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PREVENTION OF INFECTION

Efficacy of influenza vaccine in the elderly in welfare nursing homes: reduction in risks of mortality and morbidity during an influenza A (H3N2) epidemic

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The effect of influenza vaccination on the occurrence and severity of influenza virus infection in a population residing in nursing homes for the elderly was studied during an influenza A (H3N2) epidemic in Japan. Of 22 462 individuals living in 301 welfare nursing homes, 10 739 received either one dose (2027 subjects) or two doses (8712 subjects) of inactivated, subunit trivalent influenza vaccine. During the period Nov. 1998 to March 1999, there were 950 cases of influenza infection diagnosed clinically, with virus isolation or serology. There were statistically significantly fewer cases of influenza, hospital admissions due to severe infection and deaths due to influenza in the vaccinated cohort (256 cases, 32 hospital admissions, 1 death) than in the unvaccinated controls (694 cases, 150 hospital admissions, 5 deaths; reduction rates 59.8%, 76.9% and 79.1% respectively). Vaccination was almost equally effective in those who received one dose of vaccine and those who received two doses. No serious adverse reactions to vaccination were recorded. Thus influenza vaccination is safe and effective in this population, and should be an integral part of the routine care of persons aged ⩾65 years 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] and continue to cause mortality and serious morbidity among the elderly (⩾65 years in age) [2–4]. In some countries such as the USA, annual influenza vaccination is recommended for all persons aged ⩾65 years, and for persons with certain chronic medical disorders [2, 3]. More than 90% of the deaths attributed to pneumonia and influenza during epidemics occur among persons aged ⩾65 years [4]. In nursing homes for the elderly, residents live in a group and follow a similar lifestyle. Intervention to prevent infectious diseases, including influenza, is most important in this setting, where both medical care and the availability of staff for 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 an analysis of the efficacy of influenza vaccination in elderly residents of welfare nursing homes in Japan.

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Subjects and methods

The present study investigated 22 462 people over 65 years of age residing in all 301 welfare nursing homes for the elderly in Osaka Prefecture, Japan, during an influenza A (H3N2) epidemic season (Nov. 1998 to March 1999). Peak influenza A (H3N2) activity, as determined by laboratory diagnosis [5–9], occurred in Jan. 1999.

Vaccination protocol

The vaccinated group consisted of 10 739 individuals (47.8% of the whole cohort) who received, with informed consent, either one (2027 subjects) or two

(8712 subjects) doses of influenza vaccine (inactivated, killed and subunit manufactured by the Research Foundation for Microbial Diseases of Osaka University and other pharmaceutical companies in Japan; HA-influenza vaccine A,B) by subcutaneous injections as recommended [10, 11]. There were 11 723 (52.2%) unvaccinated subjects in the control group. 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 and gender ratio 0.30/0.35, respectively, for the vaccinated and control groups. 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 [5, 6].

Diagnosis of respiratory tract infections

Cases with influenza were diagnosed clinically, with virus isolation or serology as described below.

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 [7]. Serum samples were also obtained from volunteer subjects with cold symptoms, stored at -20^{o}C and assayed for the presence of haemagglutinating-inhibiting antibodies (SRL and the Research Foundation for Microbiol Diseases, Osaka University, Japan) to several viral strains, including the three viral strains contained in the vaccine [8, 9]. 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 Student's *t* test [12, 13] and data analysis was performed with statistical power calculations with the SPSS/PC statistical package, which calculates a polled rate difference, i.e., an absolute percentage reduction between the vaccinated and control groups. Confidence intervals for the ratio of mean episodes were computed with Poisson regression, with an offset reflecting the length of time available for observation. For all analyses, p values <0.05 were considered significant. The percent reduction in the mean number of episodes (reduction rate) was calculated with the following equation: $100 \times (1 - \text{the ratio of mean episodes})$.

Results

There were 950 episodes of influenza illness amongst 22 462 subjects during the study period, diagnosed clinically and with virus culture or serodiagnosis, or both. 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) (data not shown). Influenza illness was significantly less common in the vaccinated group (256 cases amongst 10 739 subjects) than in the unvaccinated control group (694 cases amongst 11 723 subjects) (Table 1). The efficacy of the vaccine was the same for both male and female subjects. Severity of illness, patient hospitalisation and mortality rates were all lower in the vaccinated group: influenza was diagnosed in 5.92% of the unvaccinated group, but only 2.38% of the vaccinated group (reduction rate 59.8%); hospitalisation rate was reduced by vaccination from 1.3 to

Table 1. Efficacy of influenza vaccine in 22 462 elderly persons in nursing homes in the 1998–1999 influenza epidemic season

Study group	Number of subjects	Age	Sex	Number (%*) of patients		Number (%*) of deaths
				with influenza	hospitalised	
Vaccinated	22 462			950 (100)	182 (19.2)	6 (0.6)
	10 739	All (⩾60)	M+F	256 (27)	32 (3.4)	1 (0.1)
		60–69	M	13	2	0
			F	21	2	0
		70–79	M	27	3	0
			F	39	4	0
		⩾80	M	59	9	0
			F	97	12	1
Control	11 723	All (⩾60)	M+F	694 (73)	150 (15.8)	5 (0.5)
		60–69	M	99	11	0
			F	83	10	1
		70–79	M	91	21	1
			F	113	24	1
		⩾80	M	125	45	1
			F	183	39	1

*Percent of all patients with influenza.

0.3% (reduction rate 76.9%) and mortality was reduced from 0.043 to 0.009% (reduction rate 79.1%). These differences between the vaccinated and unvaccinated groups were statistically significant (log rank test $p < 0.001$) (Table 2).

Influenza vaccine was effective in preventing influenza virus infection, but not other causes of respiratory tract infection. This is illustrated in Table 3, which shows representative data derived from two nursing homes for the elderly, in which epidemics of respiratory tract infection occurred. In the first of these, the epidemic was due to influenza virus, whereas in the second, the epidemic was due to adenovirus infection. The rate of illness in the latter home was the same in the vaccinated and unvaccinated groups.

Antibody responses to the influenza vaccine were investigated in some elderly people in nursing homes. The results confirmed the increase of titres of antibody responses to the vaccine >four-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 the first dose, but more than one dose was required to induce serum antibodies in the influenza B subtypes in elderly persons. Overall, after two doses of vaccine, most initially low-level or seronegative elderly persons had at least a four-fold increase in antibody titre to influenza A strains (H1N1 and H3N2) and less than half had a similar increase to influenza B subtypes (data not shown). All 10 739 vaccinated patients were monitored for 1 week after vaccination to evaluate whether there were any side-effects such as fever or local swellings, but no serious adverse events were found.

More than 3 weeks are required after immunisation for the generation of a sufficient immune response to prevent influenza [2]. To avoid contamination of the data for the vaccinated group by influenza infections occurring before acquisition of a protective immune response, the data were further analysed after eliminating the 115 cases of influenza that were detected <3 weeks after influenza vaccination. As shown in Table 4, the efficacy of influenza vaccination remained statistically significant (log rank test: $p < 0.001$). Further-

Table 2. Rates of influenza infection, hospitalisation and deaths in vaccinated and unvaccinated groups

Event	Rate (%) within vaccinated group	Rate (%) within unvaccinated group	p value*	Reduction rate† (%)
Influenza infection	2.38	5.92	<0.001	59.8
Hospitalisation	0.30	1.30	<0.001	76.9
Death	0.009	0.043	<0.001	79.1

*p value: the comparison between the vaccinated group and the control group.
†Reduction rate = % reduction: 100 × (1 − ratio of mean episodes [vaccination group/control group])

Table 3. Representative data for efficacy of influenza vaccine in elderly persons in nursing homes

	Number (%) in study group		
Clinical data	Total	Vaccinated	Control
In a nursing home with an epidemic of influenza A (H3N2)			
n =	100	38	62
Illness	38	8 (21.0)	30 (48.4)
Temperature (°C)			
⩾39	15	1	14
38–38.9	13	5	8
37–37.9	6	2	4
<37	3	0	3
Death	1	0	1
Remained healthy	62	30 (79.0)	32 (51.6)
In a nursing home with an outbreak of other virus infection			
n =	100	48	52
Illness	35	17 (35.4)	18 (34.6)
Temperature (°C)			
⩾39	9	4	5
38–38.9	13	6	7
37–37.9	11	6	5
<37	2	1	1
Death	0	0	0
Remained healthy	65	31 (64.6)	34 (65.4)

Table 4. Efficacy of vaccination in patients with onset of infection >3 weeks after influenza vaccination

Clinical criteria	Number (%) in vaccinated group			
	Total n = 10 624	1 dose n = 1997	2 doses n = 8627	Reduction rate (%)*
Influenza infection	141 (1.33)	30 (1.5)	111 (1.29)	79.5
Hospitalised	24 (0.23)	5 (0.25)	19 (0.22)	82.3
Death	0	0	0	100%

*As compared with the unvaccinated group. Comparison of data from the two subgroups showed no significant difference ($p > 0.05$).

more, it can be seen from Table 4 that there was no significant difference, in preventing influenza, between one and two doses of vaccine.

Discussion

The results obtained in this study of patients in welfare nursing homes are compatible with the findings of several recent studies (reviewed in ref [14]) on the efficacy of influenza vaccine in elderly persons. The risk of onset of illness was moderately reduced by influenza vaccination (risk reduction rate 59.8%). However, the risks for both hospitalisation due to severe illness and for mortality were reduced to a greater extent (reduction rates 76.9% and 79.1% 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], which may explain the enhanced effect of vaccination against severe illness and mortality as compared with 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 any of the 10 739 vaccinated cases. Margolis *et al*. [15] have also shown that the incidence of local and systemic side-effects in the first 48 h after vaccination was <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. Others have shown the economic benefits of this approach [16]. Almost half (47.8%) of the population in all Osaka Prefecture nursing homes for the elderly voluntarily received influenza vaccines in the 1998–1999 season in a programme supported by the Osaka Prefectural Government. This is the first and only official support in Japan for influenza vaccination of the elderly. Annual universal influenza immunisation of elderly persons in welfare nursing homes is a public health imperative that should be carried out by practising physicians and public health organisations.

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