postal questionnaire. This enabled the identification of ILI onset to be done equally for all subjects throughout an epidemic period. The postal questionnaire not only provided a similar recall stimulus to parents in both groups, but also minimized the uncertainty related to the parents' responses. Thus, it is reasonable to assume that the extent to which the ILI category included non-influenzal illnesses, and the extent to which the non-disease category included influenza *per se*, was similar in the vaccinated and non-vaccinated groups. This non-differential misclassification results in an underestimation of vaccine efficacy, but does not affect the validity of the study results.

In the present study, vaccine effectiveness for ILI was found for children under 6 years of age: 24% (12–34%) as a whole. Vaccine effectiveness for 2.0–3.9 years of age and 4.0–5.9 years of age, were 41% (26–53%) and 25% (2–42%), respectively, and were statistically significant, while it was −7% (−44 to 20%) for children <2.0 years without clear vaccine effectiveness. Thus, influenza vaccine effectiveness could not be demonstrated in this age group. In a recent randomized, controlled study of children 6–24 months of age conducted over 2 consecutive influenza seasons, the vaccine efficacy against culture-proven influenza was not consistent between the study seasons (first year: 66% (34–82%), second year: −7% (−247 to 67%)); although it should be noted that the attack rate was quite different for the 2 seasons [5]. A few factors have been identified that help explain the failure to detect vaccine effectiveness in very young children. It was reported that in children <1 year of age, the immune response to influenza vaccine was lower than in those 1–3 years of age [12]. It has also been shown that influenza epidemics often overlap with the circulation of respiratory syncytial virus (RSV) [2], which has a greater health impact in very young children than in older children [13]. An ILI defined to measure vaccine effectiveness is thus diluted more by non-influenzal illnesses among young children than among older children.

In summary, as a whole, a statistically significant protective effect of influenza vaccine against ILI was found. However, vaccine effectiveness was not clearly shown in children under 2 years of age. Further studies using different methods, in different locations, and in different seasons, are needed to clarify the effectiveness of influenza vaccine among young children.

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Confounding in evaluating the effectiveness of influenza vaccine

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ABSTRACT

Confounding is a kind of bias which occurs in a research. Confounding is less frequent in randomized controlled trials (RCT) for evaluation of influenza vaccines. However, there are obstacles or difficulties in conducting RCT for evaluation of influenza vaccines, particularly, in the elderly people. Therefore, a retrospective or prospective cohort study has been primarily performed to evaluate effectiveness of influenza vaccine in elderly people. Confounding by indication or other confounding exist in most observational studies. Accordingly, at the stage of designing or analyzing a study, confounding should be controlled with a restriction, matching, stratified or multivariate analysis technique.

1. Introduction

According to the definition in 'A Dictionary of Epidemiology' edited by Last [1], confounding is a situation in which a measure of the effect of an exposure on risk is distorted because of the association of exposure with other factor(s) that influence the outcome under study. As this pertains to evaluating the effectiveness of an influenza vaccine, a potential confounding factor may not only be related to vaccination, but also to the outcome, such as exposure to influenza viruses and manifestation of influenza-like illnesses. A confounding factor would be associated with the outcome not only in the stratum of the vaccinated group, but also in the stratum of the non-vaccinated group. A confounding factor may or may not carry some causal relationship to the outcome. If a confounding factor is not controlled or adjusted, it inevitably induces a bias in the results.

2. Confounding factors in evaluation of vaccine

Age and sex, past medical history, present health status, and previous history of vaccination, education, marital status, smoking habits, drinking habits, exercise regime, and so on are potential confounding factors which may affect evaluation of influenza vaccine [2]. Among them, relevant to present health status, confounding by indication is the most important confounding factor affecting evaluation of influenza vaccine. According to Rothman [3], confounding by indication arises from the fact that those who take medication (or influenza vaccine) generally differ from those who do not under medical indication. These differences introduce a bias in the comparison.

Confounding occurs because persons with disorder or disabilities are likely or unlikely to receive vaccination, and also likely to be infected with the influenza virus. Chronic respiratory disorders, chronic heart diseases, and reduced levels in activities of daily life (ADL) are general examples of disorders or disabilities associated with confounding by indication. As hypothetical data are shown in Table 1, influenza vaccine reduced the risk of pneumonia by 40% in the stratum of the subjects with such comorbidity, and influenza vaccine reduced the risk of pneumonia by 54% in the stratum of the subjects without the comorbidity. However, when the both strata were combined without an appropriate adjustment, influenza vaccine was found not to be associated with the reduced risk of pneumonia. This finding of no significant association is brought about by a result of no adjustment being made for confounding of indication.

3. Methods for controlling a confounding factor

There are 2 stages for controlling a confounding factor. The first stage is at the time of designing a study plan, and the second stage is at the time of data analysis. Restriction of study subjects, matching a confounding factor with the comparative groups, and randomization of the study subjects are methods for controlling a confounding factor at the stage of study design [4]. Restriction is a procedure that limits participation in the study to people who are similar in relation to the confounder. Matching is a procedure whereby controls are selected in such a way that the distribution of potential confounders among them will be identical to those of the cases. Randomization of study subjects with a reasonable sample size is

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Table 1
Hypothetical data of a cohort study on evaluation of influenza vaccine, stratified the study subjects with or without the comorbidity

	Group	Number	Pneumonia	Risk ratio of influenza vaccine	Effectiveness
Total	Vaccinated	2200	200		
	Non-vaccinated	2200	200	1.00	0%
The subjects with the comorbidity	Vaccinated	1890	190		
	Non-vaccinated	480	80	0.60	40%
The subjects without the comorbidity	Vaccinated	310	10		
	Non-vaccinated	1720	120	0.46	54%

Effectiveness: (1-risk ratio) × 100%.

the ideal method of controlling confounders because it ensures that the distribution of potential confounding variables will be similar among the groups to be compared. Randomized controlled trial (RCT) is a well-known intervention study using randomization of the study subjects.

Stratification (stratified analysis) and regression modeling (multivariate analysis) are the method for adjusting a confounding factor at the stage of data analysis [4]. Stratification is a technique in which the strength of association is measured separately within each well defined category of confounding variable, as previously shown in Table 1. Regression modeling is a sophisticated statistical method available to adjust simultaneously for various confounding factors.

4. Strengths and limitations of RCT

Because a well-conducted RCT would minimize effect of confounding, valid finding can be obtained from such a trial. However, as previously pointed out by Hak et al. [5], researchers face obstacles when planning a RCT for evaluation of influenza vaccine. Firstly, as the incidence of influenza-like illness or adverse effects of influenza vaccine are low, it would require a large number of study subjects. Secondly, several influenza seasons may need to be observed as the virulence of circulating influenza viral types is highly variables and unpredictable. Finally, ethical concerns may be raised when persons at high risk for complications to occur are involved.

Difficulties concerning recruitment for an RCT involving influenza vaccine in healthy elderly people have been also reported by Allsup and Gosney [6]. In an RCT employed for the purpose of determining the cost benefits of administrating influenza vaccination to fit healthy individuals aged 65–74 years, 6058 people were initially identified as eligible candidates for the study, but only 729 (12%) were subsequently randomized. Among individuals who returned cards indicating that they did not wish to participate, reasons why they felt unable to consent to the study included reluctance to participate in a research project (53%), concern about side effect (34%), self-perceived view of not requiring influenza vaccination (32%), and so on.

Because of obstacles and difficulties surrounding RCT on evaluation of influenza vaccine among the elderly, RCT on evaluation of influenza vaccine have been mostly conducted in children [7–9], or in health care workers [10–12]. These RCTs in health care professionals have consistently indicated that influenza vaccine is effective in reducing absence from work and mortality of their patients [10–12].

5. Controlling a confounding factor using method other than RCT

Retrospective or prospective cohort studies have been carried out for evaluation of influenza vaccine as designs other than RCT, and, confounding by indication, and other confounding has been adjusted with a technique of restriction, matching, stratified analysis, or multivariate analysis as the following articles illustrate.

A retrospective cohort study was conducted in Rotterdam, the Netherlands in 1996 to assess the effectiveness of influenza vaccination among persons aged 65 years or over [13]. Three methods, namely, matching, stratified analysis, and multivariate analysis with regression model, were used to control confounding. That is, an 8911 person vaccinated cohort and an individually age and sex matched 8911 person non-vaccinated control cohort were set up. Because the vaccinated cohort had had more diseases more frequently such as chronic respiratory diseases, cardiovascular diseases, and cancer, stratified analysis was performed after making the subgroups with and without such comorbidity as shown in Table 2. The Cox proportional hazards regression model was used for adjusting history of chronic diseases and vaccination history. As a result, influenza vaccination was associated with a significant reduction in any event of death, pneumonia, or influenza in the vaccinated elderly.

Another retrospective cohort study was conducted in England and Wales from 1989 to 1999 to assess the effectiveness of influenza vaccination among persons aged 65 years or over [14]. Namely, 692,819 person-years in vaccine recipients and 1,534,280 person-years in non-vaccine recipients were compared. As shown in Table 3, stratified analysis was carried out after making the subgroups of those subjects at a high or low risk of influenza infection. Further, Poisson regression model was used for adjusting risk category, sex, and repeat prescription. As a result, influenza vaccination was associated with a significant reduction of admission into the hospitals for treatment of acute respiratory disease in the vaccinated elderly.

A prospective cohort study was conducted in Utrecht, the Netherlands in 1995 to assess the effectiveness of influenza vaccination among persons aged 18 years or over [15]. Three methods, namely, restriction, stratified analysis, and multivariate analysis with regression model, were used to control confounding. This study restricted participants to 1696 subjects who had chronic lung disease. Among them, 1243 subjects were vaccinated, and 453 subjects were not vaccinated. Two age categories, 18–64 years and 65 years or over, were established to conduct stratified analysis. Logistic regression model was used for adjusting the prognostic confounding variables underlying lung diseases, cardiac diseases, and the number of visits to a general physician. As shown in Table 4, no effectiveness was observed in the subjects aged 18–64 years. However, in the vaccines aged 65 years or over, the occurrence of any complication of acute low respiratory tract illness, cardiac diseases, or death was significantly reduced by 46%, that is (1–0.54) × 100, as compared to those not vaccinated, after adjustment for the number of previous medical consultations, lung disease, and cardiac disease.

Another prospective cohort study involving 26,071 individuals was conducted in Rotterdam, the Netherlands from 1996 to 2002 to assess the effectiveness of influenza vaccination among persons aged 65 years or over [16]. Three methods, namely, restriction, stratified analysis, and multivariate analysis with regression model, were used to control confounding. Cox proportional hazards regres-

Table 2
Retrospective cohort study on evaluation of influenza vaccine for the defined outcome among persons aged 65 or over in Rotterdam, the Netherlands [13]

	Crude risk ratio of influenza vaccine	Adjusted# risk ratio of influenza vaccine
Total	0.83 (0.69–0.99)	0.72 (0.60–0.87)
The subjects with the comorbidity	0.86 (0.66–1.11)	0.73 (0.56–0.96)
The subjects without the comorbidity	0.74 (0.58–0.95)	0.71 (0.55–0.92)

The defined outcome: any event of death, pneumonia, or influenza.
Adjusted for age, sex, and comorbidity (respiratory tract disease, cardiac disease, hypertension, diabetes mellitus, renal dysfunction, and vaccination history).

Table 3
Retrospective cohort study on evaluation of influenza vaccine for the defined outcome among persons aged 65 or over in England and Wales [14]

	Influenza season 15 Nov–End, Apr Adjusted# risk ratio of influenza vaccine	Peri-influenza season 1 Sep–14 Nov Adjusted# risk ratio of influenza vaccine	Summer season 1 May–End, Aug Adjusted# risk ratio of influenza vaccine
Total	0.79 (0.74–0.83)	0.94 (0.88–0.99)	0.98 (0.92–1.04)
The subjects at high risk for influenza	0.79 (0.74–0.85)	0.92 (0.85–0.99)	0.92 (0.86–0.99)
The subjects at low risk for influenza	0.78 (0.71–0.86)	0.97 (0.87–1.07)	1.09 (0.98–1.20)

The defined outcome: admission to the hospitals for acute respiratory disease. High risk for influenza: chronic respiratory disease, cardiovascular, renal, and liver disease, immunosuppressive conditions, and metabolic disease.
Adjusted for age, sex, risk category, and repeat prescription.

Table 4
Prospective cohort study on evaluation of influenza vaccine for the defined outcome among persons in Utrecht, the Netherlands [15]

	Crude risk ratio of influenza vaccine	Adjusted# risk ratio of influenza vaccine
The subjects aged 18–64 years	1.30 (0.85–1.98)	0.97 (0.63–1.52)
The subjects aged ≥65 years	0.61 (0.36–1.01)	0.54 (0.32–0.93)

The defined outcome: lower respiratory tract illness.
Adjusted for number of previous consultations, lung disease, and cardiac comorbidity.

Table 5
Prospective cohort study on evaluation of influenza vaccine for the defined outcome among persons aged 65 or over in Rotterdam, the Netherlands [16]

	Crude risk ratio of influenza vaccine	Adjusted# risk ratio of influenza vaccine
Total	0.90 (0.83–0.98)	0.76 (0.70–0.83)
The subjects with the comorbidity	0.82 (0.75–0.90)	0.75 (0.68–0.83)
The subjects without the comorbidity	0.66 (0.54–0.80)	0.66 (0.54–0.80)

The defined outcome: overall death.
Adjusted for age, sex, comorbidity (respiratory tract disease, cardiac disease, hypertension, diabetes mellitus, renal dysfunction, malignancy), and vaccination history.

sion model was used for adjusting confounding variables such as age, sex, comorbidity, and vaccination history. As shown in Table 5, overall mortality was significantly reduced in the vaccinated group as compared to the non-vaccinated group.

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The effect of misclassification on evaluating the effectiveness of influenza vaccines

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ABSTRACT

Misclassification is a measurement error and can be considered a type of information bias. Misclassification can occur at both exposure and outcome levels. Nondifferential misclassification causes only a dilution effect leading to underestimation, whereas differential misclassification can have more complicated and serious consequences. To avoid nondifferential diagnosis misclassification, it is necessary to use highly specific diagnostic examinations or criteria such as virus detection to exclude 'false positive' cases, and to limit the observation period to an intensive epidemic period if using less specific diagnostic criteria such as symptoms of influenza-like illness (ILI) or absence from school or workplace. To avoid differential diagnosis misclassification, vaccinated and unvaccinated groups must be equally scrutinized, and such scrutiny is more important than the specificity of diagnosis. So, passive findings from patients with influenza at clinics can cause complicated differential misclassification despite use of highly specific diagnostic procedures because vaccinated and unvaccinated patients may participate differently. Also important is standardization of diagnostic procedure that vaccination anamnesis does not influence diagnosis of influenza, or examination of the influence. Exposure misclassification would mainly underestimate vaccine effectiveness in most situations. Consequently, misclassification of diagnosis, especially differential misclassification, affects evaluation of influenza vaccine effectiveness.

1. Introduction

Misclassification is defined as the erroneous classification of an individual, a value, or an attribute into a category other than that to which it should be assigned [1]. Misclassification is thought of as a measurement error, and can be considered a type of information bias [2]. Misclassification can occur at both exposure and outcome levels. An example of a misclassification of exposure is an incorrect recall of vaccination by a patient, while an example of a misclassification of outcome is a diagnosis of influenza-like illness (ILI) using fever and/or upper respiratory symptoms that might result in exclusion of some true influenza cases or the inclusion of other diseases.

Nondifferential misclassification indicates that the probability of misclassification is the same for all study groups, while differential misclassification indicates that the probability differs between groups [1]. When outcome misclassification is not affected by exposure (e.g., diagnosis of influenza is independent of whether the subject was vaccinated or not), the misclassification is nondifferential. Nondifferential misclassification results in a 'diluting effect' that leads to an underestimation of the strength of the association between exposure and outcome [2]. Similarly, when exposure misclassification is not associated with evaluation of outcome, it is also nondifferential.

In contrast, when an exposure misclassification is associated with outcome evaluation, or when outcome misclassification is associated with exposure, such differential misclassification may either over- or underestimate the association between exposure and outcome [2]. The direction and magnitude of the effect may be difficult to evaluate. For example, vaccinated people may visit doctors more readily when feeling ill, and consequently may be more likely to be diagnosed as having influenza than non-vaccinated people. From the viewpoint of outcome, patients with influenza may more correctly recall about their vaccination in a retrospective study than those without influenza. Thus, any misclassification may considerably influence evaluation of influenza vaccine effectiveness.

2. Sensitivity/specificity of diagnosis and nondifferential misclassification of diagnosis

Sensitivity is defined as the proportion of sick people classified as sick according to given criteria/screening among the whole sick people [2], and refers to the probability that a sick individ-

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Table 1
Sensitivity and specificity

	People with disease (1000)	People without disease (9000)	Total (10,000)
Positive to disease criteria	True positive (TP) (800)	False positive (FP) (450)	1250
Negative to disease criteria	False negative (FN) (200)	True negative (TN) (8550)	8750

Sensitivity = TP/(TP + FN) = 80%; specificity = TN/(TN + FP) = 95%; positive predictive value (PPV) = TP/(TP + FP) = 64%.

Table 2
Influence of sensitivity/specificity on evaluation of effectiveness of vaccine: underestimation of effectiveness due to nondifferential misclassification of outcome

Comparison groups		True number of patients with influenza	True relative risk (RR)	Observed number of patients with influenza diagnosed by criteria with sensitivity of 80% and specificity of 95%	Observed RR
Vaccinated	1000	50	0.25	$50 \times 0.80 + 950 \times 0.05 = 87.5$	0.44
Unvaccinated	1000	200		$200 \times 0.80 + 800 \times 0.05 = 200$	

ual will be classified as sick (Table 1). Specificity is defined as the proportion of healthy people classified as healthy according to given criteria/screening among the whole healthy people, and refers to the probability that a healthy individual will be classified as healthy. Low sensitivity and/or low specificity of diagnostic procedures causes nondifferential misclassification of diagnosis [2]. Positive predictive value (PPV) is defined as the proportion of truly sick people among those classified as sick according to the given criteria/screening, and refers the probability that criteria/screening predicts the sickness [2]. PPV depends on prevalence of sickness in study population whereas sensitivity and specificity are independent of the prevalence. For example, according to criteria with sensitivity of 80% and specificity of 95%, PPV is 64% when prevalence of sickness is 10% in study population (Table 1), while it is 14% when the prevalence is 1%.

An example of underestimation of effectiveness of influenza vaccine due to low sensitivity/specificity (nondifferential misclassification) is shown in Table 2. The observed number of patients with influenza (87.5) among vaccinated people can be calculated from the true number of patients and non-patients (50 and 950), and sensitivity and specificity of diagnostic criteria (0.80 and 0.95). The number among unvaccinated people is calculated by the same method (200). The effectiveness of influenza vaccination is presented as a ratio of rate/proportion of patients in vaccinated group relative to the rate/proportion in unvaccinated group (relative risk; RR). Although true RR is (50/1000)/(200/1000) = 0.25, the observed RR is (87.5/1000)/(200/1000) = 0.44. This difference shows the dilution effect of nondifferential misclassification.

Table 3 shows this dilution effect for various sensitivities and specificities. No effect is detected (RR = 1) when using a diagnostic criteria with a sensitivity of 0.5 and a specificity of 0.5 (diagnosis based only upon flipping a coin). Specificity is more important than sensitivity in determining the true RR. It means that exclusion of 'false positive' cases is important. Diagnostic criteria with a high specificity are likely to limit the number of patients who are diagnosed as having influenza according to the criteria, so a large initial study population is necessary. However, use of highly sensitive diagnostic criteria to gather a larger number of patients results in increase of nondifferential misclassification.

Table 3
Dilution of relative risk (RR) according to sensitivity and specificity

Sensitivity (%)	Specificity			
	100%	99%	90%	50%
100	0.25 (true RR)	0.29	0.52	0.88
90	0.25	0.29	0.54	0.90
80	0.25	0.29	0.56	0.92
50	0.25	0.32	0.67	1.00

A randomized double-blind placebo-controlled trial by Govaert et al. (Table 4) [3] adopted several influenza diagnosis criteria: serological diagnosis, symptomatic diagnosis by a family physician using the International Classification of Health Problems in Primary Care (ICHPPC-2) criteria, and diagnosis based on self-reported symptoms (mailed questionnaire) using the criteria of ICHPPC-2 and the Dutch Sentinel Stations (DSSs). Serological diagnosis, which had the highest specific criteria, showed the highest effectiveness of influenza vaccine (RR = 0.50), while family physician diagnosis showed the second (RR = 0.53), and self-reporting, which had the lowest specificity, showed the lowest effectiveness (RR = 0.69 and 0.83). The probability of 'false positive' cases as well as 'false negative' cases was similar for both vaccine and placebo groups; this was believed to be due to the double-blind vaccine/placebo inoculation methodology. Thus, misclassification derived from diagnostic procedures was nondifferential in that trial.

3. PPV and nondifferential misclassification of diagnosis

A high PPV of influenza among study subjects reduces the proportion of 'false positive' cases. It reduces nondifferential misclassification and leads to a precise evaluation of effectiveness. Govaert et al. [3] found that vaccine effectiveness was more clearly observed in the period of epidemic elevation (between week 49 in 1991 and week 6 in 1992) (Fig. 1) than over the whole study period (Table 4). This restriction increased the PPV of influenza for each criteria, and consequently reduced the nondifferential misclassification. Limiting study period is also useful when using less specific diagnostic criteria such as symptoms of ILI or absence from school

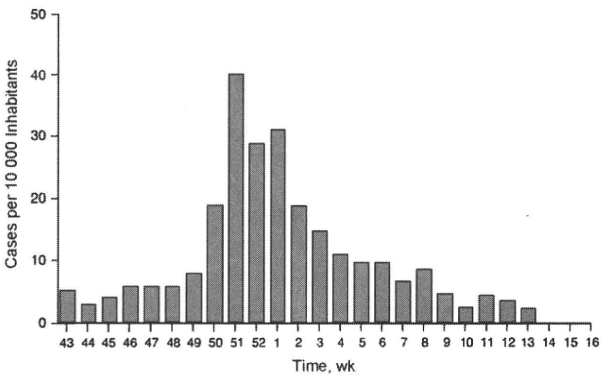

Fig. 1. Weekly influenza incidence in the Netherlands during the 1991–1992 influenza season, as reported by Govaert et al. [3].

Table 4
Modification in effectiveness of influenza vaccination according to different criteria

Influenza or influenza-like illness according to	Vaccine group no. (%) (n = 927)	Placebo group no. (%) (n = 911)	Relative risk for whole period	Relative risk for epidemic period
Serology	41 (4)	80 (9)	0.50	0.39
Family physician	17 (2)	31 (3)	0.53	0.40
DSS criteria	62 (7)	89 (10)	0.69	0.41
ICHPPC-2 criteria	108 (12)	129 (14)	0.83	0.74

Cited and reconstructed from Ref. [3].

or workplace. Study in a large outbreak season will be desired because high prevalence of target disease increases the PPV.

In conclusion, to avoid a nondifferential diagnosis misclassification, it is necessary to use highly specific diagnostic examinations such as virus detection, to limit the observation period to an intensive epidemic period, and to be conducted in a large outbreak season.

4. Differential misclassification of diagnosis

Differential misclassification results in either over- or underestimation of true association. Table 5 shows examples; the upper: relatively excess 'false positive' cases in vaccinated group leads underestimation, and the lower: those in unvaccinated leads overestimation. Relatively excess 'false negative' cases in vaccinated or unvaccinated groups will lead inverse effect, respectively.

In a cohort study, vaccinated people may more readily visit clinic and more likely to report ILI symptoms to physician than unvaccinated people because they may be more health conscious and/or because the clinic is where they were vaccinated. This leads to an increased number of influenza patients in vaccinated group, causing a differential diagnosis misclassification and underestimation of vaccine effectiveness. In contrast, if unvaccinated people fear ILI-like symptoms because they were not vaccinated, or if vaccinated people think those symptoms indicate other diseases since they were vaccinated, these tendencies would result in overestimation of the vaccine effect.

Physician behavior can also cause a differential diagnosis misclassification. A physician may be more likely to perform a virus detection test on unvaccinated compared to vaccinated patients, resulting in a greater dropout of vaccinated patients with influenza, and hence an overestimation of vaccine effectiveness. The reverse tendency would result in an underestimation. Therefore, standardization of diagnostic procedures independent of patient vaccination anamnesis is essential. If not, physicians' diagnostic procedure should be examined whether anamnesis of influenza vaccination affected the diagnostic test or diagnosis itself.

Thus, passive findings from patients with influenza who visit clinics would result in complicated differential misclassification. Especially, any information cannot be obtained from people who did not visit clinics; whether they had influenza or other diseases, died, or moved out of study area. These dropouts reduce the validity of study. Therefore, potential patients with influenza must be equally scrutinized both in vaccinated and unvaccinated cohort using the same defined criteria. This design element is more important than any others such as using highly specific examinations or criteria such as virus detection, which reduces nondifferential misclassification. In a recent prospective study in Japan [4], there was no description how investigators surveyed their all cohort members, except for devices (self-report questionnaire, phone call, or by mail). Thus, ILI patients determined in this study were derived from those who visited clinics, so that the results might be seriously distorted by diagnostic differential misclassification as well as other biases.

In a case–control study, which has been widely used in routine use, the similar problems would occur. Case–control study requires ascertaining all cases, or a representative sample of all cases, occurring in that population over the study period [5]. This assumption is not consistent with differential misclassification of diagnosis, derived from patient behavior and physicians' diagnostic procedure. The latter can be evaluated, but the former is hardly examined.

In conclusion, selective loss of patients with influenza from the vaccinated group leads to overestimation of the vaccine effect, whereas loss from the unvaccinated groups leads to underestimation. Therefore, to avoid differential misclassification of diagnosis, vaccinated and unvaccinated groups must be equally scrutinized with the same criteria. This equal observation is more important than specificity of diagnosis. In a study using passive findings from influenza patients at clinics, standardization of diagnostic procedures independent of patient anamnesis of vaccination is required, as well as examination whether diagnosis of influenza might be affected by the patients anamnesis.

5. Misclassification of exposure

When evaluating the effect of vaccines, exposure means 'vaccination', and measurement is based on medical records or self-reporting. While using medical records is the most valid method, this cannot always be achieved. Self-reporting may cause misclassification due to incorrect recall by the study subjects. Nondifferential misclassification of exposure will dilute the effectiveness of vaccine, and differential one may lead either over- or underestimation. In most situations in evaluating effectiveness of influenza vaccine, the effect of exposure misclassification will be a dilution.

Table 5
Examples of influence of differential misclassification of diagnosis

Comparison groups		True number of patients with influenza	True relative risk (RR)	Misclassification of diagnosis	Observed number of patients with influenza	Observed RR
Vaccinated	1000	50	0.25	+20	70	0.33
Unvaccinated	1000	200		+10	210	
Vaccinated	1000	50	0.25	0	50	0.21
Unvaccinated	1000	200		+30	230	

6. Conclusion

Misclassification of a diagnosis, especially differential misclassification, seriously affects the results of studies on influenza vaccine effectiveness. The following conditions must prevail in order to avoid such misclassification: equal scrutiny of outcomes in both vaccinated and unvaccinated groups and diagnosis of influenza being independent of patient vaccination status, to ascertain all cases or representative sample of influenza in the study population; and highly specific diagnostic criteria and high prevalence of influenza in the study population, to minimize 'false positive' cases.

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Ecological studies on influenza infection and the effect of vaccination: Their advantages and limitations

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ABSTRACT

Ecological studies lack the ability to control for the effects of confounding factors. The findings of a linear relationship between average exposure and disease frequency in ecological studies do not imply that such a linear relationship will be present at the individual levels. This is known as the 'ecological fallacy'. Despite these limitations, ecological studies may be the best approach to studying exposures that are easier to measure at the group rather than the individual level because most ecological studies make use of routinely collected data. They are also useful for monitoring the effectiveness of population interventions such as vaccination programs, health education campaigns and mass screening programs. Thus, ecological studies are useful epidemiologic tools for public health surveillance if we know their limitations and interpret their results carefully. Ecological studies often help to generate hypotheses, although they rarely provide a strong test of a causal hypothesis.

1. Introduction

Ecological studies are those that involve investigating the frequency of disease in relation to the average exposure level in several groups of people (i.e., population study) [1,2] or in the same group over different periods of time (i.e., time series study) [1,2]. In ecological studies, the units of analysis are groups of people rather than individuals because exposure is known only for the groups, not for the individuals in the groups [1,2]. In this paper, we introduce some examples of ecological studies on influenza infection among the elderly and the effect of vaccination on the elderly, and discuss the advantages and limitations of ecological studies.

2. Population study

The Hokkaido influenza study was conducted to evaluate the efficacy of influenza vaccination for the institutionalized elderly. We examined vaccine coverage among the residents and nursing/caring staff of each institution for the elderly in Hokkaido prefecture during the 2002–2003 influenza season [3]. We also asked each institution about the proportion of influenza-like illness among their residents and if they had any nursing/caring staff who suffered from influenza-like illness during the 2002–2003 influenza season [3]. Among 547 institutions, 409 (74.8%) agreed to participate in our study [3]. The proportion of institutions where at least one resident suffered from influenza-like illness was 28.1% while the outbreak of influenza-like illness (i.e., 5% or more residents suffered from influenza-like illness) was observed in 9.3% of the institutions [3]. In the analysis of skilled nursing homes, 51 of 191 skilled nursing homes (26.7%) revealed that at least one resident suffered from influenza-like illness during the 2002–2003 influenza season (Table 1) while the outbreak of influenza-like illness developed in 17 of 160 institutions (10.6%) (Table 2). The proportion of institutions where at least one resident suffered from influenza-like illness decreased with the vaccine coverage of their residents, although their association was not statistically significant (Table 1) [3]. The outbreak of influenza was most frequently seen in the group with the lowest vaccine coverage (Table 2).

Using the data from this survey [3], we evaluated the risk of outbreak in relation to the occurrence of influenza-like illness or influenza vaccine coverage among nursing/caring staff [4]. There was no meaningful association between the outbreak of influenza-like illness among the residents and the influenza vaccine coverage of the nursing/caring staff (Table 3), while the outbreak of influenza-like illness more frequently developed in the institutions where at least one nursing/caring staff suffered from influenza-like illness than those where no nursing/caring staff did so (Table 4). Even after controlling for other factors (i.e., the proportion of residents aged 80 and over, the proportion of demented residents, the proportion of bedridden residents, vaccine coverage,

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Table 1
The proportion of institutions where at least one resident suffered from ILI according to the vaccine coverage of the residents

Vaccine coverage of the residents	Number of institutions	Institutions where at least one resident suffered from ILI #
0–29%	6	3 (50.0%)
30–69%	19	6 (31.6%)
70%+	164	41 (24.7%)
Unknown	2	1 (50.0%)
Total	191	51 (26.7%)

Note: 31 out of the 191 institutions did not answer the proportion of the residents who suffered from ILI. ILI is the influenza-like illness, #: the values are expressed as number (%).

Table 2
The proportion of institutions with the outbreak of ILI according to the vaccine coverage of the residents

Vaccine coverage of the residents	Number of institutions	Institutions with the outbreak of ILI#
0–29%	5	2 (40.0%)
30–69%	14	0 (0%)
70%+	139	15 (10.8%)
Unknown	2	0 (0%)
Total	160	17 (10.6%)

ILI is the influenza-like illness, #: the values are expressed as number (%).

Table 3
The proportion of institutions with the outbreak of ILI according to the vaccine coverage of the nursing/caring staff

Vaccine coverage of the nursing/caring staff	Number of institutions	Institutions with the outbreak of ILI#
0–9%	33	4 (12.1%)
10–19%	13	3 (23.1%)
20–29%	12	0 (0%)
30–49%	28	1 (3.6%)
50–69%	29	1 (3.4%)
70–89%	64	10 (15.6%)
90%+	166	18 (10.8%)
Unknown	2	1 (50.0%)
Total	347	38 (11.0%)

Note: 3 out of 347 institutions did not answer whether at least one nursing/caring staff suffered from ILI. ILI is the influenza-like illness, #: the values are expressed as number (%).

and the quota of residents), occurrence of influenza-like illness in the nursing/caring staff was associated with an increased risk of the outbreak of influenza-like illness among the residents (adjusted odds ratio: 4.48, 95% confidence interval: 1.99–10.1) (Table 4) [4]. These findings may suggest that improvement of the vaccination rate among the residents as well as the prevention of influenza infection among the nursing/caring staff is important for the prevention of the outbreak of influenza-like illness in elderly care institutions.

3. Time series study

Japan has based its policy for the control of influenza on the vaccination of school children although the outbreak of influenza leads to increased mortality rates among the elderly and vaccination for the elderly is encouraged in the United States. Most Japanese school children were vaccinated against influenza from 1962 to 1987, when herd immunity was achieved in Japan. But the law was relaxed in 1987 and repealed in 1994, which made the vaccination rate drop to low levels. Reichert et al. [5] conducted a time series study to investigate the association between the excess deaths attributed to pneumonia and influenza among the elderly and the amount of influenza vaccine distributed in Japan and the United States. Their study clearly demonstrated that the excess mortality rates in Japan dropped from values three to four times those in the United States to values similar to those in the United States after the initiation of the vaccination program for school children [5]. They reported that the vaccination of Japanese children prevented about 37,000–49,000 deaths per year. In contrast, the excess mortality rates in Japan increased after the vaccination of school children was discontinued [5]. These findings may suggest that vaccinating school children against influenza provides protection and reduces mortality from influenza among the elderly in Japan. In other words, it may be beneficial to vaccinate healthy school children to prevent transmission of influenza viruses to their grandparents. However, their study had limitations [6]. First, the deaths from influenza and pneumonia may be influenced by the level of influenza-virus-circulation because influenza viruses do not usually circulate at high levels throughout the entire influenza season [6]. Second, pattern of aging, age-specific vaccine coverage and age-specific death rate were not shown in their study [6]. Third, other important variables including underlying chronic medical conditions and household structures were not addressed in their study, although underlying chronic medical conditions and three-generation households may increase the risk of influenza infection for the elderly.

Simonsen et al. [7] evaluated influenza-related excess mortality among the US elderly from 1968 to 2001. Contrary to Japan, in the United States, influenza vaccine coverage among the elderly increased from 15–20% before 1980 to 65% in 2001. However, excess mortality for influenza seasons did not change except excess mortality in A (H3N2)-dominant seasons between 1968 and the early 1980s. They attributed the decline in influenza-related mortality among the elderly in the decade after the 1968 pandemic to the acquisition of immunity to the emerging A (H3N2) virus [7]. Their study [7] failed to show the preventive effect of the influenza vaccination on excess death among the US elderly during influenza seasons after the early 1980s.

Their study showed that vaccination against influenza was less effective in preventing death among the elderly than previously assumed [7], although a meta-analysis of 20 case-control studies and cohort studies concluded that vaccination against influenza reduced half of winter deaths among the elderly in the community [8]. The results of the study by Simonsen et al. [7] have caused some confusion about whether the elderly should receive an influenza vaccine or not, but the study did not imply that the elderly should

Table 4
Odds ratios (ORs) and 95% confidence intervals (CIs) for the outbreak of ILI according to ILI among the nursing/caring staff of the institutions

Nursing/caring staff suffering from ILI	Outbreak of ILI		Crude OR (95% CI)	Adjusted OR (95% CI)
	Yes#	No#		
None	10 (4.8%)	199 (95.2%)	1.00 (reference)	1.00 (reference)
One or more	28 (20.7%)	107 (79.3%)	5.21 (2.44, 11.13)	4.48 (1.99, 10.10)

ILI is the influenza-like illness, #: the values are expressed as number (%), adjusted OR is the adjusted for the proportion of residents aged 80 and over, the proportion of demented residents, the proportion of bedridden residents, vaccine cove.

not receive influenza vaccine [9]. Although numerous studies have shown that the influenza vaccination works, it is difficult to measure the degree of the vaccine's effectiveness because influenza seasons differ each year in length and severity [9].

The study by Reichert et al. [5] demonstrated that influenza vaccination in school children reduced the influenza-related excess mortality among the elderly while the study by Simonsen et al. [7] could not show any meaningful association between influenza vaccination and influenza-related excess mortality among the elderly. The results of the former study conflict with those of the latter. It is logical that vaccinating healthy persons who have contact with high risk individuals is useful in preventing transmission of influenza viruses to the high risk group [10]. However, it seems to be strange that, although vaccinating school children reduced the influenza-related excess mortality among the elderly, vaccinating the high risk persons (i.e., the elderly) failed to do so. These findings may be due to the contradiction of ecological studies. Thus, this type of study has several limitations.

4. Advantages and limitations

Ecological studies have advantages [1,2]. First, they can be carried out quickly and inexpensively. Second, many factors can be evaluated in relation to the outcome of ecological studies. Third, most ecological studies make use of routinely collected data, and there is no need to contact the individuals involved.

However, ecological studies have disadvantages as well [1,2,11]. First, exposure levels represent average levels for each population group in ecological studies, although exposure is most often heterogeneous within a group, with some individuals not exposed at all and those exposed likely to be exposed at different levels. Thus, the findings of a linear relationship between average exposure and disease frequency in ecological studies do not imply that such a linear relationship will be present at the individual level.

A second major limitation of ecological studies is the inability to control for the effects of confounding factors. Third, exposure is most often estimated from data collected for other reasons, which generally provide only an indirect measure of possible risk factors. Therefore, we should interpret the results of ecological studies carefully because the observation of a relationship at a population level between two variables does not necessary imply that the same relationship will hold at an individual level. This is known as the 'ecological fallacy'. For these reasons, ecological studies rarely give a strong test of a causal hypothesis, but they often help to generate hypotheses.

Despite these limitations, ecological studies may be the best approach to studying exposures that are easier to measure at a group rather than an individual level [1]. For example, Wang et al. [12] demonstrated a negative but non-linear association between the concentration of fluorine in drinking water and the incidence of dental caries in 28 cities and 4 villages in China. This result may suggest that the dental caries can be reduced by drinking water with fluoridation.

Additionally, Forman et al. [13] examined the geographic association between the positive rate of Helicobacter pylori infection and the mortality rate of gastric cancer in 46 rural counties in China. They found that the counties with higher prevalence of Helicobacter pylori infection tended to have higher gastric cancer mortality although this association was not perfect [13]. This result hints that Helicobacter pylori may play a role in the development of stomach cancer.

The final example is the study by St Leger et al. [14]. They examined factors associated with cardiac mortality in 18 developed countries. They found that the countries with higher wine consumption showed lower cardiac mortality [14]. This result raises the hypothesis that alcohol protects against ischemic heart disease. Thus, ecological studies are useful in generating hypotheses, although they lack the ability to provide a strong test of a causal hypothesis.

Ecological studies are also useful for monitoring the effectiveness of population interventions such as vaccination programs, health education campaigns and mass screening programs [1]. In the United States, data from notifiable disease system have been used at the local level to document immunization effects, to demonstrate public health need, or to detect outbreaks [15]. At the national level, the data is more often used to monitor the national health condition or to detect changes in health practice [15].

Thus, ecological studies are useful epidemiologic tools for public health surveillance if we know the limitations of ecological studies and interpret the results carefully.

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Influenza vaccine effectiveness among elderly persons living in the community during the 2003–2004 season

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ABSTRACT

To examine the effectiveness of influenza vaccine among community-dwelling elderly (65–79 years old), we conducted a population-based cohort study during the 2003–2004 influenza season. A total of 4787 elderly individuals were interviewed regarding acute febrile illness, hospital visits, hospitalization and death by telephone every month. The vaccination status and physician-diagnosed clinical influenza (hereinafter referred as clinical influenza) were determined based on data obtained from the city office and hospitals, respectively. After adjusting for confounders, the odds ratio (OR) of vaccination for influenza-like illness (ILI) with high-fever, which was defined as an acute febrile illness (≥38.5 °C) during the epidemic period, was 0.38 (95% confidence interval [CI], 0.17–0.85) and the OR for clinical influenza was 0.76 (95%CI, 0.28–2.06). Due to the inadequate sample size, ORs for preventing hospitalization for influenza or pneumonia (OR, 0.37; 95%CI, 0.09–1.47) and death (OR, 3.68; 95%CI, 0.75–18.12) were not conclusive. These results suggested that vaccination was therefore effective for elderly persons living in the community.

1. Introduction

Inactivated influenza vaccination is 30–70% effective in preventing hospitalization for pneumonia and influenza among elderly persons not living in nursing homes or similar chronic-care facilities [1]. In the United States, annual vaccinations are recommended for these groups, as well as the residents of nursing homes and for groups with high-risk medical conditions, by the Advisory Committee on Immunization Practice [1]. In Japan, influenza vaccinations to elderly individuals (≥65 years old) have been subsidized by their municipality under the Preventive Vaccination Law since 2001. However, little is known about the effectiveness of influenza vaccine among community-dwelling elderly in Japan, and skepticism to effectiveness of influenza vaccination still remains.

Most observational studies about the effectiveness of influenza vaccine in community-dwelling elderly have been reported from Western countries by using large administrative databases [2–10]. Because existing administrative database cannot be used to evaluate the effectiveness of influenza vaccination in Japan, the other approach to evaluate the effectiveness of influenza vaccination is needed [11]. Ozasa et al. tried to create a framework for monitoring the effectiveness of influenza vaccine by retrospective study; however, result was not statistically significant [11]. Retrospective studies tend to have misclassification of outcomes and selection bias of study participants. The former include the recall bias of ILI, while the latter was missing of severe outcomes, such as death and hospitalizations. Those factors may affect underestimation of vaccine effectiveness. Prospective study can avoid such issues, as far as all participants are followed with an equal intensity throughout influenza season. However, such a complete study regarding community-dwelling elderly has never been previously reported [12].

2. Materials and methods

The details of study subjects and methods have been described elsewhere [12]. In brief, all study subjects were restricted to community-dwelling elderly of Saga-city, Japan, who were 65–79 years old on 1 January 2003. We selected 10,000 subjects randomly from a population registry, and sent them a letter about the explanation for the study and request for participation in it on 1 December 2003. The eligibility criteria to participate to study were as follows: not being hospitalized, not being institutionalized, not being having any long-term absence, not living alone, and possible to contact by telephone at least once a month. We asked them to answer the self-administered questionnaire about baseline characteristics that might act as potential confounders including a history of influenza vaccination, history of influenza, comorbid conditions at baseline period, such as hypertension, cardiovascular disease,

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respiratory tract disease, diabetes mellitus, cerebrovascular disease and the other, frequency of hospitalizations for pneumonia, health status, smoking habit, exercise habit, going out to a crowd, day care use, hand washing and gargling habit, and family constitution. Among 10,000 elderly citizens, 7357 responded and 4787 agreed to participate and also matched our eligibility criteria.

Some of the study subjects had been inoculated subcutaneously with 0.5 ml of a trivalent inactivated vaccine, which contained 30 μg/ml each of A/New Caledonia/20/99 (H1N1), A/Panama/2007/99 (H3N2), and B/Shandong/7/97. The vaccination status of the study subjects was identified by self-reporting verification and a list of recipients of partially funded vaccination. After all 3240 subjects (3230 subjects were self-reported and 10 subjects were known with verification) inoculated vaccine from October 1, 2003 to December 31, and the vaccination coverage was 67.7%.

We followed all study subjects prospectively. The survey period was from 1 December 2003 to 31 March 2004. If the participants had fever equal to or more than 37 °C during the survey period, they were asked to record their signs or symptoms prospectively onto the provided record sheet, including a check list of symptoms, such as cough, sore throat, nasal congestion, muscle ache and arthralgia, hospital visits, and medication. Research nurses performed telephone interviews to them or their families about the recorded symptoms, hospital visit, hospitalization and death at least once a month. If the participants had visited hospital with fever equal to or more than 37 °C as the chief complaint, we referred to their doctor for their clinical diagnosis. ILIs were defined as acute febrile illness with symptoms described above, which occurred during the epidemic period of influenza in study area. The following outcome measures were considered: ILI, clinical influenza, hospitalization for all causes, hospitalization for influenza or pneumonia (IP), and total death.

According to reports of Infectious Disease Information in Saga Prefecture as recorded by the National Epidemiological Surveillance of Infectious Disease, an influenza epidemic was experienced in Saga between 1 January 2004 and 31 March 2004, and the influenza epidemic was mild in comparison with the previous 10 seasons. The predominant influenza strain circulating all over Japan was A (H3N2), and only 10% of the Influenza A (H3N2) isolates were similar to the vaccine strain while about 90% of the isolates were similar to the drift variant, A/Fujian/411/2002 (H3N2) [13].

Student's *t*-test and the chi-square test were used to compare the baseline characteristics in vaccinated and non-vaccinated subjects. A univariate logistic regression model was used to assess the association between the vaccination uptake and baseline characteristics, as well as the association between each outcome and the vaccination status or baseline characteristics. To evaluate the vaccine effectiveness independent of confounding factors, such as significantly associated with the vaccine uptake, the adjusted odds ratio (OR) and its 95% confidence intervals (95%CI) were calculated by a multivariate analyses. Vaccine effectiveness (VE) was calculated as $(1 - \mathrm{OR}) \times 100\%$.

This study was approved by the institutional review board associated with Saga University.

3. Results

The baseline characteristics between the vaccinated group and the non-vaccinated group are shown in Table 1. In comparison to the non-vaccinated subjects, the vaccinated subjects were significantly more likely to be females, to have received the influenza vaccine in the previous season and two seasons before, to be diagnosed with influenza in the previous season, to have baseline risk conditions such as underlining hypertension, heart disease, respiratory tract disease, cerebrovascular disease and other diseases, to have been previously hospitalized for pneumonia, to have a poor health status, to regularly exercise, to use day care, and to regularly wash their hands and gargle. Non-vaccinated subjects were more likely to smoke, in contrast to vaccinated subjects.

A total of 4787 community-dwelling elderly (3240 vaccinated subjects and 1547 non-vaccinated subjects) were flowed during the 2003/04 influenza season, and sixty subjects (55 vaccinated subjects and 5 non-vaccinated subjects) among them were lost to the follow-up. Among the remaining 4709 subjects, we observed 115 cases of ILI with a fever of more than 37.8 °C, 28 cases with clinical influenza, 137 hospitalizations for all causes and 17 hospitalizations for IP and 18 deaths (two cases were due to IP).

The crude ORs of the ILI with fever differed according to fever degree (Fig. 1). The risk reduction for ILI with fever was greater

Table 1
Baseline characteristics of the study subjects before the 2003–2004 influenza season

Characteristic	Vaccinated ($n = 3240$)	Non-vaccinated ($n = 1547$)	*P* value
Mean age ± S.D. (year)	73.2 (4.0)	72.1 (4.4)	<0.0001
Female sex (%)	44.2	34.9	<0.0001
Vaccination history			
2002/03 season	59.2	4.7	<0.0001
2001/02 season	39.7	3.8	<0.0001
Clinical-diagnosed influenza			
2002/03 season	4.3	2.7	0.03
Previous diagnoses (%)			
Hypertension	39.6	27.4	<0.0001
Cardiovascular disease	17.8	12.8	<0.0001
Respiratory tract disease	7.7	3.7	<0.0001
Diabetes mellitus	12.1	10.5	0.08
Cerebrovascular disease	8.3	4.5	<0.0001
Other comorbid conditions	38.3	25.8	<0.0001
Hospitalization for pneumonia	7.9	5.5	0.003
Poor health status (%)	12.6	9.8	<0.0001
Current smoking (%)	11.0	19.3	<0.0001
Day care use (%)	6.0	3.1	0.003
Washing hand every time when they return (%)	42.8	39.0	0.0002
Gargling every time when they return	24.8	19.5	<0.0001
Living with infant or children	12.0	10.0	0.12

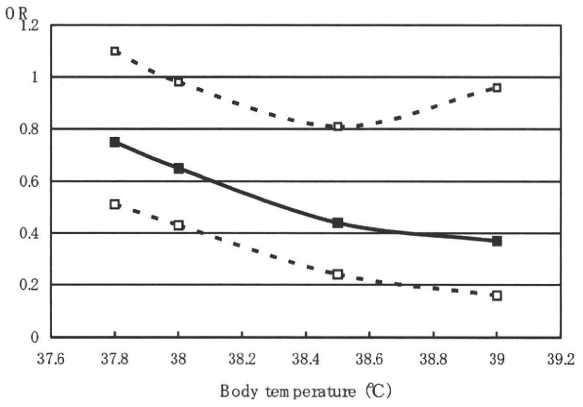

Fig. 1. Crude odds ratios (■) and their 95% confidence intervals (□) of influenza-like illness according to the degree of fever.

as fever was higher. The higher the threshold of fever, the greater the risk reduction of ILI. A statistically significant risk reduction was found when the fever was more than 38 °C. The ORs of ILI with fever more than 37.8, 38, 38.5, and 39 °C were 0.75 (95%CI, 0.51–1.10), 0.65 (95%CI, 0.43–0.98), 0.44 (95%CI, 0.24–0.81), and 0.37 (95%CI, 0.16–0.96), respectively. The OR of ILI in more than 38.5 °C fever was considered to be around 0.4, thus we defined this threshold as ILI with high-fever.

Table 2 gives the ORs and vaccine effectiveness of influenza vaccine in reducing the outcomes. The vaccination was associated with fewer ILI with high-fever, and the vaccine effectiveness for ILI was 62% (95%CI, 15–83%). Vaccination slightly reduced the risk of clinical influenza, hospitalization for all causes and hospitalization for IP, although the ORs were not statistically significant. No risk reduction in death was observed.

4. Discussion

The present study is the first study, that could detect the effectiveness of influenza vaccination in preventing ILI with a high-fever among community-dwelling elderly, as far as we know. With respect to observational studies of elderly individuals living in the community, most of them were using data-linkage from insurance-reimbursement, hospital, or primary-care databases. Jefferson et al. reviewed the evidence of efficacy and effectiveness of influenza vaccine in individuals aged 65 years or older [14]. Concerning effectiveness of vaccine against ILI, significant effect was observed among institutionalized elderly (vaccine effectiveness: 23%), although it was not observed in elderly individuals living in community (relative risk: 1.05, 95%CI: 0.58–1.89). It is difficult to certificate the effectiveness against ILI by linkage-study, because information about influenzal infection and ILI are limited to patients who had visited hospitals. The prospective cohort study can observe ILI directly, in addition, it can minimize selection bias and recall bias, in comparison to a retrospective study. However, it goes without saying that reliable and perfect follow-up of all study participants is essential. A recent internet-based prospective study in Japan could not detect the vaccine effectiveness for elderly, due to incorrect follow-up method [15]. They recruited participants before the influenza season, and gathered information of outcomes after the influenza season. The most of clinical symptoms were ascertained by self-report questionnaire. This study design might have misclassification of outcomes.

As has been discussed elsewhere [12], this study has several superiorities for follow-up method. The first is the completeness of follow-up (more than 98%), which was achieved by assignment of the eligibility criteria for participants. The second, and the most distinguished point is that we observed each individual study subject prospectively with an equal intensity throughout the epidemic period. The use of provided record sheet (symptoms diary) and every month telephone interview enabled us to observe ILI correctly. Our close observation can confirm the relationship between the ORs of ILI and the fever threshold. The OR decreased as fever threshold increased and the OR was almost 0.4, when fever was equal to and higher than 38.5 °C. We considered that the misclassification of "non-influenza" has been avoided to a great extent and that the specificity of outcome measure, which affects the effectiveness of influenza vaccine [16], has been raised, by setting a clear limit for fever. However, another possibility, such as that vaccination may also prevent higher fever itself, may consider, so that further investigations are needed.

In terms of statistical power, following situations have an advantage to detect the effectiveness of influenza vaccine; the vaccine strains are antigenically well matched to circulating strains; the epidemic is large and attack rate of influenza is high; and vaccine coverage is approximately half. In this study season, vaccine coverage of study participants was 67.7%, and that of elderly citizens in study area was 52.6%, which was higher than that of previous season (35.2%). The influenza epidemic in this season was mild, and antigenic drift strain was circulating. Thus, 2003–2004 season in study area was rather difficult to detect the vaccine effectiveness. However, this study shows significant effect of influenza vaccination in preventing ILI, due to the strong point of follow-up method discussed in above. On the other hand, we could not observe the vaccine effectiveness of the other outcomes except ILI in this study. Because the seriousness of the influenza symptoms and hospital visits are not necessarily related in Japan, a misclassification of clinical-diagnosed influenza may occur due to the fact that not every influenza patient visits a hospital. Because hospitalization from all causes included many cases of not-ILI, association with vaccination was not observed. Due to inadequate cases of influenza-related hospitalization and death, the result was inconclusive.

The potential problems of this study, related information bias and confounding by indications, were well discussed in our previous report [12]. The former was minimized by verification of vaccination status and by complete follow-up method. Regarding the latter, a multivariate analysis might not exclude all residual confounding factors. However, such confounding factors may have

Table 2
Crude and adjusted odds ratios and vaccine effectiveness for influenza-related outcomes among community-dwelling elderly

Outcomes	Vac (n = 3169)	Non (n = 1540)	Crude OR	95%CI	Adjusted OR[a]	95%CI	VE[b] (%)	95%CI
ILI with high-fever	20	22	0.44	(0.24–0.81)	0.38	(0.17–0.85)	62	(15–83)
Clinical influenza	18	10	0.87	(0.40–1.90)	0.76	(0.28–2.06)	24	(−106–72)
Hospitalization for all	92	45	0.99	(0.69–1.43)	0.72	(0.46–1.13)	28	(−13–54)
Hospitalization for IP	11	6	0.89	(0.33–2.41)	0.37	(0.09–1.47)	63	(−47–91)
Death from all causes	16	2	3.89	(0.89–16.93)	3.68	(0.75–18.12)	−268	(−1712–25)

Vac: vaccinated; Non: non-vaccinated; OR: odds ratio; CI: confidence interval; VE: vaccine effectiveness; ILI: influenza-like illness; IP: influenza or pneumonia.

[a] The odds ratios were adjusted for age and sex plus the potential confounders at baseline, which were significantly associated with the vaccine uptake.

[b] The vaccine effectiveness was calculated as (1 − adjusted OR) × 100%.

resulted in an underestimation of vaccine effectiveness. Hence, our estimates are conservative, and the real effects may actually be higher than reported herein.

In conclusion, our results indicated that, influenza vaccination had about 60% effectiveness in preventing ILI during the epidemic period in community-dwelling elderly. The results were inconclusive for preventing hospitalization and death, due to an inadequate sample size. However, our findings support that elderly individuals substantially benefit from vaccination even in a season of mild influenza activity and also when the antigenic match between the vaccine strains and the circulating strains are not closely matched.

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