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Does subsidy work? Price elasticity of demand for influenza vaccination among the elderly in Japan

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ABSTRACT

Objectives: Subsidy for influenza vaccination is often provided to the elderly in order to encourage them to receive a flu shot in developed countries. However, its effect on uptake rate, i.e., price elasticity of demand, has not been well studied.
Methods: Japan's decentralised vaccination programme allows observation of various pairs in price and uptake rate of flu shots among the elderly by the municipality from 2001/2002 to 2004/2005 season. We combine our sample survey data ($n = 281$), which monitor price, subsidy and uptake rate, with published data on local characteristics in order to estimate price elasticity of demand with panel model.
Results: We find price elasticity of demand for influenza vaccine: nearly zero in nationwide, nearly zero in urban area, and −1.07 in rural area.
Conclusions: The results question the rationale for subsidy, especially in urban area. There are cases where maintaining or increasing the level of subsidy is not an efficient allocation of finite health care resources. When organising a vaccination programme, health manager should be careful about the balance between subsidy and other efforts in order to encourage the elderly to receive shots with price elasticity in mind.

References separately shown for the purpose of anonymity:
[16] Hoshi SL, Kondo M, Okubo I. Study on pricing and uptake rate of influenza vaccination for the elderly with a simple random sampling method. Nippon Koshu Eisei Zasshi 2008;55:19–29.
[31] Hoshi SL, Kondo M, Honda Y, Okubo I. Cost-effectiveness analysis of influenza vaccination for people aged 65 and over in Japan. Vaccine 2007;25:6511–21.

1. Introduction

Seasonal influenza epidemics affect the health of population in many countries. The elderly is more vulnerable to the disease among them, which sometimes results in hospitalisation or death [1]. One way of countering this public health issue is to implement vaccination programme targeting the elderly [2], since influenza vaccine is considered as effective not only in preventing contraction of the disease [3], but also reducing risk of death after contraction [4]. Although some recent studies cast doubts as to the latter effectiveness, i.e., reducing mortality [5–7], a number of countries or regions organise such vaccination programmes [8]. In Japan, national government has set up a nationwide influenza vaccination programme for people aged 65 and over since 2001/2002 season.

These programmes usually employ several measures such as public relations or health education in order to encourage the elderly to receive shots. Subsidy is also

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provided [8], since reducing the price of a shot is believed to increase the uptake of vaccination. However, the response of the elderly as a consumer in regard to price changes, i.e., price elasticity of demand, has not been well studied. Theoretically, knowledge of price elasticity is of great help to design an efficient subsidy programme including vaccination programmes [9], but a few are reported in the literature. A correlation between subsidy levels and uptake rates is found in multinational comparison incorporating 18 developed countries [10]; a rise in uptake rate that is resulted from Medicare coverage in the U.S. [11]; the removal of fee increases uptake rate in an intervention study in Denmark [12]; price elasticity of demand, −0.022, is estimated by conjoint analysis before the launch of the national programme in Japan [13].

This lack of knowledge is probably due to the fact that such programmes usually set fixed price for all target population, which make it difficult to observe the consumer's response to price change. The current Japanese programme, however, obligates municipal authorities to manage vaccination for their aged inhabitants, and the decision of co-payment and subsidy level, that is, the price of a shot to a consumer, is devolved to municipal authorities. This arrangement makes the area of each municipality a market for flu shots, and it is possible to observe pairs of various prices and uptake rates. There is a study which reports price elasticity of −0.26 during 2001/2002 and 2002/2003 season by a survey covering 13 big cities [14]. We also take advantage of this "natural experiment", and aim to estimate price elasticity of demand for influenza vaccination among the elderly with national representative samples. The results of this study should be useful in managing vaccination programmes through price setting, and deepen the understanding of consumer behaviour toward preventive services.

2. Materials and methods

In Japan, due to the decentralised implementation of vaccination programme, price and subsidy by each municipality is not monitored or surveyed, while uptake rate by the municipality is published yearly by the central government [15]. We conducted a nationwide sample survey on price, subsidy, and uptake rate of vaccination in order to illustrate the trend of national averages, of which results were published elsewhere [16]. In this survey, operational 300 samples were randomly selected using a list of 22,671,944 people aged 65 and over inhabiting all 3252 municipalities during 2002/2003 season as a sampling frame. A questionnaire inquiring price charged to a recipient, subsidy provided by the municipality, the number of target population, and the number of vaccinated from 2001/2002 to 2004/2005 season was sent to each municipal authorities where operational samples inhabited. The use of the combination of individual level sampling frame and municipality level survey is chosen, since large-scale mergers of municipalities underwent in these years as a local government reform. 196 authorities out of 210 replied, which gave response rate of 94.0% at sample level.

In this study, we assume the operational samples of this survey as an operational panel, in which each sample faces various prices of flu shot for four times between 2001/2002 and 2004/2005 season, since the level of subsidy is usually set by a yearly negotiation between local authority and local medical association. We use uptake rates as a measure of demand assuming them as the probability of an operational sample to receive a shot.

In the literature, non-cash price such as travel cost or time cost has been proven to be significant in the demand for health care [17], including flu shots [18]. Since shots are usually provided at almost all local hospitals and clinics under cooperation with their municipal authority, we calculate the number of hospitals and clinics divided by the area of municipality to gain density of shot location as a variable of non-cash price surrogating travel cost using System of Social and Demographic Statistics (SSDS) by Statistics Bureau [19]. We added this variable to our operational panel data.

Income or budget constraint is also significant in the demand at individual level [20]. However, it is not possible to define any variable of income for our operational sample that can be combined with our operational panel data, because we construct our operational sample not through an actual observation of individuals but through an interpretation of market level observation. Average income of people aged 65 and over by the municipality is not available in SSDS, but average income per capita is available. We add this variable to our operational panel data as a controlling variable considering it as an activity level of local economy, although we do not speculate any systematic effect on the demand.

Some factors such as influenza morbidity or mortality in the previous season or current season are found influential on the demand for influenza vaccination [18,21]. In this study, however, we do not incorporate any variable that represent such factors. We also leave the level of public relations or health education untreated due to lack of data. Instead, we leave these as unobserved and intend to control their effect on the demand using panel estimation [22–24].

We specified four equations in order to estimate price elasticity as below:

$$\ln r_i = \alpha + \beta_1 \ln p_i + \beta_2 \ln d_i + \beta_3 \ln y_i + \varepsilon_t,$$
$$i = 1, \ldots, N \text{ (season model)} \quad (1)$$

where r is uptake rate, p is price of a shot, d is density of shot location, y is income per capita, ε is error term, i represents each sample in a season, and N is number of samples in a season. Uptake rate, price of a shot, and density of shot location are converted into logarithm so that we can interpret coefficient β_1 and β_2 as elasticity [25]. Income is also converted into logarithm, since unit of measurement, yen, is the same as price, while we do not interpret β_3 as income elasticity. According to this equation, season models from 2001/2002 to 2004/2005 season are estimated

$$\ln r_i = \alpha + \beta_1 \ln \frac{p_i}{c_t} + \beta_2 \ln d_i + \beta_3 \ln \frac{y_i}{c_t} + \varepsilon_i,$$
$$i = 1, \ldots, M,\ t = 1, \ldots, T \text{ (pool model)} \quad (2)$$

where c is consumer price index, t represents observed season, M represents each sample in the panel regardless of the observed season, and T is number of observed seasons.

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Table 1
Summary statistics.

	2001/2002	2002/2003	2003/2004	2004/2005	Pool
National					
Uptake rate[a]					
Obs	257	277	281	279	1094
Mean	0.2988	0.3779	0.4611	0.4960	0.4108
Std. Dev.	0.09461	0.08658	0.08360	0.07913	0.1146
Price (Yen)					
Obs	252	261	264	263	1040
Mean	1134	1135	1138	1128	1134
Std. Dev.	449.0	419.0	399.4	384.1	412.6
Density of shot location[b] (km^2)					
Obs	282	282	282	282	1128
Mean	1.995	2.021	2.041	2.066	2.031
Std. Dev.	3.113	3.145	3.178	3.220	3.160
Income (10^3 Yen)					
Obs	282	282	282	282	1128
Mean	3508	3478	3405	3367	3439
Std. Dev.	491.6	486.4	456.5	458.1	476.1
Subsidy (Yen)					
Obs	268	278	275	281	1102
Mean	2972	2955	2966	2954	2962
Std. Dev.	883.0	806.6	752.5	747.5	784.3
Subsidy level[c] (%)					
Obs	249	260	259	263	1031
Mean	72.2	71.8	72.1	72.2	72.1
Std. Dev.	12.0	12.2	10.7	10.5	11.4
Urban					
Uptake rate					
Obs	203	217	218	216	854
Mean	0.2917	0.3692	0.4546	0.4883	0.4027
Std. Dev.	0.09032	0.07792	0.07700	0.06963	0.1094
Price (Yen)					
Obs	206	211	211	210	838
Mean	1119	1120	1131	1120	1122
Std. Dev.	464.8	430.6	399.0	385.9	420.2
Density of shot location (km^2)					
Obs	218	218	218	218	872
Mean	2.503	2.536	2.564	2.595	2.546
Std. Dev.	3.366	3.399	3.435	3.480	3.415
Income (10^3 Yen)					
Obs	218	218	218	218	872
Mean	3627	3597	3514	3478	3554
Std. Dev.	477.8	456. 1	428.3	429.6	446.7
Subsidy (Yen)					
Obs	212	217	213	218	860
Mean	3074	3049	3065	3043	3057
Std. Dev.	765.5	753.8	683.7	686.7	722.1
Subsidy level (%)					
Obs	207	214	211	213	845
Mean	73.2	72.7	73.1	73.1	73.0
Std. Dev.	11.0	11.3	9.2	9.2	10.2
Rural					
Uptake rate					
Obs	54	60	63	63	240
Mean	0.3258	0.4093	0.4836	0.5225	0.4397
Std. Dev.	0.1059	0.1075	0.1008	0.1017	0.1270
Price (Yen)					
Obs	46	50	53	53	202
Mean	1201	1199	1169	1169	1183
Std. Dev.	366.4	362.9	403.4	378.1	376.2

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Table 1 (*Continued*)

	2001/2002	2002/2003	2003/2004	2004/2005	Pool
Density of shot location (km^2)					
Obs	64	64	64	64	256
Mean	0.2649	0.2688	0.2587	0.2607	0.2633
Std. Dev.	0.5284	0.5344	0.4762	0.4779	0.5020
Income (10^3 Yen)					
Obs	64	64	64	64	256
Mean	3104	3074	3032	2988	3050
Std. Dev.	372.8	352.7	339.4	334.6	350.9
Subsidy (Yen)					
Obs	56	61	62	63	242
Mean	2858	2622	2623	2648	2621
Std. Dev.	963.4	902.2	875.4	866.3	895.5
Subsidy level (%)					
Obs	42	46	48	50	186
Mean	67.3	67.4	67.6	68.5	67.7
Std. Dev.	15.5	15.2	14.9	14.5	14.9

[a] Ratio of the number of vaccinated to the target population during the season.
[b] The number of clinics and hospitals per km^2.
[c] Proportion of subsidy in the sum of price and subsidy.

Consumer price index is incorporated for the purpose of controlling the effect of inflation over the season. With this equation, we estimate pool models

$$\ln r_{it} = \alpha + \beta_1 \ln \frac{p_{it}}{c_t} + \beta_2 \ln d_{it} + \beta_3 \ln \frac{y_{it}}{c_t} + v_{it},$$

$$i = 1, \ldots, N,\ t = 1, \ldots, T \text{ (panel random effect model)} \quad (3)$$

where v_{it} represents disturbance. This equation is for panel estimation of random effect model.

$$\ln r_{it} = \alpha + \alpha_i + \beta_1 \ln \frac{p_{it}}{c_t} + \beta_2 \ln d_{it} + \beta_3 \ln \frac{y_{it}}{c_t} + u_{it},$$

$$i = 1, \ldots, N,\ t = 1, \ldots, T \text{ (panel fixed effect model)} \quad (4)$$

where α_i represents fixed effect regarding ith sample, and u_{it} represents reminder disturbance. This equation is for panel estimation of fixed effect model.

With (3) and (4), we estimate two panel models, which are compared with pool model and each other with diagnostic tests such as Hausman test of misspecification.

A previous study [14] reports price elasticity in 13 big cities, and there are some that reports the difference in utilisation of preventive services, for example, mass health examination [26], and cancer screening programme [27], between urban and rural inhabitants in Japan. Inhabitants of rural area tend to use more preventive service voluntarily compared to urban inhabitants. Taking these studies into account, in addition to estimating national models using all operational samples, urban models using only samples that live in cities, and rural models using only samples that live in towns or villages are also estimated. Because of our sampling design, both models can be interpreted as representative of each area in Japan.

Statistical package software STATA 9 is used for computation.

3. Results

Table 1 shows summary statistics of variables. National average of uptake rate, the demand, increased remarkably from 29.9% in 2001/2002 season to 49.6% in 2004/2005 season, which resulted in 41.1% over all seasons. Similar increases are also observed in urban area and rural area, while higher rates are observed in rural area than in urban area. It should be noted that the observed period is the beginning of the programme, during which there is supposed to bring about the broad diffusion of vaccination [28]. Additionally, outbreaks such as Severe Acute Respiratory Syndrome (SARS) in 2002/2003 season and avian flu in 2002/2003 season occurred, and a word, "influenza", was heavily publicised during these seasons. The need of preparation for the emergence of pandemic influenza virus was also emphasised by the government in the following years. Such information may have affect on consumers' behaviour. National average of price in all seasons is ¥1134 (US$9.86: US$1 = ¥115). The lowest price is ¥0 (US$0), and the highest ¥2500 (US$21.74). A shot is slightly more expensive in rural area than in urban area. National average of density of shot location, the non-cash price, is 2.0 per km^2, and it ranges from 0.0023 per km^2 to 20 per km^2. Urban average is smaller than rural as anticipated. National average of income, the activity level of local economy, is ¥3,439,000 (US$29,900), and it ranges from ¥2,407,000 (US$20,900) to ¥4,970,000 (US$43,200). Urban average is larger than rural as anticipated. National average of subsidy is ¥2962 (US$25.76), and it ranges from ¥0 (US$0) to ¥4599 (US$39.99), while national average of subsidy level 72.1%, from 0% to 100%. Urban municipal authorities tend to expend more subsidy than rural authorities.

Table 2 shows the results of OLS estimation of Eq. (1), season models. The demand for influenza vaccination depends significantly on price and non-cash price in the majority of models with the exception of rural 2003/2004 model and rural 2004/2005 model. Price elasticity is estimated as −0.0441 to −0.0187 in national model, −0.0384 to −0.00323 in urban model, and −0.109 to −0.0152 in rural model, of which negative signs are anticipated. Negative non-cash price elasticity is found in most of the models, which is also anticipated. Activity level of local economy

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Table 2
OLS estimation of Eq. (1).

	National 2001/2002 model		National 2002/2003 model		National 2003/2004 model		National 2004/2005 model	
	Coefficient	*t*-Statistics	Coefficient	*t*-Statistics	Coefficient	*t*-Statistics	Coefficient	*t*-Statistics
ln(price+1)	−0.0437	−2.93**	−0.0441	−4.13**	−0.0187	−1.58	−0.0358	−2.65**
ln(density)	−0.0413	−1.98*	−0.0442	−3.59**	−0.0321	−3.07**	−0.0252	−2.86**
ln(income)	−0.0953	−0.38	−0.07343	−0.50	0.0611	0.47	0.00310	0.03
Constant	−0.201	−0.10	−0.117	−0.10	−1.18	−1.11	−0.503	−0.57
	Prob > $F(3,234)$ = 0.0005		Prob > $F(3,254)$ = 0.0000		Prob > $F(3,259)$ = 0.0001		Prob > $F(3,256)$ = 0.0000	
	Adj R^2 = 0.0606		Adj R^2 = 0.1613		Adj R^2 = 0.0665		Adj R^2 = 0.0931	
	Urban 2001/2002 model		Urban 2002/2003 model		Urban 2003/2004 model		Urban 2004/2005 model	
	Coefficient	*t*-Statistics	Coefficient	*t*-Statistics	Coefficient	*t*-Statistics	Coefficient	*t*-Statistics
ln(price+1)	−0.0384	−2.44*	−0.00323	−3.03**	−0.0186	−1.27	−0.00920	−0.58
ln(density)	−0.0956	−3.19**	−0.0773	−4.62**	−0.0543	−3.82**	−0.0527	−4.47**
ln(income)	0.145	0.50	−0.0257	−0.16	0.0533	0.38	0.0647	0.56
constant	−2.20	−0.92	−0.569	−0.43	−1.10	−0.94	−1.18	−1.25
	Prob > $F(3,192)$ = 0.0001		Prob > $F(3,206)$ = 0.0000		Prob > $F(3,207)$ = 0.0000		Prob > $F(3,207)$ = 0.0000	
	Adj R^2 = 0.0867		Adj R^2 = 0.2159		Adj R^2 = 0.1279		Adj R^2 = 0.1617	
	Rural 2001/2002 model		Rural 2002/2003 model		Rural 2003/2004 model		Rural 2004/2005 model	
	Coefficient	*t*-Statistics	Coefficient	*t*-Statistics	Coefficient	*t*-Statistics	Coefficient	*t*-Statistics
ln(price+1)	−0.0985	−2.44*	−0.109	−3.47**	−0.0152	−0.69	−0.0509	−1.88
ln(density)	0.0560	1.61	−0.0223	−0.87	−0.0239	−1.00	0.00254	0.12
ln(income)	−0.254	−0.56	0.345	0.97	0.533	1.60	0.245	0.85
Constant	1.67	0.44	−3.01	−1.03	−5.00	−1.85	−2.28	−0.96
	Prob > $F(3,38)$ = 0.0434		Prob > $F(3,44)$ = 0.0057		Prob > $F(3,48)$ = 0.3864		Prob > $F(3,48)$ = 0.1599	
	Adj R^2 = 0.1266		Adj R^2 = 0.1949		Adj R^2 = 0.0019		Adj R^2 = 0.0449	

* $p < 0.05$.
** $p < 0.001$.

is not significant as a determinant of the demand in all models.

Table 3 shows the results of OLS estimation of Eq. (2), pool models. The demand depends significantly on price in national model and rural model. Price elasticity is estimated as −0.0236 in national model, −0.0113 in urban model, and −0.0626 in rural model. These values are within the range estimated in season models. Non-cash price becomes insignificant in national model and rural model. Non-cash price elasticity in rural model lessens its size and goes beyond zero, which contradicts the anticipation. With negative coefficient, activity level of local economy becomes significant as a determinant of the demand in national model and urban model.

Table 3
OLS estimation of Eq. (2).

	Coefficient	*t*-Statistics
National pool model		
ln((price+1)/cpi)	−0.0236	−2.69**
ln(density)	−0.0136	−1.48
ln(income/cpi)	−0.393	−3.55**
Constant	2.42	2.66**
	Prob > $F(3,1015)$ = 0.0000	
	Adj R^2 = 0.0524	
Urban pool model		
ln((price+1)/cpi)	−0.0113	−1.15
ln(density)	−0.0329	−2.44*
ln(income/cpi)	−0.398	−3.01**
Constant	2.36	2.19*
	Prob > $F(3,821)$ = 0.0000	
	Adj R^2 = 0.0600	
Rural pool model		
ln((price+1)/cpi)	−0.0626	−3.34**
ln(density)	0.00808	0.48
ln(income/cpi)	0.0176	0.08
Constant	−0.573	−0.31
	Prob > $F(3,190)$ = 0.0088	
	Adj R^2 = 0.0443	

cpi: Consumer Price Index.
* $p < 0.05$.
** $p < 0.001$.

Table 4 shows the results of panel estimation of Eqs. (3) and (4), random effect models and fixed effect models. Random effect models are selected over pool models by Breusch and Pagan Lagrangizan Multiplier tests, which reject null hypothesis that the variance of individual effect is zero. The demand depends significantly on price in rural model. Negative price elasticity is estimated as −0.00581 in national model, and −0.0537 in rural model, while positive price elasticity is estimated as 0.0248 in urban model, which is similar to pool models. Non-cash price elasticity becomes positive without significance in all models. With negative coefficient, activity level of local economy is significant as a determinant of the demand in national model and urban model, which is the same as pool models.

Fixed effect models are selected over pool model by *F*-tests, which rejects null hypothesis that individual effects are constant among all individual samples, and over random effect models by Hausman tests, which rejects null hypothesis that the variance of individual effect is zero. The demand depends significantly on price in rural model, of which elasticity inflates up to −1.07. Price elasticity becomes positive, 0.00221 in national model, as well as

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Table 4
Panel estimation of Eqs. (3) and (4).

	National random effect model			National fixed effect model		
	Coefficient	*t*-Statistics	95% Conf. interval	Coefficient	*z*-Statistics	95% Conf. interval
ln((price+1)/cpi)	−0.00581	−0.57	−0.02568 to 0.0140	0.00221	0.18	−0.0221 to 0.0265
ln(density)	0.0205	1.61	−0.00155 to 0.456	0.598	3.38**	0.251 to 0.945
ln(income/cpi)	−0.906	−5.95**	−1.20 to −0.607	−7.46	−17.7**	−8.29 to −6.63
Constant	6.49	5.19**	4.04 to 8.94	60.1	17.4**	53.3 to 66.8
Number of observation = 1019, number of groups = 266						
	Prob > Wald $\chi^2(3) = 0.0000$, R^2(within) = 0.3061			Prob > $F(3,750) = 0.0000$, R^2(within) = 0.3268		
	R^2(between) = 0.0.0454, R^2(overall) = 0.0416			R^2(between) = 0.0.0038, R^2(overall) = 0.0015		
F-test (pool model vs. fixed effect model): $F(265,750) = 4.06$, Prob > $F = 0.0000$						
Breusch and Pagan Lagrangizan Multiplier test for random effects: $\chi^2(1) = 52.94$, Prob > $\chi^2 = 0.0000$						
Hausman specification test: $\chi^2(3) = 352.95$, Prob > $\chi^2 = 0.0000$						
	Urban random effect model			Urban fixed effect model		
	Coefficient	*z*-Statistics	95% Conf. interval	Coefficient	*z*-Statistics	95% Conf. interval
ln((price+1)/cpi)	0.00248	0.23	−0.0190 to 0.0240	0.00323	0.26	−0.0211 to 0.0275
ln(density)	0.0112	0.62	−0.0245 to 0.0470	1.18	4.59**	0.676 to 1.69
ln(income/cpi)	−0.936	−5.36**	−1.28 to −0.594	−7.31	−15.3**	−8.25 to −6.37
Constant	6.69	4.67**	3.88 to 9.50	58.5	14.8**	50.7 to 66.3
Number of observation = 825, number of groups = 211						
	Prob > Wald $\chi^2(3) = 0.0000$, R^2(within) = 0.3330			Prob > $F(3,611) = 0.0000$, R^2(within) = 0.3543		
	R^2(between) = 0.0149, R^2(overall) = 0.0397			R^2(between) = 0.0960, R^2(overall) = 0.0157		
F-test (pool model vs. fixed effect model): $F(210,611) = 4.09$, Prob > $F = 0.0000$						
Breusch and Pagan Lagrangizan Multiplier test for random effects: $\chi^2(1) = 31.20$, Prob > $\chi^2 = 0.0000$						
Hausman specification test: $\chi^2(3) = 336.67$, Prob > $\chi^2 = 0.0000$						
	Rural random effect model			Rural fixed effect model		
	Coefficient	*z*-Statistics	95% Conf. interval	Coefficient	*z*-Statistics	95% Conf. interval
ln((price+1)/cpi)	−0.0537	−1.99*	−0.107 to −0.000736	−1.07	−3.24**	−1.72 to −0.416
ln(density)	0.0266	1.02	−0.0248 to 0.0780	−0.0521	−0.22	−0.519 to 0.415
ln(income/cpi)	−0.422	−1.23	−1.09 to 0.251	−6.10	−6.36**	−7.99 to −4.20
Constant	2.94	1.05	−2.57 to 8.44	55.5	7.15**	40.1 to 70.8
Number of observation = 194, number of groups = 55						
	Prob > Wald $\chi^2(3) = 0.1406$, R^2(within) = 0.2784			Prob > $F(3,136) = 0.0000$, R^2(within) = 0.2987		
	R^2(between) = 0.0.0454, R^2(overall) = 0.0416			R^2(between) = 0.0109, R^2(overall) = 0.0340		
F-test (pool model vs. fixed effect model): $F(54,136) = 4.17$, Prob > $F = 0.0000$						
Breusch and Pagan Lagrangizan Multiplier test for random effects: $\chi^2(1) = 13.30$, Prob > $\chi^2 = 0.0003$						
Hausman specification test: $\chi^2(3) = 57.08$, Prob > $\chi^2 = 0.0000$						

cpi: Consumer Price Index.
* $p < 0.05$.
** $p < 0.001$.

0.00323 in urban model, which are nearly zero. Positive and relatively large non-cash elasticity is estimated with significance in national model and rural model, while negative and insignificant in rural model. The former results contradict our anticipation. With negative coefficient, activity level of local economy is significant as a determinant of the demand in all models.

4. Discussion

We estimate price elasticity of demand for influenza vaccine among the elderly in Japan with national representative panel data: nearly zero in nationwide, nearly zero in urban area, and −1.07 in rural area. The selection of fixed effect models among models estimated by diagnostic tests is not unexpected, when the rise in uptake rates through a process of diffusion and relative invariability of variables such as price, density of shot location, and average income per capita, are taken into account. The estimators in fixed effect models should be most statistically efficient among those models, and the figures of price elasticity can be considered as estimators after controlling not only observed factors but also unobserved ones.

The almost totally price inelastic result at national level is probably due to the contribution by urban samples, of which number is much larger than rural. Price elasticity of nearly zero in urban area is surprising, which contrasts with the previously reported relatively elastic −0.26 in 13 big cities in 2001/2002 season and 2002/2003 season [14]. Even if we limit by the season for the sake of comparison, our results, −0.00323 to −0.0384 is obviously less elastic. Perhaps this difference is explained by the difference in 'urban area' surveyed. In our survey, only 14.5% of urban samples inhabit the 13 big cities surveyed by the previous study.

Highly elastic result in rural area may be explained by a lower income of the elderly compared to those of urban area, which is suggested by our observation of the activity level of local economy. An opportunity cost of the difference in price around ¥1183 (US$10.29) may be higher in rural

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area. A previous study on participation in cancer screening in Japan [27] discussed that a small fee, arguably similar to the price in this study, seemed to have nothing to do with higher participation rate observed in rural communities, and ignored price as a determinant of participation in their analysis. Our results, however, implies that subsidy that reduce price to a consumer might be effective in such situation.

The unanticipated positive non-cash price elasticity in urban fixed effect model is not so surprising, since it is not difficult to imagine the easy geographical access in concentrated urban area that a consumer may not pay much attention to travel cost when seeking health care. Positive non-cash elasticity at national level is probably due to the contribution by the large number of urban samples, as well.

The sampling method used in the survey data of this study, simple random selection using individual level sampling frame, is chosen for the purpose of studying the expected level of price faced by an 'average' aged person, overcoming concurrent municipality mergers. Simple random selection at an individual level is rarely used in nationwide surveys, while the combination of selection using list of municipality as a frame and estimation with population weights is more frequently used mainly because of practicality [16,29,30]. Our approach, however, does not accompany any bias, and it is therefore methodologically rigorous as the other approach.

The results of this study question the rationale for subsidy in influenza vaccination programme targeting the elderly. The elderly is not sensitive to price change especially in urban area, which means that reducing the price does not encourage them more to receive a shot. A benefit-cost analysis of current Japanese programme speculates potential benefit gain obtainable from increasing subsidy based on the estimation of price elastic demand in big cities [14]. But given the price inelastic results of this study, it is not recommendable to hastily raise the subsidy level at least in urban area. Since we demonstrate the cost-effectiveness of current programme with average subsidy level of 71%, of which results unchanged even when the effectiveness of reducing mortality is assumed negligible, elsewhere [31], more effort on public relations or health education without the increase of subsidy level may be a preferred policy in urban area. There may be some potential benefit gain by increasing subsidy in rural area.

5. Conclusions

Our finding shows that demand for influenza vaccination among the elderly can vary from elastic to inelastic depending on the characteristics of locality, and there are cases where subsidy cannot be effective. This addresses implications for developed countries where similar vaccination programmes are implemented. There are cases that maintaining or increasing level of subsidy is not an efficient use of finite health care resources. When organising a vaccination programme, managers should be careful about the balance between subsidy and other efforts, by taking the characteristics of the locality into account and with price elasticity of demand in mind. Further studies looking at income elasticity of demand or the effect of other efforts to encourage people to receive a shot, which this study does not model directly, are awaited.

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Original Article

Attenuated Antibody Reaction for the Primary Antigen but not for the Recall Antigen of Influenza Vaccination in Patients with Non-Hodgkin B-Cell Lymphoma after the Administration of Rituximab-CHOP

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To assess the humoral response to the influenza vaccine in patients undergoing R-CHOP therapy (rituximab combined with cyclophosphamide, doxorubicin, vincristine, and predonisolone) for non-Hodgkin lymphoma (NHL), the anti-hemagglutinin (HA) titer in 7 NHL patients undergoing therapy was compared with those in 10 control group subjects in the 2005/2006 season. Four weeks after vaccination, the HA titers against the influenza type A H1N1 and type B antigens, the same antigens that had been used in the previous seasons, were elevated in all patients treated with R-CHOP. In contrast, there was no increase in the geometric mean titer for type A H3N2 antigen, which was newly included in 2005/2006 season, in the patients treated with R-CHOP, while there was a significant increase in the 10 control subjects ($p = 0.014$). This study showed that vaccination against influenza virus generated an appreciable humoral response to recall antigens in NHL patients treated with R-CHOP therapy, but not to the primary antigen. [*J Clin Exp Hematopathol 49(1) : 9-13, 2009*]

Keywords: R-CHOP, non-Hodgkin lymphoma, influenza vaccination, primary antigen, recall antigen

INTRODUCTION

Influenza is one of the most common infectious diseases, affecting people of all age groups and influencing morbidity and mortality worldwide. To date, the most effective method of protection against infection with the influenza virus is influenza vaccine, and annual vaccination for immunocompromised patients is recommended.[1] Patients with non-Hodgkin lymphoma (NHL) are at special risk of influenza virus infection because of a constitutive immunodeficiency, intensified by immunotherapy, chemotherapy, or radiotherapy and usually old age, which may also adversely affect the immunological response to viral infections, thereby inhibiting the immune response to vaccines. However, the data on the immunogenicity of influenza vaccination in patients with NHL tend to vary greatly. In some studies, the influenza vaccine has been reported to be less immunogenic in NHL patients in comparison to healthy people, despite appropriate vaccination,[2-5] while in another study the influenza vaccination was reported to induce a sufficient immune response in patients with NHL, irrespective of any previous chemotherapy.[6]

Rituximab, a chimeric monoclonal antibody directed against the cell surface antigen CD20 of B cells, has been demonstrated to be an effective treatment for non-Hodgkin B-cell lymphoma, in which CD20 is expressed at the surface of malignant cells, and treatment with rituximab combined with CHOP (cyclophosphamide, adriamycin, vincristine, and prednisolone) (R-CHOP), is now recognized as the standard therapy for CD20-positive aggressive B-cell lymphoma.[7,8] Although rituximab induces an almost complete depletion of normal B lymphocytes in the peripheral blood for an average of 6-9 months, it is unusual for treatment by rituximab alone to result in suppression of serum immunoglobulin or infective complication.[9] However, data on the effect of R-CHOP therapy on the immune response to active immunization with influenza vaccine in NHL patients are scarce. Therefore, we

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conducted a preliminary investigation to evaluate the effect of R-CHOP therapy on the immunogenicity of vaccination against influenza and to assess vaccination safety in NHL patients.

PATIENTS AND METHODS

Characteristics of patients and control subjects

The patient characteristics are shown in Table 1. Seven patients with NHL (age, 39-71 years ; median, 49 years ; 3 with diffuse large B-cell lymphoma, 3 with follicular lymphoma, and 1 with small lymphocytic lymphoma) were treated with 6 cycles of CHOP therapy combined with rituximab (R-CHOP) (375 mg/m^2 intravenously, 6 doses, every 3 weeks). Three patients were vaccinated during the 6 cycles of R-CHOP therapy, 3 within 2 months after the 6th cycle, and one 11 months after the R-CHOP therapy. Two patients with NHL (62 and 64 years of age, respectively), treated with only 6 cycles of CHOP therapy (one was in the course of the CHOP therapy and the other was 1 year after the CHOP therapy) without rituximab (CHOP alone), were compared as a control. Rituximab was not used for the latter patient because rituximab was not yet available at that time. To confirm the immunogenicity of the vaccine, 8 healthy subjects were also included as healthy controls (age, 31-45 years ; median, 39 years). The vaccinations consisted of 0.5 mL split virion inactivated vaccine for 2005-2006 (Hokken, Saitama, Japan) containing a 15 mg hemagglutinin (HA) dose of A/New Caledonian/20/99 (NC, H1N1), A/New York/55/04 (NY, H3N2), and B/Shanghai/361/02 (SHAN), administered subcutaneously.

Hemagglutination inhibition test

The immunogenicity of the vaccine was tested by the hemagglutination inhibition (HI) test. HI antibody titers were measured just before vaccination and 28 days later. The serum samples were separated and stored frozen at -20°C until tested. For the HI test, the serum samples were serially diluted from 1:10 to 1:1,280 and co-incubated with 0.5% turkey red blood cells and influenza strains. The HI titer was determined as the reciprocal of the highest serum dilution causing complete inhibition of the agglutination of red blood cells.

The humoral response to the 3 antigens contained in the influenza vaccine was assessed by calculating the following parameters : geometric mean titers (GMT), mean fold increase (MFI), the seroresponse rate (the percentage of subjects with a 4-fold or more increase), and the seroprotection rate (the percentage of subjects with an HI titer of at least 1 : 40) in the HI titers.

Outcomes of the study

A satisfactory humoral response was defined as either a positive seroresponse or positive seroprotection. The titer of an antiserum not showing any inhibition was recorded as $< \times 10$. A complete blood count was done for all treated patients to assess the total lymphocyte count.

Upon requesting influenza vaccination, appropriate informed consent was obtained from each of the subjects involved in this pilot study.

Statistical methods

The statistical significance of the comparisons of the mean values was assessed by either the non-parametric Mann-

Table 1. Characteristics of patients at baseline (day 0)

Clinicohistological findings	R-CHOP (n = 7)	CHOP alone (n = 2)	Healthy control (n = 8)
Age (years)	54.4 ± 11.0	63	41.4 ± 11.7
Male, sex	4	1	8
Histology			
DLBCL	3	1	
FL	3	0	NA
SL	1	0	
PT	0	1	
Lymphocytes (/μL)	644 ± 221	1,254	NE
Serum IgG levels (mg/dL)	930 ± 359	771	1,059 ± 224

Data are shown as mean ± SD. DLBL, diffuse large B-cell lymphoma ; FL, follicular lymphoma ; SL, small lymphocytic lymphoma ; PT, peripheral T-cell lymphoma ; R-CHOP, CHOP therapy with rituximab ; CHOP alone, CHOP therapy without rituximab ; CHOP denotes cyclophosphamide, dexorubicin, vincristine, and prednisone ; NE, not examined ; NA, not applicable

Whitney U test or two-tailed Fisher's exact test. Probability (p) values < 0.05 were considered to be statistically significant.

RESULTS

At the time of vaccination, lymphocytopenia (< 1,000/μL) was seen in 5 of 7 patients treated with R-CHOP (Table 1). Two patients who were within 2 months of the completion of R-CHOP therapy showed a low titer of IgG, although there was no significant difference in the IgG value between the R-CHOP group and the non-R-CHOP group, which included healthy subjects. Six patients (85.7%) treated with R-CHOP, 1 patient (50.0%) treated with CHOP alone, and 8 (100%) healthy subjects had a history of influenza vaccination in the last few years before the 2005-2006 season.

The GMT, MFI, and rates of seroprotection and seroresponse of the patients treated with R-CHOP, CHOP alone, and the healthy controls are shown in Table 2. There were no significant differences in the pre-vaccination GMT of the HI antibodies, e.g. as a result of previous infection or vaccination between the patients with the R-CHOP therapy and the non-R-CHOP group, which included healthy subjects. The two patients treated with CHOP alone, who lacked a history of vaccination, were negative for all of the antibodies before vaccination. Four weeks after vaccination, positive seroprotection was seen in 6 of 7 against the influenza type A H1N1 (NC) and in all 7 against type B (SHAN) antigens in patients treated with R-CHOP, for which the same antigens had been used in the previous seasons. There was no significant difference in the GMT among the R-CHOP group and the non R-CHOP control group (Table 2). In contrast, there was no increase in the GMTs of the HI antibody for the type A H3N2 (NY) antigen, which was newly included in the 2005-2006 season, by the patients treated with R-CHOP, but there was a significant increase for the healthy controls (p = 0.029) and for all 10 control subjects, including the two patients who were treated with CHOP alone (p = 0.014), thus suggesting a satisfactory immunogenicity of the NY antigen. The MFI was significantly lower for the R-CHOP group than for the healthy control subjects (p = 0.014) and for all control subjects (p = 0.0007). The response of the NY antigen was significantly lower for patients treated with R-CHOP (1 of 7, 14.2%) in comparison to that of the control subjects (8 of 10, 80.0%) (p = 0.015). Only 1 patient treated with R-CHOP showed a positive titer for the H3N2 (NY) antigen (1:40) at the time of vaccination, thus suggesting a previous exposure to the antigen. A response to more than 1 antigen was obtained by all but 1 of the R-CHOP patients, and all of the 10 control subjects. No difference was noted between the R-CHOP and the control group subjects in the response rate to all 3 antigens or to none of them. In the patients receiving R-CHOP therapy, there was no apparent association between the humoral response and age, gender, disease duration, histology of lymphoma, or the time interval since receiving the last rituximab. In addition, vaccination against influenza was not associated with a significant worsening of clinical or laboratory indices such as fever or liver dysfunction and none of the patients receiving R-CHOP therapy developed influenza during this influenza season.

DISCUSSION

Vaccination against influenza generated a humoral response for 2 of the 3 antigens tested (NC and SHAN but not NY) in NHL patients treated with R-CHOP therapy, suggesting that the vaccine was not uniformly immunogenic among the antigens. The immune responsiveness for the recall antigens (NC and SHAN) that had been used in the previous season was comparable to the control group, and achieved titers of functional antibodies greater than the protective threshold, irrespective of previous chemotherapy administration. In contrast, the antibody titer against the primary antigen (NY), which was a newly included antigen in the 2005-2006 season, was not elevated (< ×40) in any of the patients treated with R-CHOP.

The immune responsiveness of patients treated with rituximab has been addressed by several studies of patients with lymphoma. Horwitz *et al.* evaluated the ability of 35 patients with lymphoma, who were being treated with rituximab and cyclophosphamide, to respond to vaccination against tetanus, *Haemophilus influenzae*, and pneumococcus administered at 6 and 9 months after their last rituximab infusion.[10] Most of the patients produced protective antibody levels against hemophilus and tetanus but not against pneumococcus, and the pre-existing antibody levels against tetanus and pneumococcal polysaccharide were shown to be unaffected by a single course of rituximab. Interestingly, results similar to our observations have also been reported in other studies. van der Kolk *et al.*[11] reported the effect of treatment with rituximab on the humoral immune response to 2 primary antigens (keyhole limpet hemocyanin and hepatitis A vaccine) and 2 recall antigens (tetanus toxoid and poliomyelitis vaccine) in 11 patients with relapsed, low-grade lymphoma. None of the patients responded to the primary antigens before or after the treatment. In contrast, all patients responded to recall antigens, although the response was significantly lower than that before treatement.[11] Oren *et al.* reported that rheumatoid arthritis patients treated with rituximab had low response to a different H3N2 antigen (California) than the one used in the present study, that was included in the vaccine of the 2005-2006 season, while the response rate to the other 2 antigens was similar among all patients.[12] These results suggest that lower responsiveness to primary antigens may be common to rituximab treatment.

The two recent studies may explain in part why the re-

Table 2. Antibody kinetics in patients with R-CHOP therapy and control vaccinated against influenza in the epidemic season 2005-2006

Subjects	GMT	MFI	Protection	Response
A/New Caledonia/20/99 (H1N1)				
Pre-				
R-CHOP	36.23			
CHOP alone	14.14	NA	NA	NA
Healthy donor	80.00			
Control, total	56.57			
28 days post-				
R-CHOP	48.76	1.49	86%	29%
CHOP alone	28.28	2.00	50%	0%
Healthy donor	95.14	1.19	88%	13%
Control, total	74.67	1.32	80%	10%
A/New York/55/04 (H3N2)				
Pre-				
R-CHOP	13.46			
CHOP alone	14.14	NA	NA	NA
Healthy donor	11.89			
Control, total	12.31			
28 days post-				
R-CHOP	13.46	1.00	29%	0%
CHOP alone	56.57	4.00	50%	100%
Healthy donor	47.57[a]	4.00[c]	63%	75%
Control, total	49.25[b]	4.00[d]	60%	80%[e]
B/Shanghai/361/02				
Pre-				
R-CHOP	36.23			
CHOP alone	10.00	NA	NA	NA
Healthy donor	47.57			
Control, total	34.82			
28 days post-				
R-CHOP	53.84	1.81	100%	29%
CHOP alone	40.00	4.00	50%	100%
Healthy donor	61.69	1.35	100%	0%
Control, total	56.57	2.00	90%	20%

GMT ; geometric mean titer, MFI ; mean fold increase, NA ; not applicable, R-CHOP ; CHOP therapy with rituximab, CHOP alone ; CHOP therapy without rituximab. CHOP denotes cyclophosphamide, dexorubicin, vincristine, and prednisone. The differences between groups were tested in Mann-Whitney unpaired test (a-d) or Fisher's exact test (e), and $p < 0.05$ was considered as significant.

sponse to the recall antigen is maintained to some degree after treatment with rituximab. Mamani-Matsuda *et al.* demonstrated the persistence of $CD27^+IgG^+$ memory B cells in the spleen in contrast to the decrease or depletion of memory B cells in the peripheral blood after the treatment with rituximab.[13] Ahuja *et al.* demonstrated that the plasma cells, which pool in spleen and bone marrow, do not need a significant supply from memory B cells for their maintenance and that they live long enough to maintain the antibody titers over a long period without renewal.[14] These findings suggest that depletion of memory B cells in peripheral blood with rituximab should have no effect on either the number of $CD27^+$ IgG^+ memory B cells or long-lived plasma cells, thus leading to the maintenance of the response to the recall antigen.

The roles of CHOP therapy and rituximab in response to the vaccination profiles remain to be elucidated. It is not

certain whether antibody production after influenza vaccination was attenuated by the effect of both CHOP and rituximab, or only by rituximab. However, the normal antibody production after vaccination of the NY antigen in the 2 NHL patients who were treated with CHOP alone suggests that rituximab was responsible for the attenuation of the response to the primary antigen.

This preliminary study demonstrates that the vaccination of B-cell lymphoma patients against influenza is safe. These findings also suggest that an appreciable humoral response to recall antigens, but not to the primary antigen, is generated in NHL patients treated with R-CHOP. Larger studies to evaluate the respective impact of rituximab and CHOP on the immunogenicity of influenza vaccination are necessary to confirm these findings.

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Effectiveness of an acellular pertussis vaccine in Japanese children during a non-epidemic period: a matched case-control study

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SUMMARY

The number of pertussis cases in Japan has decreased dramatically following the nationwide use of an acellular pertussis vaccine combined with diphtheria-tetanus toxoids (DTaP vaccines) which began in 1981. However, the effectiveness of the DTaP vaccine has not been systematically evaluated using appropriate epidemiological methods during a non-epidemic period in Japan. We evaluated the vaccine effectiveness (VE) of the Kaketsuken DTaP vaccine which contains two-component pertussis antigens in Japanese children from 1999 to 2001 using a matched case-control design and data from the Basic Resident Registration and Maternal and Child Health Handbooks. The DTaP vaccination history of 15 children with pertussis and 59 controls was obtained. The VE of 3 or 4 pertussis vaccinations compared with non-vaccination (baseline) was 96·9% for coughing attacks that lasted ⩾7 days, 96·4% for those lasting ⩾14 days, and 95·9% for those lasting ⩾21 days. These findings suggest that DTaP vaccination effectively prevented pertussis during a non-epidemic period in Japan.

INTRODUCTION

Acellular pertussis (aP) vaccination in Japan was introduced in 1981 after confirmation of antibody production in vaccinees and demonstration of the vaccine's clinical safety [1] and prophylactic effect on secondary infection in family members [2]. A number of randomized controlled trials (RCT) were conducted later, mainly in Europe, to evaluate aP vaccines. Since then, aP vaccines have been used in many countries [3, 4].

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Several observational studies have been conducted worldwide to evaluate the effectiveness of aP vaccine. However, most studies evaluated vaccine effectiveness (VE) during pertussis epidemics. Effectiveness of aP vaccine in a non-epidemic period has been evaluated in only a few studies [5, 6]. By 1987, a Japanese observational study on secondary infection in family members reported the effectiveness of aP vaccine during an epidemic. The National Epidemiological Surveillance of Infectious Diseases showed that the number of reported cases of pertussis decreased dramatically as the vaccination rate increased, suggesting the effectiveness of the aP vaccine. No increases in the number of infected patients suggestive of apparent pertussis outbreaks have been reported since 1997 [7].

No observational study to directly evaluate the effectiveness of aP vaccine has been conducted since the number of reported cases of pertussis started to decrease in Japan.

In addition to the fact that pharmacoepidemiology in Japan is still an underdeveloped discipline, the lack of a database of personal vaccination histories may explain why so few observational studies of VE have been conducted in Japan. Accurate information about individual vaccination status is indispensable for observational studies of VE. In the United States, influenza vaccination information is recorded in the HealthPartners computerized influenza vaccination database and has been used for a cost-effectiveness study [8]. The General Practice Research Database (GPRD) in Great Britain contains vaccination information which has been used for a case-control study [9]. However, such an electronic database has not been developed in Japan. Instead, all parents living in Japan are required to keep their children's vaccination records in their Maternal and Child Health (MCH) Handbooks according to the Maternal and Child Health Law. Parents in Japan therefore have reliable information on their children's vaccination status [10]. Data from the MCH Handbooks could be used to check vaccination status and therefore be used in research studies.

Another limitation on observational studies to evaluate VE in Japan is the need for population sampling. In order to conduct an observational study in the general population, researchers need to check the personal vaccination statuses of individual residents. A telephone survey might be an effective way to collect such information; however, it requires tremendous time and effort to select appropriate subjects based on their age and sex. Many of the existing Japanese observational studies were therefore conducted in patients seeking treatment at hospitals without attempting to survey a representative and unbiased population sample. Fortunately, information such as individual residents' address, name, age, and sex can be obtained for each household from the Basic Resident Registration in Japan. Therefore, efficient random sampling of study subjects is possible if a copy of the resident card is available [11]. We therefore conducted a matched case-control study in Japanese children to evaluate the effectiveness of aP vaccine during a non-epidemic period based on data from MCH Handbooks and the Basic Resident Registration.

METHODS

Paediatricians at 57 medical institutions and paediatric general practitioners participated in the study. We recruited the paediatricians from the members of the Kitakyushu City Medical Association, via an invitation explaining the purpose and plan of our study. Of the paediatricians belonging to the Kitakyushu Medical Association, 66% (57/86) collaborated with our study. Cases and controls were selected from children who lived in Kitakyushu City (population 1·01 million in 1999). Based on a VE of 0·96, which was estimated in a previous small-scale pilot study (K. Okada *et al.*, unpublished data), three controls were selected for each case to ensure a statistical power of 90%.

Vaccine studied

aP vaccines combined with diphtheria-tetanus (DT) toxoids (DTaP) were available in Japan from six manufacturers when the study was conducted. The DTaP vaccine produced by The Chemo-Sero-Therapeutic Research Institute (Kaketsuken; Kumamoto, Japan) was estimated to have been given to >95% of children in Kitakyushu City. The rate of use of the Kaketsuken vaccine was estimated from the total number of units supplied by the manufacturer in the city of Kitakyushu divided by the total number of DTaP vaccines that children received in the city of Kitakyushu. The Kaketsuken vaccine, a two-component aP vaccine, contains a modified formulation of the original aP vaccine; its pertussis toxin (PT) and filamentous haemagglutinin (FHA) were isolated by affinity chromatography to obtain a constant ratio of 1:4 PT to FHA [12]. The standard immunization schedule for DTaP in Japan is an initial dose given three times from ages 3 to 12 months followed by a single booster injection given between 12 and 18 months.

Patients, controls, and diagnosis

From April 1999 to March 2001, the participating paediatricians registered 116 children with clinically suspected pertussis who had attended their hospital or paediatric clinic, and definitive diagnoses were made by another paediatrician responsible for case diagnosis. Clinically suspected pertussis was determined by the participating paediatricians according to the reporting standards used for Japan's pertussis

surveillance, i.e. coughing lasting >1 week with either: (*a*) coughing episodes with staccato, whooping, or paroxysmal cough at night and/or (*b*) neonates or children with otherwise unexplained vomiting or apnoea after cough. For these cases, we examined bacterial isolates from nasopharyngeal swab samples, PT paired serum, and levels of antibody to the fimbriae antigen which is not included in the two-component vaccine, in addition to WBC count and lymphocyte count. After these tests, the paediatrician responsible for case diagnosis reviewed the diagnosis of pertussis on the basis of patient files and test results supplied by the participating paediatricians, and definitively diagnosed pertussis in 15 children. Definitive diagnosis was based on the following: (1) characteristic coughing attacks (repeated staccato, whoop or paroxysmal cough that lasted ⩾7 days and (2) either isolation of *Bordetella* pertussis, serodiagnosis (at least fourfold increase of PT-IgG or agglutinin titre) or contact with a family member with confirmed pertussis.

Controls were randomly selected from the Basic Resident Registration of Kitakyushu City. In Japan, all citizens are registered on the Basic Resident Registration. Individuals can view details including names, dates of birth, sex and address. Controls [matched by age (±6 months of the date of birth) and sex] were selected who were living in the same residential area as the cases during the study period.

The number of vaccinations was defined as the number of vaccinations received at least 28 days before definitive case diagnosis. A period of 28 days was chosen as the valid period to allow for the development of antibodies (around 14 days) and the normal incubation period (14 days). The age of cases at the time of the valid period was used in the data analysis.

Study method and questionnaires

The study description and a questionnaire with a manual were sent to parents of potential controls between October and December 2005. In a previous small-scale pilot study (using the same method), a 43% valid response rate from the parents of 30 children was achieved. Based on this response rate, we randomly selected nine candidates, which included 'reserves' if additional mailing of questionnaire forms was needed, for each case from the Basic Resident Registration. Questionnaire forms were sent according to the selection order to the first six consecutive candidates per case. If valid responses from three or more controls for each case were not received within 2 weeks, questionnaires were sent to the three 'reserve' candidates. The study description and general information on pertussis were posted on the Kitakyushu Medical Association website to provide information for parents.

The questionnaire sent to the parents of candidate controls included questions on: (1) the history of DTaP vaccination (date, vaccine manufacturer and lot number), (2) whether the control child was born in Kitakyushu City or had moved from another city (in which case the date of arrival was requested), and (3) any history of pertussis, including the date of diagnosis and name of diagnosing institution if available. Parents who consented to taking part in the study also copied the history of DTaP vaccination from their MCH Handbooks. Questionnaires could be returned to the Kitakyushu Medical Association by fax or mail.

The same definitions of number of vaccination and age used for the cases were applied to the controls. The exclusion criteria for controls were as follows: (1) onset of pertussis before the definitive diagnosis of pertussis in the matched case, (2) moving to Kitakyushu City after the onset of pertussis in the matched case, and (3) use of vaccines other than Kaketsuken DTaP vaccine.

The reason for this 4-year delay in surveying controls after the identification of the cases is that there was a change in the method of identifying control subjects. Initially, we planned to collect hospital-based controls, but we received advice from our statistician that the collection of community-based controls would be more appropriate. However, the method of collecting community-based controls in Japan was not established at that point, and it took some time to change the research protocol. Moreover, due to the enactment of the Protection of Personal Information Act in Japan, obtaining permission to view the Basic Resident Registration from the local government also takes a long time. Therefore, there was a delay between collecting the cases and starting to identify suitable controls.

The controls were surveyed in accordance with the 'Ethical Guidelines for Epidemiological Studies' issued by the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare in July 2002. The study protocol was approved by the ethical committee of the Public Health Research Foundation.

Table 1. *Age of children and number of DTaP vaccinations*

	0†		1		2		3		4		Total	
Age*	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control
<1 yr	7	20	0	4	0	3	1	5	0	0	8	32
1 yr	3	0	0	0	0	1	1	12	0	2	4	15
2 yr	1	0	0	0	0	0	0	2	0	5	1	7
3 yr	1	0	0	0	0	0	0	0	0	1	1	1
5 yr	0	0	0	0	0	0	0	0	0	2	0	2
6 yr	0	0	1	0	0	0	0	0	0	2	1	2
Total	12	20	1	4	0	4	2	19	0	12	15	59

* Age of children.
† Number of DTaP vaccinations.

Statistical analysis

We used SAS software (SAS Institute Inc., Cary, NC) and a conditional logistic regression model to calculate the matched odds ratio (OR) and two-tailed 95% confidence interval (CI) for pertussis events by number of vaccination [1–2 vaccination(s) or 3–4 vaccinations]. The formula $(1-\mathrm{OR})\times 100$ was used to calculate VE. This was stratified according to the duration of coughing attacks: ⩾7 days, ⩾14 days, or ⩾21 days.

RESULTS

Questionnaires for cases

During the study period, 15 children, aged 4 months to 6 years, received a definitive diagnosis of pertussis. Eight of the children were aged <1 year [their ages were 4 and 10 months (one case each) and 5, 6 and 7 months (each in two cases)], four were aged 1 year, and the remaining three were aged 2, 3, and 6 years (Table 1). Six were boys and nine were girls. Twelve had never been vaccinated, while one child had been vaccinated once and two children had been vaccinated three times.

Ten children had persistent staccato cough, six whooped, 14 had nocturnal paroxysmal cough, two had cyanosis (lasting 1 day and 3 days respectively) and one patient presented with apnoea. Coughing attacks lasted 10–90 days, with one child having coughing attacks that lasted 7–13 days, two children having attacks that lasted 14–20 days, and 12 children having attacks that lasted >21 days. One patient was admitted to hospital. The WBC count was ⩾15000/μl in 11 children, and the percentage of lymphocyte was ⩾70% in three.

The definitive diagnosis of pertussis was based on *Bordetella* pertussis isolation in two children, on positive PT-IgG antibody titre or significant increase in antibody level in 10 children, and on positive agglutinin titre or its significant increase in three children. No child had contact with a family member with confirmed pertussis. However, of the 15 confirmed cases, 10 had siblings, and among these, three had a sibling who showed signs of pertussis (i.e. consistent coughing lasting ⩾14 days), and could have been an infection source.

Questionnaires for controls

For four cases, valid responses were not received within 2 weeks of sending questionnaires from three or more matched controls, so questionnaires were also sent to the parents of the 'reserve' candidates until valid responses were received from three or more controls for each case.

The questionnaire return rate was 69·6% (71/102). We received valid responses from the parents of 59 children; this amounted to three controls for six cases, four controls for four cases, and five controls for five cases. The age of the control children ranged between 4 months and 6 years: 32 were aged <1 year; 15 were aged 1 year; seven were aged 2 years; one was aged 3 years; two were 5 years and two were 6 years (Table 1). Of the controls, 25 were boys, and 34 were girls. Twenty had never been vaccinated, four had been vaccinated once, four twice, 19 three times, and 12 four times.

Twelve children were excluded from the efficacy analysis: one had an onset of pertussis before the onset in the matched case, four had moved to Kitakyushu City after the onset of pertussis in the

Table 2. *Effectiveness of aP vaccine*

Case definition	No. of subjects: Case	No. of subjects: Control	No. of vaccinations	OR*	95% CI	VE* (%)	95% CI
⩾7 days cough	15	59	1–2	0·132	0·010–1·690	86·8	−69·0 to 99·0
			3–4	0·031	0·003–0·378	96·9	62·2 to 99·7
⩾14 days cough	14	56	1–2	0·140	0·011–1·742	86·0	−74·2 to 98·9
			3–4	0·036	0·003–0·465	96·4	53·5 to 99·7
⩾21 days cough	12	46	1–2	0·161	0·013–2·075	83·9	−107·5 to 98·7
			3–4	0·041	0·003–0·539	95·9	46·1 to 99·7

* Effectiveness of acellular pertussis vaccinations compared with non-vaccination.

matched cases, and seven had been vaccinated with vaccines other than the Kaketsuken DTaP vaccine.

Age of children and number of vaccinations

The rate of vaccination with Kaketsuken DTaP was 87% (comprising a total of 136 injections) in the 67 children (obtained from the 71 completed questionnaires excluding the four children who had moved to Kitakyushu City after the study period).

Vaccination status by age (defined as having received at least one vaccination) was 1/8 in children aged <1 year, 1/4 in children aged 1 year, 0/1 in the children aged 3 or 5 years, and 1/1 in the child aged 6 years (Table 1). Vaccination status in control children was 12/32 in those aged <1 year, 15/15 in those aged 1 year, 7/7 in those aged 2 years, 1/1 in the child aged 3 years, and 2/2 in children aged 5 or 6 years. Based on the number of vaccinations by age, the vaccination rate was lower in the cases than in the controls.

Effectiveness of pertussis vaccine

The cases were divided into three groups based on the duration of coughing attacks characteristic of pertussis: ⩾7 days, ⩾14 days, and ⩾21 days. The cases were further divided into two groups, depending on whether they had received one or two vaccination(s), or three or four vaccinations, to estimate VE by using a conditional logistic regression model (Table 2). The VE of three or four vaccinations compared with non-aP vaccination (baseline) was 96·9% (95% CI 62·2–99·7) for coughing attacks that lasted ⩾7 days, 96·4% (95% CI 53·5–99·7) for ⩾14 days, and 95·9% (95% CI 46·1–99·7) for ⩾21 days. The point estimate of VE for one or two vaccination(s) was 86·8–83·9%. However, the number of subjects who received only one or two vaccination(s) was small, and therefore the confidence interval was large. Therefore, comparing the effectiveness of one or two with three or four vaccinations was difficult.

DISCUSSION

The effectiveness of DTaP vaccine has never previously been evaluated using appropriate epidemiological methods in Japan. We surveyed the DTaP vaccination history of children with pertussis who had coughing attacks that lasted >7 days and of controls who were matched by age and sex in Kitakyushu City. The effectiveness of the DTaP vaccine used in more than 95% of children living in the region for prevention of pertussis was 95·9–96·9% in children who had received three or four vaccinations, equivalent to VE of 96·0% (95% CI 67·4–99·5) in the practice-based controls (children who, for reasons other than pertussis, visited the hospital where the cases received treatment for pertussis around the same time and had the same background as the cases) in the previous study.

A case-control study on DTaP vaccine was conducted in Munich, Germany, from 1993 to 1995. In the cases who were defined as having continual cough for at least 21 days, the VE of three DTaP vaccinations was 93% (95% CI 63–99) [13], which is comparable to the VE of three or more DTaP vaccinations in patients who had continual cough for ⩾21 days estimated in our study (95·9%, 95% CI 46·1–99·7). The Centers for Disease Control and Prevention (CDC) in the United States conducted a case-control study in children aged 6–59 months in seven states and territories by using two types of whole-cell pertussis vaccines combined with DT toxoids (DTwP) and three types of DTaP vaccines

from 1999 to 2000 [14]. The VE estimated in the US study was also comparable to that in our study: 95·4% (95% CI 88·7–98·2) with three DTaP vaccinations and 96·7% (95% CI 90·8–98·8) with four vaccinations.

Since 1991, large-scale field RCTs and cohort studies on DTaP vaccines including aP vaccines developed in Japan have been conducted in children in Europe and Africa. These studies used different designs and case definitions. When evaluated based on the case definition most similar to that used by the World Health Organization (WHO), most DTaP vaccines (with two or more components) showed >80% effectiveness [15].

Thus, the VE reported in the case-control studies are higher than that reported in the RCTs or cohort studies. Pertussis symptoms are often milder in vaccinated children than in their unvaccinated counterparts. VE may therefore be overestimated if the definition 'moderate-to-severe pertussis' is used in the study [16]. Liese *et al.* estimated VE separately based on two sets of definitions, 'pertussis with paroxysmal cough' and 'pertussis with cough', and reported a higher VE among patients who met the stricter criteria [13]. The high VE estimated in our study may be due to the fact that the majority of patients included in the analysis had more severe forms of pertussis (Table 2).

We consider the wide confidence intervals and relatively high point estimates for the effectiveness of one or two doses of vaccine are due to the small number of cases included. However, a similar case-control study conducted in the United States reported the effectiveness of a single vaccination to be 70%, and two doses to be 89%; and they therefore reported similar effectiveness for one or two doses as the present study, i.e. 86% [14].

The effectiveness of aP vaccines in the Japanese population was evaluated based on secondary infection within families in the studies conducted during the pertussis epidemic in the 1980s [17, 18]. However, no placebo-controlled RCT or cohort study was done. In overseas studies, effectiveness of aP vaccines has been evaluated by individual brands. However, other than the study conducted by Kato *et al.* [18], previous Japanese studies on secondary infection within families did not distinguish vaccines by brand.

An RCT or cohort study is ideal for evaluating aP VE. However, because the number of pertussis cases in Japan has decreased substantially due to the increased vaccination rate [19], conducting a cohort study is difficult. Additionally because infant pertussis vaccination is generally recommended in Japan, a randomized study would be unethical. Fine pointed out that the study design for evaluation of secondary infection within families included potential biases that might affect study results [20]. Thus, in the present study, we believe that our use of a case-control design using aP vaccine was the most appropriate to evaluate the effectiveness of DTaP vaccine during a non-epidemic period.

We inspected a copy of the Basic Resident Registration to identify a random sample of control candidates from the community. Sampling efficiency with this method was considered far superior to a telephone survey since control candidates could be matched with cases based on their date of birth and sex provided in the Basic Resident Registration. Unlike authors of studies conducted in Europe and the United States where databases of personal vaccination statuses are available, we used MCH Handbooks kept by parents of study participants as information sources. In Japan, all pregnant women receive an MCH Handbook, and these are retained by most parents or guardians at least until the child reaches the sixth grade of elementary school, which is the end of last required periodical vaccination in Japan. Several reports have been published on epidemiological studies in which MCH Handbooks were used [21, 22]. Documentation of health-care records of mothers and their children including infant vaccination status (including a record of the type of vaccine, manufacturer, lot number, date of vaccination, and administering physician) in MCH Handbooks by physicians is required under Japanese law. Since we asked the parents to copy the details such as manufacturer, lot number and date of vaccination from their MCH Handbooks onto questionnaire forms, the information obtained in the survey was thought to be more reliable than that which could have been obtained from telephone interviews. The study method based on the Basic Resident Registration and MCH Handbooks used in this case-control study on paediatric aP vaccine could therefore be used in Japan as an alternative to the database-oriented study method used in Europe and the United States. The Basic Resident Registration and MCH Handbooks could also be used in other epidemiological studies in Japanese children.

Our study suggests that the Kaketsuken DTaP vaccine effectively prevented pertussis in Japanese children during a non-epidemic period. However,

because this study was conducted in a specific region and had a small number of cases, further research is needed to reach a definitive conclusion.

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DECLARATION OF INTEREST

None.

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