

## Vaccine effectiveness for influenza in the elderly in welfare nursing homes during an influenza A (H3N2) epidemic

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### SUMMARY

Influenza vaccine effect on the occurrence and severity of influenza virus infection in a population residing in nursing homes for the elderly was studied as a cohort study during an influenza A (H3N2) epidemic in Japan. Of 22462 individuals living in 301 welfare nursing homes, 10739 voluntarily received inactivated, sub-unit trivalent influenza vaccine in a programme supported by the Osaka Prefectural Government. There were statistically significantly fewer cases of influenza, hospital admissions due to severe infection, and deaths due to influenza in the vaccinated cohort compared to the unvaccinated controls. No serious adverse reactions to vaccination were recorded. Thus influenza vaccination is effective for preventing influenza disease in persons aged 65 years and over, and should be an integral part of the care of this population residing in nursing homes.

### INTRODUCTION

Influenza A and B viruses are among the most common causes of respiratory tract illnesses that bring elderly persons to seek medical care [1]. Influenza infections more commonly result in medical consultation than do infections with other respiratory viruses [1]. In some countries such as the United States of America, annual influenza vaccination is recommended for all persons aged 65 years and older, and for persons with certain chronic medical disorders [2–4], but there remains a question as to the efficacy of influenza vaccination in persons over 65 years in Japan and no official support by the government for influenza vaccination for them had been established. More than 90% of the deaths attributed to pneumonia and influenza during epidemics occur among persons aged 65 years and older [5]. Influenza viruses continue

to cause mortality and serious morbidity among the elderly (65 years or more in age) [2–5]. In nursing homes for the elderly, residents live in a group in a similar lifestyle. Intervention to prevent infectious diseases including influenza, is most important for the elderly in welfare nursing homes, where both medical care and the availability of staff for the residents are at lower quantitative levels than would be the case in hospitals. Currently available influenza vaccines are effective only against infecting viral strains with haemagglutinins of similar antigenic characteristics. This study provides a cohort study of an analysis of the efficacy of influenza vaccination in elderly residents of welfare nursing homes in Japan.

### METHODS

#### Subjects and methods

We studied 22462 people over 65 years of age residing in all 301 welfare nursing homes for the elderly in

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Osaka Prefecture, Japan, during an influenza (H3N2) epidemic season (November 1998 – March 1999). Peak influenza A (H3N2) activity, as determined by laboratory diagnosis [6–10], occurred in January 1999.

### Vaccination protocol

This study with a programme supported by the Osaka Prefectural Government for influenza vaccination of the elderly was announced and recommended for all people ( $n = 22462$ ) residing in welfare nursing homes ( $n = 301$  nursing homes) for the elderly in Osaka Prefecture, using lectures and written materials equally. The vaccinated group consisted of 10739 persons (47.8% of the whole cohort) who voluntarily received, always with informed consent, either one (2027 subjects) or two (8712 subjects) doses of influenza vaccine (inactivated, killed and sub-unit, manufactured by the Research Foundation for Microbial Diseases of Osaka University and other pharmacological companies, Japan, HA-influenza vaccine A, B) by subcutaneous injections as recommended [11, 12]. There were 11723 (52.2%) unvaccinated persons in the control group. Vaccine strains used in this study were influenza A/Beijing/262/95 (H1N1), A/Sydney/05/97 (H3N2), and B/Mie/1/93 virus culture extracts with chick cell agglutinin in egg allantoic fluid [6, 7].

### Diagnosis of respiratory tract infections

Cases with influenza in this study were diagnosed clinically, and in active surveillance with virus isolation and/or serology as described below [8–10]. Staff at the study-site nursing homes were instructed to collect specimens for virus culture from symptomatic subjects within 4 days of onset of an illness presenting with any of the following: fever, runny nose or nasal congestion, sore throat, cough, headache, muscle aches, chills, vomiting, decreased activity, irritability, wheezing, shortness of breath, and pulmonary congestion. Rhesus monkey kidney cell cultures were inoculated with fresh respiratory secretions within 4 h of collection or as soon as possible thereafter, for culture of influenza viruses [6]. Serum samples were also obtained from volunteer subjects with cold symptoms, stored at  $-20^{\circ}\text{C}$ , and assayed for the presence of haemagglutinating-inhibiting antibodies (SRL and the Research Foundation for Microbial

Diseases of Osaka University, Japan) to several viral strains, including the three viral strains contained in the vaccine [9, 10]. Reports of illness provided by study-site staff also included whether or not patients were treated by a primary care provider; if so, the provider's diagnosis and treatment were recorded.

### Statistical analysis

Statistical analyses were based on logrank-test method [13, 14] and data analysis was performed with statistical power calculations using the SPSS/PC statistical package [6], which calculates a pooled rate difference, that is, an absolute percentage reduction between the vaccinated and control groups. Confidence intervals for the ratio of mean episodes were also computed with Poisson regression. For all analyses,  $P$ -values less than 0.05 were considered significant. The percent reduction in the mean number of episodes (vaccine effectiveness) was calculated with the following equation:  $100 \times (1 - \text{the ratio of mean episode [vaccination group/control group]})$ .

## RESULTS

There were 950 episodes of influenza illness among 22462 subjects during the study period, diagnosed clinically, and some in active surveillance with virus culture and/or serodiagnosis. The temporal distribution of influenza episodes in the study cohort was similar to the overall epidemic curve as defined by isolations of influenza A (H3N2) which was the serological match to the vaccine strains used in this study in Japan (data not shown). Influenza illness in the study cohort was significantly less common in the vaccinated group (256 cases amongst 10739 subjects) than in the unvaccinated control group (694 cases amongst 11723 subjects, Table 1). Differences in the mean age and gender ratios between these two groups were not statistically significant: mean age 79.3/80.0 for men, 83.4/82.3 for women, 82.6/81.4 for total subjects respectively for the vaccinated and control groups, and gender ratio (male/female) 0.30/0.35 respectively for the vaccinated and control groups. Also, vaccine effectiveness was not significantly different in males and females. In both groups, other informations such as previous influenza vaccination status, underlying diseases like diabetes, prevalence of dementia were not monitored in this study. Severity of illness, patient hospitalization and mortality were all lower in the vaccinated group. Influenza was diag-

Table 1. Characteristics of the 22462 elderly persons in nursing homes in 1998–9 influenza epidemic season in this study

	Total	Vaccine group (n = 10739)			Control group (n = 11723)				
		Age	Male	Female	Age	Male	Female		
Number of patients									
Total influenza patients	950(100%)	256(27.0%)	60–69 70–79 80–	13/913 27/1661 59/1007	21/1306 39/3738 97/2917	694(73.0%)	60–69 70–79 80–	99/896 91/1541 125/916	83/1940 113/3442 183/2948
Hospitalization due to severe illness	182(19.2%)	32(3.4%)	60–69 70–79 80–	2/913 3/1661 9/1007	2/1306 4/3738 12/2917	150(15.8%)	60–69 70–79 80–	11/896 21/1541 45/916	10/1940 24/3442 39/2948
Number of death due to influenza	6(0.6%)	1(0.1%)	60–69 70–79 80–	0 0 0	0 0 1/2917	5(0.5%)	60–69 70–79 80–	0 1/1541 1/916	1/1940 1/3442 1/2948

Influenza attack number of denominator population for each cell is shown.

Table 2. Ratios of the cumulative incidences of cases to the total number of people in the vaccinated and unvaccinated (control) groups

Event	Attack rate (%) within vaccinated group	Attack rate (%) within unvaccinated group	P-value*	Vaccine effectiveness†
Onset of influenza	2.38	5.92	< 0.001	59.7
Hospitalization	0.30	1.30	< 0.001	76.7
Death	0.009	0.043	< 0.001	78.2

\* P-value: the comparison between the vaccinated group and the control group.

† Vaccine effectiveness = percent reduction (%):  $100 \times (1 - \text{the ratio of mean episodes [vaccination group/control group]})$ .

nosed in 5.92% (694/11723, episode cases/total number of the group) of the unvaccinated group, but only 2.38% (256/10739) of the vaccinated group (reduction rate 59.7% for prevention of influenza); hospitalization rate was reduced by vaccination from 1.3 to 0.3% (reduction rate 76.7% for prevention of hospitalization), and death was reduced from 0.043 to 0.009% (reduction rate 78.2% for prevention of death). These differences between the vaccinated and unvaccinated groups were statistically significant (Table 2) for risks of both mortality and morbidity.

Antibody responses to the influenza vaccine were investigated preliminary in elderly persons in nursing homes. We confirmed the increase of titres of antibody responses to the vaccine more than 32-fold, and detected better responses to the influenza A strains (H1N1 and H3N2) than influenza B subtypes (data not shown). The vaccine used in this study was highly immunogenic for the influenza A strains (H1N1 and H3N2) after first dose for elderly persons (data not shown). We monitored the post-vaccination reactions in all 10739 cases in this study for 1 week to evaluate whether there were any side effects due to the influenza

vaccination such as fever or local swellings and pains, but no serious adverse events such as anaphylaxis were found in any case, except a sore arm with local swellings and pains within 48 h which recovered completely after 3 days.

More than 3 weeks after immunization are required for sufficient immunogenic activity to prevent influenza [3–5]. To avoid contamination of the data for the vaccinated group by influenza infections prior to acquisition of a protective immune response, we further analysed the data of cases of influenza that were detected more than 3 weeks after influenza vaccination. As shown in Table 3, the effectiveness of influenza vaccination for risks of both mortality and morbidity remained statistically significant. Furthermore, it can be seen from Table 3, that there was no significant difference, in preventing influenza, between one and two doses of vaccine.

## DISCUSSION

The results in this study of patients in welfare nursing homes are compatible with the findings of several

Table 3. *Vaccine effectiveness in patients with influenza onset over 3 weeks after influenza vaccination (n = 10624)*

	Number (%) of cases in vaccinated group*	Mean % of cases in the vaccinated group	Vaccine effectiveness† (%)
Onset of influenza	(a) 30/1997 (1.50%) 141/10624‡ (b) 111/8627 (1.29%)	1.33 %	79.5
Hospitalization	(a) 5/1997 (0.250%) 24/10624§ (b) 19/8627 (0.220%)	0.23 %	82.3
Death	0	0%	100

\* (a) patients with 1-dose of injection (percentage against the number of subjects with 1 dose vaccination:  $n = 1997$ ); (b) patients with 2-dose of injection (percentage against the number of subjects with 2 doses vaccination:  $n = 8627$ ). Comparison of data from subgroup (a) and (b) reveals no significant difference ( $P > 0.05$ ).

† As compared to the unvaccinated group.

Influenza attack number of denominator population for each cell is shown.

‡ Age 60–69: 21/2103, age 70–79: 69/5211, and age 80–: 51/3310.

§ Age 60–69: 3/2103, age 70–79: 12/5211, and age 80–: 9/3310.

recent studies (reviewed in [15]) on the efficacy of influenza vaccine in elderly persons. This study is not a randomized controlled trial but a cohort analysis and that there may be biases that are not recognized that may have accounted for the findings. The risk of onset of illness was moderately reduced by influenza vaccination (vaccine effectiveness = risk reduction (%):  $100 \times [1 - \text{the ratio of mean episodes}] = 59.7\%$ ). However, the risks for both hospitalization due to severe illness, and for mortality were reduced to a greater extent (vaccine effectiveness 76.7 and 78.2% respectively). It is known that inactivated vaccines induce serum antibody responses that can inhibit diffusion and replication of influenza viruses, but they do not induce strong local immune responses to prevent infection [11, 12], which may explain the enhanced effect of vaccination against severe illness and mortality as compared to infection. The clinical illnesses were distributed in time in parallel to isolations of influenza virus and the known epidemic period within this study. There were no serious adverse events identified through monitoring of post-vaccination reactions for 1 week in all 10739 vaccinated cases. Margolis and colleagues [16] have also shown that the incidence of local and systemic side effects in the first 48 h after vaccination was less than 5%.

In summary, this study has demonstrated that when influenza vaccine is administered before an epidemic, and the vaccine strain is closely related to the epidemic strain, serious morbidity and mortality in nursing

homes for the elderly are significantly reduced. Nichol and colleagues have shown the efficacy and cost-effectiveness of vaccination against influenza among elderly persons living in the community: for elderly citizens living in the community, vaccination against influenza is associated with reductions in the rate of hospitalization and in deaths from influenza and its complications, as compared with the rates in unvaccinated elderly persons, and vaccination produces direct dollar savings (direct savings per year averaged \$117 per person vaccinated) [2]. Others have shown the economic benefits of this approach [17]. Almost half (47.8%) of the population in all nursing homes in Osaka Prefecture for the elderly voluntarily received influenza vaccines in the 1998–9 season in a programme supported by the Osaka Prefectural Government, and more (59.3%) in the 1999–2000 season. This is the first and only official support in Japan for influenza vaccination for the elderly at the present time in Japan. Annual universal influenza immunization of elderly persons in welfare nursing homes is a public health imperative that should be carried out by practicing physicians and public health organizations.

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