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History of influenza vaccination programs in Japan

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ABSTRACT

In 1976, influenza mass vaccination among schoolchildren was started under the Preventive Vaccination Law, which was intended to control epidemics in the community. However, in the late 1980s, questions about this policy and vaccine efficacy arose, and a campaign against vaccination began. In 1994, influenza was excluded from the target diseases list in the Preventive Vaccination Law, without considering the immunization policy with respect to the common indications in high-risk groups. In 2001, the Law was again amended, specifying target groups, such as the elderly aged 65 or over, for influenza vaccination. In the 2005–2006 season, vaccine coverage among the elderly reached 52%. This shows that the need for vaccination has gradually become understood. However, the anti-vaccination campaign, which claims that the influenza vaccine has no efficacy, is still active. Vaccine efficacy studies that were not properly conducted are also being reported. In 2002, the Ministry of Health, Labor, and Welfare organized a research group on vaccine efficacy consisting of epidemiologists. The present symposium, as part of the 9th Annual Meeting of the Japanese Society for Vaccinology in 2005, was planned to further introduce epidemiological concepts useful in studying influenza vaccine efficacy.

1. Introduction

Japan is the only country in the world to have adopted mass vaccination of schoolchildren for influenza control, which resulted in an anti-vaccination campaign that still continues and claims that influenza vaccine has no efficacy. This has resulted in two peculiar circumstances in Japan. First, many people are concerned about influenza vaccine efficacy, whether or not they have the specialized knowledge required to understand the issue. Second, self-proclaimed specialists, who often lack specialized knowledge, nevertheless consider themselves specialists. As a result, people interested in influenza vaccine efficacy hear contradictory comments from real specialists, would-be specialists, and lay people, with lay people having the loudest voice.

The present symposium was planned to summarize the essential knowledge needed to understand the issues involved in influenza vaccine efficacy. Here, as a prologue to the symposium, we will briefly review the history of influenza vaccination programs in Japan, so that international readers can appreciate how lack of knowledge has contributed to difficulties in program implementation.

2. The beginning of influenza mass vaccination

In Japan, the Preventive Vaccination Law was promulgated in 1948, although influenza was not listed at that time. After the great impact of the 1957 Asian flu pandemic, a special program to promote influenza vaccination among schoolchildren was started in 1962, though it was not mandated by the Law. After the 1968 Hong Kong flu pandemic, the government was determined to establish further effective countermeasures against influenza. However, the rationale behind influenza control, which is to prevent severe complications and death among high-risk individuals, was not reflected in the vaccination strategy, and schoolchildren continued to be the sole target of active influenza vaccination. This somewhat one-sided policy gradually became entrenched, and studies that supported the approach were emphasized [1]. In 1976, the Preventive Vaccination Law was amended to include influenza among the target diseases, and mass vaccination of schoolchildren was started. This policy was intended to control influenza epidemics in the entire community by suppressing transmission in schools, while in Western countries, on the other hand, influenza vaccine was being given mainly to high-risk individuals, such as the elderly, at that time [2]. This was the beginning of chaos in influenza vaccination policy and in the influenza vaccine efficacy

Abbreviations: CI, confidence interval; MHW, Ministry of Health and Welfare; MHLW, Ministry of Health, Labor, and Welfare.

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debate that took place during the following 20 or more years in Japan.

3. Effect of mass vaccination on influenza impact

The unconventional policy of mass vaccination of schoolchildren attracted attention about whether it could actually mitigate the impact of influenza. However, no positive result of the policy was clearly shown [3]. A recent study reported that mass vaccination of schoolchildren reduced influenza mortality among the elderly; excess deaths among the elderly were lower during mass vaccination and then increased after discontinuation of the program [4]. However, this finding was criticized from several perspectives, including the increase in the elderly population, the rapid increase in the number of nursing homes and other living centers for seniors, and the definition of the influenza season [5]. Another study inferred that the discontinuation of mass vaccination among schoolchildren was responsible for an increase in influenza-associated deaths among young children [6]. On the other hand, a study focusing on the elderly in the United States failed to correlate increased vaccine coverage with a decline in mortality in any age groups [7]. In any case, these studies, whether the results were positive or negative, cannot provide solid evidence for influenza vaccine efficacy both at the population level and at an individual level, because they are "ecological studies." The subtlety involved in interpreting such studies has been discussed elsewhere [8].

4. Scepticism about influenza vaccine efficacy

From 1976 to 1987, more than 10 million schoolchildren annually received influenza vaccine, with the peak of 16.5 million vaccinees in each of 1983 and 1984. However, seasonal epidemics continued to occur, the elimination of which had been the objective of the mass vaccination policy. Furthermore, in Japan, individuals use the term "Kaze" (meaning cold) almost interchangeably with flu, and would say "I contracted Kaze, even though I received an influenza vaccine" [9]. School physicians, who were mostly private community practitioners who were in charge of school mass vaccination, were often asked about influenza vaccine efficacy by parents and teachers. This was an unexpected question for these frontline clinicians, since they had seldom been queried about the other vaccines. Many of them decided to study influenza vaccine efficacy by comparing the frequencies of Kaze, severe Kaze, or absenteeism due to Kaze between vaccinees and non-vaccinees in the school setting. Many such studies failed to detect vaccine efficacy due to misclassification of disease; however, they played an important role in stigmatizing influenza vaccine. Thus, in the late 1980s, two issues arose: whether influenza mass vaccination effectively prevents community epidemics; and whether influenza vaccine effectively prevents influenza attacks in individuals. With the blending of these two questions by the campaign against influenza vaccination, which involved the mass media, teachers' union, consumers' union, and other groups, influenza vaccine coverage among schoolchildren declined steeply from about 80% at its peak to 18% in 1992.

5. Discontinuation of mass vaccination programs

In contrast to the many reports that alleged that influenza vaccine had little or no efficacy, three quality Japanese studies were also published. The first one, a randomized, controlled study, was done among high school students during the 1968–1969 season. This study demonstrated that vaccine efficacy against serologically confirmed infection was 80% ($P < 0.001$) for A(H3) and 43% ($P < 0.01$) for B [10]. The second study, a case–control study among elementary schoolchildren, was done during the 1988–1989 season when A(H1) viruses were predominant. After adjusting for several confounders, the odds ratio of vaccination against influenza-like illness with fever $\geq 39\,^{\circ}C$ was calculated to be 0.33 (95% confidence interval (CI): 0.14–0.78) [11]; of interest, this finding was wrongly cited in a recent systematic review article [12]. The third study, an observational follow-up study among asthmatic children aged 2–14 years in the clinic setting, showed that vaccine efficacy against infection was 67.5% ($P < 0.01$) for A(H3), 43.7% ($P < 0.01$) for B, and 42.1% ($P < 0.01$) for both A(H3) and B combined [13]. However, these scientific reports were not considered when the vaccination program was being evaluated, since the vaccination policy and vaccine efficacy were being studied and discussed mainly by pediatric practitioners, who had an interest in school health, and by microbiologists, who were interested in the vaccine. In June 1994, the Preventive Vaccination Law was amended to exclude influenza from the list of target diseases without considering an immunization policy that would be based on the common indications for high-risk groups. Thus, influenza mass vaccination among schoolchildren that had lasted for nearly 20 years under the Law was discontinued. This is in striking contrast to what happened in the United States, where, in 1993, the federal government's Medicare program started reimbursement for the cost of influenza vaccine and its administration.

6. The pendulum swings back

At a time when interest in influenza disease and the influenza vaccine was extraordinarily low, several authors reviewed the misunderstandings about the vaccine and vaccination strategy [9,14]. Then, in 1997, the first Committee for Influenza Pandemic Preparedness was established by the Ministry of Health and Welfare (MHW) and clearly specified the rationale of influenza control and influenza vaccine efficacy, given the results of the three above-mentioned studies [10,11,13]. The committee also reviewed the frequency of influenza vaccine side effects, which had been officially recognized and compensated for during the mass vaccination era (1977–1994): 116 events among 329,339,615 vaccinations, that is "0.35×10^{-6} (95% CI: 0.29×10^{-6} to 0.42×10^{-6}) per vaccination", which can also be stated as "0.07×10^{-6} per week after vaccination", assuming that the maximum duration between vaccination and the onset of side effects is 35 days. Once again, the mass media began to show their interest in influenza, and newspapers headlined influenza deaths in nursing homes. Thus, it appeared as if the pendulum were swinging back, though the negative view of influenza vaccine persisted. At that time, there was an article published in a magazine alleging that the group of people with favorable views towards influenza vaccine had been the result of collaboration among vaccine manufactures, scientifically biased researchers, and the MHW [15]. It also presented survey data on influenza attack rates (vaccinees 71.0%, non-vaccinees 75.4%) and absenteeism due to influenza (vaccinees 73.3%, non-vaccinees 72.8%) and concluded that it would be hard to accept that influenza vaccine is effective. Fortunately, unlike the period from the late 1980s to the early 1990s, few people agreed with this view, but unfortunately, there were still only a few individuals who could instantly understand the drawbacks of such data reported in the magazine. It is quite clear that the survey data reported suffered substantially from misclassification of disease due to loose criteria, such as "Kaze", particularly when compared to the reported attack rates (45–60%) among schoolchildren during the 1957 Asian flu pandemic.

7. A new vaccination strategy and the present status

During the 1996–1997 influenza season, the MHW issued a notice to all prefecture governments that welfare institutes were to make the necessary arrangements to ensure that all residents could receive influenza vaccine. In 1999, the MHW and the Japan Medical Association collaborated on a campaign whose slogan was, "Don't confuse influenza with Kaze. Don't underrate influenza." Finally, in 2001, the Preventive Vaccination Law was amended to again include influenza, specifying two target groups: the elderly aged 65 or older and those aged 60–64 years with heart, kidney, lung, and other chronic disorders. Under this Law, more than 99% of eligible persons are elderly, since the 60–64-year-old age group is normally classified as the disabled people who are officially registered for special welfare services. Under the Law, municipalities have to take responsibility for offering vaccinations to the target groups. The cost of providing the influenza vaccine, including not only the cost of the vaccine and the cost of its administration, but also a health consultation fee to determine whether it is indicated, is roughly 5000 Japanese Yen (¥); the municipality provides a subsidy (¥4000), and the individual contributes a self-payment (¥1000). The cost and the division of the cost are not equal among the municipalities, but they depend on the agreement between the municipal government and the community medical association. The relatively high cost of vaccination reflects the need to deal with the negative perception of influenza vaccine safety, since the anti-vaccination campaign always exaggerates the side effects of the vaccine.

Since 2001, vaccine coverage among the target population has been consistently increasing: 28% in 2001–2002, 35% in 2002–2003, 45% in 2003–2004, 47% in 2004–2005, and 52% in the 2005–2006 season. These figures reflect the coverage among the elderly aged 65 or over, since they account for almost all of the target population. Thus, the significant health impact of influenza and the important role that vaccination plays have gradually become understood by the general public. Geriatric hospital physicians have played an important role in disseminating information about influenza vaccine efficacy. They closely observe each patient throughout the influenza season, since influenza-related complications, such as pneumonia, are critical issues in their hospitals. They can, therefore, themselves observe the reduction in severe complications and death among vaccinated patients compared to non-vaccinated patients. This situation is quite different from that of the school physicians who were previously engaged in mass vaccination; they only had contact with the children who visited their clinics during influenza season. Many or almost all such children suffering from flu symptoms had received influenza vaccine due to the high vaccine coverage rates that had been achieved with the mass vaccination programs.

8. Recent developments surrounding influenza vaccine

In Japan, while anti-vaccination campaigns are still active, they have weakened and have some peculiar features. The opposition is based upon the view that influenza vaccine has a little or no efficacy but a high risk of side effects, and that influenza is not a serious disease for which preventive intervention is required. It is really regrettable that there are physicians who inexplicably share the views of the anti-vaccination activists and object to influenza vaccination. This situation is in sharp contrast with that in Western countries where the major reasons for refusing vaccination are typically religious beliefs or personal principles.

Many physicians and pediatricians still feel frustrated by the degree of efficacy of the present influenza vaccine. They usually make apologies when administering influenza vaccine, explaining that "Every vaccine recipient cannot necessarily avoid contracting influenza." To resolve this dilemma, they perform their own studies of vaccine efficacy. They believe that the failure to detect vaccine efficacy during the mass vaccination era was solely due to the use of a clinically defined outcome. Now, they are confident that laboratory-confirmed influenza can be identified in their clinics using a newly developed commercial rapid diagnostic kit. Thus, they tend to first register vaccinated and non-vaccinated subjects before the influenza season, and then simply calculate the proportion of clinic visitors with positive rapid antigen tests among the initially enrolled subjects by vaccination status; they do not include any information on non-clinic visitors. It appears difficult for front-line clinicians to recognize that observing individual study subjects with equal intensity is of paramount importance in these types of studies. As in the 1980s, although fewer in number, several studies have been conducted by clinicians who lack even a rudimentary appreciation of epidemiologic principles, including selection bias, confounding, and misclassification. Of even greater concern is that there are few Japanese researchers who can critically review such flawed studies, which results in the presentation at scientific meeting or publication in journals of fundamentally flawed studies [16].

Thus, in 2002–2004, the Ministry of Health, Labor, and Welfare (MHLW: the former MHW was reorganized in 2001) created a research group consisting of epidemiologists, for the "Appraisal of influenza vaccine efficacy and vaccination policy in conformity with evidence-based medicine", and granted them a total of ¥99,750,000. This was the first research group created by the MHLW that focused on the epidemiological aspects of influenza vaccine. The formation of this group attracted the attention of epidemiologists to influenza vaccine. Most of the epidemiologists had never considered that vaccine research was a field in which they could be involved. It is also undeniable that pediatricians and microbiologists had considered influenza vaccine to be their own exclusive research area and felt reluctant to work with epidemiologists. Several epidemiologists in the research group took a great interest in the field and have successfully conducted studies of vaccine efficacy [17–20].

Following the success of the first research group, in 2005–2007, the MHLW set up a successor group for "Analytical epidemiologic study on the effectiveness of influenza and other vaccines and vaccination policy" and has already granted ¥94,900,000 for the first 2 years. In this second research group, the epidemiologists who gained experience doing influenza research in the first group are expected to expand their investigations in close cooperation with pediatricians, physicians, and microbiologists, as well as to transfer their epidemiological knowledge and skills to their co-researchers. Thus, as a result of the common perception of the vaccine efficacy study, the present symposium on influenza vaccine from the epidemiological viewpoint was held at the 9th Annual Meeting of the Japanese Society for Vaccinology in Osaka on October 15–16, 2005. The following articles dealing with the topics covered at the symposium were collected to serve as the basis to convey the essential knowledge of epidemiology, to review the prior studies for use as a reference, and to present community-based studies recently carried out by epidemiologists with the cooperation of clinicians and virologists.

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Essential tools for assessing influenza vaccine efficacy in improperly conducted studies: A Japanese perspective

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ABSTRACT

The fundamental issue in assessing influenza vaccine efficacy is to observe all study subjects with equal intensity throughout the surveillance period. The case definition can be adopted within the scope of the budget and the logistics of the study; however, there is no doubt that culture-proven influenza is currently the best outcome index. More pronounced vaccine efficacy can be detected if stricter case definition criteria are applied and/or if observations are confined to the peak epidemic period. Patients identified through passive case-finding in clinics do not properly represent all influenza cases that occur in the study subjects. Almost all non-randomized studies which have so far been conducted by Japanese clinicians do not take confounders into consideration. Even though laboratory-confirmed influenza is identified, vaccine efficacy should primarily be estimated based on the presence of any influenzal illness, since efficacy calculated by virus type or subtype often results in loss of statistical power. The results from post hoc subgroup analysis may not offer a solid base for assessing vaccine efficacy and should be cautiously interpreted.

1. Introduction

During the height of the influenza anti-vaccination campaign in the 1980s, many pediatricians working in school health conducted studies of vaccine efficacy based on their extensive clinical experience. The studies they designed were done in the school setting, and information on vaccination status and outcomes, such as cold symptoms or absenteeism, were obtained. However, most of the studies failed to detect vaccine efficacy due to the diluting effect of outcome misclassification. With the availability of rapid influenza diagnostic test kits, pediatricians and other physicians who had been discouraged by the difficulties involved in proper case definition were delighted; they immediately began to perform studies of influenza vaccine efficacy using these kits. Vaccinees and nonvaccinees were enrolled before the influenza season. Subjects who visited their clinics during the influenza season were tested with the rapid diagnostic kits, and the proportions of positive test results in the vaccinated and nonvaccinated groups were simply compared. The principal outcome of these studies was "laboratory-confirmed influenza". However, subjects that were lost to follow-up and those that died tended not to be properly handled, and no information was obtained about illness attacks among subjects who did not visit their clinics [1]. Such studies are typical of those that have been recently reported from Japan. Both the researchers and the readers are impressed by "laboratory-confirmed influenza" as the outcome, and overlook the fact that a study must "observe all study subjects with equal intensity throughout the surveillance period." Regrettably, it is not rare that journal reviewers and chairpersons of scientific sessions fail to identify this fatal flaw in such studies.

2. Studies of acellular pertussis vaccine

In Japan, there is a long-standing notion that the inactivated influenza vaccine has little or no efficacy. However, worldwide, the efficacy of acellular pertussis vaccine compared to that of whole-cell vaccine has been the most widely debated, as has been previously discussed in detail [2].

In Europe and Africa between 1985 and 1993, nine major studies on the efficacy of acellular pertussis vaccine were conducted, including a case–control study. They differed in many aspects, including study design, case definition, surveillance methods, and choice of comparison group. In these studies, the duration of surveillance or observation ranged from 7.2 to 25.6 months. The surveillance/follow-up methods included: telephone interviews every 2 weeks, every month, or every 6–8 weeks; clinic visits at 5, 12, and 18 months; or weekly home visits by field workers. How-

Abbreviations: CI, confidence interval; HMO, Health Maintenance Organization; ICD, International Classification of Diseases; ILI, influenza-like illness.

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ever, initial efficacy results were not consistent in judging whether acellular or whole-cell vaccines were superior, since the estimation of vaccine efficacy is strongly influenced by case definition [2].

In 1991, the World Health Organization convened an expert committee to formulate a pertussis case definition that would be used in vaccine efficacy studies. The definition included "at least 21 days of paroxysmal cough plus bacteriological, serological, or epidemiological confirmation." Using this case definition, it became possible to obtain stable estimates of pertussis vaccine efficacy and to compare these estimates among different studies. Thus, compared to whole-cell vaccine, acellular pertussis vaccine was found to have nearly the same efficacy (75–90% vs. 85–95%) and fewer adverse events (about one-third in frequency); acellular pertussis vaccine has replaced the whole-cell vaccine and is widely used [2].

The process of studying acellular pertussis vaccine offers two key lessons. First, all study subjects, both vaccinees and nonvaccinees, must be observed with equal intensity throughout the surveillance period. Second, the case definition that is used to assess vaccine efficacy is not identical to the one used in clinical settings. Thus, after satisfying the first condition, which requires full observation, case definition(s) can be adopted within the scope of the study's budget, logistics, and other relevant parameters.

3. Selected studies demonstrating the principles of study methods

There have been several studies that satisfy the essential criteria for assessing influenza vaccine efficacy. The four studies mentioned below are especially recommended to Japanese researchers, since they were well designed, well performed, well analyzed and well interpreted; they contain all of the requisites that are often overlooked in Japanese studies.

3.1. Belshe et al. (1998)

This was a randomized, multi-center, double-blind, placebo-controlled trial using live attenuated, cold-adapted influenza virus vaccine in children 15–71 months old [3]. Study subjects were assigned to a vaccine group ($n = 1070$) or a placebo group ($n = 532$). They were then observed during the period from vaccination up to the end of influenza outbreaks at the study sites during 1996–1997 season. Parents were contacted by telephone every 2 or 3 weeks until the beginning of an influenza epidemic, and then weekly during the epidemic. The staff at the study sites collected viral-culture specimens from symptomatic subjects. From among a total 3005 specimens, 109 culture-positive cases were identified. Thus, a case was defined as any patient with an illness detected by active surveillance that had a positive culture. Vaccine efficacy was reported to be 93% (95% confidence interval (CI): 88–96%) based upon the attack rates of 1.3% (14/1070) in the vaccine group and 17.9% (95/532) in the placebo group.

This can be regarded as one of the best studies on influenza vaccine efficacy reported to date. Most Japanese readers would first consider that the outcome (culture-confirmed influenza) confers the greatest value to this study. In fact, there is currently no doubt that culture-confirmed influenza is the best outcome measure for studying influenza vaccine efficacy. However, it is also important to note that active case-finding was successfully performed by telephone contact on a weekly basis. The collection of specimens from symptomatic subjects and the performance of virus culture examinations only became meaningful after thorough case finding had been conducted. It is also noteworthy that a total of 3005 specimens were collected from symptomatic subjects due to the active case-finding procedure. This means that each child under 6 years of age presented with influenza-like symptoms approximately twice during the season.

3.2. Govaert et al. (1994)

This was a randomized, multi-center, double-blind, placebo-controlled trial using inactivated influenza vaccine in elderly individuals aged 60 years or older [4]. The subjects were assigned to a vaccine group ($n = 927$) or a placebo group ($n = 911$) and observed for attacks or infections up to 5 months after vaccination during the 1991–1992 season. Four outcomes were compared between the groups: (1) serologically confirmed influenza infection; (2) physician-diagnosed influenza-like illness (ILI), based on the *International Classification of Health Problems in Primary Care (ICHPPC-2-Defined)*, made at the time the subject visited the participant's clinic; (3) ILI based upon the information obtained from postal questionnaires sent 10 and 23 weeks after vaccination that collected self-reported ILI episodes classified using the criteria of the Dutch Sentinel Stations; (4) similarly, self-reported ILI defined by the *ICHPPC-2-Defined* based on the questionnaire information. Paired sera were collected from 97% of all subjects; the response to the questionnaires was 98% and 96% at the first and second mailings, respectively.

For the outcomes (1)–(4) listed above, the relative risks of vaccination were 0.50 (95% CI: 0.35–0.61), 0.53 (0.39–0.73), 0.69 (0.50–0.87), and 0.83 (0.65–1.05), respectively. When observation was confined to the peak epidemic period of 10 weeks, lower relative risks for the outcomes (1)–(4) were obtained: 0.39 (0.22–0.68), 0.40 (0.19–0.87), 0.41 (0.28–0.61), and 0.74 (0.24–1.00), respectively.

This study highlights important aspects of assessing influenza vaccine efficacy. It clearly demonstrates that a more pronounced efficacy can be detected if stricter criteria are applied to measure the outcome and if the observations are confined to the influenza peak epidemic period. This is attributed to the increase in specificity of classifying non-diseased subjects as a negative outcome, which clinicians usually consider achievable only by applying more sophisticated laboratory tests. Moreover, this study implicitly indicates the authors' profound knowledge on a randomized controlled trial. The authors did not perform statistical significance testing to compare the distribution of subjects' baseline characteristics between vaccine and placebo groups; they conducted multivariate analysis to consider potential confounding effects. The authors recognized that the imbalances that do occur in a randomized study are due to chance and therefore one cannot reject the null hypothesis.

The authors also performed subgroup analyses and reported the relative risks of vaccination for two different age groups, e.g., 0.43 (0.28–0.67) for ages 60–69 and 0.77 (0.39–1.51) for ages 70 or older. They stated, "The post hoc analysis suggests that the efficacy may be lower in those aged 70 years and older, and therefore further evaluation of this group would be interesting." At that time, some anti-vaccination activists in Japan cited this data and wrongly asserted that influenza vaccine had no efficacy among those aged 70 or older, since the relative risk decrease was not statistically significant.

3.3. Nichols et al. (1994)

This was a retrospective cohort study among elderly individuals aged 65 or older that used information collected during three seasons (1990–1991, 1991–1992, and 1992–1993) in the administrative database of a large Health Maintenance Organization (HMO) in the United States [5]. The outcome included hospitalizations for pneumonia and influenza, all acute and chronic respiratory condi-

tions, and congestive heart failure. Cases were identified using the *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM). Information about potential confounders was also obtained from the same database. The observation period lasted from the date of the first influenza virus isolation in the community through March in each season. For example, during the 1991–1992 season, 15,288 vaccinees and 11,081 nonvaccinees were identified in the database, and the outcome frequencies were compared. The adjusted difference in hospitalization was: 5.8×10^{-3} (95% CI: 3.0×10^{-3} to 8.5×10^{-3}) for pneumonia and influenza; 15.3×10^{-3} (8.2×10^{-3} to 22.4×10^{-3}) for all acute and chronic respiratory conditions; 2.3×10^{-3} (0.1×10^{-3} to 4.4×10^{-3}) for congestive heart failure. Vaccination was also effective in preventing death from all causes; the adjusted odds ratios were 0.49 (0.35–0.70) in 1990–1991, 0.46 (0.35–0.61) in 1991–1992, and 0.61 (0.47–0.81) in 1992–1993.

This study is quite instructive for Japanese researchers. First, in applying passive case-finding, the authors chose hospitalization as a study outcome, not the influenza illness attack confirmed in the outpatient clinic. In an HMO, disease severity requiring hospitalization can be judged fairly consistently. Therefore, it seems unlikely that many patients who did not require hospitalization were actually hospitalized, and that many patients who required hospitalization were not hospitalized. This means that the both sensitivity and specificity of the outcome (hospitalization) were properly maintained, and the diluting effect of misclassification was minimized. On the other hand, the use of influenza illness attacks identified in the clinic through passive case-finding causes a biased estimate of vaccine efficacy, since, other than in young children, visiting a clinic due to uncomplicated influenza is strongly affected by factors other than illness severity. With passive case-finding as is used in Japan, it can become extremely difficult to ensure the homogeneity of the outcome and to minimize non-differential/differential misclassification of the outcome, not only for illness attacks but also for hospitalizations. This is because, in principle, the Japanese health insurance system guarantees the patient's freedom to choose the medical institution, whether a clinic or hospital, that they attend and makes a payment according to the amount claimed by the doctor.

Second, in this study, outcome measures were adjusted for potential confounders, such as age, gender, diagnoses indicating high risk, use of medications, and previous use of health care services. Almost none of the influenza vaccine efficacy studies so far conducted by Japanese clinicians have taken into consideration the confounding effects of other factors, despite their non-randomized observational designs.

3.4. Hoberman et al. (2003)

This was a randomized, double-blind, placebo-controlled trial using inactivated influenza virus vaccine in children 6–24 months old during the 1999–2000 and 2000–2001 seasons; the study was originally designed to evaluate vaccine efficacy against acute otitis media (AOM) [6]. Children were assigned to receive either vaccine or placebo in a 2:1 ratio (273:138 in the first season, and 252:123 in the second season) and were followed to the end of March with biweekly visits. Parents were instructed to contact study staff if their children developed any signs or symptoms so that an interim visit could be arranged. Throat culture specimens were collected during visits if the patients showed symptoms or signs of an upper respiratory tract infection accompanied by fever $\geqq 38\,^{\circ}C$, AOM, or both. There were a total of 1260 episodes of illness, from which 1113 specimens (88%) were obtained. In the first season, the frequency of culture-proven influenza was 5.5% in the vaccine group and 15.9% in the placebo group; in the second season, the corresponding figures were 3.6% and 3.3%, respectively. Accordingly, the efficacy of the vaccine to prevent culture-proven influenza was calculated to be 66% (95% CI: 34% to 82%) in the first season, and −7% (−247% to 67%) in the second season. No efficacy against AOM was detected.

This study shows that even well-designed studies using a proper protocol do not always consistently detect influenza vaccine efficacy. This tendency is particularly marked in studies focused on young children and/or studies done during a season with low-influenza activity. Several factors make it difficult to detect vaccine efficacy among very young children, including, among others: a low-immune response to the vaccine possibly due to the child's unique biological characteristics or less previous exposure to influenza viruses or antigens; susceptibility to co-circulating infectious agents; the illness definition used to measure the outcome event; the method used to obtain clinical information. In addition, antigenic similarity between circulating viruses and vaccine strains differs every year. Therefore, a randomized, controlled study investigating influenza vaccine efficacy cannot have results that are as conclusive as other randomized trials dealing with other preventive or curative interventions. Furthermore, observational studies of the influenza vaccine are even less likely to obtain stable results. Thus, to demonstrate influenza vaccine efficacy, particularly among young children, repeated studies in different populations under varying circumstances using a variety of methods are needed.

4. Discussion and conclusion

Belshe et al. appear to achieve almost perfect case-finding by observing all study subjects with equal intensity throughout the season and by detecting culture-proven influenza. Hoberman et al. also successfully performed surveillance, although active contact by study staff was biweekly as compared to the weekly contact in the study by Belshe et al. It should also be noted that the postal questionnaire sent 10 and 23 weeks after vaccination used in the study by Govaert et al. is an appropriate instrument for observing subjects equally and can thereby secure the validity of the study. However, the use of self-reported influenza-like illnesses (ILI) is likely to underestimate vaccine effectiveness due to the non-differential misclassification of the outcome. Although dilution is unavoidable, self-reported ILI can provide fairly accurate results if efforts are made to enable frequent contact, such as with telephone interviews or postal questionnaires on a weekly basis, and/or if the observation of the occurrence of outcomes is confined to the peak epidemic period [4,7]. In the study by Nichols et al., hospitalization was retrospectively identified using the HMO database; this is also considered to be a valid estimate of vaccine efficacy in the light of the severity of the outcome and the parameters of the HMO health insurance system scheme. Japanese researchers should not simply use passive case-finding to identify the outcome, since the Japanese health insurance system strongly affects patients' behavior in choosing to consult a doctor, and the doctors' approach to practicing medicine. Readers should take a critical view of Japanese studies that compare outcomes identified using passive case-finding.

Even in studies that are based on laboratory confirmation, the primary outcome should be the presence of any illness, regardless of virus type or subtype, as in the studies by Belshe et al., Govaert et al., and Hoberman et al.; type- or subtype-specific illness should be treated as a secondary outcome. This approach can be rationalized as follows. When the attack rate is 10% in vaccinees and 20% in nonvaccinees, statistically significant vaccine efficacy can be detected if 199 subjects are enrolled in each group, under the conditions of $\alpha = 5\%$ and $(1 - \beta) = 80\%$. If the attack rate decreases to 5% in vaccinees and 10% in nonvaccinees by comparing virus type- or

subtype-specific diseases, 435 subjects are required in each group using the same conditions. Thus, vaccine efficacy calculated by virus type or subtype is not always as straightforward to interpret as vaccine efficacy calculated against any illness; however, virus type or subtype-specific estimates may provide further biological insight.

The conservative and careful interpretation by Govaert et al. of the relative risk of vaccination for the ages 70 or older subgroup is a good example to researchers, since the results were obtained from a post hoc subgroup analysis. Such data cannot offer a solid basis for determining vaccine efficacy, whether they do or do not favor the vaccine. In Japan, medical professionals who have an interest in influenza often mistakenly argue about vaccine efficacy among young children relying on data from subgroup analyses with limited numbers of subjects, as if such data could provide a solid basis for discussion. The level of knowledge among such medical professionals seems unlikely to be different from that of anti-vaccination activists who wrongly alleged, citing Govaert's article, that influenza vaccine has no efficacy among the elderly (aged 70 years or over).

There have been many Japanese observational studies that have not taken confounders into consideration; the need to do so has not been appreciated by so-called influenza specialists. This is likely due to the fact that few epidemiologists have been involved in vaccine research. All Japanese medical professionals who are interested in and involved in discussing influenza vaccine efficacy should recognize the elegance of the study by Govaert et al., who performed a multivariate analysis of the results of their randomized, controlled trial. Currently in Japan, it is unfortunate that proficient researchers are sometimes censured by so-called influenza specialists as being anti-vaccination activists when they criticize studies that report vaccine efficacy but overlook significant confounding effects.

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Ecological fallacy and scepticism about influenza vaccine efficacy in Japan: The Maebashi Study

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ABSTRACT

In 1979, Maebashi City discontinued influenza mass vaccination immediately after a case of vaccine-related convulsion occurred. A research group of the Maebashi City Medical Association studied the effects of mass vaccination on influenza activity in two cities without mass vaccination programs and three cities with mass vaccination programs (Maebashi Study). Due to possible issues of validity arising from the non-randomized design of the study, the authors of the Maebashi Study reserved discussion on the vaccine efficacy that they calculated from the attack rates among the non-vaccinees and vaccinees. Instead, they compared the overall attack rates in Maebashi and among the twice-vaccinees in the cities with mass vaccination programs. The authors limited their discussion to the fact that influenza activity in Maebashi was not materially different from that in cities with mass vaccination programs. Anti-vaccination activists misconstrued this to mean that the absence of a correlation between attack rate and vaccine coverage implies that influenza vaccine has no efficacy. This is a good example of the "ecological fallacy", which refers to the fact that a relationship between two variables at the population level does not necessarily imply the same relationship at an individual level.

1. Introduction

It has been said that one report played a decisive role in instilling scepticism about influenza vaccine efficacy in Japanese society. The study, known as the "Maebashi Study", was performed by a research group organized by the Maebashi City Medical Association and was conducted primarily between 1981 and 1986.

The Maebashi Study is almost always cited by anti-vaccination activists, as well as by medical professionals, as evidence that influenza vaccination is not effective. During the 1979–1980 season, Maebashi City discontinued its influenza mass vaccination program for school children when a case of severe convulsion occurred in a child after the first dose; the second dose inoculation program was cancelled that season. Subsequently, the Medical Association investigated influenza vaccine efficacy. The results of the study were published in 1987, in a report entitled "Influenza Epidemics in a Non-vaccinated Area" [1]. However, it is important to note that most influenza specialists have never read this report; they simply believe that, based on mass media reports, the Maebashi Study demonstrated that influenza vaccine had little or no efficacy.

In the preface to the report, the authors stated the background and aim of their study as follows:

> "...We have no intention of fully investigating the protective effect of influenza vaccine against infection or attack. However, we are greatly concerned with whether vaccination of pupils and students would provide any protection against an influenza epidemic. Now is the time to review the compulsory mass vaccination program for these age groups."

Thus, it is clear that the aim of the Maebashi Study was to investigate the effect of mass vaccination on influenza activity in the community, as shown by the title of the report "Influenza Epidemics in a Non-vaccinated Area."

2. An outline of the Maebashi Study

2.1. Subjects and methods

Most of the study was done during the 1984–1985 season, which had a type B virus epidemic, and during the 1985–1986 season, when A(H3) viruses were circulating. The attack rate in all school children was investigated in five selected cities in the Gunma Prefecture: Maebashi and Annaka, which had discontinued mass vaccination; Takasaki, Kiryu, and Isesaki, which were still continuing mass vaccination. Information on influenza attacks was

Abbreviation: ILI, influenza-like illness.

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retrospectively collected from more than 99% of the subjects. An influenza-like illness (ILI) was defined as "fever ≧ 37 °C plus absenteeism ≧ 2 consecutive days" or "absenteeism ≧ 3 consecutive days" during an influenza outbreak in the appropriate school. An outbreak was characterized as the period during which the proportion of absenteeism due to influenza symptoms among school children was 2% or more.

The authors again emphasized in the beginning of this section that:

> "...The vaccine effectiveness we discuss hereafter indicates the one relevant to the group of people, not to the individuals."

2.2. Results and discussions

The main results of the Maebashi study are shown in Tables 1 and 2.

First (noted by superscript "b" in the Table), the authors pooled the data for the three cities that were still continuing with mass vaccination and calculated the attack rate as a whole for the 1984–1985 season (Table 1); it was 54.7% (3962/7241) among non-vaccinees and 40.6% (13,255/32,641) among twice-vaccinees, for an estimated effectiveness of twice-vaccination of 25.8% [(54.7–40.6)/54.7]. The corresponding attack rates for the 1985–1986 season (Table 2) were 33.3% (2564/7702) among non-vaccinees and 20.3% (5729/28,207) among twice-vaccinees, for a vaccine effectiveness of 39.0% [(33.3–20.3)/33.3]. At this point, the authors recognized that the non-randomized study design could have introduced a validity problem. They suggested that asthmatic children, who usually account for about 5% of Japanese school children, were likely not vaccinated; of note, the Japanese vaccination guideline includes asthma as well as egg allergy as conditions that require special attention if influenza vaccine is to be given. The authors also believed that children in poor health might not have been vaccinated if they had symptoms at the time that the vaccine was being given. Thus, the non-vaccinated group was thought to include more subjects that were prone to develop influenza symptoms, which would have led to vaccine effectiveness being overestimated. Thus, the authors undertook additional analyses.

Second (noted by superscript "a" in the Table), the authors regarded the overall attack rate in Maebashi city as the reference rate (non-vaccinated area), and compared it with the attack rate among all twice-vaccinees in the three cities that continued their mass vaccination programs (vaccinated area). In the 1984–1985 season (Table 1), the comparison of the attack rates between the non-vaccinated (42.8%) and vaccinated areas (40.6%) showed that vaccination program was associated with an absolute risk reduction of 2.2% points, with a prevented fraction of 5% (calculated in the same way as ordinary vaccine efficacy). In the 1985–1986 season (Table 2), comparison of the two attack rates (27.7% vs. 20.3%) demonstrated an absolute risk reduction of 7.4% points, with a prevented fraction of 2.7%. Thus, the vaccination program appeared to have only a limited effect.

3. Interpretation by the research group

When interpreting the results of their first analysis, the authors emphasized that the groups had an imbalance of characteristics, though they did not use the term "confounding." Had a more complete epidemiological analysis been done, it would have adjusted for the confounding effects, using the information on potential confounders collected initially. Of note, it should be emphasized that, even 20 years after the Maebashi Study, the issue of confounding is not often adequately addressed in vaccine efficacy studies done by Japanese clinicians.

With respect to the study's second analysis, it seems unlikely that attack rates in the non-vaccinated and vaccinated areas were sufficiently comparable, since influenza activity is a phenomenon that is time- and place-specific. In addition, the unit of observation was changed from individuals in the first analysis to groups in the second analysis. Had the authors contrasted the overall attack rate between the non-vaccinated and vaccinated areas, as would be done in an ordinary ecological study, they would have noticed that their analysis was illogical, given that the comparison showed that the vaccination program had a negative effect (Table 1): a 42.8% attack rate in Maebashi and a 43.7% attack rate in the three cities that were grouped together as the vaccinated area during the 1984–1985 season.

The authors avoided discussing vaccine efficacy at the individual level, as they mentioned in the preface to the report and in the beginning of the main chapter. Based upon the slight effect of the vaccination program shown in their second analysis, they concluded:

> "...Influenza activity in Maebashi in non-vaccinated areas did not show any material difference from that in vaccinated areas. We therefore believe that the idea of preventing an influenza epidemic in the community by using school children as a breakwater has been proven a complete failure."

Thus, the authors interpreted their study's results carefully, recognized that it had some limitations, and never deviated from scientifically sound principles in explaining influenza vaccine efficacy.

4. Ecological fallacy drawn from the Maebashi Study

Anti-vaccination activists incorrectly cite the Maebashi Study in their campaign and have put the following statement on their website:

> "...The doctors of the Maebashi City Medical Association ... thoroughly surveyed absenteeism and illness attack rates in the vaccinated and non-vaccinated areas. This outstanding epidemiologic study comparing 45,000 school children in a vaccinated area with 25,000 school children in a non-vaccinated area revealed that influenza vaccine cannot prevent epidemics, not only in the community but also among children, and the efficacy of vaccine was thus negated."
>
> "...As shown by the data of the 1984–1985 season with type-B virus circulation, ... vaccine coverage was 0.1% in Maebashi as compared to 91.5% in Takasaki, but the actual incidence was nearly the same, 42.8% and 40.1%, respectively. The situation was similar in cities other than Takasaki. These data demonstrate good reasons for concluding that influenza vaccine has no efficacy."

In their statements, the activist group compared the attack rate in relation to the vaccine coverage; the unit of observation was each city, not the individual, although the original data had included information on each individual subject. To assert that influenza vaccine had no efficacy provides a good example of the "ecological fallacy." On the other hand, the authors of the Maebashi Study carefully focused their discussion on the effect of mass vaccination programs.

5. Consideration

The Maebashi Study group conducted a large-scale survey, though there were some limitations. They must be respected for the enormous effort they made to conduct the study and for their pru-

Table 1
Influenza vaccination and attack rates of influenza-like illness (ILI) among school children in the 1984–1985 season (Maebashi Study)

City	Vaccination	Number of subjects (distribution%)	Number of ILIs (attack rate%)
Cities with no mass vaccination			
Maebashi	Total	25,122 (100)	10,743 (42.8)[a]
	Non-vaccinees	25,101 (99.9)	10,738 (42.8)
	Once-vaccinees	18 (0.1)	5 (27.8)
	Twice-vaccinees	3 (0.0)	0 (0)
Annaka	Total	4,021 (100)	1,832 (45.6)
	Non-vaccinees	4,021 (100)	1,832 (45.6)
	Once-vaccinees	0 (0)	0 (0)
	Twice-vaccinees	0 (0)	0 (0)
Cities with mass vaccination			
Total	Total	45,336 (100)	19,817 (43.7)
	Non-vaccinees	7,241 (16.0)	3,962 (54.7)[b]
	Once-vaccinees	5,445 (12.0)	2,603 (47.8)
	Twice-vaccinees	32,641 (72.0)	13,255 (40.6)[a,b]
Takasaki	Total	22,119 (100)	8,865 (40.1)
	Non-vaccinees	1,887 (8.5)	1,017 (53.9)
	Once-vaccinees	1,291 (5.8)	597 (45.9)
	Twice-vaccinees	18,941 (85.6)	7,254 (38.3)
Kiryu	Total	12,374 (100)	5,324 (43.0)
	Non-vaccinees	2,751 (22.2)	1,425 (51.8)
	Once-vaccinees	2,318 (18.7)	1,039 (44.8)
	Twice-vaccinees	7,305 (59.0)	2,860 (39.2)
Isesaki	Total	10,843 (100)	5,628 (51.9)
	Non-vaccinees	2,603 (24.0)	1,520 (58.4)
	Once-vaccinees	1,836 (16.9)	967 (52.7)
	Twice-vaccinees	6,395 (59.0)	3,141 (49.1)

ILI: "fever ≧ 37 °C plus absenteeism ≧ 2 consecutive days" or "absenteeism ≧ 3 consecutive days." Observations from January 8, 1985 to February 28, 1985.
[a] Compared in the second analysis.
[b] Compared in the first analysis.

Table 2
Influenza vaccination and attack rates of influenza-like illness (ILI) among school children in the 1985–1986 season (Maebashi Study)

City	Vaccination	Number of subjects (distribution%)	Number of ILIs (attack rate%)
Cities with no mass vaccination			
Maebashi	Total	24,266 (100)	6,714 (27.7)[a]
	Non-vaccinees	24,249 (99.0)	6,709 (27.7)
	Once-vaccinees	10 (0.0)	5 (50.0)
	Twice-vaccinees	7 (0.0)	0 (0)
Annaka	Total	4,071 (100)	903 (22.2)
	Non-vaccinees	4,056 (99.6)	899 (22.2)
	Once-vaccinees	11 (0.3)	3 (27.3)
	Twice-vaccinees	4 (0.1)	1 (25.0)
Cities with mass vaccination			
Total	Total	43,687 (100)	10,513 (24.1)
	Non-vaccinees	7,702 (17.6)	2,564 (33.3)[b]
	Once-vaccinees	7,778 (17.8)	2,220 (28.5)
	Twice-vaccinees	28,207 (64.6)	5,729 (20.3)[a,b]
Takasaki	Total	21,381 (100)	4,481 (21.0)
	Non-vaccinees	2,063 (9.6)	637 (30.9)
	Once-vaccinees	2,106 (9.8)	640 (30.4)
	Twice-vaccinees	17,212 (80.5)	3,204 (18.6)
Kiryu	Total	11,657 (100)	2,933 (25.2)
	Non-vaccinees	2,628 (22.5)	846 (32.2)
	Once-vaccinees	3,470 (29.8)	817 (23.5)
	Twice-vaccinees	5,559 (47.7)	1,270 (22.8)
Isesaki	Total	10,649 (100)	3,099 (29.1)
	Non-vaccinees	3,011 (28.3)	1,081 (35.9)
	Once-vaccinees	2,202 (20.7)	763 (34.7)
	Twice-vaccinees	5,436 (51.0)	1,255 (23.1)

ILI: same as Table 1. Observations from November 3, 1985 to December 28, 1985.
[a] Compared in the second analysis.
[b] Compared in the first analysis.

dent attitude in interpreting the results. On the other hand, many so-called influenza specialists, who misunderstand the Maebashi Study based on the mass media information, simply believe that the study raised doubts about influenza vaccine efficacy. Needless to say, they have not delved into the details of the study itself, nor have they noticed its important message on case definition, confounding, selection bias, surveillance with equal intensity, among others.

The ecological fallacy that has been intentionally drawn from the data in the Maebashi Study has been spread by the anti-vaccination campaign. Currently, only a few influenza specialists can differentiate between inferences drawn from an ecological study and those drawn from ordinary, analytical epidemiological studies. Influenza specialists involved in vaccination programs should be expected to acquire such basic knowledge and to use it to correctly inform the general public about the propaganda against the influenza vaccine. Influenza specialists, both in Japan and in other countries, must understand the advantages and disadvantages of ecological studies, in the light of recent ecological studies and their impact [2,3].

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Selection bias in evaluating of influenza vaccine effectiveness: A lesson from an observational study of elderly nursing home residents

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ABSTRACT

Selection bias is of critical concern in the study of influenza vaccine effectiveness when using an observational study design. This bias is attributable to the inherently different characteristics between vaccinees and non-vaccinees. The differences, which are related both to vaccination and signs of clinical disease as an outcome, may lead to erroneous estimation of the effectiveness. In this report, we describe how selection bias among elderly nursing home residents may lead to a spurious interpretation of the protective effect of influenza vaccine. Our results should be a lesson in the importance of regarding selection bias when assessing influenza vaccine effectiveness.

1. Introduction

Selection bias is a kind of systematic error in epidemiologic studies. The common element of selection bias is that the relationship between exposure and disease is different between participants and non-participants in the study. As an example, one may imagine "self-selection bias" or "healthy worker effect" [1]. Using the study of influenza vaccine effectiveness, we adopt influenza-like illness (ILI) as an outcome measure. The inherently different characteristics between vaccinated and non-vaccinated group may be obvious. Specifically, vaccinees may be health-conscious and have behavior that decreases the risk of ILI. Therefore, the vaccinated group might be expected to have a lower rate of ILI for reasons that are unrelated to the vaccination. The opposite assumption is that the vaccinees may have underlying disease that predisposes to a higher rate of ILI, and puts them in a higher risk group than non-vaccinees. The different characteristics between the groups, as related both to vaccination and the clinical disease status as an outcome, may lead to erroneous estimation of the vaccine effectiveness.

Such a systematic error is regarded as confounding if distortion due to the error is able to be accurately controlled for in the analysis. However, since variables potentially confounding the association of interest are not always possible to identify and quantify, this error may exert unpredictable effect as selection bias [2]. In general, the preferred epidemiologic study design for minimizing the extent of selection bias in assessing vaccine is the randomized controlled trial [3]. Nevertheless, specific characteristics of naturally occurring seasonal influenza epidemics make it difficult to obtain conclusive findings from a single field trial. Namely, the unpredictable nature of time and intensity of the influenza occurrence, the presence of different virus strains in an epidemic, and antigenic differences between the vaccine strains and epidemic viruses, are all factors that can affect the outcome of a vaccine trial [4]. Taken together with the recent ethical concerns regarding the use of placebo in vaccine trials, cost issues, and logistic problems, it is now the norm to use a non-experimental study design [5]. Although several methods have been proposed to address the issues of systematic errors [5–7], no definitive resolution has emerged.

In this report, we present an experience from a prospective cohort study to evaluate the influenza vaccine effectiveness in elderly nursing home residents. In our study, we detected possible spurious protective effects due to selection bias. By estimating vaccine effectiveness during different periods of the influenza season, we became aware of the existence of the bias.

2. Materials and methods

All residents in an elderly nursing home, located in Nagoya City, Japan, as of 1 December 2003 were included in this study.

Abbreviations: OR, odds ratio; CI, confidence interval; ILI, influenza-like illness.

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Table 1
Baseline characteristics of vaccinees and non-vaccinees

Variable	Vaccinees (N = 166)	Non-vaccinees (N = 118)	P-value[a]
Sex (male)	49(30)	36(31)	0.858
Age (years): median (25, 75 percentile)	84(77,90)	86(78,92)	0.344[b]
Smoking (yes)	10(6)	7(6)	0.974
Heart disease (yes)	101(61)	77(65)	0.449
Lung disease (yes)	42(25)	28(24)	0.762
Cerebro-vascular disease (yes)	98(59)	66(56)	0.602
Diabetes mellitus (yes)	28(17)	17(14)	0.576
Hypertension (yes)	83(50)	55(47)	0.573
Steroid/immnosuppesunt use (yes)	3(2)	4(3)	0.455
Functional status (bedridden)	107(64)	96(81)	0.002
Dementia (required assistance)	74(45)	75(64)	0.002
Albumin level (<3.8 g/dl)	106(64)	99(84)	0.0002

Note: The distribution of subjects by vaccination status is expressed as number and percentage in parenthesis, otherwise indicated.
[a] Chi square test or Fisher exact test, except for age.
[b] Wilcoxon rank sum test.

A total of 284 residents (mean age, 85 years; 85 men, 199 women) were enrolled. Based on institutional policy, only residents who were able to provide informed consent could receive the vaccine. Informed consent provided by family members was not acceptable. Vaccination with a commercial inactivated influenza vaccine was done in 166/284 residents. A 0.5 ml dose contained 15 μg each of A/New Caledonia/20/99(H1N1), A/Panama/2007/99(H3N2), and B/Shandong/7/97 antigens. Subcutaneous injections of 0.5 ml were given once before the influenza season.

For baseline data, we collected information from medical records on demographic characteristics, smoking status, underlying medical conditions (heart disease, lung disease, cerebrovascular disease, diabetes mellitus, and hypertension), steroid/immunosuppressant use, functional status (bedridden or not), dementia (required assistance or not), and clinical laboratory results. The defined outcomes in the study were febrile illnesses of ≥38 °C and ≥39 °C, pneumonia, and death by all causes.

During the typical 17-week influenza season, from 1 December 2003 until 28 March 2004, specifically from the 49th week of 2003 to the 13th week of 2004, we prospectively surveyed the weekly occurrence of each outcome. For febrile illness, the highest temperature during a week was recorded. The physician in charge took throat swabs from residents whenever influenza was suspected and swabs were tested immediately using a rapid antigen test (Capilia Flu A + B, Nippon Becton Dickinson Company, Ltd.). If the result was positive, viral cultures were done. The study protocol was approved by the ethics committee at the Osaka City University Graduate School of Medicine.

SAS Version 8.2 (SAS Institute, Inc., Cary, North Carolina) was used for statistical analyses. Logistic regression was used to estimate vaccine effectiveness by calculating adjusted odds ratios (ORs) and 95% confidence intervals (95% CIs). All explanatory variables, except for age, were dichotomized when included in the model. To account for the time necessary for the vaccine to induce effective antibody, outcomes that occurred within 14 days after vaccination were excluded. All P values are two-sided, the level of significance was 5%, and a value of $0.05 < P < 0.1$ was considered as marginally significant.

3. Results

All participants were followed until either the end of the 2003–2004 influenza season or death, if it occurred during the study period. An influenza outbreak in the nursing home was not virologically confirmed since none of the patient samples were positive by the influenza viral antigen rapid test.

Baseline characteristics between vaccinated and non-vaccinated group were documented (Table 1). A significantly higher proportion of non-vaccinees were bedridden or had dementia that required assistance as compared to vaccinees (81% vs. 64%, $P = 0.002$; and 64% vs. 45%, $P = 0.002$, respectively). A significantly higher proportion of non-vaccinees had lower serum albumin levels (84% vs. 64%, $P = 0.0002$) than vaccinees. There were no significant differences between groups for any of the other variables studied.

The vaccine effectiveness for each of four outcomes was evaluated (Table 2). Based on the observations made during the entire 17-week influenza season, the multivariate analysis revealed that vaccination was effective at preventing febrile illness of ≥38 °C (adjusted OR, 0.48; 95% CI, 0.26–0.90; $P = 0.022$) and ≥39 °C (OR, 0.44; 95% CI 0.17–1.14; $P = 0.091$), and all causes of death (OR, 0.37; 95% CI, 0.12–1.15; $P = 0.084$) with at least marginal significance. The adjusted OR did not reach statistical significance ($P = 0.121$) for an association with preventing pneumonia, but the point estimate of the OR (0.42) suggested a protective effect.

We performed an additional analysis to detect if vaccine effectiveness was more pronounced [8,9] when observations were confined to the intensive influenza season. The two types of epidemic curves representing the reported number of clinically diagnosed influenza cases per sentinel from 70 surveillance sites in the community, and the number of residents with febrile illness of ≥38 °C in the nursing home are shown in Fig. 1. In the community,

Table 2
Outcome occurrence and corresponding vaccine effectiveness[a]

Outcome	Vaccinees (N = 166), n(%)	Non-vaccinees (N = 118), n(%)	Crude OR (95%CI)	P-value	Adjusted OR[b] (95%CI)	P-value
All febrile illness (≥38 °C)	29(17)	38(32)	0.45 (0.26–0.78)	0.004	0.48 (0.26–0.90)	0.022
All febrile illness (≥39 °C)	9(5)	14(12)	0.43 (0.18–1.02)	0.055	0.44 (0.17–1.14)	0.091
Pneumonia	6(4)	11(9)	0.37 (0.13–1.02)	0.054	0.42 (0.14–1.26)	0.121
All causes of death	6(4)	14(12)	0.28 (0.10–0.75)	0.011	0.37 (0.12–1.15)	0.084

[a] Analysis during the entire 17-week influenza season from the 49th week of 2003 to the 13th week of 2004.
[b] Adjusted for sex, age (continuous variable), smoking status, underlying medical conditions (heart disease, lung disease, cerebrovascular disease, diabetes mellitus, and hypertension), steroid/immunosuppressant use, functional status (bedridden or not), dementia (required assistance or not), and albumin level (<3.8 or ≥3.8 mg/dl).

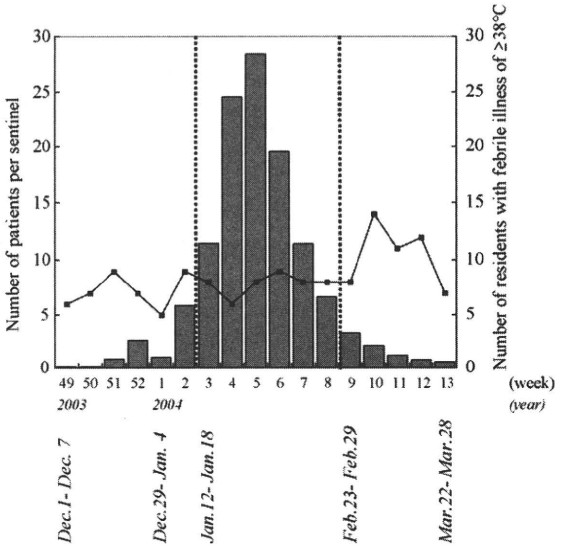

Fig. 1. Changes in the number of clinically diagnosed influenza patients per sentinel reported weekly from 70 surveillance sites in Nagoya city (bar), and the number of residents with febrile illness of ≥38 °C in the nursing home (line) during the 2003–2004 season.

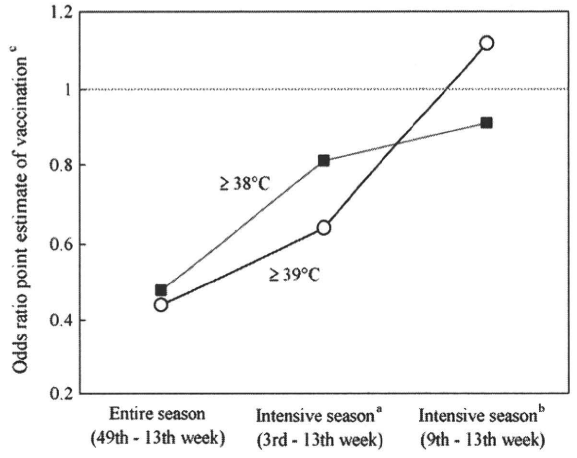

Fig. 2. Change of odds ratio point estimate of vaccination for all febrile illness of ≥38 °C (square) and ≥39 °C (circle) during three different periods of the season. [a]Period that the reported number of clinically diagnosed influenza patients per sentinel was 10 or more persons, based on the weekly report from 70 surveillance sites in Nagoya city during the 2003–2004 influenza season. [b]Period defined as a small peak in a fever curve which presented the number of residents with febrile illness of ≥38 °C in the nursing home. [c]Adjusted for sex, age (continuous variable), smoking status, underlying medical conditions (heart disease, lung disease, cerebrovascular disease, diabetes mellitus, and hypertension), steroid/immunosuppressant use, functional status (bedridden or not), dementia (required assistance or not), and albumin level (<3.8 or ≥3.8 mg/dl).

there were less than 10 patients per sentinel until the 2nd week of 2004. In the nursing home, a small peak appeared after the 9th week in 2004. We interpreted this data as meaning that the peak of the influenza epidemic in the community started from the 3rd week of 2004 on 12 January and that the period following 11 weeks represented the intensive influenza season. Furthermore, from the 9th week of 2004, beginning on 23 February, a second period of the intensive influenza season was noted.

Table 3 shows the outcome occurrence between vaccinated and non-vaccinated groups during the entire season, as well as for the two different periods of the intensive influenza seasons. Based on the comparisons made during the entire season, a significantly higher proportion of non-vaccinees had febrile illness as compared to those receiving vaccine ($P = 0.004$–0.049). However, such differences became smaller and lost statistical significance as we limited the comparisons to the later periods of the season.

The corresponding adjusted odds ratios were calculated during three different periods of the season (Fig. 2). Since there were very few subjects with pneumonia or death, especially in the later period of the season, only febrile illness was considered in the multivariate analysis. Both ORs for febrile illness of ≥38 °C and ≥39 °C were shifted toward the null value, indicating no effect, later in the influenza season.

4. Discussion

In this study, there are different baseline characteristics between vaccinated and non-vaccinated groups. Variables such as being bedridden, having dementia that requires assistance, and lower serum albumin levels, occurred more frequently among non-vaccinees than vaccinees. Functional and nutritional status has been reported as potential confounder in determining either effectiveness or the nature of the immune response of influenza vaccine

Table 3
Outcome occurrence during three different periods of the season

Outcome	Vaccinees ($N = 166$), n (%)	Nonvaccinees ($N = 118$), n (%)	P-value[c]
Entire season (49th–13th week)			
All febrile illness (≥38 °C)	29(17)	38(32)	0.004
All febrile illness (≥39 °C)	9(5)	14(12)	0.049
Pneumonia	6(4)	11(9)	0.046
All causes of death	6(4)	14(12)	0.007
Intensive season[a] (3rd–13th week)			
All febrile illness (≥38 °C)	26(16)	25(21)	0.232
All febrile illness (≥39 °C)	8(5)	10(8)	0.213
Pneumonia	5(3)	6(5)	0.534
All causes of death	4(2)	6(5)	0.328
Intensive season[b] (9th–13th week)			
All febrile illness (≥38 °C)	16(10)	14(12)	0.548
All febrile illness (≥39 °C)	5(4)	7(4)	1.000
Pneumonia	2(2)	3(2)	1.000
All causes of death	2(2)	1(1)	0.572

[a] Period that the reported number of clinically diagnosed influenza patients per sentinel was 10 or more persons, based on the weekly report from 70 surveillance sites in Nagoya city during the 2003–2004 influenza season.

[b] Period defined as a small peak in a fever curve which presented the number of residents with febrile illness of ≥38 °C in the nursing home.

[c] Chi square test or Fisher exact test.

in the elderly [10,11]. Since such differences were likely to contribute to overestimation of vaccine effectiveness, we adjusted for these variables in the analysis [5]. However, adjustment did not significantly reduce systematic error.

Our conclusion that selection bias was the most plausible explanation for the spurious results regarding vaccine was based on the following information. Despite the fact that we did not virologically confirm the influenza outbreak, a protective effect of vaccination was suggested when we considered outcome occurrences during the entire influenza season. Unexpectedly, these effects disappeared when we analyzed the intensive period of the influenza season as a separate entity. Most outcome occurrences among non-vaccinees developed in the initial period. This is likely to be the result of the institutional consenting policy. Since participation was limited to those who were able to give informed consent by themselves, the non-vaccinated group included both individuals too frail to be consented, as well as those who elected not to participate. Those individuals were likely to be at high risk for significant clinical outcomes early in the influenza season.

In addition, a recent study has suggested the influence of bias in study of influenza vaccine effectiveness among elderly [12]. In this study, the relative risk was estimated separately before, during, and after the influenza season. The authors pointed out the movement of the effectiveness of vaccine toward null later in the season, and concluded that relatively healthy seniors prefer to receive vaccine. Although the process to define each period of the season for additional analysis was different from our study, the approach to identify the possible existence of bias was similar.

Alternative explanations for our unexpected findings should also be considered. First, we cannot exclude that an influenza epidemic in the nursing home had occurred before the entire season as defined in this study. If the timing of the outbreak was prior to the season, it would be reasonable to expect that vaccine effectiveness would disappear if the observation period was limited to the later period. However, since nosocomial infectious disease is monitored in the nursing home throughout the year, the assumption of a prior epidemic is unlikely. Second, older persons might have lower post-vaccination antibody titers than healthy young adults [13]. In a randomized trial, vaccine efficacy among persons aged $\geq$70 years was lower compared with relatively younger seniors [9]. Besides, a major limitation of this study was that non-specific outcomes were adopted as end-points, rather than ILIs, which are usually defined as illnesses with rhinorrhea, sore throat, and/or cough, plus fever [8,14]. This limitation was because many of the patients were bedridden or had dementia that required assistance. Those who were bedridden commonly have rhinorrhea and a cough. It is also difficult for those with dementia to reliably report the presence of sore throat. Thus, to prove vaccine effectiveness among elderly nursing home residents may be complicated.

Despite the limitations, selection bias seems to be a reasonable interpretation for our findings. The key message is the importance of analyzing the data from multiple angles, whether or not positive results are obtained. To estimate vaccine effectiveness during different periods of the season may be the most informative approach. Further exploration and discussion are needed avoid introducing inappropriate inferences in the study of influenza vaccine effectiveness.

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Influenza vaccine effectiveness and confounding factors among young children

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ABSTRACT

This study, done during the 2002–2003 season among children <6 years of age to investigate influenza vaccine effectiveness and confounding factors, involved 2913 children (1512 vaccinees, 1401 non-vaccinees) recruited from 54 paediatric clinics. Between December 2002 and April 2003, parents reported their children's maximum body temperatures weekly. Influenza-like illness (ILI) was defined as an acute febrile illness (≥38.0 °C) during the peak epidemic period. Adjusted odds ratios (ORs) for ILI were obtained using a logistic regression model. In analysis for total subjects, the ORs were significantly decreased for vaccinees (OR: 0.76, 95% CI: 0.66–0.88) and significantly increased for younger age groups, including children aged 2.0–3.9 years (1.42, 1.18–1.72) and those <2.0 years (2.02,1.61–2.54), compared to those between 4.0 and 5.9 years. ORs were significantly increased for children who visited a physician within the last 6 months for a cold (1.27, 1.08–1.50), attended preschool (1.72, 1.45–2.04), and had ≥3 siblings (1.42, 1.15–1.74). These confounding factors are suggested to be considered in estimating vaccine effectiveness among young children. In subgroup analysis by age groups, significantly decreased ORs were seen in 2.0–3.9-year-old (0.59, 0.47–0.74) and 4.0–5.9-year-old (0.75, 0.58–0.98) vaccinees; no significant vaccine effectiveness was detected for those <2.0 years (1.07, 0.80–1.44). Thus, among very young children vaccine effectiveness could not be demonstrated.

1. Introduction

It has been reported that healthy children less than 2 years of age have high influenza related hospitalization rates, that are, in fact, similar to the hospitalization rates among older adults for whom annual influenza vaccination is recommended [1,2]. Recently, the US Advisory Committee on Immunization Practices recommended that, beginning with the 2006–2007 season, influenza vaccine be administered to all children under 5 years of age. This expands on the recommendation to vaccinate only children aged 6–23 months in the previous two seasons [3].

Previous studies have investigated the efficacy of influenza vaccine among young children [4–6], but their results are not consistent. In addition, few studies have investigated the factors that influence influenza vaccine effectiveness among young children. Therefore, this study was conducted during the 2002–2003 season to assess the effectiveness of influenza vaccine and to identify the confounding factors that distort the estimated influenza vaccine effectiveness among children under 6 years of age.

2. Material and methods

Details of the study have been previously described [7]. Briefly, the study subjects were children under 6 years of age who were recruited from 54 paediatric clinics located in 8 different areas of Japan, between October 1, 2002 and December 15, 2002. A total of 2934 children (1521 vaccinees and 1413 non-vaccinees) were enrolled in this study. At each clinic, the children who received vaccine on parental request were entered into the vaccinated group. The unvaccinated group consisted of the one or two children who visited the paediatrician after each vaccinee and whose parents did not request to have their children vaccinated. For vaccinees, two doses of vaccine, containing A/New Caledonia/20/99(H1N1), A/Panama/2007/99(H3N2) and B/Shandong/7/97, were given subcutaneously. Children under 1 year of age received a 0.1 ml dose, while children 1 year of age and older received a 0.2 ml dose.

Physical and environmental data were obtained using self-administered questionnaires completed by parents or guardians at the time of enrolment. The data collected included: date of birth; gestational age; birth weight; preschool attendance; number of family members; number of siblings; number of rooms; total room space of the residence; disease onset during the previous influenza season and history of hospitalization; and influenza vaccinations

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within the last 3 years. The information about health-related conditions collected from the children's paediatricians using a structured questionnaire included: vaccination status; vaccine manufacturer and lot number if vaccinated; current body weight; physician visits within the previous 6 months (for cold symptoms, otitis media, digestive symptoms, or other reasons); underlying conditions (nine diseases); and long-term treatment with corticosteroids or aspirin.

With respect to the follow-up survey, the parents were requested to report the child's maximum body temperature every week. This questionnaire was to be returned to the paediatrician's office each week from the 51st week of 2002 to the 15th week of 2003. An influenza-like illness (ILI) was defined as an acute febrile illness that occurred during the highest epidemic period of influenza recorded in each study area. All subjects were classified into 3 categories according to the highest body temperature reported during the peak epidemic period: non-disease with fever <38.0 °C; ILI with fever 38.0–38.9 °C; and ILI with fever ≥39.0 °C.

To compare the characteristics of vaccinees and non-vaccinees, Chi-square or Fisher's exact test, and the Wilcoxon rank-sum test were employed. In order to assess independent associations between each outcome of ILI and the vaccination status or confounding factors, adjusted odds ratios (ORs) and 95% confidence intervals (95% CI) were calculated by a proportional odds model or a binary model on logistic regression. The stepwise method with default P values of 0.05 to enter and remove was used to determine the final model. Vaccine effectiveness was equivalent to $(1 - \text{OR}) \times 100\%$. All reported P values are two-sided. All data analyses were carried out using the SAS statistical software package (Version 9.1; SAS Institute, Inc., Cary, NC, USA).

3. Results

Data from 2913 subjects were analyzed; 21 subjects were excluded from the initial 2934 due to non-participation in the follow-up survey. The mean age of the vaccinees was 3.4 years, and the mean age of the non-vaccinees was 2.8 years. Among the vaccinees, 52% were male; among the non-vaccinees, 53% were male. The baseline characteristics that were statistically significantly different between the two groups are shown in Table 1. Older age, heavier current body weight, smaller family size, fewer siblings, preschool attendance, and previous vaccinations were more frequent in the vaccinated group. The univariate analysis results for all these factors are shown in Table 2.

In the first analysis, crude and adjusted ORs for ILI were calculated using a proportional odds model with a three-level outcome variable (maximum body temperature: <38.0, 38.0–38.9, ≥39.0 °C) (Table 2). Five explanatory variables (vaccination, age, number of siblings, physician visits for cold symptoms within the last 6 months and preschool attendance) were selected. When analyzed as an entire sample, the adjusted OR of vaccinees decreased significantly to 0.76 (95% CI: 0.66–0.88). Thus, vaccine effectiveness was estimated to be 24% (95% CI: 12–34%). Increased adjusted ORs were observed for the younger age groups of <2.0 years (OR: 2.02, 95% CI: 1.61–2.54) and 2.0–3.9 years (OR: 1.42, 1.18–1.72), preschool attendance (OR: 1.72, 1.45–2.04), having 3 or more siblings (OR: 1.42, 1.15–1.74), and physician visits within the last 6 months for a cold (OR: 1.27, 1.08–1.50). Significant dose–response relationships with increasing adjusted ORs were shown for both a decrease in age and an increase in the number of siblings (P = 0.000 and 0.001, respectively).

Secondly, same as the first analysis proportional odds model were also used to calculate adjusted ORs by age group (Table 3). Significantly decreased ORs of vaccination were observed for the 2.0–3.9 age group (OR: 0.59, 0.47–0.74) and the 4.0–5.9 age group (OR: 0.75, 0.58–0.98). In contrast, the adjusted OR was 1.07 (0.80–1.44) among those aged <2.0 years; a decreased OR was not observed.

Table 1
Baseline characteristics of the study participants by vaccination status

Characteristics	Vaccinee (n = 1512)	Non-vaccinee (n = 1401)	P value[a]
Health-related conditions collected from parents or guardians			
Age (years)	3.4	2.8	0.000
Birthweight (%)			
<2000 g	2	1	0.026
2000–2499 g	8	7	
2500–2999 g	40	36	
3000–3499 g	38	42	
3500–3999 g	11	13	
>4000 g	1	1	
Influenza vaccination within last 3 years (%)	70	9	0.000
Disease onset in previous season[b] (%)	42	39	0.044
History of hospitalization (%)	33	23	0.000
Health-related conditions collected from paediatrician			
Current body weight[b] (kg)	14.5	13.1	0.000
Physician visits within last 6 months (%)			
For otitis media	9	7	0.018
For cold symptoms	76	74	0.292
Underlying illnesses (%)			
Atopy	7	11	0.000
Environmental characteristics collected from parents or guardians			
Preschool attendance (%)	62	46	0.000
Number of family members	4.2	4.4	0.000
Number of siblings	1.9	2.0	0.000
Number of rooms	4.4	4.3	0.010
Total room space (m^2)	76.1	69.1	0.000

Except where indicated otherwise, values are mean.
[a] χ^2 test or Wilcoxon rank-sum test.
[b] One subject was excluded as data was missing.

In the third analysis, the ORs were calculated using binary models with combinations of two-level outcomes (<38.0 °C versus ≥38.0 °C, <39.0 °C versus ≥39.0 °C). In these computations, the same explanatory variables as those in the first analysis for total subjects were considered for adjustment. The adjusted ORs of vaccination for all subjects were 0.77 (0.66–0.90) for <38.0 °C versus ≥38.0 °C, and 0.74 (0.62–0.88) for <39.0 °C versus ≥39.0 °C.

In the fourth analysis, adjusted ORs were calculated for age groups comparing <38.0 °C versus ≥38.0 °C and <39.0 °C versus ≥39.0 °C. The adjusted ORs for 2.0–3.9 years were 0.62 (0.48–0.79) for <38.0 °C versus ≥38.0 °C and 0.53 (0.40–0.70) for <39.0 °C versus ≥39.0 °C; for 4.0–5.9 years, the adjusted ORs were 0.75 (0.58–0.99) for <38.0 °C versus ≥38.0 °C and 0.76 (0.55–1.04) for <39.0 °C versus ≥39.0 °C. Even when different outcome definitions were used, significantly or marginally significantly decreased ORs were observed for the older 2 age groups. ORs in the lowest age group were 1.05 (0.76–1.44) for <38.0 °C versus ≥38.0 °C and 1.10 (0.78–1.55) for <39.0 °C versus ≥39.0 °C; decreased ORs were not observed in this age group.

4. Discussion

This study was conducted using a non-randomized design, in which vaccination or non-vaccination was self-selected by the parents. Therefore, it is essential to consider potential confounders that could have been unequally distributed between the groups. In fact, Table 2 shows that vaccine effectiveness in all subjects was

Table 2
Odds ratios for ILI by vaccination status and characteristics of children under 6 years of age, calculated using a proportional odds model with a three-level outcome

Vaccination status and characteristics	Crude OR			Adjusted OR		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Non-vaccinee	1.00			1.00		
Vaccinee	0.73	0.64–0.84	0.000	0.76	0.66–0.88	0.000
Age (years)						
<2.0	1.45	1.21–1.74	0.000	2.02	1.61–2.54	0.000
2.0–3.9	1.09	0.92–1.29	0.307	1.42	1.18–1.72	0.000
4.0–5.9	1.00			1.00		
		Trend $P=0.000$			Trend $P=0.000$	
Birthweight (g)						
<2500	1.00					
2500–2999	1.05	0.81–1.37	0.700			
3000–3499	1.12	0.87–1.45	0.389			
>3500	1.10	0.81–1.50	0.530			
		Trend $P=0.364$				
Influenza vaccination within last 3 years						
No	1.00					
Yes	0.68	0.59–0.79	0.000			
Disease onset in previous season						
No	1.00					
Yes	1.23	1.07–1.42	0.004			
History of hospitalization						
No	1.00					
Yes	1.11	0.95–1.29	0.196			
Current body weight (kg)						
<10.1	1.00					
10.1–12.5	0.86	0.69–1.07	0.178			
12.6–15.7	0.78	0.63–0.96	0.018			
>15.8	0.67	0.55–0.83	0.000			
		Trend $P=0.000$				
Physician visits within last 6 months for otitis media						
No	1.00					
Yes	1.48	1.15–1.90	0.003			
Physician visits within last 6 months for cold						
No	1.00			1.00		
Yes	1.34	1.14–1.58	0.001	1.27	1.08–1.50	0.005
Atopy						
No	1.00					
Yes	1.19	0.93–1.52	0.173			
Preschool attendance						
No	1.00			1.00		
Yes	1.26	1.09–1.45	0.002	1.72	1.45–2.04	0.000
Number of family members						
<4	1.00					
4	0.99	0.83–1.19	0.935			
>5	1.20	0.99–1.45	0.060			
		Trend $P=0.041$				
Number of siblings						
1	1.00			1.00		
2	1.06	0.90–1.26	0.491	1.14	0.96–1.36	0.135
>3	1.37	1.12–1.67	0.002	1.42	1.15–1.74	0.001
		Trend $P=0.003$			Trend $P=0.001$	
Number of rooms						
<4	1.00					
4	0.93	0.78–1.11	0.408			
5–6	0.97	0.81–1.17	0.761			
>7	0.90	0.70–1.16	0.421			
		Trend $P=0.496$				
Total room space (m^2)						
<41.0	1.00					
41.0–57.3	0.95	0.77–1.17	0.628			
57.4–81.9	1.00	0.82–1.23	0.989			
>82.0	0.98	0.81–1.20	0.875			
		Trend $P=0.972$				

Table 3
Odds ratios of vaccination for different outcome definitions of ILI among children under 6 years of age by age group

Age (years)	Proportional model				Binary model (<38.0 °C vs. ≧38.0 °C)				Binary model (<39.0 °C vs. ≧39.0 °C)			
	Crude		Adjusted		Crude		Adjusted		Crude		Adjusted	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
0–5.9[a]	0.73 (0.64–0.84)	0.000	0.76 (0.66–0.88)	0.000	0.74 (0.64–0.86)	0.000	0.77 (0.66–0.90)	0.001	0.72 (0.61–0.85)	0.000	0.74 (0.62–0.88)	0.001
<2.0[b]	1.18 (0.89–1.56)	0.255	1.07 (0.80–1.44)	0.653	1.16 (0.86–1.57)	0.323	1.05 (0.76–1.44)	0.772	1.20 (0.87–1.66)	0.271	1.10 (0.78–1.55)	0.582
2.0–3.9[c]	0.60 (0.48–0.75)	0.000	0.59 (0.47–0.74)	0.000	0.63 (0.50–0.79)	0.000	0.62 (0.48–0.79)	0.000	0.54 (0.41–0.70)	0.000	0.53 (0.40–0.70)	0.000
4.0–5.9[c]	0.78 (0.61–1.01)	0.060	0.75 (0.58–0.98)	0.034	0.78 (0.60–1.02)	0.065	0.75 (0.58–0.99)	0.040	0.79 (0.58–1.08)	0.137	0.76 (0.55–1.04)	0.081

Note: The distribution of subjects by body temperature is expressed as number and percentage in parenthesis. OR, Odds ratio; CI, confidence interval.
[a] Explanatory variables: vaccination, age, siblings, physician visits for cold symptoms within the last 6 months and preschool attendance.
[b] Explanatory variables: vaccination, siblings, preschool attendance, vaccine dosage (or age).
[c] Explanatory variables: vaccination, siblings, physician visits for cold symptoms within the last 6 months and preschool attendance.

decreased by 11% (from 27 to 24%) after adjustment, and derived vaccine effectiveness was shifted toward a null value. A previous study suggested the importance of considering confounding effects when estimating influenza vaccine effectiveness. It was found that after adjustment for functional limitation, the OR for death in vaccinated subjects compared to unvaccinated subjects was closer to null (OR: 0.71, 0.47–1.06) than an unadjusted estimate (OR: 0.59, 0.41–0.83) [8]. In a randomized control trial of influenza vaccine efficacy, the characteristics of vaccinees and non-vaccinees were compared; the adjusted relative risks were calculated and compared to unadjusted values, and they were confirmed to be similar [9]. Indeed, particularly in the present non-randomized study, confounding factors that could influence influenza vaccine effectiveness should be considered in analysis.

Four confounding factors were simultaneously considered in our analysis of vaccine effectiveness. These confounding factors also affect as risk factors of ILI. Firstly, younger age was an increased risk of ILI. This indicates a significant change in susceptibility to illness as children age. This result is consistent with a previous study of children aged 6 months to 8 years, which reported that children 6–11 months and 12–23 months of age had a higher risk of ILI than a reference group of 7–8 year olds (adjusted hazard rate ratio: 5.32 (4.51–6.27), 3.68 (3.16–4.27), respectively) [9]. In another study, subjects' age were older than the present study; nevertheless, elementary school children in higher grades had a significantly decreased risk of ILI (mild ILI, OR: 0.4 (0.2–0.9); severe ILI, 0.2 (0.1–0.6)) [10].

Secondly, variables related to viral exposure increased the risk of ILI. Children with more than 3 siblings had an increased risk of ILI (OR: 1.42, 1.15–1.74). Similar findings were reported in a case–control study in elementary schools, where large family size (≥5 members) increased the risk of ILI (OR: 1.93, 95% CI: 1.10–3.37) [10]. Both the number of siblings and the number of family members indicate the degree of crowding present in the family setting, which can be interpreted as the presence of household contacts increases the probability of influenza infection from infected individuals. Our study also shows that preschool attendance increases the probability of such infectious contacts, as shown by an increased risk of ILI for preschool attendance (OR: 1.72, 1.45–2.04).

It has been reported that children with high risk conditions have an increased risk of influenza-associated outpatient visits and hospitalisations [11]. In addition, significantly increased risks of ILI among elementary school children were found for children with easily inflamed tonsils and with a history of physician-diagnosed asthma [10]. In the present study, physician visits for a cold within the last 6 months were associated with an increased risk of ILI, although no association was found between underlying illnesses and ILI. This is perhaps due, in part, to the fact that most subjects were healthy children. However, the increased risk associated with physician visits for a cold prior to the epidemic seasons may indicate an association between children's general health status and ILI.

Four factors (age, sibling number, preschool attendance, and physician visits for a cold within the last 6 months) except for vaccination status were selected for the final model. Since these factors were associated with an increased risk for ILI, the estimated vaccine effectiveness in this study would be distorted unless an adjustment for these factors were made. Although we carefully considered it in our analysis, there is a limitation to this study, as has been discussed elsewhere [7]. In this study, it is inevitable that non-influenzal illnesses were included in the definition of ILI, which would have affected the results. This is due to the definition of ILI as an acute febrile illness reported during an epidemic peak. In order to measure the onset of a febrile illness, information about the maximum body temperature each week was prospectively collected using a