

Epidemiological Report

Evaluation of a Mass Influenza Vaccination Campaign

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SUMMARY: Kawaura, a rural town in Kumamoto Prefecture, Japan, population approximately 6,800, started a mass influenza vaccination campaign in the 1999-2000 season for all residents ≥ 3 years of age. The town provided free vaccinations to children ≤ 13 years and the elderly ≥ 65 years. Only 900 yen (US\$8.80) was charged to the other residents for two vaccinations. In the 1999-2000 season, a total of 5,563 doses of vaccine were administered to 2,952 residents. Over 90% of the vaccinees received two doses. The program resulted in a vaccination rate of 43% of all residents. The vaccination rates for females and males were 40.7% and 36.8%, and for those of 3-14 years, 15-64 years, and ≥ 65 years population were 75%, 31%, and 55%, respectively. The town spent a total of 5.78 million yen (US\$56,700) for the campaign. The per-shot cost was estimated as 1,683 yen (US\$16.50). From December 1999 through March 2000, a total of 233 town residents (15-101 years old, median 72) were admitted to the town hospital. Of these 233 inpatients, 22 (66-98 years old, median 78) developed respiratory illness, with 4 fatal outcomes. Of these 22 cases, 3 had been vaccinated twice, while 19 had not been vaccinated at all. The relative risk of vaccinees' hospitalization due to respiratory illness decreased to 0.13 compared with that of non-vaccinees (3/1,203 versus 19/1,003, vaccine efficacy = 0.87). Likewise, the relative risk of vaccinees death due to respiratory illness decreased to 0.28 compared with that of non-vaccinees (1/1,203 versus 3/1,003). The results of the Kawaura town's initiative should be helpful for better modeling of mass influenza vaccination campaigns.

INTRODUCTION

The magnitude of the efficacy of influenza vaccines has been vigorously debated in Japan. This debate has focused on how well vaccinations protect the elderly, the group most at risk of severe illness and death. It is commonly believed that the diminished immune systems of the elderly may respond to influenza vaccines, but conflicting results have been published concerning sufficient immune protection of the elderly compared to young subjects (1). Japanese studies of antibody response to influenza vaccine in the elderly, however, have shown rises in antibody levels similar to those in younger individuals (2,3), and, more important, protection from illness (2-4). These and similar data in many industrialized countries have indicated the desirability of widespread vaccination of older adults and the elderly. In the United States (U.S.), 67% of the population ≥ 65 years of age was vaccinated in preparation for the 1998-1999 influenza season (5). For the 1999-2000 season, over 77 million doses of vaccine were produced for the U.S. population of 274 million (6). In 1995, the U.S. had a vaccine distribution of 239 doses per 1000 population (7). In contrast, in Japan, in preparation for the 1999-2000 influenza season, some 3.5 million vials of vaccine were produced for the Japanese population of 127 million (Fig. 1). Japanese vaccination rates among the elderly and general popu-

lation are lower than those in other industrialized countries. Following the 1992 abandonment of widespread vaccination of school children, the vaccine distribution in 1995 was only 8 doses per 1,000 population (7), one thirtieth that of the U.S.

Why low influenza vaccination rates persist in Japanese elderly population despite data from Japan and other industrialized countries supporting vaccination is puzzling. It is clear that excess death of the Japanese elderly during influenza seasons is significant, especially since A/H3 strains have become epidemic (8). Among the elderly in the U.S., it is estimated that more than 40% of the 110,000 hospitalizations are related to influenza during an average influenza season, and that more than 90% of the 20,000 deaths are associated with influenza (9). Were vaccination rates not so high, morbidity and mortality would be worse, and the U.S. Centers for Disease Control and Prevention (CDC) estimates that for every 1 million elderly persons vaccinated, 1,300 hospitalizations and 900 deaths are averted.

Although the elderly, who are most likely to contract microbial infections, benefit the most from influenza vaccination, other groups are also protected by vaccination. The U.S. guidelines recommend vaccination of those ≥ 50 years of age with a variety of chronic illnesses (9). Healthy, younger people, however, are also protected by vaccination, and whether one vaccinates these groups is largely a matter of cost-effectiveness and individual preference.

One reason why vaccination of the Japanese population, especially the elderly, is not more strongly supported may be

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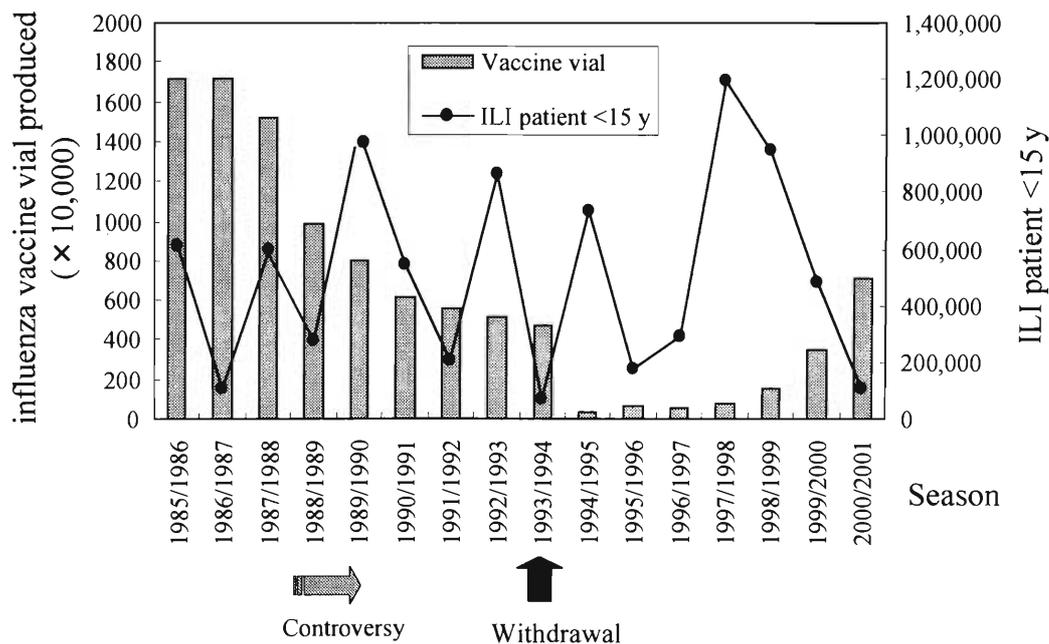


Fig. 1. Influenza vaccine production and pediatric influenza-like illness (ILI) <15 years old, 1985-2001, Japan.

that relatively few Japanese studies of vaccine efficacy have been carried out (4), and that, perhaps as a result, the national guidelines in recent years have not strongly endorsed vaccine administration (10). As there is little public funding support for vaccination and because vaccination is relatively expensive (US\$25-35 per shot), it may be no surprise that tepid national recommendations for a relatively expensive vaccine result in poor vaccination coverage. The high expense of the vaccine has been caused, in part, by the Japanese policy of using two doses of vaccine administered 1-4 weeks apart compared to the one-dose regimen that is used in other industrialized nations. Even assuming that an appreciation of vaccine efficacy becomes more widespread in Japan, the effectiveness of mass immunization for influenza needs to be established. How does one effectively immunize large sections of the population? And what groups should be targeted?

Kawaura town is located in a rural area of the Amakusa Peninsula in Kumamoto Prefecture. The town has a population of 6,865, which is engaged primarily in agricultural and fishery businesses. Severe influenza activity occurred in Japan during the 1997-1998 and 1998-1999 seasons (11,12), resulting in considerable morbidity in the town. However, despite the increase in the number of deaths associated with influenza, the outbreak was not as severe as in other towns, likely because residents at the town nursing home have received influenza vaccinations free of charge for nearly two decades. Following the 1998-1999 season, the mayor and town council were startled by the differences in morbidity between the vaccinated and unvaccinated, and to avoid increase in morbidity in 1999-2000, a mass vaccination campaign was planned for all residents ≥ 3 years of age for 1999-2000. Through evaluation of this unique effort, we have investigated questions concerning mass influenza vaccination in Japan.

MATERIALS AND METHODS

Initially, town-wide meetings were held to explain the decision and to gather support, which became widespread. Residents were mailed information about the campaign

whether they wished to receive the vaccine or not. Records of these responses were used to plan for the purchase of sufficient vaccine well in advance of the time it was needed, as a vaccine shortage was expected. The town designated seven vaccination sites at schools and public venues such as community centers, which were geographically separated, so that all citizens, in particular the elderly, could conveniently be vaccinated on vaccination days.

Three months before the mass vaccination, Kawaura town ordered Influenza HA vaccine (1 ml vial contains A/Beijing/262/95 200CCA/ml, A/Sydney/5/97 350CCA/ml, and B/Shangdong 300CCA/ml; Kaketsuken, Kumamoto) from a wholesale distributor. On the vaccination day (November 17, 1999), volunteers together with town officials, obtained written informed consent. After taking anamneses and performing a physical examination, the physician administered the vaccine subcutaneously (adults 0.5 ml, 6-12 years of age 0.3 ml, 3-5 years of age 0.2 ml), accompanied by one or two nurses and staff. Vaccinated persons spent approximately 10 min after vaccination at the site to ensure that there were no immediate hypersensitive reactions to the vaccine. Approximately 4 weeks after the initial vaccination, residents were eligible for the second dose, and community efforts to administer the second dose were similar to those for the first.

Residents were charged the wholesale cost of the vaccine (450 yen, or US\$4.40 per dose). Children ≤ 13 years and the elderly ≥ 65 years of age received the vaccination free of charge. Because the vaccinations were performed at schools or community centers, there was no cost for the facilities. Distribution and administrative costs as well as the cost of syringes, needles and administration were borne by the town. Town physicians supported the vaccination effort, and they were paid an hourly rate by the town.

During December 1, 1999 through March 31, 2000, name, age, sex, period of hospitalization, diagnosis, underlying conditions, medical expenses, and vaccination record of all those ≥ 15 years who were hospitalized in the town hospital were investigated from clinical charts. None were admitted anywhere other than the town hospital. Pediatric patients less

than 15 years old were not investigated because most of them were referred out of town.

To estimate the vaccine efficacy, a vaccination request list used for the mass vaccination campaign was categorized according to those who were immunized and those who were not. To compare the attack rate for influenza-like illness (ILI), 200 vaccinees (4-81 years old, median 45 years old, 95 males, and 105 females) and 200 non-vaccinees (3-84 years old, median 42 years old, 102 males, and 98 females) were randomly selected by the local health center from the vaccination request list. Those selected residents were requested to answer: 1) how many doses of the vaccine did you receive, and 2) did you experience ILI between December 1999 and March 2000. ILI was defined as fever >38°C with cough or muscle/joint pain, plus either headache, appetite loss, or general fatigue.

Local influenza activity was monitored by the national influenza sentinel and laboratory surveillance.

RESULTS

A total of 5,563 doses of vaccine were administered to 2,952 residents aged ≥ 3 years. The program resulted in a vaccination rate of 43% for all residents. The female vaccination rate (40.7%) was higher than that for males (36.8%). The vaccination rates of the population aged 3-14 years, 15-64 years, and ≥ 65 years were 75%, 31%, and 55%, and the vaccination rates according to the four communities were 35.3%, 37.7%, 40.4%, and 40.6%, respectively (those who stayed at the hospital and nursing facilities were excluded). Over 90% of individuals receiving one dose of vaccine received a second. Except for local reactions such as soreness and redness (3), no severe adverse effects were reported.

The town spent a total of 5.78 million yen (US\$56,700) for the mass vaccination. The per-shot cost was estimated as 1,683 yen (US\$16.50).

National influenza sentinel and laboratory surveillance revealed that influenza activity was significantly less than in the previous two seasons. In early February, 2000, increased titers for influenza A/Beijing/262/95(H1) were observed in sera drawn from unvaccinated children in the Amakusa area. Vaccine strains were antigenically similar to the epidemic strains.

During the observation period, a total of 233 town residents (15-101 years old, median 72) were admitted to the town hospital. Of the 233 inpatients, 22 (66-98 years old, median 78) developed respiratory illness (13 were pneumonia cases),

with 4 fatal outcomes. Of the 22 cases, 3 had been vaccinated twice, while 19 had not been vaccinated at all. The relative risk of vaccinees' hospitalization due to respiratory illness decreased to 0.13 compared with that of non-vaccinees (3/1,203 versus 19/1,003). Among the 4 fatal cases, 1 had been vaccinated twice, while 3 had not. The relative risk of vaccinees death due to respiratory illness decreased to 0.28 compared with that of non-vaccinees (1/1,203 versus 3/1,003). Among the 11 fatal cases due to non respiratory illness, 3 had been vaccinated, and 8 had not. The relative risk of vaccinees death due to non respiratory illness decreased to 0.31 compared with that of non-vaccinees (3/1,203 versus 8/1,003).

Of the 5,568 town residents ≥ 15 years of age, 2,242 received vaccinations. Among the vaccinees, 27 were hospitalized due to non respiratory illness. The relative risk of vaccinees' hospitalization due to non respiratory illness decreased to 0.44 compared with that of non-vaccinees (27/2,242 versus 91/3,326). If focusing only on the population ≥ 65 years old, the relative risk decreased to 0.32 (26/1,203 versus 68/1,003) (Table 1).

Among the 200 vaccinees and 200 non-vaccinees selected for vaccination and ILI queries, a total of 241 (60.25%), aged 4-78 years (median 39 years old, 108 males and 133 females) responded. Of these, 3 receiving two vaccinations presented ILI, 112 receiving two vaccinations did not present ILI, 5 receiving a single vaccination presented ILI, 41 receiving a single vaccination did not present ILI, 4 receiving no vaccination presented ILI, and 66 receiving no vaccination did not present ILI. Ten responses were invalid. The vaccine efficacy for those receiving two doses of vaccine was estimated to be 54%. Likewise, the vaccine efficacy for those receiving either one or two doses of vaccine was calculated to be 13%. However, these results were not statistically significant (Table 2).

The medical costs were estimated based on the medical expenses claimed to medical insurance for treatment of inpatients with acute respiratory illness. The medical expenses of 2 inpatients were not calculable because the respiratory illness was complicated by underlying conditions, which entailed costs for rehabilitation over a month. The rest of the 17 inpatients' costs were calculated to be 73,000-813,080 yen (mean \pm SD = 260,339 \pm 175,830 yen, days of hospitalization: 4-30, median 11). If these 19 inpatients had been vaccinated, 87% (1-0.13) (17 inpatients) might have been able to avoid hospitalization due to influenza followed by acute respiratory illness. If so, approximately 4.4 million yen, which is 76% of the campaign cost, would have been saved.

Table 1. Influenza vaccine efficacy in relation to selected outcome events

Outcomes	Proportion of events Vaccinee vs. Non-vaccinee	Relative risk (95% CI*)
Respiratory diseases hospitalization**	3/1,203 vs. 19/1,003	0.13 (0.04-0.44)
Respiratory diseases death**	1/1,203 vs. 3/1,003	0.28 (0.03-2.67)
Non respiratory disease hospitalization ≥ 15 years old	27/2,242 vs. 91/3,326	0.44 (0.29-0.67)
Non respiratory diseases hospitalization ≥ 65 years old	26/1,203 vs. 68/1,003	0.32 (0.20-0.50)
Non respiratory diseases death**	3/1,203 vs. 8/1,003	0.31 (0.08-1.18)

*CI: confidence interval

**all cases were at 65 years old or older

Table 2. Influenza vaccine efficacy in relation to influenza-like illness (ILI)

Vaccination	Attack rate ILI/ Total (%)	Relative risk (95% CI*)
None	4/70 (5.7)	1 -
Once	5/46 (10.9)	1.90 (0.54-6.71)
Twice	3/115 (2.6)	0.46 (0.11-1.98)
All vaccinees	8/161 (5.0)	0.87 (0.27-2.79)

Vaccine efficacy (Twice vs. None): $1 - 0.46 = 54\%$

*CI: confidence interval

DISCUSSION

How strongly Japanese public health authorities endorse the administration of influenza vaccine, in whom, and whether to financially support these recommendations, will remain contentious issues until data addressing the costs and value of vaccination are available and fully reviewed; the Kawaura town effort may assist in making these decisions. While the Kawaura town data do not allow the full evaluation of vaccine efficacy due to incomplete response rates and reliance on a simple questionnaire to judge the attack rates. However, relative risk for hospitalization and death for both respiratory and non respiratory illness supports this evidence. In particular, the relative risk for hospitalization for respiratory illness (relative risk = 0.13, vaccine efficacy = 87%) shows that influenza vaccination is a very effective prevention measure.

In addition to demonstrating the level of vaccine efficacy, this study uniquely shows the value of a community approach to vaccination. The Kawaura town recognized the impact that influenza had on their community the preceding year and organized a community-wide effort to prevent a similar occurrence. Through these community efforts, an estimated 43% of the population received vaccine, and over 90% of these received two doses. This was a well-organized, effective public health campaign.

The use of two vaccine doses, as recommended for the 1999-2000 season, considerably increased the cost of the vaccination campaign. Recent Japanese studies indicate that two doses of vaccine offer no additional immunogenicity compared to a single dose (3,14). For example, Horie et al. have found that a single dose of trivalent vaccine raises the reciprocal geometric mean H1N1 hemagglutination titers from a prevaccination level of 61.5 to 668.4, compared to a rise from 85.7 to 637.7 following two doses in 71 working adults from 20-60 years of age (14). Similarly, one dose of vaccine appears to be as protective as two doses in the elderly. In a large study of 22,462 elderly subjects living in nursing homes, it was found that vaccination with one or two doses, compared to results with nonimmunized individuals, results in 59.8% reductions in cases of influenza diagnosed by serology or culture; a 76.9% decrease in hospitalization; and a 79.1% decrease in death (4). Protection was similar between those who received one and those who received two doses. Another recent study of elderly bedridden patients receiving a single dose showed protection from illness, although perhaps not hospitalization (15).

The similarity of immunogenicity and protection from one dose of vaccine compared to two doses is reflected in the guidelines from the Japanese Ministry of Health, Labour and Welfare for the 2000-2001 influenza season. These guidelines recommend, for the first time, that physicians use either a single dose of vaccine or two doses for children and adults

≥13 years of age, and have assured a single dose for the elderly ≥65 years (10). This new guidance should have significant impact on the use, and thus effectiveness, of the influenza vaccine in Japan, if the use of a single dose of vaccine is widely adopted. Patients will need to pay for only one clinician visit and one dose of vaccine, so costs will be considerably reduced. Also important for ambulatory patients will be the impediment that two visits to the doctor now impose with regard to scheduling visits, taking time off from work (for patients or, in some cases, children to assist parents), etc. These benefits may well lead to a much greater vaccination coverage for the Japanese population.

Unfortunately, there remains skepticism among the medical profession and the public about the efficacy of vaccine protection. This skepticism may be due to confusion about what, clinically, influenza is. The common cold, "kaze", is often confused in Japan with influenza (16). It is easy for professionals and the public to misunderstand the degree of protection afforded by the influenza vaccine. Efforts by public health authorities to provide a better understanding of the meaning of kaze, and the efficacy of the influenza vaccine, to both the medical community and the public would undoubtedly help to increase vaccine coverage of the Japanese population.

In addition, the efforts would become increase recognition that the vaccination may ameliorate the clinical severity of influenza, even if it does not prevent it. Some health professionals assert that the efficacy of the influenza vaccine, even at 50-60%, is not high enough to support a policy of universal vaccination (17). But such an argument likely does not include the additional benefits of clinically milder influenza in some vaccinated individuals, even if they are not fully protected against infection.

The effort in Kawaura town was broad and included individuals not currently recommended for vaccination in Japan, e.g., school children and working adults. Prior to 1994, the vaccine was recommended for school children by the national immunization law. The policy was discontinued, however, because of an apparent lack of evidence of effectiveness, but confusion with kaze surely contributed to this belief. The belief became widespread, and vaccination coverage among this group declined from about 80% in the latter 1970s to 18% in 1992 (16). The current national recommendations for administration of vaccine includes school children and working adults who wish to be vaccinated. Individuals in these groups may, however, choose to be vaccinated and those will not only decrease influenza morbidity in their own age groups (18,19), but also reduce mortality among older persons (20): this study suggests that with efforts to vaccinate school children, many people are protected from influenza, leading to cost savings, e.g., children did not miss school, parents did not miss work, and medical costs were avoided. For high-risk groups, more cost savings were realized because more severe complications, due to infection from family and those who came into contact with them were avoided.

Our cost analysis did not, however, result in the Kawaura town effort being cost effective, i.e., saving money, primarily because the two-dose vaccination policy nearly doubled the campaign costs. If a single-dose policy had been employed, approximately 40% of the cost would have been saved, and the campaign might have been cost-effective. Secondly, the influenza was less active in this season, although the influenza vaccine was antigenically similar to the virus strain recovered from the area. Thirdly, we could not calculate the medical expenses of two inpatients; thus, our estimation of medical

expenses might have been less than actually paid. In addition, we did not include the medical expenses for the outpatient clinic and pediatrics. These limitations compromised the cost-effectiveness results in the Kawaura effort. A recent U.S. cost analysis of working adults, for example, has shown that vaccinated adults report 34% fewer influenza illnesses, 42% fewer physician visits, and 32% fewer lost work days compared to nonvaccinated controls (21). Despite these benefits, when direct (medical care costs) and indirect (the benefits of fewer work days lost) medical costs were evaluated, the program cost US\$11.17 per person, i.e., it did not save money in this population. Nevertheless, a community may decide that such an expenditure is worthwhile, and it is their responsibility to determine how they wish to spend their money. In addition, the Kawaura town effort provided vaccine at 75-90% less cost than would have been possible if there were no community effort. This significant decrease in the cost of providing vaccine means further savings were realized among the high-risk, i.e. elderly population, whose vaccination rate remained at 55%, and that savings were likely realized for low-risk populations. Thus, when the entire population of persons vaccinated in Kawaura town is considered, it is likely that there were considerable cost-savings with the entire program. In addition, people enjoyed better health, an intangible cost benefit that is so difficult to include in cost-effectiveness analyses.

Future efforts to evaluate the efficacy and effectiveness of similar vaccination efforts would provide invaluable assistance to determining the optimal vaccination strategy for Japanese citizens.

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