenza and pneumococcal vaccines.   The formula (B), on the other hand, is employed to estimate ICER of the combined vaccination in comparison with the influenza-vaccine-only approach.
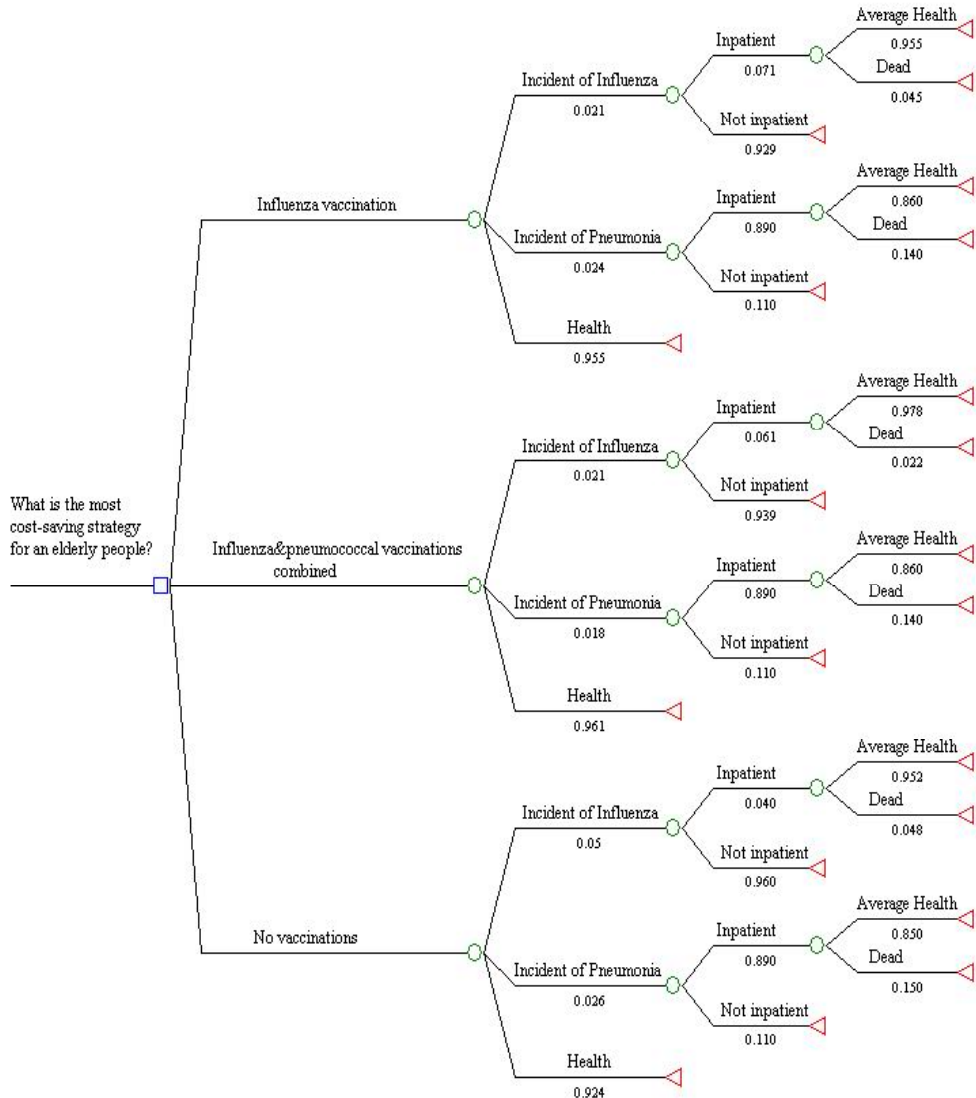
FIG. 1. The decision tree of influenza/pneumococcal vaccination for elderly people in Japan.

The decision tree representation, flowing from left to right, of three alternative strategies involving influenza and pneumococcal vaccinations. The immediate decision to choose from one of the three strategies is represented by the square on the left-hand side(□: decision node), while ellipsoids to the right stand for the events caused by chance(○: chance node), whose branches are mutually exclusive. Hence, the numeral assigned to each branch coming out of one chance node represents a probability of the event assigned to each branch. To keep the mutual exclusiveness of probability, the numerals assigned at the right-side of one chance node must be equal to one when summed them up summed up to 1. (For example, the sum of the numerals such as 0.021, 0.024, 0.955 comes to 1 at the chance node uppermost in the second depth.) Lastly, the triangular shape represents end node, each of which is a terminal point of respective strategy. The probabilities shown were calculated using available data (7)(23).

Validation of Cost

Categories and estimates of key costs have been constructed for this study as shown in Table I. Japanese Yen (JPY) is used as a currency for costing. (Note: one US dollar is almost equivalent to 120 JPY in our study.)

1) Vaccination cost

Based on Immunization Law in Japan, starting in 2001, people over 65 years of age can be inoculated with the influenza vaccine for 1,000 JPY.   Without any financial assistance, a person wishing for the same vaccine would pay 4,300 JPY (28).   In this study, the cost of the vaccine without financial assistance from the public sector is taken into account with respect to the social cost.   As stated earlier, when it comes to vaccines for pneumococcal disease, however, there is no public funding available to support the elderly in Japan.   The fee for the pneumococcal vaccine without public assistance is 6,000-9,000 JPY, which is the amount that an elderly person wishing for this inoculation would pay from his/her own pocket.

2) Cost of medical treatment

This category of cost refers to the expense that is spent for treating people who are not hospitalized, and also inpatients suffering from influenza and pneumonia.   The data from the Ministry of Health, Labour, and Welfare on acute upper respiratory infections for the year 2002 were used to approximate the cost of care for influenza.   For the same disease, the average cost for outpatient visit and over the counter (OTC) (assumed as 2,000 JPY) was calculated using the data, and it was estimated to be 6,238 JPY.   The cost to treat an inpatient suffering from influenza was assumed as 201,664 JPY.   For pneumonia, an outpatient treatment cost was reckoned to be about 24,964 JPY, while the hospitalization fee was estimated to be 335,578 JPY.   Based on the study conducted by Okubo and Hoshi, 1,000,000 JPY was estimated for the cost of medical treatment for influenza till death (28), and the same estimate was adopted for the cost of treating pneumonic patients who eventually died.

3) Loss of productivity due to hospitalization

In Japan, about 20 percent of people over 65 years of age are employed.   It is important to heed that when one is hospitalized or incapacitated, one inevitably loses his/her productivity, which results in absence of economic output to the society, not to mention the cost for the patient himself/herself who may not have income in the meantime.   From a societal perspective, the lack of labor is a cost to the society as well as to the individual. Regarding the average wage of the aged, the data in the Basic Survey on Wage Structure 1999 Census was employed to obtain an estimate: the amount is 535 JPY per hour.   The estimate on average working time is set at 153.1 hours per month.

According to the Survey of Medical Care Activities in Public Health Insurance 2002, the average length of hospitalization for pneumonia was 43.3 days, during which a hospitalized elderly person infected with pneumonia would miss his/her work.   For influenza, however, the average length of hospitalization for acute upper respiratory infections (13.3 days) was used as a substitute.   No outpatient visit of the elderly who received vaccination was assumed, because of the activated immune system.

The Japanese Respiratory Society published pneumonia prevention and treatment guidelines for adults (2000) and hospitals (2002).   Nonetheless, they contain neither data nor information on the ailment from the perspective of health economics.   They, however, contain information about a short-term patient survey carried out by the Ministry of Health, Labour, and Welfare.   Our estimates related to pneumonia, such as the total medical cost,

hospital admission criteria, medical cost due to hospitalization, and outpatient medical cost, are based on the Survey of Medical Care Activities in Public Health Insurance 2002.

TABLE 1. Key Costs and assumed values

Cost	Base Estimate (JPY)	Reference No.
Cost of influenza vaccine	4,300	(28)
Cost of pneumococcal vaccine	7,000	Assumed
Inpatient cost of influenza	201,664	(21)
Inpatient cost of pneumonia	335,578	(21)
Cost of influenza (not inpatient)	6,238	(21)
Cost of pneumonia (not inpatient)	24,964	(21)
Medical treatment cost till death	1,000,000	(28)
Hourly wage of employed elderly people	535	(25)

The table shows the estimated or assumed costs of vaccinations, treatments, and hourly wage of the elderly.

Simulation analysis

In order to assess the probable range of outcomes, computing simulations were conducted. Using the software called Crystal Ball 2000 Professional Edition (v5.2), which enables various computing simulations, the above-mentioned algorithms and the estimates were applied to carry out the Monte Carlo simulation, through which pseudo random numbers for multiple scenarios were generated. It allowed for the quantification of uncertain variables. The variables as well as constants used in the simulation are listed in Table II and III. The variables were assumed to be in accordance with normal distributions. Under these conditions, the simulation was repeated with the trials of 10,000 times. Utilizing the Monte Carlo simulation, a sensitivity analysis was also conducted.

TABLE 2. Variables used in simulation with initial values

Variables	Vaccination Strategies			Assumed distribution	Reference No.
	Influenza vaccination only	Combined vaccinations	No vaccination		
Mortality of inpatients with influenza	0.045	0.022	0.048	Normal	(7)
Hospitalized proportion of incident with influenza	0.071	0.061	0.040	Normal	(7)
Incident probability of Influenza	0.021	0.021	0.050	Normal	(7)
Mortality of inpatients with pneumonia	0.140	0.139	0.150	Normal	(7)
Hospitalized proportion of incident with pneumonia	0.890	0.890	0.890	Normal	(23)
Incident probability of pneumonia	0.024	0.018	0.026	Normal	(7)
Hospitalization days of influenza	13.3days	13.3days	13.3days	Normal	(23)
Hospitalization days of pneumonia	43.3days	43.3days	43.3days	Normal	(23)

The table shows 8 variables for each strategy used in the Monte Carlo simulation. These were adopted from previous studies, whose reference numbers (initial values for the simulation) are indicated in the table. Utilizing these values, the Monte Carlo simulation repeatedly runs generating a value for each variable in accordance with the normal distribution assumed in computing.

TABLE 3. Constants used in simulation

Constants	Base Estimate	Reference No.
Labour force participation rate	20.2%	(34)
Life expectancy of aged≥65yrs people	13.3years	(28)
Monthly working time of elderly people	153.1hours	(24)

The table shows the constants, showing the estimates of 3 parameters. These constants, in conjunction with the variables in TABLE 2, are used in the Monte Carlo simulation.

RESULTS

The result of the Monte Carlo simulations for the three strategies was shown in Table IV.

According to the results of the simulations, the cost-effectiveness ratio was calculated. For per 100,000 elderly people, the CER of influenza vaccine only was about 516,332 JPY/YOLS. For the combined vaccine strategy, on the other hand, the CER was about 459,874 JPY/YOLS for the same number of elderly people. The smaller CER obtained for the combined strategy in comparison with the influenza-vaccine-only approach indicates the better cost-effectiveness of the combined strategy.

Moreover, the ICER of the combined vaccinations versus the influenza-vaccination-only was 426,698 JPY / YOLS per 100,000 elderly people. It means that the addition of 426,698 JPY to the cost for the influenza-vaccine-only approach would enable the combined vaccine to augment one YOLS for 100,000 elderly people.

As a result of the sensitivity analysis of the Monte Carlo simulation, it was revealed that the most influential factors affecting the outcomes of the simulation were the incident probability of pneumonia and also the hospitalized proportion of incident with pneumonia. The results indicated superior health economic impacts of the combined vaccination over the other alternatives.

TABLE 4. The result of the Monte Carlo simulation for 100,000 people

Strategies	COST (Lower limit, Upper limit)	YOLS (Year)	CER (JPY/YOLS)	ICER (JPY/YOLS)
No vaccinations	1,125,362,258 (639019631, 1737952651)	0	-	-
Influenza only	1,445,642,749 (1006363352, 1987630080)	620.3	516,332	-
Combined	1,896,064,977 (1532818110, 2286978986)	1675.9	459,874	426,698

The table shows the results of the Monte Carlo simulation, encompassing YOLS and the key costs of each of the three alternative strategies. The indicators CER and ICER were calculated with the aforementioned formulas in the rest and the values obtained in the simulation.

DISCUSSION

A society's standard or criteria for hospitalization usually differ from those of another society.   This fact, along with some other factors, does influence the hospitalization rate. For instance, the hospitalization rate from pneumonia in the United Kingdom (UK) was 32 percent, while in the United States of America (USA) it was approximately 20 percent. Nevertheless, the counterpart for Japan was about 70 percent (13).   The sensitivity analysis of the Monte Carlo simulation suggests that such a high proportion of hospitalization from pneumonia in Japan may be carefully reviewed in relation to the benefit of vaccination.

One of the critical challenges that Japan faces is to deal effectively with the low inoculation of pneumococcal vaccine among the elderly.   The high cost of the vaccine, particularly from the standpoint of the consumers, is certainly one of the factors that play a role in the low inoculation rate.   One of the reasons for the high cost may be that there has been no public assistance for the expenses needed to implement a pneumococcal vaccination program.   In turn, one possible explanation for the lack of funding may be that, in some previous studies, the questions with regard to the preventive effects of pneumococcal vaccines remain inconclusive.   In response, this makes policy/decision-makers reluctant to mobilize public funding.   As the Swedish study established the evidence of effectiveness and also, our studies indicate the cost-effectiveness of the combined strategy, it becomes important to increase the inoculation rate for pneumococcal diseases along with that for influenza, while also informing the public about the diseases and the cost-effective approach to tackle the diseases.

Sisk et al. found that pneumococcal vaccination against pneumococcal bacteremia among the elderly was cost-effective: a person over 65 years of age vaccinated with it saved $8.27 and gained 1.21 quality-adjusted days (32).   Since there were no data on pneumococcal bacteremia available in Japan, this study is not inclusive of the possible health-economic outcomes of the disease.   Moreover, although the potency of pneumococcal vaccine may last for five years, the analytical span of this study is set to the period of one year due to the limitation of data availability.   Despite these limitations, it is possible to conjecture that given the cost-effectiveness of pneumococcal vaccination against pneumococcal bacteremia, the inclusion would have beneficial increment to the cost-effectiveness of the combined approach as investigated in this study.

As the results of this study suggest the cost-effectiveness of a joint-vaccination to protect the elderly from influenza and pneumonia, and reaching the decision for allocating funds to launch the joint-vaccination program are the foremost steps to be taken in Japan at this point. After such an achievement is made, it will be necessary to address the questions as to how it would be possible to promote and encourage the elderly to take the vaccines.   These questions have been addressed by some researchers in other countries.   For instance, While et al. indicated that tactics such as flyers, personal invitations, and doctors' recommendations were efficient to enhance the proportion of receiving inoculation with the vaccination (37). In addition, one randomized controlled study conducted by Berg et al. in the USA found that direct mail-marketing, encouraging the recipients to receive vaccinations for influenza and pneumococcal disease, worked successfully and increased the vaccination rate as compared to the control group (4).   It is also important not only for physicians or professionals in the field of healthcare, but also for policy/decision-makers to be sensitive to the specific needs of the elderly, taking into account such factors as their socio-economic status, psychosocial needs, their opinions or beliefs about their own lives as well as health.   The health and well-being of the elderly and cost-effectiveness are not mutually exclusive.   It is important

also to note that cost-effectiveness, as described in this paper, is different from cost-saving. In particular, the strategy (iii) will be more costly as compared to the strategy (ii). Nevertheless, the effectiveness obtained from the strategy (iii) is more beneficial than that of the strategy (ii) despite the cost constraint required to implement (iii).

Our study, of course, has limitations which include the structure of decision tree for analysis, limited availability of data assigned to the decision tree, availability and reliability of clinical/epidemiological data for pneumococcal vaccination in Japan, and so on. The Monte Carlo simulation is one of the therapeutic treatments and methods to overcome the limitations of data including cost measurement.

In Japan, it is estimated that the number of people over the age of 65 will reach 31,880,000 by the year 2015. At the current rate, it is evident that social as well as economic needs for this population group will be enormous. In particular, health care costs related to influenza and pneumonia for this specific population in the future will be more demanding and certainly require a cost-effective, as well as efficient, approach. In conclusion, it was suggested that the combined use of influenza and pneumococcal vaccines should be adopted for the elderly with respect to increasing the benefit in public health.

ACKNOWLEDGEMENTS

REFERENCES

1. **Allsup, S., Gosney, M., Haycox, A., Regan, M.** 2003. Cost-benefit evaluation of routine influenza vaccination in people 65-74 years of age. Health Technol Assess. **7**:1-65

2. **Allsup, S., Gosney, M., Haycox, A., Regan, M.** 2004. Is influenza vaccination cost effective for healthy people between ages 65 and 74 years? A randomized controlled trial. Vaccine. **16**:639-645

3. **Barros, M.M., Cartagena, S.C., Bavestrello, F.L.** 2005. Prevention of community-acquired pneumonia in adults. Revista Chilena de Infectologia. **22**:67-74

4. **Berg, G.D., Thomas, E., Silverstein, S., Neel, C.L., Mireles, M.** 2004. Reducing medical service utilization by encouraging vaccines: randomized controlled trial. American Journal of Preventive Medicine. **27**:284-288

5. **Centers for Disease Control and prevention**: 1998. Influenza and pneumococcal vaccination levels among adults ≥65 years. MMWR. **47**:797-802

6. **Chen YH, Liou SH, Chou CC, Su WL, Loh CH, Lin SH.** 2004. Influenza and pneumococcal vaccination of the elderly in Taiwan. Vaccine. **22**:2806-2811.

7. **Christenson, P., Hedlund, B., Lundbergh, J., and Ortqvist, A.** 2004. Additive preventive effect of influenza and pneumococcal vaccines in elderly persons. Eur Respir J. **23**:363-368.

8. **Christenson, P., Lundbergh, J., Hedlund, B., and Ortqvist, A.** 2001. Effects of a large-scale intervention with influenza and 23-valent pneumococcal vaccines in adults aged 65 years or older: a prospective study. Lancet. **357**:1008–1011.

9. **De Graeve D, Lombaert G, Goossens H.** 2000 Cost-effectiveness analysis of pneumococcal vaccination of adults and elderly persons in Belgium. Pharmacoeconomics. **17**:591-601.

10. **Fedson, D.S.**, 1996. Evaluating the impact of influenza vaccination: A North American perspective. Pharmacoeconomics. **9**:54-61

11. **Fedson, D.S.**, 1997. Pneumococcal vaccination: four issues for western Europe. Biologicals. **25**:215-219.

12. **Fletcher**, **T.J., Tunnicliffe**, **W. S., Hammond, K.**, **Roberts, K.**, **Ayres, J.G**. 1997. Simultaneous immunisation with influenza vaccine and pneumococcal polysaccharide vaccine in patients with chronic respiratory disease. British Medical Journal. **314**:1663.

13. **Fukuda,Y., Yanagihara,K., Kawano,s.** 2004. Haienn no Iryo Keizai. Geriat. Med. **42**:587-592. [in Japanese] [Health economics of pneumonia (Title translation by the authors)]

14. **Gross, P.A., Hermogenes, A.W., Sacks, H.S., Lau, J. La vandowski RA.** 1995. The efficacy of Annals of Inter influenza vaccines in elderly persons: A meta-analysis and review of the literature. Intern Med. **123**: 518-527.

15. **Hedlund, J., Christenson, B., Lundbergh, P., Ortqvist, A.** 2003. Effects of a large-scale intervention with influenza and 23-valent pneumococcal vaccines in elderly people: a 1-year follow-up. Vaccine. **21**:3906-3911.

16. **Honkanen P.O., Keistinen, T., Kivela, S.L.** 1996. Reactions following administration of influenza vaccine alone or with pneumococcal vaccine to the elderly. Arch Intern Med. **156**:205-208.

17. **Infectious Disease Surveillance Center of Japan** 2004.The Topic of This Month. **25**:297 Web information: http://idsc.nih.go.jp/iasr/25/297/tpc297-j.html

18. **Ishida T, Hashimoto T, Arita M, Ito I, Osaka M.** 1998. Etiology of community-acquired pneumonia in hospitalized patients. A 3-year prospective study. Chest. **114**:1588-1593

19. **Jonkers, R.E., Boersma, W.G.** 2003. Pneumococcal vaccination in adults. Ned Tijdschr Geneeskd. **147**:437-441

20. **Kashiwagi, S.** 1998. Influenza among the elderly. Rinsho to Kenkyu. **75**:74-75. [in Japanese]

21. **Ministry of Health, Labour and Welfare** 2002. Survey of medical care activities in public health insurance. Web information: http://wwwdbtk.mhlw.go.jp/toukei/data/650/2002/toukeihyou/0004469/t0093191/ji41_002.html

22. **Ministry of Health, Labour and Welfare.** 2002.Vital statistics of Japan. Web information: http://www1.mhlw.go.jp/toukei-i/toukeihp/9nenpo_8/deth2.html

23. **Ministry of Health, Labour and Welfare.** 2002. Patient survey. Web information: http://wwwdbtk.mhlw.go.jp/toukei/data/150/2002/toukeihyou/0004584/t0094266/j48_001.html

24. **Ministry of Health, Labour and Welfare.** 2002. Monthly labor survey statistics. Web information: http://wwwdbtk.mhlw.go.jp/toukei/kouhyo/indexkr_1_4.html

25. **Ministry of Labor.** 1999. Basic survey on wage structure. Web information: http://wwwdbtk.mhlw.go.jp/toukei/kouhyo/indexkr_4_5_1.html

26. **Nichol, K.L.** 1999. The additive benefit of influenza and pneumococcal vaccinations during influenza seasons among elderly persons with chronic lung disease. Vaccine **17**:91–93.

27. **Nichol, K.L., Goodman, M.** 2002. Cost effectiveness of influenza vaccination for healthy persons between ages 65 and 74 years. Vaccine. **20**:21-24

28. **Okubo, I., Hoshi, S.** 2002. 65-sai ijyo kourei sha e no Influenza yobou seshy no hiyou kouka bunnseki. [in Japanese]. [Cost-effectiveness analysis of influenza vaccination among the elderly over 65 years of age. (Title translation by the authors)] Web

information: http://mhlw-grants.niph.go.jp/niph/search/NIDD00.do

29. **Postma MJ, Heijnen ML, Jager JC.** 2001. Cost-effectiveness analysis of pneumococcal vaccination for elderly individuals in The Netherlands. Pharmacoeconomics. **19**:215-222

30. **Salo, H., Sintonen, H., Pekka, N.J., Linna, M., Nohynek, H., Verho, J., Kilpi, T.** 2005. Economic evaluation of pneumococcal conjugate vaccinations in Finland. Scand J Infect Dis. **37**:821-832

31. **Shorr AF.** 2005. Preventing pneumonia: the role for pneumococcal and influenza vaccines. Clin Chest Med. **26**: 123-134.

32. **Sisk JE, Moskowitz AJ, Whang W, Lin JD, Fedson DS, McBean AM, Plouffe JF, Cetron MS, Butler JC.** 1997. Cost-effectiveness of vaccination against pneumococcal bacteremia among elderly people. JAMA. **278**:1333-1339.

33. **Socan, M., Frelih, T., Janet, E., Petras, T., Peternelj, B.** 2004. Reactions after pneumococcal vaccine alone or in combination with influenza vaccine. Vaccine. **22**: 3087-3091.

34. **Statistical Survey Department, Statistics Bureau, Ministry of Public Management, Home Affairs, Posts and Telecommunications.** 2003. Labour force participation rate. Labour force by age group and Labour force status. Web information: http://www.stat.go.jp/data/nenkan/zuhyou/y1602000.xls

35. **Tateyama, M.** 2002. Kourei sha haienn no tiryou sennryaku. Geriat Med. **40**:1585-1591. [in Japanese] [Prevention and treatment of pneumonia among the elderly. (Title translation by the authors)]

36. **Weaver M, Krieger J, Castorina J, Walls M, Ciske S.** 2001. Cost-effectiveness of combined outreach for the pneumococcal and influenza vaccines. Arch Intern Med. **161**:111-120.

37. **While, A., George, C., Murgatroyd, B.** 2005. Promoting influenza vaccination in older people: rationale and reality. Br J Community Nurs. **10**:427-430