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Vaccine 30 (2012) 7630–7636

Contents lists available at SciVerse ScienceDirect

Vaccine

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

Effectiveness of an influenza A (H1N1) 2009 monovalent vaccine among Japanese pregnant women: A prospective observational study assessing antibody efficacy

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ARTICLE INFO

Article history:
Received 21 June 2012
Received in revised form 3 October 2012
Accepted 5 October 2012
Available online 18 October 2012

Keywords:
Influenza vaccine
Effectiveness
Pregnant women
Antibody efficacy
Pandemic influenza

ABSTRACT

In order to estimate the effectiveness of an influenza A (H1N1) 2009 monovalent vaccine among pregnant women, we prospectively observed 135 Japanese pregnant women who received an influenza A (H1N1) 2009 monovalent vaccine during November 2009. We calculated an index of "antibody efficacy", in which the medical visits for respiratory illnesses were compared between those with and without post-vaccination hemagglutination inhibition (HI) titer ≥1:40. The product of antibody efficacy and achievement rate is theoretically equivalent to the vaccine effectiveness. Among all subjects, an inverse but non-significant relationship during the epidemic period was observed between post-vaccination HI titer ≥1:40 and medical visits for respiratory illnesses. After stratification by trimester at recruitment, a significant inverse association during the epidemic period was found among subjects in the first or second trimester (antibody efficacy: 91%, vaccine effectiveness: 79%). The influenza A (H1N1) 2009 monovalent vaccine administered in the first or second trimester reduced medical visits for respiratory illnesses among Japanese pregnant women.

1. Introduction

It is widely known that pregnant women are at increased risk of complications from influenza. Severe influenza illness and fatality among pregnant women were observed during the most recent 2009 pandemic of influenza A (H1N1) [1–10], as well as during previous pandemics [11–14]. Even in the inter-pandemic periods, rates of medical visits for acute respiratory diseases attributable to influenza were greater among pregnant women than non-pregnant women [15]. The rate of hospitalization during influenza season due to respiratory illness or acute cardiopulmonary disease increased at the later stages of pregnancy [16,17]. Elevated risk for influenza among pregnant women is likely due to alterations in cardiovascular and respiratory systems, including increased heart rate, stroke volume, oxygen consumption, and decreased lung capacity [18]. Immunologic changes during pregnancy may also contribute to increased susceptibility to influenza viruses, because of suppression of cell-mediated immunity while retaining normal humoral immunity [19].

Several guidelines or statements recommend receiving inactivated influenza vaccination during any trimester of pregnancy [20,21]. Previous studies showed adequate immune response and safety of maternal influenza vaccination [22–26]. A recent publication also confirmed that immunogenicity of an influenza A (H1N1) 2009 monovalent vaccine was excellent in Japanese pregnant women [27,28]. Regarding the vaccine effectiveness, there has been a growing number of reports that influenza vaccination during pregnancy was associated with a reduced risk of influenza virus infection or hospitalization in infants [29–32]. On the other hand, few studies have assessed the effectiveness of maternal influenza vaccination in protecting pregnant women from influenza-related outcomes, and the findings were inconsistent [29,33]. Because the current recommendation with regard to influenza vaccination during pregnancy seems to be dependent on health impact, immunogenicity and safety data, additional findings of vaccine effectiveness in pregnant women are needed to support the recommendation.

During the 2009 influenza pandemic, the Ministry of Health, Labor and Welfare in Japan stated that pregnant women were one of the initial target groups for receiving a 2009 influenza A (H1N1) monovalent vaccine. This statement placed ethical

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http://dx.doi.org/10.1016/j.vaccine.2012.10.027

constraints on the use of a randomized controlled trial to evaluate efficacy of maternal immunization. It was also not easy to obtain a sufficient number of unvaccinated pregnant women to evaluate vaccine effectiveness, in which the outcome occurrence is compared between vaccinee and non-vaccinee, because of the vaccination efforts of both pregnant women and obstetricians. An index of "antibody efficacy", in which the outcome occurrence is compared between those with and without a protective level of post-vaccination hemagglutination inhibition (HI) titer, has been shown to be a valid alternative to evaluate vaccine effectiveness [34–36].

An influenza pandemic is likely to provide an ideal opportunity for evaluating influenza vaccine effectiveness. However, if a large-scale pandemic occurs, the anticipated vaccine supply is substantially delayed. On the other hand, the pandemic may subside when the vaccine is sufficiently distributed. Such trade-off might partly explain the fact that, to the best of our knowledge, there has been no prospective study of vaccine effectiveness among pregnant women during the 2009 influenza pandemic. In this prospective observational study assessing antibody efficacy, our objective was to estimate the effectiveness of an influenza A (H1N1) 2009 monovalent vaccine in Japanese pregnant women.

2. Methods

2.1. Study subjects and vaccination

Eligible subjects were pregnant women who were willing to receive an influenza A (H1N1) 2009 monovalent vaccine at two medical institutions in Osaka, Japan, during November 2009. A total of 150 pregnant women were recruited. Subjects were excluded if they had an episode of prior 2009 influenza A (H1N1) infection, an acute febrile illness or signs of severe acute illness at the time of vaccination, a history of anaphylaxis due to vaccine components, or other conditions which precluded them from receiving vaccination. None of the subjects met the exclusion criteria. All subjects gave written consent prior to their participation in this study. The study protocol was approved by the ethics committee of Osaka City University Faculty of Medicine.

During recruitment, from November 7–27, 2009, all subjects received the first dose of subcutaneous injections of an influenza A (H1N1) 2009 monovalent inactivated vaccine into their arms. A 0.5 mL prefilled syringe type vaccine was used (Lot. NM001A, Kitasato Institute, Japan). Each dose contained 15 μg of hemagglutinin antigen. The seed virus was prepared from reassortant vaccine virus A/California/7/2009 NYMC X-179A (New York Medical College, Valhalla, NY) distributed by the Centers for Disease Control and Prevention in the United States (US). The vaccine contained neither preservative (thimerosal) nor adjuvant. During December 3–18, 2009, the subjects received a second dose of vaccine after a 3-week interval from the first vaccination.

As of November 11, 2009, Ministry of Health, Labor and Welfare in Japan stated that one dose of an influenza A (H1N1) 2009 monovalent vaccine was thought to be enough to induce a sufficient immune response for pregnant women. However, this issue was still controversial when we started recruitment. Thus, we asked the subjects in this study to receive vaccination twice.

2.2. Information collection at recruitment and follow-up

A self-administered questionnaire was used to collect a subject's baseline characteristics at recruitment such as age, height and body weight before pregnancy, underlying medical conditions, food/drug allergies, smoking history, number of family members, reproductive history and years of schooling. Underlying medical conditions were defined as chronic pulmonary disease (including asthma), cardiovascular disease (excluding hypertension), renal disease, hepatic disease, hematological disease, diabetes, neuromuscular disease, immunocompromised conditions, malignant tumors, connective tissue disease, or atopy. The subjects were also asked to provide a history of their 2009–2010 seasonal influenza vaccination, their 2008–2009 seasonal influenza vaccination, and a physician diagnosis of influenza during the 2008–2009 season. The obstetrician in charge provided information regarding the subject's gestational age and maternal disorders predominantly related to pregnancy.

We prospectively conducted weekly follow-up surveys using a self-administered postal questionnaire. The subjects were requested to report medical visits for respiratory illnesses and hospitalization until the end of this study (March 28, 2010). In addition, the date of delivery was provided by the obstetrician in charge.

2.3. Serum specimen and HI titer measurement

The subjects provided serum samples at three time points: before vaccination; 3 weeks after the first dose; and 4 weeks after the second dose. Serum was frozen at −80 °C until assayed simultaneously at the Kitasato Institute in February 2010. Serum HI titers were measured using a standard method with the same antigens that were in the vaccine.

In this study population, we confirmed that a single dose of influenza A (H1N1) 2009 monovalent vaccine induced an adequately protective level of immunity in accordance with the international licensing criteria, and that a second dose conferred little additional induction of antibodies [27,37,38]. We therefore compared the outcome occurrence between those subjects with and without an HI titer $\geq$1:40 at 3 weeks after the first vaccination (hereafter referred to as "post-vaccination titer").

2.4. Regional epidemic and observation period

Influenza is designated as one of the target diseases of the sentinel surveillance program in Japan. During 2009, Osaka prefecture had 305 sentinel medical institutions for influenza that should report the number of influenza patients aggregated by sex and age groups. Fig. 1 shows the number of reported influenza patients per sentinel in Osaka prefecture during the study period. Based on the epidemic curve, antibody efficacy was examined for the following three periods: (1) the entire period (from 3 weeks following the first vaccination until March 28, 2010); (2) period A, when the number of reported patients per sentinel was at least one (until February 21, 2010); and (3) period B, when the number of reported patients per sentinel was at least five (until January 31, 2010). All influenza viruses isolated in Osaka prefecture during the period were 2009 pandemic influenza A (H1N1) virus strain.

2.5. Statistical analysis

The outcome measures for this study were medical visits for respiratory illnesses and hospitalization for reasons other than delivery. We considered outcome occurrence from 3 weeks following the first vaccination to March 28, 2010, regardless of the subject's delivery. If a subject experienced the outcome once or more during the pre-specified observation period, we considered the subject as having the outcome occurrence. Logistic regression analyses were employed to estimate odds ratios (ORs) of those with post-vaccination HI titer $\geq$1:40 and the 95% confidence intervals (CIs). An antibody efficacy was calculated as $[1 - \mathrm{OR}] \times 100\%$ [34–36]. The product of antibody efficacy and achievement rate (i.e., the proportion of those who achieved post-vaccination HI titer

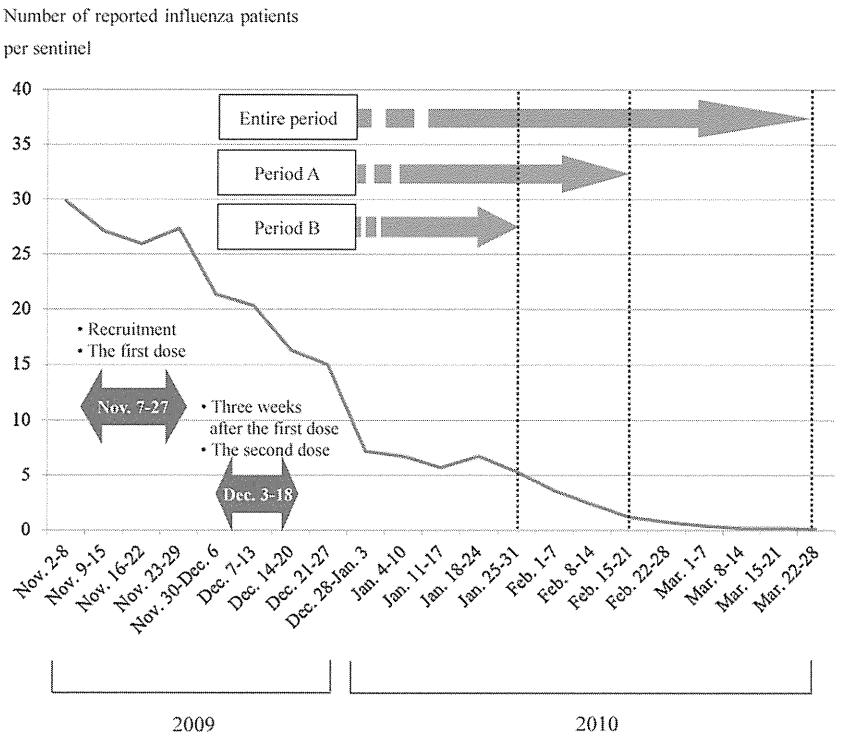

Fig. 1. Number of reported influenza patients per sentinel in Osaka prefecture during the study period. Three observational periods were defined as follows: the entire period, from 3 weeks following the first vaccination until March 28, 2010; period A, until February 21, 2010 (the period during number of reported patients per sentinel ≥1); and period B, until January 31, 2010 (the period during number of reported patients per sentinel ≥5).

≥1:40 among those with HI titer <1:40 before vaccination) is theoretically equivalent to the vaccine effectiveness [35].

The primary multivariate model included adjustments for age (continuous) and trimester (first: <14 weeks/second: 14–27 weeks/third: ≥28 weeks). The fully adjusted model additionally incorporated body mass index (BMI) before pregnancy (continuous), smoking (never smoked/current or former smoking), 2009–2010 seasonal influenza vaccination (yes/no) and physician diagnosis of influenza during the 2008–2009 season (yes/no). Factors included in the multivariate model were those with a *P* value of <0.20 in the univariate analysis irrespective of the observation periods (i.e., the entire period, period A, or period B), as well as clinically important variables from a previous report whether statistically significant or not. All hypothesis testing was conducted assuming a 0.05 significance level and a two-sided alternative hypothesis. SAS software version 9.1 (SAS Institute, Inc., Cary, NC) was used throughout the analyses.

3. Results

Because one subject reported that she experienced a physician-diagnosed influenza A virus infection during the 3 weeks following the first vaccination, the subject was excluded from the analysis. Also excluded were 14 subjects with incomplete weekly follow-up survey data (response rate: 135/149, 91%). Analysis was therefore carried out with 135 subjects. A total of 125 subjects (93%) had an HI titer <1:40 before vaccination. Of these, 109 subjects (87%) achieved a post-vaccination HI titer ≥1:40.

At recruitment, the median age of subjects was approximately 30 years, and approximately half of the subjects were in the third trimester (Table 1). Compared to those with a post-vaccination HI titer ≥1:40, those with a HI titer <1:40 were more likely to report having received a 2009–2010 seasonal influenza vaccine. Most of the subjects did not have underlying medical conditions or maternal disorders predominantly related to pregnancy.

A total of 18 subjects (7 subject in the first or second trimester and 11 subjects in the third trimester at recruitment) reported medical visits for respiratory illnesses (Table 2). These visits occurred during the postpartum period in 9 subjects (1 subject in the first or second trimester and 8 subjects in the third trimester at recruitment), and 5 subjects experienced more than one visit. Compared to subjects with a post-vaccination HI titer ≥1:40, medical visits for respiratory illnesses were frequently found in those with a HI titer <1:40, irrespective of the observation period (19–31% vs. 8–11%, respectively). After stratification by trimester at recruitment, similar findings were obtained among those subjects in the first or second trimester (30% vs. 6–8%, respectively), but not among those in the third trimester (0–33% vs. 9–14%, respectively). Of 11 subjects who experienced hospitalization other than delivery, 3 subjects (1 subject in the first or second trimester and 2 subjects in the third trimester at recruitment) experienced hospitalization during the postpartum period. One subject experienced more than one hospitalization. The number of subjects with hospitalization was too small to conduct multivariate analyses.

Among total subjects, an inverse relationship with marginal significance during the entire period was observed between a post-vaccination HI titer ≥1:40 and a medical visit for respiratory illnesses (fully adjusted OR: 0.28, 95%CI: 0.06–1.24, $P = 0.08$) (Table 3). During period A and period B, a decreased OR was obtained but was not statistically significant (OR: 0.35–0.47). When assessing only the subjects in the first or second trimester at recruitment, an inverse association was more pronounced during all the observation periods, and a lower OR with significance was observed during period A and period B (fully adjusted OR: 0.09, 95%CI: 0.004–0.93). The corresponding antibody efficacy and vaccine effectiveness against medical visits for respiratory illnesses were 91% ($[1 - 0.09] \times 100$) and 79% ($91\% \times 0.87$), respectively. Analysis limited to the subjects in the third trimester was not applicable during period A or period B because of no outcome occurrence.

Table 1
Characteristics of study subjects.

Variable at recruitment	Post-vaccination HI titer[a]		*P* value[b]
	<1:40 (*N* = 16)	≥1:40 (*N* = 119)	
Age (years)	30 (21–37)	31 (17–41)	0.52
Body mass index before pregnancy (kg/m^2)	19 (18–22)	20 (17–31)	0.28
Underlying medical conditions[c] (present)	0 (0)	8 (7)	0.60
Food/drug allergy (present)	2 (13)	24 (20)	0.74
Smoking			
Never	15 (94)	77 (65)	
Former	1 (6)	37 (31)	
Current	0 (0)	5 (4)	0.06
2009–2010 seasonal influenza vaccination (vaccinated)	8 (50)	25 (21)	0.03
2008–2009 seasonal influenza vaccination (vaccinated) – no./total no. (%)	8/16 (50)	45/118 (38)	0.36
Physician diagnosis of influenza during 2008–2009 season (yes) – no./total no. (%)	1/16 (6)	7/117 (6)	1.00
Number of family members	3 (1–5)	3 (1–7)	0.43
Number of past pregnancies	1 (0–4)	1 (0–8)	0.50
Number of past deliveries	1 (0–3)	1 (0–4)	0.46
Period of schooling (years)	14 (10–16)	14 (9–20)	0.33
Trimester			
First	4 (25)	17 (14)	
Second	6 (38)	36 (30)	
Third	6 (38)	66 (55)	0.30
Maternal disorders predominantly related to pregnancy			
Hypertension (present) – no./total no. (%)	0/16 (0)	1/117 (1)	1.00
Anemia (present) – no./total no. (%)	0/16 (0)	4/117 (3)	1.00
Diabetes (present) – no./total no. (%)	0/16 (0)	0/116 (0)	–

HI, hemagglutination inhibition. Values are expressed as median (range) or no. (%), unless otherwise indicated.
[a] HI titer at 3 weeks after the first vaccination.
[b] Continuous variables were assessed by Wilcoxon rank sum test, and categorical variables by Chi-square test or Fisher's exact test.
[c] Chronic pulmonary disease (including asthma), cardiovascular disease (excluding hypertension), renal disease, hepatic disease, hematological disease, diabetes, neuromuscular disease, immunocompromised conditions, malignant tumors, connective tissue disease, or atopy.

Of 135 subjects in this study, 4 subjects did not receive the second dose and 5 subjects did not provide a serum specimen at 4 weeks after the second dose. After excluding these 9 subjects, we examined how the second dose affected the HI titer and the outcomes among 126 subjects. Of 117 subjects who had an HI titer <1:40 before vaccination, 105 subjects (90%) achieved a HI titer ≥1:40 at 4 weeks after the second dose. Thus, achievement rate was slightly higher than that at 3 weeks after the first dose (87%). When HI titer at 4 weeks after the second dose was used for calculating antibody efficacy and the follow-up was started at 4 weeks after the second dose, a decreased OR was observed for medical visits due to respiratory illnesses during period A and period B among the subjects in the first or second trimester at recruitment (age-adjusted OR: 0.29, 95%CI: 0.02–6.77). However, because a shorter observation period resulted in a smaller number of outcome occurrences, CIs were very wide and the fully adjusted model was not fitted.

4. Discussion

To date, this is the first prospective study to explore the effectiveness of an influenza A (H1N1) 2009 monovalent vaccine among pregnant women. Because all the study subjects were vaccinated, effectiveness was estimated using an index of antibody efficacy. Our results showed that the influenza A (H1N1) 2009 monovalent vaccine administered in the first or second trimester reduced medical visits for respiratory illnesses during the epidemic period among Japanese pregnant women. The corresponding antibody efficacy and vaccine effectiveness were 91% and 79%, respectively.

The strength of our study is mainly attributable to the fact that all subjects received an influenza A (H1N1) 2009 monovalent vaccine. The subjects seemed to have equal stimulus to report an outcome occurrence. Observational studies that compare vaccinated and unvaccinated populations are likely to be subject to selection

Table 2
Attack rate for two post-vaccination HI titer[a] levels.

Outcome	Entire period (until March 28, 2010[d])		Period A[b] (until February 21, 2010[d])		Period B[c] (until January 31, 2010[d])	
	<1:40	≥1:40	<1:40	≥1:40	<1:40	≥1:40
Medical visits for respiratory illnesses						
Total subjects	5/16 (31)	13/119 (11)	3/16 (19)	10/119 (8)	3/16 (19)	9/119 (8)
First or second trimester	3/10 (30)	4/53 (8)	3/10 (30)	3/53 (6)	3/10 (30)	3/53 (6)
Third trimester	2/6 (33)	9/66 (14)	0/6 (0)	7/66 (11)	0/6 (0)	6/66 (9)
Hospitalization						
Total subjects	1/16 (6)	10/119 (8)	0/16 (0)	8/119 (7)	0/16 (0)	6/119 (5)

HI, hemagglutination inhibition. Values are expressed as no./total no. (%).
[a] HI titer at 3 weeks after the first vaccination.
[b] Period during number of reported patients per sentinel ≥1 in Osaka prefecture.
[c] Period during number of reported patients per sentinel ≥5 in Osaka prefecture.
[d] The follow-up was started at 3 weeks after the first vaccination.

Table 3
Odds ratio of subjects with post-vaccination HI titer ≥1:40[a] for medical visits due to respiratory illnesses.

	Entire period (until March 28, 2010[d])	Period A[b] (until February 21, 2010[d])	Period B[c] (until January 31, 2010[d])
Total subjects			
Crude OR (95%CI)	0.27 (0.08–0.96)	0.40 (0.11–1.94)	0.35 (0.09–1.75)
Adjusted OR (95%CI)[e]	0.24 (0.07–0.91)	0.41 (0.10–2.07)	0.38 (0.09–1.97)
Adjusted OR (95%CI)[f]	0.28 (0.06–1.24)	0.47 (0.09–2.84)	0.35 (0.06–2.24)
First or second trimester			
Crude OR (95%CI)	0.19 (0.03–1.13)	0.14 (0.02–0.88)	0.14 (0.02–0.88)
Adjusted OR (95%CI)[g]	0.16 (0.03–1.01)	0.13 (0.02–0.83)	0.13 (0.02–0.83)
Adjusted OR (95%CI)[h]	0.16 (0.02–1.34)	0.09 (0.004–0.93)	0.09 (0.004–0.93)
Third trimester			
Crude OR (95%CI)	0.32 (0.05–2.51)	NA	NA
Adjusted OR (95%CI)[g]	0.32 (0.05–2.51)	NA	NA
Adjusted OR (95%CI)[h]	0.36 (0.05–3.30)	NA	NA

OR, odds ratio; CI, confidence interval; HI, hemagglutination inhibition; NA, not applicable.
[a] HI titer at 3 weeks after the first vaccination.
[b] Period during number of reported patients per sentinel ≥1 in Osaka prefecture.
[c] Period during number of reported patients per sentinel ≥5 in Osaka prefecture.
[d] The follow-up was started at 3 weeks after the first vaccination.
[e] Adjusted for age (continuous) and trimester (first/second/third).
[f] Adjusted for age (continuous), trimester (first/second/third), body mass index before pregnancy (continuous), smoking (never smoked/current or former smoking), 2009–2010 seasonal influenza vaccination (yes/no) and physician diagnosis of influenza during 2008–2009 season (yes/no).
[g] Adjusted for age (continuous).
[h] Adjusted for age (continuous), body mass index before pregnancy (continuous), smoking (never smoked/current or former smoking), 2009–2010 seasonal influenza vaccination (yes/no) and physician diagnosis of influenza during 2008–2009 season (yes/no).

biases or confounded by indication [39–41]. However, choosing a randomized controlled trial is ethically unfeasible in most settings in evaluating influenza vaccine efficacy because the US Advisory Committee on Immunization Practices recently recommended universal influenza vaccination for all persons aged ≥6 months [20]. It has been pointed out that an index of antibody efficacy has rarely been used in estimating influenza vaccine effectiveness due to practical difficulties in confirming the strain-specific disease corresponding to each of the vaccine-induced antibodies [35,36]. The 2009 pandemic influenza might have provided a unique opportunity for the index because the influenza A (H1N1) 2009 vaccine was monovalent, and almost all circulating influenza viruses around the world were 2009 pandemic influenza A (H1N1).

Our study findings are limited by several factors. First of all, the influenza epidemic had passed its peak at the time of study recruitment. The majority of subjects in this study acquired protective levels of HI titers, which may have resulted in a low number of outcome occurrences. Another limitation is that sample size was small, because initial vaccine supply was very limited. All outcome occurrences were self-reported, and laboratory-confirmed influenza was not evaluated. Although hospitalizations for reasons other than delivery were considered to be an outcome event in this study, we did not conduct multivariate analyses because of small numbers of these events. Even if the number of events was greater, we would fail to show any impact of higher HI titers on more severe forms of respiratory illnesses because there was no differentiation between hospitalizations for respiratory causes or other non-delivery reasons. Finally, designing the study to enroll non-vaccinated pregnant women would have strengthened our results. However, we were not able to assure recruitment of the same numbers of non-vaccinees as vaccinees due to a nationwide growing tendency to receive an influenza vaccine without delay.

Approximately 25% of the subjects in this study reported medical visits for respiratory illnesses during the entire period. This figure is in agreement with a large population-based cohort study in Canada (25.2%) [17]. Because our study subjects had regular contact with obstetricians via antenatal examination, we cannot rule out the possibility that those with respiratory illnesses, even if mild, were likely to complain to their obstetricians in charge. Provided that such complaints were also reported, medical visits in this study may be over reported. However, all the subjects in this study received the influenza A (H1N1) 2009 monovalent vaccine and did not know their HI titer. The over reporting may, therefore, be non-differential.

Recently, there has been a growing number of reports that influenza vaccination during pregnancy was associated with a reduced risk of influenza virus infection or hospitalization in infants [29–32]. On the contrary, few studies evaluated the effectiveness of maternal influenza vaccination in protecting pregnant women from influenza-related outcomes. In a randomized controlled trial in Bangladesh, a developing country where the circulation of influenza virus is perennial because of the tropical location, maternal influenza vaccination significantly prevented one-third of febrile respiratory illnesses among the mothers. The vaccine effectiveness against clinic visits with respiratory illness was 25%, but not statistically significant [29]. A large observational study using data from Kaiser Permanente Northern California across five influenza seasons (1997–1998 to 2001–2002) found that the risk of medical visits for influenza-like illness was not different between women who received influenza vaccine during pregnancy and women who did not receive vaccine. The number of subjects with hospitalization for influenza or pneumonia was extremely rare in the population [33].

In this study, a significant antibody efficacy was observed among pregnant women in the first and second trimester at recruitment, but not among those in the third trimester. None of the previous studies evaluated the influenza vaccine effectiveness among pregnant women separately by trimester. We confirmed that, in this study population, a single dose of influenza A (H1N1) 2009 monovalent vaccine induced sufficient immunity in accordance with the international licensing criteria, and that the responses were robust irrespective of trimester [27,37,38]. Regarding the subjects in the third trimester at recruitment, we found that the majority of medical visits for respiratory illnesses occurred during the postpartum period (8 out of 11 subjects, 73%). In contrast, the corresponding figure was quite low among subjects in the first or second trimester at recruitment (1 out of 7 subjects, 14%). Postpartum women might be less susceptible to influenza illness than pregnant women, although it has been reported that postpartum women, as well as pregnant women, are at increased risk for severe influenza infection or influenza-related complications [2,5,10,14,20].

We found that, compared to those with a post-vaccination HI titer ≥1:40, those with a HI titer <1:40 were more likely to report having received a 2009–2010 seasonal influenza vaccine. Although this is the subject of another article previously published [27], it is worth considering along with recent reports to assess whether the immunogenicity of seasonal and A (H1N1) 2009 monovalent vaccine is affected by the order of vaccination in healthy adult volunteers. In a randomized controlled trial from China, compared to administration of A (H1N1) 2009 monovalent vaccine followed by seasonal vaccination, the immune responses to pandemic H1N1 antigen was significantly reduced when the seasonal vaccine was administered prior to the A (H1N1) 2009 monovalent vaccination. The order of vaccination did not affect the response to seasonal H1N1 antigen [42]. Another randomized controlled trial in Japan reported that immunogenicity to pandemic H1N1 antigen was inhibited among subjects with seasonal vaccination followed by A (H1N1) 2009 monovalent vaccination but not among subjects with vaccinations in the reverse order [43]. Immunological mechanisms for this interference are still unclear, although several authors discussed a potential explanation, the phenomenon of "original antigenic sin" [42–44].

In conclusion, we found that an influenza A (H1N1) 2009 monovalent vaccine administered in the first or second trimester reduced medical visits for respiratory illnesses among Japanese pregnant women. Given the limited data currently available, further accumulation of evidence regarding vaccine effectiveness, immunogenicity and safety among pregnant women is needed to promote maternal influenza vaccination strategy.

Acknowledgments

The authors would like to thank all the medical staff of the Department of Obstetrics and Gynecology, Osaka City Juso Hospital and the Kawabata Women's Clinic for their valuable contribution during the data collection and data management.

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, Labor and Welfare, Japan (grant H20-SHINKO-IPPAN-002).

Contributors: Dr. Fukushima had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Conception and design*: Fukushima, Ohfuji, Yoshida, Maeda, and Hirota. *Acquisition of data*: Fukushima, Ohfuji, Deguchi, Kawabata, Hatayama, and Yoshida. *Analysis and interpretation of the data*: Fukushima, Ohfuji, Maeda, and Hirota. *Drafting the article*: Fukushima. *Revising it critically for important intellectual content*: Fukushima, Ohfuji, Deguchi, Kawabata, Hatayama, Yoshida, Maeda, and Hirota. *Final approval of the version to be submitted*: Fukushima, Ohfuji, Deguchi, Kawabata, Hatayama, Yoshida, Maeda, and Hirota. *Conflict of interest*: None declared.

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PEDIATRICS INTERNATIONAL Official Journal of the Japan Pediatric Society

Pediatrics International (2012) **54**, 758–761 doi: 10.1111/j.1442-200X.2012.03691.x

Original Article

IgG3 deficiency and severity of 2009 pandemic H1N1 influenza

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Abstract ***Background***: The severity of the 2009 pandemic H1N1 influenza (H1N1 pdm 09) in immune deficient children is unknown. The aim of the present study was to investigate this in a case of complete IgG3 deficiency complicated by pneumonia and asthma attack.

Methods: The clinical parameters of the IgG3 deficiency patient were compared with those of four control patients using 95% confidence intervals. These control patients were selected from 71 patients admitted due to pneumonia or bronchitis caused by H1N1 pdm 09, and were chosen according to age, absence of pretreatment with oseltamivir before admission, presence of a past history of asthma, use of antibiotics, and combination of inhalation of a beta2 agonist and treatment with i.v. methylprednisolone for asthma attack.

Results: The IgG3 deficiency patient had significantly longer duration of admission and period of oseltamivir, with a significantly decreased pulse oxygen saturation and increased maximum serum C-reactive protein, creatine kinase and urinary excretion of β2-microglobulin/creatinine, compared with the controls ($P < 0.05$).

Conclusions: Complete IgG3 deficiency is possibly associated with severity of the clinical course of pneumonia and asthma attack in children suffering from H1N1 pdm 09.

Key words admission duration, asthma, IgG3 deficiency, influenza H1N1 pdm 09, pneumonia.

The 2009 pandemic H1N1 influenza (H1N1 pdm 09) was first reported in Mexico at the end of March 2009,[1] and spread all over the world in approximately 2 months as a new pandemic influenza. With this new influenza infection, a high incidence of admission of respiratory failure patients was reported compared to seasonal influenza in many countries including Mexico,[2] and the USA.[3] Especially, it was noted that young people, including small children, were admitted due to pneumonia in the early stage of infection.[4] The reason for this was speculated to be the strong invading characteristics of the pandemic influenza virus in the lungs.[5] Recently, host adaptive immune deficiency was reported in severe pandemic influenza.[6] Gordon *et al.* reported that severe H1N1 infection was associated with IgG2 deficiency.[7] The severity of the H1N1 pdm 09 in children with an IgG deficiency, however, is unknown. Here, we report a case of complete IgG3 deficiency complicated by pneumonia and asthma attack caused by the H1N1 pdm 09.

Methods

A total of 71 Japanese patients (46 male, 25 female) were admitted to Minoh City Hospital suffering from mild pneumonia caused by influenza-like illness (ILI) between September 2009 and January 2010, including one patient with complete IgG3 deficiency. The patient was a 5-year-old boy who had a past history of asthma. He was previously healthy and had no history of admission. All of the patients were found to be infected with influenza A on immunologic rapid test. The diagnosis of influenza A was made using the Espline immunologic rapid test (Fujirebio, Tokyo, Japan). We measured the serum levels of IgG subclasses in 45 of these patients using nepherometry (BML, Japan). The presence of pneumonia was confirmed by chest roentgenogram on admission. We treated all patients with an anti-influenza neuraminidase inhibitor (oseltamivir or zanamivir) and Mao-to.[8] Mao-to is a Japanese traditional herbal medicine, which was reported to be effective against seasonal influenza infection.[8] This protocol was approved by the review board of the Clinical Ethics Committee of Minoh City Hospital.

Parameters investigated in the aforementioned 45 patients included presence or absence of >38°C fever; cough; nausea/vomiting; pulse oxygen saturation (SpO_2) level; and duration from the onset of clinical signs and symptoms of influenza to admission. The latter included the worst clinical data on admission, for example maximum body temperature, respiration and pulse rate, the time necessary for defervescence below 37.5°C and the period of oseltamivir. We also investigated laboratory data such as white blood cell count (WBC) with the percentage of granulocytes, platelet number, biochemical markers including serum C-reactive protein (CRP), lactate dehydrogenase (LDH), creatine kinase (CK), IgG subclasses (IgG1, IgG2, IgG3 and IgG4) and urinary β2-microglobulin/urinary creatinine.

We selected four clinical controls who were matched to the present complete IgG3 deficiency patient according to age,

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Received 15 February 2011; revised 27 February 2012; accepted 1 June 2012.

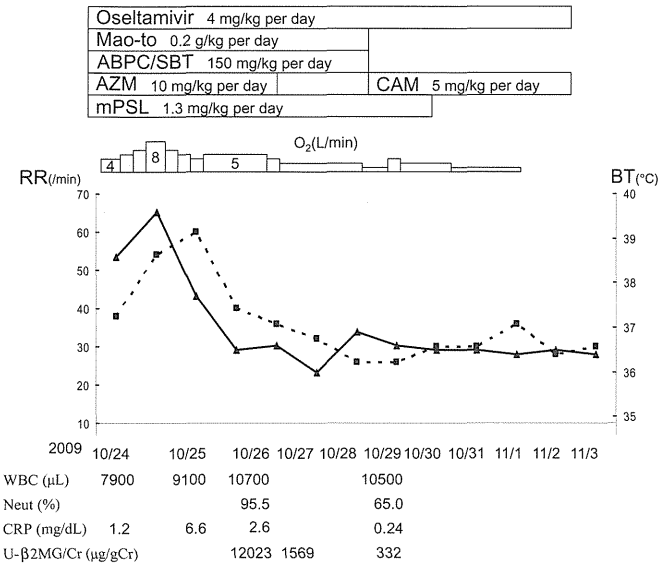

Fig. 1 Clinical course. Oseltamivir, mao-to, antibiotics and steroid hormone were given. Note that the patient needed high-volume oxygen at first and low-volume oxygen was continued for 1 week to maintain SpO_2 >95%. ABPC, aminobengel penicillin; AZM, azisuromicine; BT, body temperature; CAM, clarithromycine; CRP, C-reactive protein; mPSL, methylprednisolone; neut, neutrophils; RR, respiratory rate; SBT, sulbactum; SpO_2, pulse oxygen saturation; U-β2MG, urinary β2-microglobulin. ··■··, respiratory rate; —▲—, body temperature.

absence of pretreatment with a neuraminidase inhibitor before admission, presence of a past history of asthma, use of antibiotics either orally or i.v. and therapy for asthma on admission such as inhalation of a beta2 agonist combined with infusion of methylprednisolone for asthma attack. We then calculated 95% confidence intervals (95%CI) for each parameter to compare the corresponding data with those of the present IgG3 deficiency patient. Data are given as mean and 95%CI using JMP 8.02 (SAS, Cary, NC, USA)

Results

Complete IgG3 deficiency: Clinical profile

The patient was a 5-year-old boy. He was brought to a family doctor complaining of high fever and severe cough on 23 October 2009. Physical examination showed retraction with a decreased SpO_2 level of 92%. An influenza rapid test was negative. He was the first child of healthy and unrelated parents without a past history of recurrent infectious diseases such as pneumonia or sinusitis. He suffered from asthma, and serum IgE was found to be elevated (447 UA/mL). He was referred to Minoh City Hospital for pneumonia treatment on 24 October. On admission, he was pale and a roentgenogram indicated bilateral pneumonia (Fig. 1). Venous gas analysis was as follows: pH 7.376; PCO_2, 31.7 mmHg; HCO_3, 18.2mEq/L, base excess, 5.7. We gave him a maximum 8 L/min oxygen to keep SpO_2 >95%. On 25 October an immunologic rapid test for influenza showed influenza A, which proved to be the H1N1 pdm on polymerase chain reaction. The worst data for WBC and percentage of granulocytes were 10 700/μL and 95.5%, respectively, with normal platelet levels. With regard to biochemical markers, maximum CRP was 6.6 mg/dL with normal levels of LDH, CK, Na and albumin. In contrast, maximum urinary β2-microglobulin/urinary creatinine was 12 023 μg/gCr (Fig. 2). On 26 October, serum IgG, IgM and IgA were 718 mg/dL, 133 mg/dL and 168 mg/dL, respectively. Serum concentration of IgG subclasses was as follows: IgG1, 393 mg/dL; IgG2, 204 mg/dL; IgG3, undetectable (<4 mg/dL) and IgG4, 13 mg/dL. IgG1, IgG2 and IgG4 were within normal range according to the corresponding Japanese data.[9] No pathological bacteria were isolated from the nasopharyngeal specimen on culture. Also, a rapid test for pneumococcus infection was negative for the urine specimen. No bacteria were isolated from blood specimen. We reconfirmed a positive result for immunologic rapid test for influenza A on 29 October, but we had no data to prove prolonged viral shedding thereafter.

On admission, treatment was started with a combination of a neuraminidase inhibitor (oseltamivir), Japanese herbal medicine (Mao-to),[8] several antibiotics, inhalation of a beta2 agonist in a continuous nebulized formulation and i.v. methylprednisolone. Following this, body temperature returned to normal within 1 day, but it took a total of 3 days for respiration rate to normalize. Also, low-volume oxygen was given for 1 week because of the asthma attack and the patient had to stay in hospital for 12 days (Fig. 2).

Comparative study: IgG3 deficiency patient vs clinical controls

Table 1 lists only the statistically significant data ($P < 0.05$) for the clinical signs and symptoms of influenza on admission and the worst clinical data during the hospital stay. These were duration of admission; SpO_2 level on admission; biochemical markers CRP, CK, urinary β2-microglobulin/urinary creatinine; serum IgG3 concentration; and the period of oseltamivir.

Discussion

This study has shown for the first time that complete IgG3 deficiency affects the clinical course of H1N1 pdm 09 and pneumonia. Recently, immunodeficiency was reported as a risk factor for

Table 1 Significant clinical data: IgG3 deficiency patient vs clinically matched controls

Parameters	Present case	Control patients ($n = 4$) 95%CI
IgG3 (mg/dL)	<4	14–39
SpO_2 on admission (%)	90	92–97
CRP (mg/dL)	6.6	−2.4 to 6.0
CK (IU/L)	618	57–278
U-β2-microglobulin/creatinine (μg/gCr)	12023	878–4729
Duration of oseltamivir (days)	10	3.4–8.1
Duration of admission (days)	12	6.5–10.6

Only the parameters with $P < 0.05$ are shown. Mean age, 5.5 years; 95% CI, 4.2–6.9 years. CI, confidence interval; CK, creatine kinase; CRP, C-reactive protein; SpO_2, pulse oxygen saturation; U, urinary.

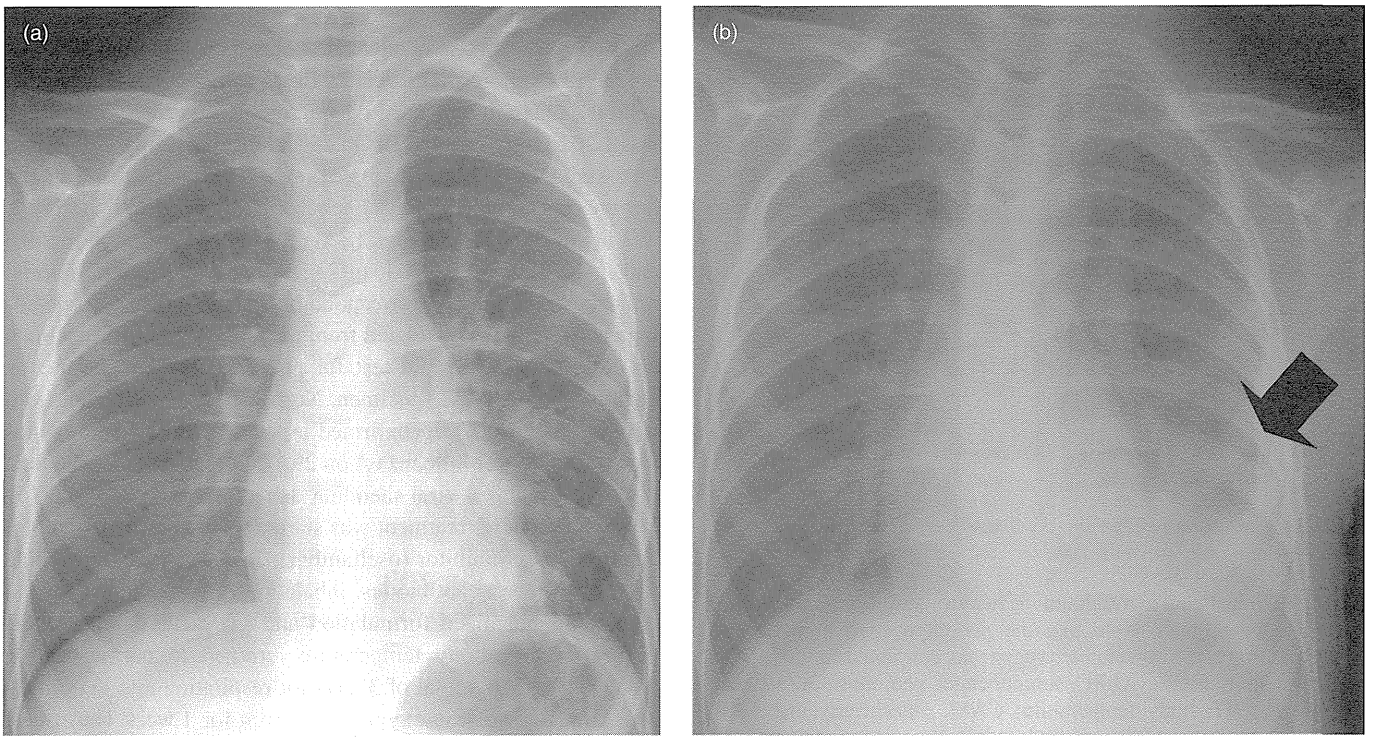

Fig. 2 Chest roentgenogram. (a) Bilateral pneumonia is present on admission. (b) On the second hospital day, pneumonia in the left side extended to the lower one-third area with pleural fluid (arrow).

H1N1 pdm 09,[10] but no studies have been done on the clinical outcome of children with IgG3 deficiency in H1N1 pdm 09. This was probably because IgG3 deficiency is relatively rare in children compared to adults.[11]

Asthma has been reported as a risk factor for H1N1 pdm 09.[12] Also, asthma is a complication of IgG3 deficiency.[13] In the present case, the duration of admission, which is a possible hallmark of the severity of H1N1 pdm 09, was significantly longer than that of clinical controls. It was difficult, however, to indicate that this was caused by asthma because it was adjusted as one of the baseline characteristics in the present study. In addition, the present IgG3 deficiency patient needed a longer period of oseltamivir to treat the influenza compared to the clinical control patients. Thus, these data may be due to the prolonged virus shedding as seen in the other immunocompromised patients in H1N1 pdm 09,[14] although we had no data to prove the hypothesis. On the basis of these data, we postulate that immunodeficiency due to complete IgG3 deficiency clearly affects the severity of the clinical course of children suffering from pneumonia and asthma caused by H1N1 pdm.

Although the precise mechanism for this are unclear, two hypotheses are plausible. One is that immunodeficiency makes a patient susceptible to bacterial infection, but we found no abnormality in culture analysis of blood and upper respiratory swabs. Thus, the first hypothesis is likely to be implausible, although we could not completely exclude the possibility. The second is a decreased immunological defense ability to eradicate the influenza virus from the body. IgG3 has been suggested to be associated with the primary response in respiratory viral infection.[15] In the present case, we treated all the patients admitted due to H1N1 pdm 09 with oseltamivir and Mao-to, a Japanese herbal medicine. The usefulness of this kind of combination therapy has been reported in the case of seasonal influenza.[8]

We found no abnormality in serum IgG2 level, which was reported by Gordon *et al.*[7] This discrepancy was thought to be derived from the difference in the clinical severity and age of the patients; the present children with pneumonia stayed on a regular floor without mechanical respiratory assistance in a municipal hospital, compared to adult patients with severe respiratory failure, who were admitted to the intensive care unit in a center hospital.

The evidence in the present report is limited, and it was unclear whether the severity of the clinical course for pneumonia and asthma attack in this case was derived from H1N1 pdm 09 influenza or influenza itself. Although the patient had no past history of pneumonia caused by seasonal influenza, he was the only patient with IgG3 deficiency in our experience. Thus, we could not conclude whether the relatively severe clinical course in this case was caused by H1N1 pdm 09. Frequency of IgG3 deficiency in children, however, is relatively low,[11] and the importance of IgG3 deficiency has recently been suggested in recurrent infections.[13] Thus, we thought it worthwhile to report our experience and preliminary analyses even in a single case of complete IgG3 deficiency. Further study is necessary to elucidate the mechanism of IgG3 deficiency complicated by pneumonia and asthma attacks in the severity of H1N1 pdm 09.

In conclusion, complete IgG3 deficiency is possibly associated with severity of the clinical course of pneumonia in children suffering from H1N1 pdm 09.

Acknowledgments

We thank the many co-medical staff working in Minoh City hospitals for their clinical cooperation.

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Kondo et al. BMC Health Services Research 2012, 12:313
http://www.biomedcentral.com/1472-6963/12/313

BMC
Health Services Research

RESEARCH ARTICLE Open Access

Demand for pneumococcal vaccination under subsidy program for the elderly in Japan

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Abstract

Background: Vaccination programs often organize subsidies and public relations in order to obtain high uptake rates and coverage. However, effects of subsidies and public relations have not been studied well in the literature. In this study, the demand function of pneumococcal vaccination among the elderly in Japan is estimated, incorporating effects of public relations and subsidy.

Methods: Using a data from a questionnaire survey sent to municipalities, the varying and constant elasticity models were applied to estimate the demand function. The response variable is the uptake rate. Explanatory variables are: subsidy supported shot price, operating years of the program, target population size for vaccination, shot location intensity, income and various public relations tools. The best model is selected by c-AIC, and varying and constant price elasticities are calculated from estimation results.

Results: The vaccine uptake rate and the shot price have a negative relation. From the results of varying price elasticity, the demand for vaccination is elastic at municipalities with a shot price higher than 3,708 JPY (35.7 USD). Effects of public relations on the uptake rate are not found.

Conclusions: It can be suggested that municipalities with a shot price higher than 3,708 JPY (35.7 USD) could subsidize more and reduce price to increase the demand for vaccination. Effects of public relations are not confirmed in this study, probably due to measurement errors of variables used for public relations, and studies at micro level exploring individual's response to public relations would be required.

Keywords: Demand, Elderly, Vaccination program, Pneumococcal polysaccharide vaccine (PPV), Price elasticity, Public relations, Subsidy

Background

The administration of 23-valent pneumococcal polysaccharide vaccine (PPV) has been proven to be effective in reducing the incidence of invasive pneumococcal disease caused by Streptococcus pneumoniae (*S. pneumoniae*) among the elderly by 50% to 70% [1,2]. It is also effective in reducing mortality from severe community acquired pneumonia that requires hospitalization [3,4]. Several developed countries have implemented national pneumococcal vaccination programs for the elderly in order to prevent the disease and improve its outcomes [5-8], although the incidence of the disease varies worldwide [9].

Such programs target high uptake rates and coverages [10,11], for which subsidies and public relations (PR) are often organized in order to encourage the elderly to get vaccinated. However, the effects of subsidies and PR in publicly funded vaccination program have not been studied well in the literature. Al-Sukhni et al. (2008) found that in Canada, physician's face to face advocacy inside the consultation room is important for the elderly to decide for influenza vaccination or pneumococcal vaccination [12]. Li, Norton, and Dow (2004) examined the threat-responsiveness hypothesis among the elderly and their decision to obtain influenza vaccination or pneumococcal vaccination in the U.S., and found that an increased associated mortality in the previous year does not significantly affect the demand for pneumococcal vaccination but significantly affect the demand for influenza vaccination [13]. Nevertheless, no studies have

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been reported on the effect of subsidy, or the price elasticity of demand for pneumococcal vaccination. This lack of knowledge is probably due to the fact that usually, immunization programs set fixed subsidized vaccine price for target population, and this makes it difficult to observe the consumer's response to price changes.

In Japan, despite of the fact that pneumonia has been the fourth leading cause of death among the elderly aged 65 or over since 1975 [14], and that *S. pneumoniae* is the most common etiologic agent of community acquired pneumonia which accounts for 38.7% of such cases [15], a national pneumococcal vaccination program is yet to be set. In 2001, however, one town initiated a pneumococcal vaccination program for the elderly, under which aged inhabitants were encouraged to receive a subsidized PPV shot. Subsequently, several municipalities introduced similar programs, and by 2007, those amounted to 63 out of all 1,821 municipalities [16]. These programs set various levels of subsidized shot price and organized various PR at municipality's own discretion, which enable us to observe consumers' response, that is, the uptake rate, to subsidized price and PR.

We take advantage of this Japanese context, and aim to estimate a demand function for pneumococcal vaccination with price elasticity and effects of various PR tools on the uptake rate. The results of this study should deepen our understanding of consumer's behavior towards preventive health care, and have implications for health managers in charge of vaccination programs to organize more effective programs, not only in Japan but also in other developed countries.

Methods

A questionnaire survey was carried out to all municipal authorities operating pneumococcal vaccination programs in 2008. At the time of the survey, 63 municipalities operated programs and the response rate was 100%. In the survey, following questions were asked: operating years of the program, definition and size of the target population, uptake population, price to get one vaccine shot, number of health facilities providing shots, and PR tools taken for promoting vaccination. The type of PR tools included:

To target population

"House-to-house delivery of brochures (PR1)", "Distribution of brochures at health facilities (PR2)", "Distribution of brochures at public facilities (PR3)", "Insert articles in newsletters (PR4)", "Upload information to websites (PR5)", "Hold public events (PR6)", "Local cable broadcasting (PR7)"

To physicians

"Distribution of brochures to their health facilities (PR8)", "Hold information events (PR9)", "Communication in regular meetings (PR10)"

To health nurses & care givers

"Distribution of brochures to their health facilities (PR11)", "Hold information events (PR12)", "Communication in regular meetings (PR13)"

These questions were asked on a Yes/No basis. With this municipal based data, we assume each municipality as a market for vaccination and examine the effects of PR tools implemented by the municipality and subsidy supported shot price on the vaccine uptake rate.

Descriptive statistics are reported in Table 1. Due to missing or inadequacy values for data analysis, 39 out of the 63 municipalities were chosen for the estimation. Inadequacy values included the price of a shot if it was

Table 1 Descriptive statistics

					n = 39
	Ratio	**Mean**	**Min.**	**Max.**	**S.d.**
Uptake rate		0.268	0.007	0.991	0.223
Shot price (1,000 JPY)		3.556	0.000	6.500	1.310
Operating years (year)		2.128	1.000	5.000	1.341
Target population (1,000 persons)		3.625	0.217	44.353	7.139
Location intensity (per km^2)		0.474	0.002	9.966	1.599
Income (1,000,000 JPY)		1.233	0.564	4.984	0.732
Implemented PR tools:					
To target population (Count PR1-7)		3.667	1.000	7.000	1.284
PR1	0.564				
PR2	0.718				
PR3	0.538				
PR4	0.795				
PR5	0.513				
PR6	0.205				
PR7	0.333				
To physicians (Count PR8-10)		0.897	0.000	3.000	0.968
PR8	0.487				
PR9	0.077				
PR10	0.333				
To nurses & care givers (Count PR11-13)		0.385	0.000	2.000	0.747
PR11	0.179				
PR12	0.077				
PR13	0.128				
Total (Count PR1-13)		4.949	1.000	11.000	2.176

changed many times during the operating years of the program, or if the municipality had set fixed subsidies to health care providers and had them decide their own retail shot prices that reflected discretional technical service fees. The "Uptake rate" is the uptake population divided by the target population for vaccination during the operating years of the program. A municipality with 0.991 in the maximum shows that vaccination program had run successfully, meaning that 99.1% of the target population had been vaccinated. The "Shot price" is individual cost burden for receiving one shot. The 0 in the minimum means that the individual shot price is fully covered by the subsidy, and on the other hand, 6.500 in the maximum implies that the price is not fully covered and an individual has to pay 6,500 Japanese yen (JPY) (62.5 USD; 1USD = 104JPY in 2008 annual average) for vaccination. The "Operating years" is the length of operating the program. Note the maximum is 5 years, meaning that the data taken is the first 5 years from the beginning of the vaccine program, therefore there is no individual who has taken the shot twice. This is because effectiveness of PPV shot is said to last for 5 years [1] and revaccination was prohibited in Japan at the time of the survey. That is to say, the demand for vaccination would be decided by the shot price, PR, etc., and not by some sentiment from previous shot experience. The "Target population" is defined by the age criteria: ≥ 65, ≥ 70, or ≥ 75 years old, depending on the municipality. The difference of 0.217 in the minimum and 44.353 in the maximum is not because of age criteria chosen by municipalities, such as ≥ 75 in the minimum and ≥ 65 in the maximum, but of the population size: one with 0.217 shows a small village and the other with 44.353 shows a big city. The "Location intensity" is the number of health facilities providing vaccination per km^2 in the municipality. The "Income" is the average income per capita by municipality obtained from System of Social and Demographic Statistics by Statistics Bureau [17]. The demand function requires a budget constraint information such as income [18], however, we cannot define the value from our municipal based questionnaire survey data. And there was no available income data on the targeted elderly but only of the entire citizen in the municipality. The "PR1 to 13" are binary or dummy variables which take 1 if the municipality implements the PR tool and take 0 otherwise. 79.5% of the municipalities take PR4, while only 7.7% take PR9 and PR12. "To target population", "To physicians", "To nurses & care givers" and "Total" show the number of PR tools implemented by the municipality during the operating years of the program; PR1 to PR7, PR8 to PR10, PR11 to PR13 and PR1 to PR13, respectively. 3.667 in the mean of "To target population" describes that municipalities implement on the average of 3 or 4 PR tools among PR1 to PR7.

The "Uptake rate" is the response variable in our demand function, and we have "Shot price" and "Income" as explanatory variables [18]. As considered to affect the response variable, "Operating years", "Target population", "Location intensity" and "PR1 to 13"; "To target population", "To physicians", and "To nurses & care givers", and "Total" are also included into the demand function. If the program has been operating for a long period of time, it would have become more common and high uptake rate is expected, in regards to "Operating years". The "Target population" is regarded as nature of works which municipal authorities have to undertake to promote vaccination. It would be an extreme example, but making an effort to increase the uptake rate for a target population of one person is much easier than for a target population of 10,000 persons. The "Location intensity" is regarded as the non-cash price such as travel or time cost which has been proven to be significant in the demand for health care [19] including vaccination [20]. Investigating the effects of PR tools on the uptake rate is the aim of this study, therefore, we include "PR1 to 13" as dummy variables to examine which PR tools are effective to increase the uptake rate. In addition, the number of PR tools implemented by the municipality is considered as another PR scale, because it may reflect the intensity of PR within the municipality.

We assume a linier demand function, then the estimation form is expressed as [21]:

$$Y_i = \beta_0 + \beta_1 x_{1i} + \beta_2 x_{2i} + \ldots + \beta_p x_{pi} + \varepsilon_i \, (i = 1, \ldots, n),$$

where Y is the response variable "Uptake rate" in this study, $x_j (j = 1, \ldots, p)$ are explanatory variables, $\beta_j (j = 0, \ldots, p)$ are the constant and coefficients, ε is the error term, and n is the sample size. Three models are estimated: "Shot price", "Operating years", "Target population", "Location intensity", "Income" in all three models; "Total" is added in model 1; "To target population", "To physicians" and "To nurses & care givers" are added in model 2; and "PR1 to 13" are added in model 3.

In order to examine the effects of explanatory variables, especially the effects of each PR tool on the "Uptake rate", the best model is selected by c-AIC from model 3 as a full model, with a restriction to keep "Shot price" and "Income". This is because "Shot price" and "Income" are conventional variables in the theory of demand [18]. Then c-AIC is calculated for all possible regressions with combinations of 16 explanatory variables. 'c-AIC' is the Akaike Information Criterion (AIC) for small sample data: the smaller the value of c-AIC, the better the model [22]. Sugiura (1987) suggested that AIC may perform poorly if there are too many parameters in relation to the size of the sample [23]. Our

sample size is 39 and small, while parameters are 20, quite large, in model 3. The best model is created as model 4.

The price elasticity calculated from the estimation results of model 1, model 2, model 3, or model 4 is written as [18]:

$$\delta_v = \frac{\partial Y}{\partial x_1} \cdot \frac{x_1}{Y} = \hat{\beta}_1 \cdot \frac{x_1}{\hat{Y}} \quad (1)$$

where x_1 is the "Shot price", $\hat{\beta}_1$ is the estimated coefficient of the "Shot price", and $\hat{Y}$ is the expected value of the "Uptake rate" at x_1. From equation (1), model 1, model 2, model 3, or model 4 is called as the varying elasticity model since the price elasticity can vary in response to changes in x_1 and $\hat{Y}$ [24]. Meanwhile, the constant elasticity model takes $\log(x_1)$ and $\log(Y)$, instead of taking x_1 and Y in the varying elasticity model [24]. That is:

$$\log(Y_i) = \beta_0 + \beta_1 \log(x_{1i}) + \beta_2 x_{pi} + \ldots + \beta_p x_{pi} + \varepsilon_i \, (i = 1, \ldots, n)$$

Then the constant price elasticity is expressed as:

$$\delta_c = \frac{\partial Y}{\partial x_1} \cdot \frac{x_1}{Y} = \frac{\partial \log(Y)}{\partial \log(x_1)} = \hat{\beta}_1 \quad (2)$$

We focus to the best model, which is model 4, and estimate the varying and constant price elasticities, using a command "margins" in the software STATA12 [25]. The $\hat{Y}$ is calculated with all explanatory variables except x_1, fixed at their means by using a command "atmeans". Model 5 is created as the constant elasticity version of model 4 for reference.

Regarding research ethics, this study is not an experimental research nor carried on humans. It also falls outside of the guidelines of health research ethics in Japan. The data used for this study is openly available, and we received permission to use this data by all respondents' municipalities.

Results

Estimation results are listed in Table 2. Model 1, model 2 and model 3 suggest that "Operating years", "Target population", "Location intensity", "Income", "Total", "To target population", "To physicians", "To nurses & care givers" "PR1 to 13" do not affect the uptake rate, while "Operating years" in model 1 and "PR5" in model 3 are significant at 10%. "Shot price" is negatively significant in all four models, which confirms a negative relation between the "Shot price" and the "Uptake rate".

Comparing c-AIC, model 4 has the smallest value and is regarded as the best among four models. The AIC and adjusted R^2 also imply that model 4 is the best, however,

Table 2 Estimation results

	Uptake rate				$n = 39$ log (Uptake rate)
	Model 1	Model 2	Model 3	Model 4	Model 5
Consent	0.557***	0.618***	0.641**	0.662***	−1.023***
Shot price (1,000 JPY)	−0.090***	−0.089***	−0.079**	−0.069***	
log (Shot price) (1,000 JPY)					−0.148*
Operating years (year)	0.042*	0.038	0.032		
Target population (1,000 persons)	−0.007	−0.003	0.000		
Location intensity (per km^2)	−0.018	0.028	0.015		
Income (1,000,000 JPY)	0.075	−0.029	0.007	−0.016	−0.008
Implemented PR tools:					
To target population (Count PR1-7)		−0.008			
PR1			0.058		
PR2			−0.117***	−0.117***	−0.762**
PR3			0.007		
PR4			−0.059		
PR5			−0.147*		
PR6			0.165		
PR7			0.101		
To physicaians (Count PR 8–10)		−0.056			
PR8			−0.036		
PR9			−0.027		
PR10			−0.145		
To nurses & care givers (Count PR11-13)		−0.006			
PR11			−0.167		
PR12			0.041		
PR13			0.295		
Total (Count PR1-13)	−0.024				
c-AIC	−3.608	2.611	49.812	−11.124	113.527
AIC	−8.408	−5.246	3.145	−12.942	111.709
Adjust R^2	0.235	0.201	0.111	0.274	0.142

Signif codes: 0.01 '***' 0.05'**' 0.1'*'.

the difference in AIC between −8.408 in model 1 and −12.942 in model 4, 4.534, is smaller than the corresponding difference in c-AIC, 7.516, which tells us that c-AIC performs better than AIC in selecting the best model. The coefficient of the "Shot price" in model 4, −0.069, explains that the uptake rate is decreased by 6.9% with an increase of the shot price at 1,000 JPY (9.6 USD). Contrary to our expectations, "Operating years", "Target population", and "Location intensity" are not selected by c-AIC, and "Income" is not found statistically significant, which implies that these variables have little effect on the uptake rate. Only "PR2" is selected by c-AIC but its coefficient sign is negative, however. It is not clear whether any of these PR tools promotes the increase in uptake rate.

Model 5 is the estimated result of constant elasticity model. The coefficient of the "log(Shot price)", −0.148, is regarded as the constant price elasticity, and it is larger than −1 and smaller than 0, which implies that the demand for vaccination is inelastic.

Figure 1 describes varying and constant price elasticities calculated from estimation results of model 4 and model 5, respectively. From (1) and the negative coefficient value of the "Shot price" in model 4, −0.069, the varying price elasticity becomes negatively larger as "Shot price" takes larger positive value. The shot price is 3,708 JPY (35.7 USD) at unit elasticity, i.e., $\delta_v = -1$. Therefore, the demand for vaccination is inelastic at the mean price of 3,556 JPY (34.2 USD), and becomes elastic at more than 3,708 JPY (35.7 USD).

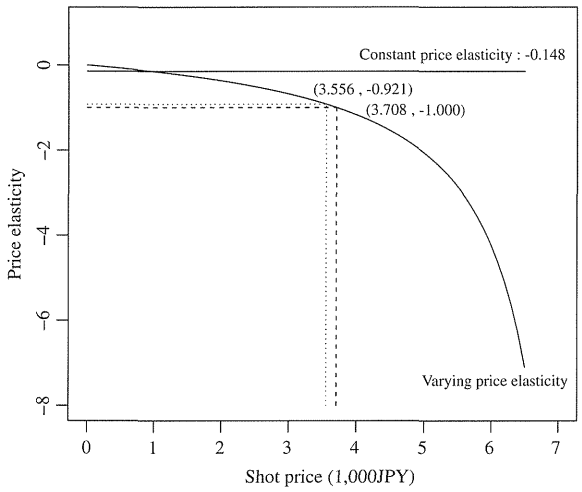

Figure 1 Price elasticity Vs Shot price. Relations between varying or constant price elasticity and shot price, according to the estimation results from model 4 or model 5, respectively. Solid lines show constant and varying price elasticities. Dashed and dotted lines show the unit elasticity and the elasticity at mean shot price on the varying price elasticity, respectively.

Discussion

We estimate the demand function for pneumococcal vaccination under subsidy programs incorporating the shot price, various PR tools and other factors considered to affect the demand, i.e., the uptake rate. The uptake rate is found to depend significantly on the shot price. Therefore, reducing the shot price by subsidy is an effective implementation to achieve higher coverage. Additionally, we estimated price elasticity of the demand, which has not been studied well in the literature. According to the varying price elasticity of demand, the demand is inelastic, more than − 1, when the shot price is reduced, supported by larger subsidy. And it is elastic, less than − 1, when the price is higher with smaller subsidy. Unitary elasticity is estimated at 3,708 JPY (35.7 USD), so municipalities offering higher than 3,708 JPY (35.7 USD) for a shot can expect substantial gains in uptake rates by reducing shot prices.

Since only subsidized shot price is available for our analysis, it is not possible to discuss the direct link between subsidy and demand. We can, however, give a probable breakdown of subsidy and shot price. The National Health Insurance price list gave 4,835 JPY (46.9 USD) for 23-valent PPV at the time of the survey, although municipalities or vaccination providers might have purchased at a discounted price for such public health program that is not covered by the National Health Insurance reimbursement. And arguably, it can be assumed that the technical service fee for administrating one shot levied by physicians is around 5,000 JPY (48.1 USD). Therefore, the municipality are likely to expend 10,000 JPY (96.2 USD) to 3,500 JPY (33.7 USD) per shot as subsidy in order to set the price of a shot at 0 JPY (0 USD) to 6,500 JPY (62.5 USD).

Although we anticipated a result that the demand increases by implementing more PR tools, their effectiveness is not found. Furthermore, any positive effect of each PR tool on the demand is not observed. However, we do not think that these results suggest that PR is ineffective in organizing vaccination programs. On the contrary, these failures could be attributable to the measurement errors of variables we used, which are difficulties inherent in this study. 13 PR tools had been asked on only a Yes/No basis in the survey because there was no a priori knowledge about PR practices in this context. One possible account is a lack of appraisal of actual contents of each PR tool. It can be assumed that the contents are divided into two types: information about arrangement and procedure of the program including the shot price; and information about risk and benefit of vaccination, that is, health education. PR tools containing price information could cause negative effects on the uptake rate. And PR tools containing health education information might also not work well as it may

cause irrational response among people with aversion to vaccination. It is known that there is a negative attitude towards vaccination among Japanese health professionals compared to those of overseas [26]. Their aversion to vaccination has been firmly rooted by the anti vaccination campaign in the 1990s in Japan [27], where both the public [28] and physicians [26] have become to fear its adverse effects. Therefore, the use of PR in order to dispel this negative attitude could prompt the demand.

The effects of the operating years of the program and target population size to the uptake rate were not found, which could be explained that communicating to the aged inhabitants may be similar among the municipalities irrespective of time span or size. The location intensity may be failing in measuring the travel cost. The travel cost to the elderly may not be just direct distance to health facilities. It depends more on the access assured by public transportation, or consulting their home doctor to make their decision in their regular doctor visits, which cannot be caught by number of health facilities providing a shot per km^2.

In addition to the lack of contents and information regarding PR tools and the travel cost, the number of usable observations of only 39 municipalities is small, even though we used the data set with 100% response rate and took statistical technique for small samples, i.e., c-AIC. This may be another reason why anticipated results were not found in this study.

It is notable that the estimated price elastic demand for pneumococcal vaccination contrasts with the price inelastic demand for influenza vaccination among similar population [29]. These two vaccinations for the elderly are also found differently in the threat-responsiveness hypothesis about demand in the U.S. [13]. Comparative study between the two vaccinations is awaited to deepen our understanding about this difference.

This study leaves a room for further study. Particularly, effects of PR on the demand would be of interest to academics as well as to health managers currently in practice. Our experience in this study suggests that rigorous PR measurements for estimating the demand function across diverse municipal programs is quite difficult unless any contextual opportunity is offered. Studies at micro level exploring individual's response to PR could be one of the possible approaches to obtain some evidence.

Conclusions

The elderly's demand for pneumococcal vaccination under subsidy programs in Japan is found price-sensitive. Subsidy works, and setting the appropriate level of price for a shot is important in organizing such programs. High gains in uptake rates and coverage are expected by increasing subsidy when the price of a shot is higher than 3,708 JPY (35.7 USD). The role of PR or its effectiveness in obtaining high uptake rates and coverage could not be confirmed in this study.

Competing interests

Authors declare there is no conflict of interest.

Authors' contributions

MK, SH, and IO were involved in conception and design of this project, while MK and MY were involved with the implementation of the project and analysis and interpretation of the data. MK and MY have drafted the manuscripts while IO had provided critical comments. "All authors read and approved the final manuscript."

Acknowledgements

This study was partly supported by Japan's Ministry of Health, Labour and Welfare research grant for Research on Emerging and Re-emerging Infectious Diseases, led by principal investigator: Prof. Yoshio Hirota, Osaka City University.

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Received: 26 January 2012 Accepted: 7 September 2012
Published: 12 September 2012

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doi:10.1186/1472-6963-12-313
Cite this article as: Kondo *et al.*: Demand for pneumococcal vaccination under subsidy program for the elderly in Japan. *BMC Health Services Research* 2012 **12**:313.

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

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Abstract

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

Introduction

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

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

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

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Key words: cost-effectiveness, invasive pneumococcal disease, polysaccharide pneumococcal vaccine, vaccination program, subsidy

Conflict of interests: the authors report no potential conflict of interests

Funding: This study is funded by the Ministry of Health, Labour and Welfare grant for *the Influenza Vaccine Epidemiology Study* (2009), led by principal investigator: Prof. Yoshio Hirota, Osaka City University.

Received for publication: 26 September 2011.
Revision received: 27 March 2012.
Accepted for publication: 7 May 2012.

Ageing Research 2012; 4:e8
doi:10.4081/ar.2012.e8

Materials and Methods

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

Program and decision

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

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

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

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

Markov model

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