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Two Outbreaks of Influenza A (H3N2) in a Japanese Nursing Home in the Winter of 1996–1997, with Differing Vaccine Efficacy

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[1]*Department of Public Health and* [2]*Department of Internal Medicine, Niigata University School of Medicine, Niigata 951-8510,* [3]*Department of Virology, National Institute of Infectious Diseases, Tokyo 162-8640,* [4]*Clinical Research Division, Sendai National Hospital, Sendai 982-0045, and* [5]*Sun-Plaza Nagaoka, Nagaoka 940-2111*

MURAYAMA, N., SUZUKI, H., ARAKAWA, M., NEROME, K., MIZUTA, K. and KAMEYAMA, K. *Two Outbreaks of Influenza A (H3N2) in a Japanese Nursing Home in the Winter of 1996-1997, with Differing Vaccine Efficacy.* Tohoku J. Exp. Med., 1999, **188**(4), 289–298 —— Sixty of 128 (46.9%) residents of a nursing home were immunized with two doses of the trivalent split influenza vaccine. They developed 7.4–11.5-fold antibody increases, with a 69–82% protection rate, presenting good immune response rates to the influenza vaccine. Two outbreaks of influenza A (H3N2) occurred. There were no significant antigenic differences among the vaccine strain and the strains isolated from both outbreaks in haemagglutination-inhibition tests, suggesting that the second might have been a reoccurrence. There were no residents who were infected in both outbreaks. The vaccine efficacy against clinical illness in the first outbreak of typical influenza-like-illness (ILI) was 51% (relative risk: 0.49), and the febrile period was reduced significantly by vaccination. In the second outbreak, however, in which all patients had atypical ILI with a high fever but not respiratory symptoms, vaccine efficacy was not apparent for unknown reason. ———— influenza; vaccine efficacy; aging; immunization

Influenza has consistently been associated with excess mortality observed mainly in patients aged 65 or older. Influenza vaccines are strongly recommended for any person aged over 6 months who is at increased risk for complications in developed countries (Fedson et al. 1997). This is particularly the case for aged people over 65 years old. Influenza vaccination of aged people is available in Japan on a voluntary basis, but hardly any elderly Japanese have ever been vaccinated. Historically, the main target group for influenza vaccination in

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Japan was school children until June 1994. This is because it was considered that influenza epidemics in the entire community could be controlled through suppressing transmission in schools.

Outbreaks of influenza at aged people's nursing homes in many areas were reported in the 1996–1997 season, and the Government advised practitioners and local policy-makers to immunize those people. However, little has been studied on influenza immunization among aged people in Japan. This paper reports the results of a prospective non-randomized controlled trial in a nursing home in order to propose the introduction on the vaccination program for elderly persons.

Materials and Methods

We conducted a non-randomized, controlled trial in a nursing home in the winter of 1996–1997.

Study subjects

Residents of the nursing home were offered immunization against influenza. Sixty of 128 residents agreed to participate and immunize as a vaccinated group, and others were classified as a control group (Table 1). There were no significant differences in the proportions of men and women (chi-square test), mean ages (t-test), or risk status between these groups. After obtaining written informed consent from all vaccinees and/or their family members, two doses (0.5 ml per dose) were given subcutaneously on December 6 and 20, 1996 as ordinary influenza immunization procedure in Japan. Past vaccination history of all residents was asked and recorded in nursing charts. From those, none of the residents on the nursing home had previously received influenza vaccination as is usual for elderly Japanese. The commercial trivalent split influenza vaccine licensed in Japan for the 1996–1997 winter season was used (Biken, Osaka). It contained 300 chick cell agglutinating (CCA)/ml hemagglutinin (HA) of A/Yamagata/32/89 (H1N1), 300 CCA/ml of A/Wuhan/359/95 (H3N2), and 250 CCA/ml HA of B/Mie/1/93.

Table 1. *Charactaristics of study subjects*

		Vaccined group	Control group
No.		60	68
Age	Mean±S.D. (range)	84.2±6.7 (71–99)	84.7±5.5 (70–96)
Sex	Male	11 (18.3%)	21 (30.9%)
	Female	49 (81.7%)	47 (69.1%)
Risk status	Cardiac disease	4 (6.7%)	5 (7.4%)
	Pulmonary disease	2 (3.3%)	2 (2.9%)
	Diabetes mellitus	7 (11.7%)	9 (13.2%)

S.D., standard deviation.

The vaccinated group was compared with the control group with respect to the incidence of influenza-like-illness (ILI). International Classification of Health Problems in Primary Care (ICHPPC-2-defined) criteria was applied for its diagnosis. It requires one of the following: (1) viral culture or serological evidence of influenza virus infection, (2) influenza epidemic plus four of the criteria in 3, or (3) six of the following: sudden onset, cough, rigors or chills, fever, prostration and weakness, myalgia, widespread aches and pains, no significant physical signs other than erythema of nasal mucous membrane and throat, and influenza in close contact (Classification Committee of WONCA 1983). Body temperatures were routinely taken and recorded by the nursing staff for any residents who appeared ill.

An "outbreak" was defined on the basis of an overall attack rate of at least 10% in the nursing home within any seven-day period (Patriarca et al. 1985; Arden et al. 1995). The "duration" of an outbreak was defined by the number of days in which one or more cases of ILI occurred, and was considered to be over when there were no additional cases with for 3 consecutive days.

Laboratory investigations

Virus isolation and identification. During the study period, throat swabs were obtained from residents with febrile and/or symptoms of upper respiratory tract infection among both vaccinated and control groups. Virus isolation was performed using the microplate method (Numazaki et al. 1987). Four cell types were used, namely human embryonic fibroblasts, Hep-2, Vero, and Madin-Darby canine kidney (MDCK) cells. Influenza virus was cytopathic effect (CPE) positive with MDCK cells, and identified by the hamagglutination-inhibition (HI) test with standard strain antiserum to influenza viruses.

HI test. Pre-phase serum was collected before the first vaccination, and post-phase serum was obtained 3 weeks after the second vaccination. Acute-phase serum obtained from those who were ill, and convalescent-phase serum was obtained 3–4 weeks later. All sera were frozen upon collection and kept at −20°C until use. Commercial hemagglutinating antigens and the antiserum of vaccine strains and receptor destroying enzyme (Denka Seiken, Tokyo), infected ferret's serum, and guinea pig and goose red blood cells were used for the tests. Serological diagnosis was performed with paired sera collected from vaccinees and residents with ILI by standard microtiter assay for the HI test (Tobita et al. 1975). Serological titers were expressed as the reciprocal of the last serum dilution showing complete inhibition of hemagglutination. The initial serum dilution used was 1 : 8 and two-fold serial dilution were carried out to 1 : 1024. For calculation of geometric mean titers, $<1:8$ was considered as positive at 1 : 4. A four-fold or greater increase in HI antibody titer to (epidemic) influenza A or B viruses was regarded as positive.

Vaccine efficacy. All residents' physical charts indicating age, diagnosis and

clinical manifestations were reviewed after outbreaks. To estimate the clinical effectiveness of the influenza vaccine, the incidence rate of ILI and the length of the febrile period were compared between the vaccinated group and the control group. Vaccine efficacy was calculated with the following formula: 1-(incidence in the vaccinated group/incidence in the control group)×100 (Longini et al. 1988).

Statistical analysis. The chi-square test was used to calculate a 95% confidence interval of odds ratio, the Pearson's correlation coefficient for linear regression, and Student's *t*-test for evaluation of differences in mean values.

Results

Immune responses to influenza vaccine

Sixty of 128 (46.9%) residents were immunized with two doses of the trivalent split influenza vaccine two weeks apart, as is the ordinary influenza immunization procedure in Japan. Serious side effects of the influenza vaccination were not observed in any of the vaccinated residents. The geometric mean antibody titer rise of the HI antibody against the three vaccine components were 8.9-fold against A/Yamagata/32/89 (H1N1), 11.5-fold against A/Wuhan/359/95 (H3N2), and 7.4-fold against B/Mie/1/93 (Table 2). Based on the assumption that HI antibody titers of $\geq 1:64$ are protective, the proportion of subjects (%) protected were 50% against A/Yamagata/32/89 (H1N1), 56% against A/Wuhan/359/95 (H3N2), and 69% against B/Mie/1/93.

The outbreaks

There were two outbreaks (Fig. 1). The first occurred from December 25th, 1996 to January 14th, 1997, and 40 (31.3%) of 128 residents had typical ILI. The second occurred from February 19th to 26th, 1997, and in that case 23 (18.1%) of

Table 2. *HI antibody responses to three vaccine components in subjects vaccinated in 1996 with a trivalent split influenza vaccine*

Antigen	GMT		Mean fold increase	Proportion of subject (%) protected		Response rate (%)
	Before	After		Before	After	
A/Yamagata/32/89 (H1N1)	7.1	62.4	8.9	3.6	50.2	69.1
A/Wuhan/359/95 (H3N2)	6.3	72.6	11.5	3.6	56.4	81.8
B/Mie/1/93	11.2	83.4	7.4	10.9	69.1	76.4

GMT, geometric mean titre.

Proportion of subject (%) protected: percentage of subjects with an antibody titre $\geq 1:64$.

Response rate: percentage of subjects showed antibody titre rise at or above four-fold.

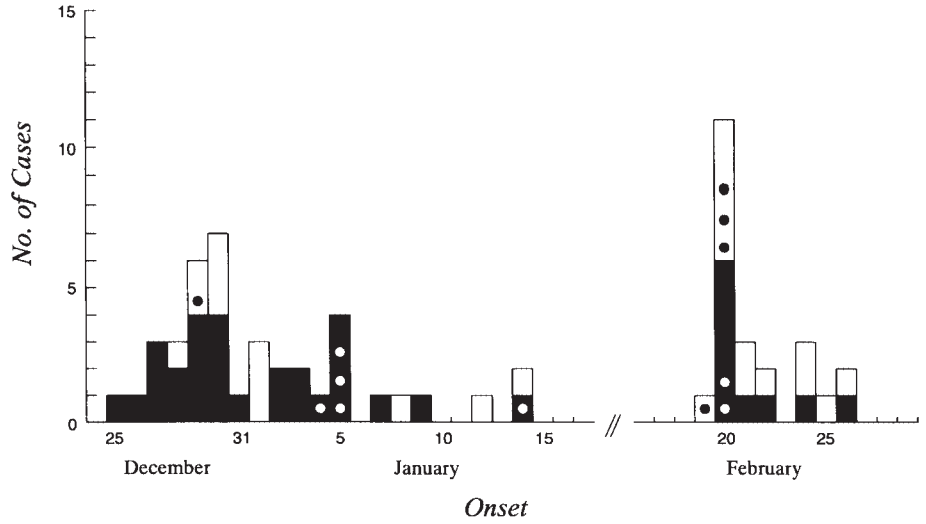

Fig. 1. Cases of influenza-like illness among residents of nursing home by the date of onset, December 1996– February 1997.
■, Control group ($n=68$); □, Vaccinated group ($n=60$); ○ or ●, Virus isolated.

127 residents had illness with elevated body temperature but no documented respiratory symptoms.

Five and seven influenza A (H3N2) viruses were isolated from vaccinated and control groups respectively in the two outbreaks (Fig. 1). The antigen analysis with sera of ferrets suggested that there were no significant antigenic differences among the vaccine strain and those isolated from the outbreaks by the HI test (Table 3). Paired acute- and convalescent-phase sera of patients of vaccinated and control groups for both outbreaks were available (20/23, 87%), demonstrating a significant increase in HI antibody titers against only influenza A/Wuhan/359/95 (H3N2) (Fig. 2). Based on the above observations, the second outbreak appeared to be a reoccurrence of influenza A (H3N2). We could not isolate other respiratory viruses, such as adenovirus, RS virus, and rhinovirus during the study period. In the two outbreaks none of offered individuals had used amantadine hydrochloride for prophylactic or therapeutic purposes as is often the case for elderly Japanese.

Vaccine efficacy

In the first outbreak, the vaccine efficacy against clinical illness was 51% (relative risk [RR]: 0.49), and the febrile period was reduced significantly by vaccination (Table 4). The number of hospitalizations did not differ significantly between the vaccinated and control groups, and there was only one death case in the vaccine group. In the second apparent reoccurrence of influenza A (H3N2), however, the febrile period was not reduced significantly by vaccination and no vaccine efficacy was shown (RR: 1.45).

TABLE 3. *Hemagglutination-inhibition titres of influenza viruses with serum specimens from infected ferrets*

Viral antigen	Ferret antiserum					
	A/Yamagata/32/89 (H1)	A/Beijing/262/95 (H1)	A/Wuhan/359/95 (H3)	A/Kitakyushu/159/93 (H3)	A/Yamagata/56/93 (H3)	B/Mie/1/93
Reference antigens						
A/Yamagata/32/89	256	4096	<8	<8	<8	<8
A/Wuhan/359/95	<8	<8	4096	256	256	<8
A/Kitakyushi/159/93	<8	<8	32	4096	2048	<8
B/Mie/1/93	<8	<8	<8	<8	<8	<8
Our isolates						
1st Outbreak	<8	<8	2048	256	512	<8
2nd Outbreak	<8	<8	2048	256	256	<8

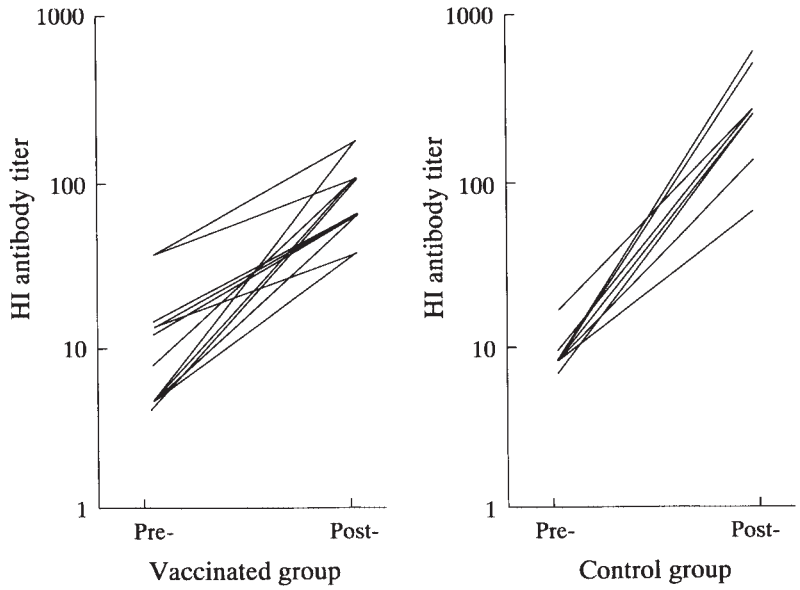

Fig. 2. Serum HI antibody titer of influenza A (H3N2) from residents infected during second outbreak.

TABLE 4. *Attack rates, vaccine efficacies, febrile periods, No. of hospitalizations*

		First outbreak	Second outbreak
Attack rate	Vaccine group	12/60	13/60
	Control group	28/68	10/67
		$p<0.05$*	n.s.
Vaccine efficacy (Relative risk)		51% (0.49)	−45% (1.45)
Febrile period	Vaccine group	2.8±1.7 (1- 5)	5.4±4.3 (2-16)
Mean±S.D. (range)	Control group	6.65±3.9 (1-16)	7.0±4.4 (2-14)
		$p<0.05$	n.s.
No. of hospitalization	Vaccine group	2	2
	Control group	3	2
		n.s.	n.s.
No. of death	Vaccine group	0	0
	Control group	1	0
		n.s.	n.s.

*odds ratio=0.35, 95%, confidence interval=0.16-0.78.
S.D., standard deviation.

DISCUSSION

During our study period, there were two influenza outbreaks with a one-month interval. In any single winter season, several respiratory agents are usually present and cause illness, and they have been shown to co-circulate during influenza virus epidemics. Therefore, appropriate laboratory studies must be conducted to fully characterize the infectious virus, responsible for an epidemic of respiratory illness. We used the microplate method with four kinds of cell cultures to cover most respiratory viruses, but could isolate only the influenza A (H3N2) virus from both the control and vaccinated groups in the two outbreaks. Furthermore, the antigen analysis with the sera of ferrets suggested that there were no significant antigenic differences from the vaccine strain and those isolated from both outbreaks by the HI test. The fact that serum HI antibody titers against

influenza A (H3N2) of patients in the second outbreak demonstrated a significant increase strongly suggested a reoccurrence of influenza A (H3N2). We did not conduct a bacteria study, but based on our observations together with the findings of the virological examination, it is unlikely that the outbreak was caused by bacteria.

The present prospective non-randomized, controlled trial in a nursing home indicated that the clinical manifestations and vaccine efficacy against influenza A (H3N2), were different in the two outbreaks which occurred in one season. In the first outbreak with typical ILI clinical manifestation, the vaccine efficacy was 51% (RR: 0.49), and febrile period were reduced significantly by vaccination, in line with earlier reports (Patriarca et al. 1985; Gross et al. 1987; Nichol et al. 1994). In contrast, febrile period was not reduced significantly and no vaccine efficacy was shown with the reoccurrence of influenza A (H3N2). Atypically, the patients had high fever, but not respiratory symptoms. Although, many of the residents were mentally impaired and might not have correct verbalize information about myalgia, aches and pains, and weakness. There were no residents who were infected in both outbreaks, suggesting strong protection by natural immunity. As we did not carry out a detailed sero-epidemiological study, differences in reaction to the virus could not be further elucidated. We need further epidemiological studies to confirm the vaccine efficacy among aged people in Japan.

The two-dose administration with a two-week interval used in this study is the standard method in Japan. Fully vaccinated residents in an nursing home developed 7.4–11.5-fold antibody increases, and showed 69–82% protection, presenting good immune response rates in agreement with those reported in other countries (Peters et al. 1988; Gross et al. 1989; Glathe et al. 1993; Gorse et al. 1996). It is considered that a supplemental dose of the vaccine has no booster effects, and it is not recommended for ages of 9 years or above in the United States (Mackenzie 1977; Gross et al. 1987; Glathe et al. 1993; Advisory Committee on Immunization Practices 1998). In a preliminary study, we obtained similar results with both one and two doses (data not shown), and it is recommended that the two-dose standard vaccination method for the elderly in Japan be changed to a single dose administration.

In conclusion, we found that influenza vaccination in the elderly was effective against ILI. The epidemic curve of the first outbreak suggested person to person spread, with the number of cases increasing slowly, leveling off, and then slowly decreasing (Fig. 1). In contrast, that of the second outbreak in which the number of cases rose, peaked, and fell rapidly, suggested transmission from a point source, probably from health care workers on the fourth floor. In this context the report by Potter et al. (1997) that vaccination of health care workers against influenza is associated with reduced rates of mortality and ILI in geriatric medical long-term-care patients, is of interest.

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