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Three year follow up study of national influenza vaccination practices in Japan

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Abstract

Study objective **– To evaluate new national influenza vaccination practices which were started in 1987 under a revised law in Japan.**

Design **– This was a three year, nonrandomised cohort study with information collected by questionnaire between 1989 and 1991.**

Setting **– Eight primary schools in the city of Yonago, Tottori, Japan. These schools were selected from 23 schools in the city.**

Participants **– Altogether 4251 pupils (1355 boys and 2896 girls) in years 1–4 of the eight primary schools were included in this study, and followed up. Three years later, data for 1619 pupils (768 boys and 851 girls) were obtained and analysed.**

Main results **– The one-winter seasonal incidence rates of influenza-like disease were 13·4%, 29·9%, and 10·3% in 1989, 1990, and 1991 respectively. The incidence rate of influenza-like disease in fully vaccinated pupils was significantly lower than that in unvaccinated pupils in 1990, but not in 1989 or 1991. Stepwise multiple regression analysis showed that the incidence of influenza-like disease had a statistical relationship with the frequency of vaccination and the school year (R^2 was 0·0148). Standardised parameters of the frequency of vaccination and the school year were −0·089 and −0·080 respectively.**

Conclusions **– The preventive effects of influenza vaccine are not strong. There must be some unknown factors that affect the incidence of influenza. This vaccine is useful for pupils in the early school years who seem to have less resistance. All pupils should not be inoculated with the vaccine to reduce influenza transmission in the community or school.**

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In Japan, vaccination against influenza has been carried out since 1976 as part of a national programme under the Preventive Vaccination Law. Influenza vaccination is performed annually in children of 3–15 years. These target groups for influenza vaccination were selected as a result of the findings of an epidemiological study carried out in 1957,[1] which showed that kindergarten, and primary and secondary schoolchildren were infected with influenza in the early stages of epidemics and were therefore major sources of infection in the community. At that time, the philosophical and conceptual basis of the influenza vaccination programme was that routine immunisation against influenza in children, as a collective preventive measure, would benefit the whole community by reducing influenza transmission. Thus, influenza vaccination was considered to be mandatory for the target groups.

Japanese practice differs from that operating in the United States and in Europe, and in Japan itself there have been arguments for and against it.[2–7] An expert team from the United States who visited Japan and researched the benefits of Japanese influenza vaccination practice[8] concluded that the lack of data on the effects of annual vaccination in reducing influenza associated morbidity and mortality made evaluation difficult. Some Japanese researchers have since carried out epidemiological studies to evaluate the efficacy of the vaccination programme. Because difficulty in obtaining an unvaccinated control group has made the studies biased, proper evaluation has been problematic. However, since no alternative method has been proposed, the same epidemiological approach to influenza vaccination has continued in Japan.

In the middle of the 1980s, the occurrence of side effects of influenza vaccine were the subject of judicial decisions, and these resulted in public campaigns against influenza vaccination. The Ministry of Health and Welfare changed the Preventive Vaccination Law in 1987, introducing new regulations that weakened its obligatory nature. The regulations made it easy for parents of children aged 3–15 years to refuse influenza vaccination for their children, and resulted in large differences in vaccination rates in kindergartens and primary and secondary schools.

We believed that this situation provided the conditions for a "natural experiment", and presented us with a good opportunity to evaluate the preventive effects of influenza vaccination practice.[9] We therefore carried out an epidemiological study with the cooperation of the Departments of Health and Education of the city of Yonago, Tottori Prefecture, Japan.

Methods

This follow up study was carried out between March 1989 and March 1991. The subjects were pupils in years 1–4 of eight primary schools in Yonago in 1989. There were 4251 pupils – 1355 boys and 2896 girls. These eight

Table 1 Influenza virus strains used in vaccines and isolated from children with influenza-like disease between 1989 and 1991

Year	Strains	Vaccines	Isolated virus
1989	A(H1N1)	A/Yamagata/120/86	A/Yamagata/120/86, A/Tottori/61/89
	A(H3N2)	A/Fukuoka/C29/85	
	A(H3N2)	A/Sichuan/2/87	
	B	B/Nagasaki/1/87	
1990	A(H1N1)	A/Yamagata/120/86	
	A(H3N2)	A/Sichuan/2/87	A/Sichuan/2/87, A/Hokkaido/20/89, A/Tottori/3/90
	B	B/Yamagata/16/88	Unknown B strains
	B	B/Aichi/5/88	
1991	A(H1N1)	A/Yamagata/32/89	
	A(H3N2)	A/Kishu/54/89	A/Guizhou/54/89, A/Tottori/1/91
	B	B/Hong Kong/22/89	
	B	B/Aichi/5/88	

schools were selected from 23 primary schools in the city according to the vaccination rates of the pupils (percentage of children who received two shots of the vaccine) in 1988. Four schools with high vaccination rates (51·7%–81·5%) and four schools with low vaccination rates (9·9%–25·1%) were selected.

In March every year between 1989 and 1991, questionnaires were given to the pupils by their teachers, filled in by the parents, and then collected by the teachers. The questionnaire included the following items: name of pupil; age; sex; name of school; school year; history of common cold incidence in that year; symptoms of common cold; history of influenza vaccination in that year; occurrence of side effects from the influenza vaccination; history of nephritis, asthma, or allergic diseases; number of days absent from school in that year; type of heating systems; and family histories of common cold incidence in that year. Any completed questionnaires in which information on the name of the child, sex, name of school, school year, incidence of common colds in the year, or history of influenza vaccination in the year was missing were excluded from the evaluation.

The response rates (number of fully completed questionnaire/number of distributed questionnaire) were 77·8%, 80·1%, and 83·6% in 1989, 1990, and 1991, respectively.

The influenza vaccine used in this study was

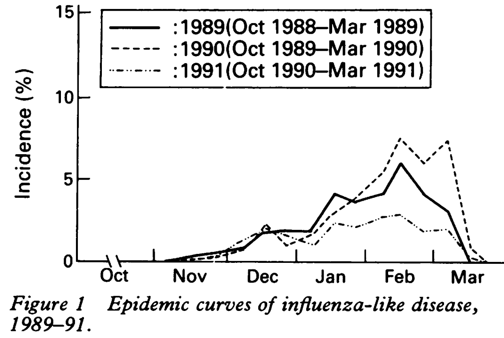

Figure 1 Epidemic curves of influenza-like disease, 1989–91.

Table 2 The one-winter seasonal incidence rates (%) of influenza-like disease by sex and vaccination status, 1989–91

	1989		1990		1991	
	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated
Boys	9·8	12·1	14·7	26·2	4·4	7·1
Girls	15·4	13·7	15·2	28·1	5·5	6·6

a split virus vaccine. The vaccine is made every year from subunit of A/USSR, A/Hong Kong, and B strains. Table 1 shows the strains which were used to make the influenza vaccines in October 1989, 1990, and 1991, and also those strains which were isolated from pharyngeal mucus of children who had influenza-like disease in Tottori Prefecture between October 1989 and March 1991.

By March 1991, we had completed three year questionnaires from 1619 pupils – 768 boys and 851 girls. They consisted of 396, 364, 424, and 435 pupils in the third, fourth, fifth, and sixth years in 1991. These pupils were the subjects of the analysis in this study.

A reduction in the seasonal incidence of influenza is an appropriate measure of the preventive effects of the vaccination. The seasonal incidence of influenza could not be obtained, however, unless all the sick pupils in the city visited their doctor and had a blood test in a winter season. This was not possible. Thus, instead of the incidence of influenza, we examined the rate of influenza-like disease. The definition of influenza-like disease was a history of common cold with a fever higher than 38°C; cough or sore throat, and a duration of symptoms longer than three days.

The χ^2 test, Wilcoxon rank sum test, and multiple regression analysis were used to determine relationships between influenza vaccination and the incidence of influenza. Dummy variables were used for binary variables and categorical variables in multiple regression analysis. These analyses were carried out on SAS software.[10]

Results

ONE-WINTER SEASONAL PREVENTIVE EFFECT

Epidemics of influenza-like disease in the eight schools began at the start of November and ended in late March, showing peaks in the middle of February in all three years. Figure 1 shows the incidence rate (new cases per 10 days) of the disease. The one-winter seasonal incidence rates of influenza-like disease in these schools were 12·7%, 23·0%, and 6·3% in 1989 (October 1988 to March 1989), 1990 (October 1989 to March 1990), and 1991 (October 1990 to March 1991) respectively. The highest and lowest rates in the different schools were 19·3% and 6·48%, 36·0% and 15·7%, and 11·1% and 4·7%, in 1989, 1990, and 1991 respectively.

The rates of influenza-like disease in vaccinated boys and girls (who had received two shots of the vaccine) were significantly lower than those in unvaccinated boys and girls (who did not receive any shot of the vaccine) in 1990. In 1989 and 1991, however, there was no statistical difference in the rates between vaccinated and unvaccinated boys and girls (table 2). The effect index:

$$\text{Effect index } (\%) = (1 - \text{attack rate in vaccinated population})/(\text{attack rate in unvaccinated population}) \times 100$$

was used for quantitative estimation of effect of

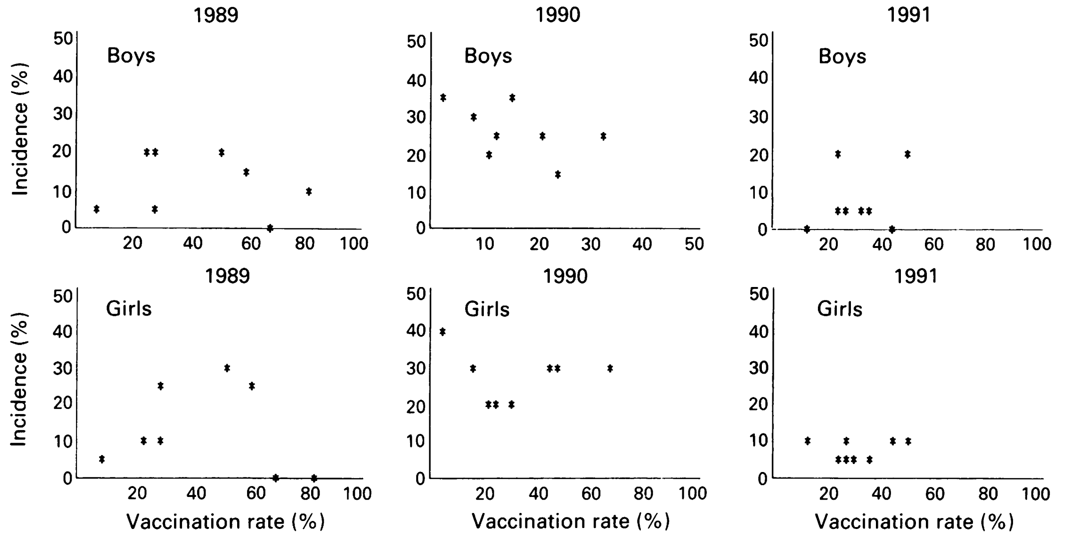

Figure 2 Incidence rates of influenza-like disease in unvaccinated boys and girls, 1989–91.

the vaccine. An index of zero per cent indicates an identical infection rate in vaccinated and unvaccinated children, and 100% indicates a zero infection rate in vaccinated children. The effect indices of the vaccine against influenza-like disease in boys and girls respectively were 19·0% and 0·0%, 43·9% and 45·9%, and 38·0% and 16·7% in 1989, 1990, and 1991, respectively. To assess "herd immunity", the incidence rates of influenza-like disease in unvaccinated boys and girls were compared in the eight schools (fig 2). Spearman's rank correlation coefficients between the incidence rates of these diseases in unvaccinated boys and girls, and the vaccination rates in the schools were −0·14 and −0·61, −0·57 and −0·12, and 0·05 and 0·47 in 1989, 1990, and 1991, respectively: none of these were statistically significant.

The incidence of vaccine side effects was very low in the three year period. The most frequent side effect was swelling around the injection site, followed by redness of the injected region and then general fatigue. The incidences of swelling were 14·3%, 10·4%, and 8·8% in 1989, 1990, and 1991, respectively. None of the subjects showed serious reactions during the study period.

THREE-WINTER SEASONAL CUMULATIVE PREVENTIVE EFFECT

The incidence of influenza-like disease in fully vaccinated pupils (pupils who received six shots of the vaccine over the three years) and unvaccinated pupils (pupils who did not receive any shot of the vaccine in three years) was compared (table 3). The incidence rates of influenza-like disease in boys and girls respectively were 27·7% and 28·0% in the fully vaccinated group and 38·2% and 40·6% in the unvaccinated group. The incidence in fully vaccinated boys and girls was significantly lower than that in unvaccinated boys and girls. The same results were obtained with the Wilcoxon rank sum test for the data in table 3. The mean frequency of contracting influenza-like disease over the three years in the fully vaccinated boys and girls was lower than that in unvaccinated boys and girls.

Stepwise multiple regression analysis was carried out. The dependent variable was the frequency of influenza-like disease and the independent variables were frequency of vaccination, sex, school year, history of asthma, history of allergic diseases, number of days absent from school in a year, and type of heating systems. The results of this analysis showed that the regression model which included the frequency of vaccination, sex, and school year was the most appropriate. In this model, the incidence of influenza-like disease had a statistical relationship with the frequency of vaccination and the school year (table 4). The more frequently pupils were vaccinated, the less frequently they had influenza-like disease, and the higher the school year they were in, the less frequently

Table 3 Incidence of influenza-like disease in three-winter seasons by sex and vaccination status

	Total	*Incidence in three years* 0	1	2	3
Fully vaccinated:					
Boys No	130	94	30	6	0
(%)	(100·0)	(72·3)	(23·1)	(4·6)	(0·0)
Girls No	143	103	35	4	1
(%)	(100·0)	(72·0)	(24·5)	(2·8)	(0·7)
Unvaccinated:					
Boys No	238	147	77	12	2
(%)	(100·0)	(61·8)	(32·4)	(5·0)	(0·8)
Girls No	266	158	85	22	1
(%)	(100·0)	(59·4)	(32·0)	(8·3)	(0·4)

Table 4 Analysis of variance table for multiple regression

Source of variation	*df*	*Sums of squares*	*F value*	*p*
Regression	3	10·899	9·65	0·001
Residual	1615	726·181		
Total	1618	737·080		

Variable	*Estimated parameter*	*T value*	*p*	*Standardised parameter*
Intercept	0·555	13·75	0·001	0
Vaccine*	−0·051	−3·93	0·001	−0·089
Year*	−0·044	−3·54	0·004	−0·080
Sex*	0·041	1·50	0·135	0·034

Coefficient of determination = 0·0148.
* Dependent variable; Incidence of influenza-like disease
Vaccine; Frequency of vaccination
Year; School year
Sex; Dummy variable, indicates a girl.

they had the disease. The standardised parameter of the frequency of vaccination was −0·089, and that of the school year was −0·080. The relationship between the frequency of vaccination and the incidence of influenza-like disease was stronger than the relationship between the school year and the disease. The coefficient of determination was 0·0148, however, which indicated that there were many other unknown risk factors for influenza-like disease. The other independent variables, which were sex, history of asthma, history of allergy diseases, absence days from school in a year, and type of heating system did not have any statistically significant relationship with the incidence of influenza-like disease.

EPIDEMIOLOGICAL DATA FOR COMMON COLDS IN FAMILIES

To investigate the epidemiology of influenza in families, we focused on those family members who had common colds earliest in the winter season period. The analysis showed that the subject pupils or siblings of the subject pupils were the family members who most frequently exhibited this feature (table 5). Our data showed that 60·1% of these siblings were pupils of primary schools. These data showed that pupils of primary schools were the family members who had common colds earliest in the winter season. This finding in young schoolchildren indicated that they were the source of the amplification of influenza epidemics in communities, even at present.

Discussion

This study aimed to determine the efficacy of national influenza vaccination practices in pupils in a Japanese city. Information on the history of influenza vaccination and the incidence of influenza in this population were required for this purpose. To obtain precise information on the incidence of influenza, however, all target pupils must visit their doctors and have blood tests when they have a common cold. This is possible in epidemiological studies in a small population, but not in a large one. If the preventive effect of influenza vaccination is great, epidemiological studies, even in a small population, will detect statistical differences in incidence between vaccinated and unvaccinated groups. As we have already stated, however, the effect of influenza vaccination was not thought to be large, so we decided to carry out a study in a large population, and instead of examining influenza, we studied influenza-like disease, which has sometimes been investigated in epidemiological studies in large populations.[11–14]

Table 5 Number and component ratio of the first patient with a common cold in families, by family members, 1989–91

Year	Total	Subject	Siblings	Parents	Other	No patients
1989 No	1641	588	378	358	89	288
(%)	(100·0)	(35·8)	(23·0)	(21·8)	(5·5)	(13·9)
1990 No	1641	615	435	336	125	130
(%)	(100·0)	(37·5)	(26·5)	(20·5)	(7·6)	(7·9)
1991 No	1641	372	476	421	204	168
(%)	(100·0)	(24·1)	(30·8)	(27·2)	(7·0)	(10·9)

In this study, to minimise the inclusion of non-influenza cases, we applied strict criteria to define influenza-like disease, and where information was doubtful, the case was excluded. This procedure cannot, however, exclude *all* non-influenza cases from influenza-like disease. As a result, the power of the study to detect a protective effect of the vaccine would presumably be reduced.

Recall bias is possible in this study. There may be some parents who forgot their children's history of common cold incidence, symptoms of common cold, or history of influenza vaccination. In general, however, parents take their children's health seriously, and the number of parents who cannot recall their children's exact history should be small.

Although the response rates in three years were high (77·8%, 80·1%, and 83·6%), the rate of pupils who could be followed up over the three years was not high (1619/4251). The reasons for this low follow up rate were non-response, change of schools, or inaccuracy of replies to items in the questionnaire. The relatively high response rates and low follow up rate indicate that non-respondent pupils were not constant, that they varied with the years. There may be no bias caused by non-response, but it is possible in this study.

Many strains of influenza virus were isolated from pharyngeal mucus of children who had influenza-like disease in Tottori Prefecture between October 1988 and March 1991 (table 1). The isolation rates of influenza virus from children with influenza-like disease were 50%, 30%, and 60% in these three years respectively.[15–18] These data indicated differences in the isolation rates of influenza virus in calendar years, but not in cities/towns in a year. We assumed that the rate of influenza virus in a school in one winter season was almost stable between vaccinated and unvaccinated pupils, and that difference in incidence rates of influenza-like disease showed differences in the rates of influenza between the two groups of pupils.

Our first analysis showed that not only was the preventive effect of the influenza vaccination not very high (even in the most effective year the effect index was only 45·9%) it was also inconsistent (in the worst year the effect index was 0·0%). The influenza vaccine used currently is a split virus vaccine. This was developed to reduce side effects and has been used since 1972 in national influenza vaccination practice. Before the introduction of the split virus vaccine, whole virus influenza vaccine was used, and studies showed that it had a high preventive effect against influenza.[19 20] It was only after the split virus vaccine became widely used, however, that it was found that its preventive effect was not very high and that it was also inconsistent. The one-winter seasonal effect indices ranged from 0% to 60%.[21–24] Our results here agreed with these earlier studies, and indicated the appropriateness of the method of this study. We think the inconsistency indicates an unstable immunological relationship between the strains of epidemic influenza viruses and the inactivated viruses in the vaccine.

The analysis did not show that the routine immunisation of many pupils reduced the incidence of influenza-like disease in those who were unvaccinated. It did not indicate that routine immunisation resulted in "herd immunity" by reducing influenza transmission. Nor did our analysis support the philosophical and conceptual basis of the programme, which held that routine immunisation against influenza in childhood could benefit the community. A theoretical epidemiological study has indicated that herd immunity can be obtained only if the effect index of the vaccine exceeds 60% and the vaccination rate exceeds 80%.[6] In our study, the effect indices ranged from 0·0% to 45·9%, and vaccination rates ranged from 15·8% to 81·5% (table 2). Our analysis indicated therefore that present routine immunisation against influenza in childhood brought about no benefit for communities. This analysis does not, however, exclude the existence of herd immunity to influenza when both the effect index and the vaccination rate are high.

All side effects described in the questionnaires were slight and did not require treatment. The national surveillance for side effects has shown the incidence of serious side reactions such as encephalopathy, encephalitis, and epilepsy, to be very low.[25] Since the sample size in this study was too small to detect these side effects, it is not surprising that we saw no serious reactions during the study period.

Our second analysis showed the preventive effects of influenza vaccination after three seasonal influenza epidemics. This result was different from that obtained by Hoskins, whose studies showed no preventive effect of the vaccination after six years' observation.[26,27] There are three explanations for this inconsistency. Firstly, in Hoskins' studies the vaccines used had been prepared from influenza virus strains that had been epidemic in the previous year. Currently, however, these vaccines are made from strains that scientists "suspect" may become epidemic in the next season; these strains are detected through worldwide surveillance.[28,29] The currently used influenza vaccines must therefore be more effective than those used in Hoskins' time. Secondly, Hoskins' study was carried out in a boarding school in which pupils had to sleep in a dormitory. This increased the probability of influenza virus transmission and the incidence rates of influenza in vaccinated pupils whose antibody titre was not high enough. Thirdly, the analytic method used in this study was more sensitive than the method in Hoskins' study. In the latter study, analysis in which two probabilities were compared was used. Here, we used more sensitive stepwise multiple regression analysis. If multiple regression analysis had been used in Hoskins' study, weak preventive effects of influenza vaccination might have been shown. There are no epidemiological studies, other than this report and that of Hoskins, in which the same cohorts have been followed to evaluate the efficiency of influenza vaccination over a few years. It is desirable, especially in Japan, that our results be confirmed.

This analysis showed that not only influenza vaccination, but also the school year, were related to the incidence of influenza-like disease. The same result was obtained in a case-control study in Japan, in which multivariate analysis was used.[30] We believe that some kinds of immunity develop with age, and that older pupils are more resistant to influenza infection. We recommend that younger pupils should be inoculated with influenza vaccine rather than older pupils. This analysis showed that girls were more susceptible to influenza-like disease. This result cannot be explained by virology. The immunological response of girls to vaccination must be the same as that of boys. This analysis also showed that there must be some unknown factors which affect the incidence of the disease. These unknown factors might include child rearing practices, playing in homes, and treatment in an early stage of diseases. A history of asthma and other allergic diseases was suspected of being related to the incidence of common colds. However, the number of children in our population who had this history was small, and the analysis did not show any such relationship.

Our third analysis indicated that schoolchildren were the source of amplification of influenza epidemics in communities. This result indicates that the reasoning behind the vaccination programme in Japan is relevant. If more pupils are inoculated with a more effective influenza vaccine, epidemics would become smaller, not only in schools, but also in communities. Our first and second analyses indicated that the effectiveness of the current influenza vaccine was insufficient to bring this about. A more effective influenza vaccine that does not cause severe side effects must be made available if the vaccination programme is to achieve its aims.

The analyses suggest that the preventive effect of influenza vaccination in pupils under the current programme is inconsistent and weak. Even if the effectiveness of the vaccine is low, however, it still helps to prevent influenza. The results of our multiple regression analysis suggest that inoculating young schoolchildren with the vaccine was especially useful. But it cannot be expected that influenza vaccine will prevent unvaccinated schoolchildren or adults in the community from getting influenza. As stated before, the Ministry of Health and Welfare changed the regulations of the Preventive Vaccination Law, and weakened the obligatory aspect of influenza vaccination. Under the new rules, influenza vaccination is still mandatory for pupils but our results show that this is not enough, and that the obligational concept of the vaccination might be cut off. Unless an influenza vaccine with greater effectiveness and more consistent results becomes available, there is no point in recommending that all pupils be inoculated to protect themselves and also their communities. Similar cohort studies are necessary to confirm our results, because any change in the national influenza vaccination programme should be made cautiously.

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