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Basic principle of population-based cohort study to evaluate influenza vaccine effectiveness among elderly Japanese

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ABSTRACT

Influenza vaccines minimize the risk of influenza-related morbidity, complication, and death in elderly people. Although evaluating vaccine effectiveness (VE) is important for promoting immunization programs and coping with influenza epidemics, it is difficult to evaluate its effectiveness in Japan, where no frameworks to use large databases, such as a vaccination registry and health maintenance organization datasets, are available. Therefore, another analytic epidemiological investigations to evaluate VE in Japan are required. Herein, we describe the basic principles of a cohort study, which might be the most comprehensive, but expensive, study design. It is particularly important to be aware of the potential bias and confounding factors that should be minimized in the study design and analysis. We focus on "laboratory-confirmed influenza" and "influenza-like illness", and discuss why it is important to follow up with equal intensity, and how to control for bias; problems that often arise in population-based observational cohort studies.

1. Introduction

Influenza is an infectious disease, and vaccination is available; however, epidemiological evidence of vaccine effectiveness (VE) of influenza vaccine among elderly people is insufficient in Japan. In 1994, influenza was excluded from target disease list in the Japan's Preventive Vaccination Law. This owed to governmental and medical distrust of the vaccine's VE. Suspicions about VE caused a reduced vaccination coverage in Japan around 2001, when the Preventive Vaccination Law was amended to include influenza for those aged 65 years or above and for those aged 60–64 years at high-risk again [1]. To promote vaccination and to cope with a potential influenza epidemic, evidence for VE among elderly people in Japan is needed. In 2002, the Ministry of Health, Labour and Welfare organized a research group on VE in Japan.

Among the epidemiological study designs, randomized controlled trials that measure laboratory-confirmed influenza virus infections as the outcome are the most persuasive for obtaining reliable evidence of VE. However, such trials cannot be conducted ethically among groups recommended to receive vaccination annually, because those assigned to control groups will thereby miss their opportunity for vaccination. Longitudinal cohort studies provide clear information about the vaccination and outcome. Most cohort studies among community-dwelling older people were reported in Western countries [2–9]. They were conducted by record linkage studies, using large existing administrative datasets, such as health maintenance organizations, Medicare, Medicaid, national health insurance schemes, general practice research databases, population and mortality registries, as well as a vaccination registry database. The VE against serious outcome measures such as influenza-related pneumonia, hospitalization, and death were usually evaluated in those studies, but the VE against clinically diagnosed influenza was rarely detected. Because clinically diagnosed influenza was detected only among patients who had visited medical institutions, this was considered an inappropriate indicator. Additionally, most linkage studies did not control adequately for differences in the propensity for healthier persons to be more likely to receive vaccination than less healthy persons.

In Japan, there is no vaccination registry and it is difficult to use health maintenance organization datasets, owing to the Privacy Protection Law and the nature of the Japanese health care system. In principal, the Japanese health insurance system guarantees a

Abbreviations: VE, vaccine effectiveness; ILI, influenza-like illness.

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patient's freedom to choose a medical institution; thus the seriousness of influenza symptoms is not necessarily related with visiting medical institutions. Therefore, special epidemiological investigations to evaluate VE in Japan are needed. In this article, we describe the basic principles and several potential pitfalls of population-base cohort studies, which are the most comprehensible study design, with reference to our previous report [10].

2. Basic principle of cohort studies for VE

Vaccine efficacy and VE were first described by Greenwood and Yule in 1915 [11]. In observational studies, VE is the percent reduction in the incidence of disease in vaccinated subjects (I_{vac}) compared with the incidence of disease in unvaccinated subjects (I_{unv}): $VE = \{(I_{unv} - I_{vac})/I_{unv}\} \times 100 = \{1 - (I_{vac}/I_{unv})\} \times 100 = \{1 - \text{risk ratio (RR)}\} \times 100$. For ease of understanding, Fig. 1 shows the concept and an example of VE. A reduction in the incidence of disease in I_{vac} was "20%–6%", which accounts for "{(20%–6%)/20%} × 100 (%) = 70 (%)" of I_{unv}. Therefore, a VE of 70% does not mean that 70% of vaccinated subjects will not develop influenza. The concept of RR might make it easy to understand VE. Assuming I_{unv} to be 1, then I_{vac} will be 0.3, the ratio of the incidence of vaccinated subjects compared with unvaccinated subjects.

It is an essential point that all cohort studies for evaluating VE need to observe the target outcome in both vaccinated and unvaccinated subjects over time with "equal intensity". "Laboratory-confirmed influenza" virus infections as the outcome are the most persuasive evidence of VE, because this reduces the risk of misclassification of outcome for infection. However, laboratory-confirmed influenza virus infections are not always ideal outcomes for population based cohort studies. In general, they are diagnosed only when subjects' specimens are collected at medical institutions. Because the likelihood of visits to medical institutions when patients present symptoms depends not only on symptom severity, but also on patient characteristics, laboratory-confirmed influenza may induce ascertainment bias in population-based cohort studies. Unvaccinated subjects might visit medical institutions more frequently when they have influenza-related symptoms as compared with vaccinated subjects, because they might worry about influenza. Thus, unvaccinated subjects tend to be diagnosed as having laboratory-confirmed influenza by passive surveillance in clinical settings, causing VE to be overestimated. To avoid such bias by using laboratory-confirmed influenza as an outcome, active surveillance with a weekly survey for symptom and specimen collection should be performed. To the best of our knowledge, only one randomized controlled trial among children demonstrated VE using laboratory-confirmed influenza [12]. The researchers contacted all study participants every week to obtain information regarding the onset of influenza-like illness (ILI) during an epidemic period, and once they ascertained ILI, they collected respiratory specimens from every participant within a few days, and identified influenza virus infection. However, because such a study requires huge effort and cost, it is not easy to adopt for the study on evaluation of VE. The case definition, which can collect all outcomes from both vaccinated and unvaccinated subjects with an "equal intensity", should be made.

3. Case definition and standardized active surveillance

As already mentioned, the case definition is an essential element for studies. A case definition that poorly represents the disease might cause a differential misclassification of the outcome, leading to imprecise estimates of VE. Additionally, if infection or disease is differently diagnosed in vaccinated and unvaccinated subjects, potential bias may occur. Thus, the case detection must be made independent of vaccination history, and can be adopted within the scope of the budget and logistics of the study. To ascertain influenza onset with equal intensity in a population-based study, active surveillance requires contact with all study participants at regular intervals via mail [13] or telephone [10,12]. In this situation, ILI during an influenza epidemic can be available for the outcome. Although using ILI is likely to lead to underestimating VE because of the non-differential misclassification of true influenza, it is more favorable than using biased outcomes.

In our previous study of the 2003–2004 influenza season [10], we asked participants to measure their body temperature prospectively and record all sudden onset fever ≥37.0 °C with any symptoms onto a special diary sheet, that we provided before follow-up. The diary sheets included a checklist of symptoms, such as cough, sore throat, nasal congestion, muscle ache and arthralgia, hospital visit, and medication. Active surveillance through monthly phone calls by nurses was conducted to ascertain outcomes with equal intensity throughout the influenza season. The subjects or their family members reported their outcomes with reference to the records on their diary sheet. The collected information was as follows: all acute febrile illness ≥37.8 °C with any symptoms in the list, visits to medical institutions owing to these symptoms, hospitalization for all causes, hospitalization for influenza or

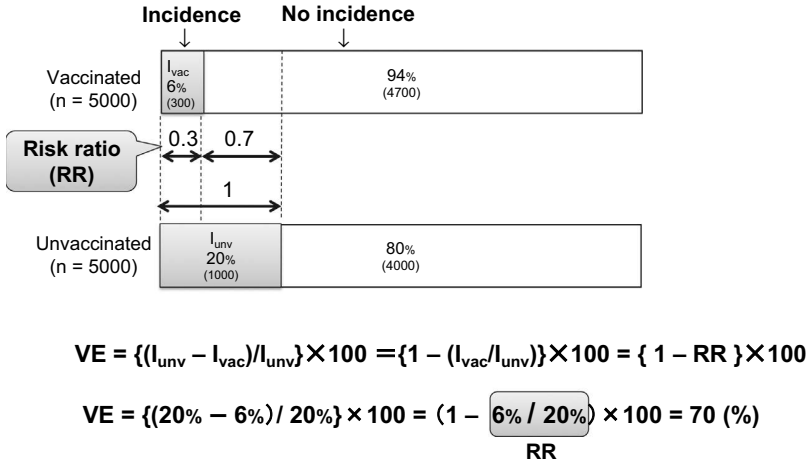

Fig. 1. Concept of vaccine effectiveness (VE). VE refers to the percent reduction in the incidence of disease in vaccinated individuals (I_{vac}) compared with the incidence of disease in unvaccinated individuals (I_{unv}). RR, risk ratio.

pneumonia, and total deaths. After the follow-up, the ILI was defined by limiting the acute febrile illness to cases occurring during the influenza epidemic in the study field. To increase the specificity of ILI, we analyzed the RR of vaccination according to fever degree and defined the ILI with high fever. Self-reported medical institution visits and hospitalization were identified by review with physicians to verify clinically diagnosed influenza and hospitalization for all causes and those for influenza or pneumonia. Death was certificated using the population registry.

4. Study setting and eligibility criteria for participation

Based on the characteristics of influenza, a VE study needs to specify the season, place, and population, because epidemic strains of influenza differ by season and place; the proportion of susceptible individuals differs by the season, place, and population; and vaccine strains differ by season. In our previous study of the 2003–2004 influenza season, we set a fixed cohort of older persons aged 65–79 years in the southern Japanese city of Saga [10]. In addition to explaining the study purpose and receiving written consent to study participation, we set the eligibility criteria for study participation to complete follow-up with equal intensity as follows: possible to contact by telephone at least once a month, living with family, not being hospitalized, not being institutionalized, and not having any long-term absence. We were also permitted to inquire about their information at Basic Resident Register city offices, when we failed to contact them during the follow-up period.

5. Sample size calculation and making a list to enroll older subjects

The parameters we used for sample size calculation were vaccination coverage (40–60%), VE (30–50%), and proportion of primary outcome onset among unvaccinated subjects (3–7%). If we set α-error and β-error as 0.05 (for a two-sided test) and 0.10, respectively, the total numbers of participants were estimated to be 5000–6000. When we take into account a participation proportion of 50% to 60%, then almost 10,000 older persons must be enrolled.

Because Japan has a Privacy Protection Law, we could not obtain electronic datasets from the population registry of the city office, even though the study protocol was approved by an institutional ethical committee. We selected 10,000 community-dwelling older persons randomly from the Basic Resident Register, and traced their name, sex, address, and birth date to form the study list.

6. Confounding and misclassification of vaccination status

Because VE can be determined by comparing the incidence of disease among vaccinated and unvaccinated individuals, potential bias may occur if any of the following conditions occur: there is unequal opportunity for exposure to people with influenza that encourages individuals to self-select for vaccination, and taking action to receive vaccination systematically differs between healthy and diseased persons. Confounding factors by indication induce a bias in the comparison. For example, older persons with any disease might be diagnosed as influenza, as well as be vaccinated, more frequently than a person without any disease, because they visit to a medical institution regularly (Fig. 2). Therefore, confounding factors might lead to the reduction of VE. Factors such as age, sex, race, socioeconomic status, residence, comorbid conditions, day care use, health-conscious behavior, and vaccination history of influenza may be independently related to both risk of influenza and vaccination status. Therefore, we asked subjects

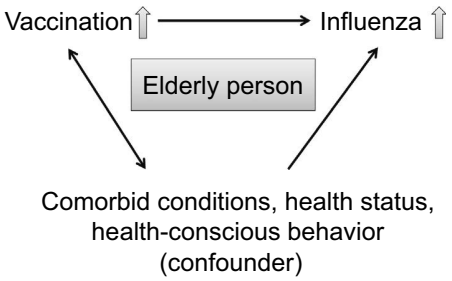

Fig. 2. Confounding factors on vaccine effectiveness in elderly persons.

about these factors using a self-administered questionnaire at the beginning of the study, and adjusted them by multivariate analysis.

Misclassification of vaccination status by self-reporting may also influence VE. Non-differential misclassification of vaccination status can dilute the VE, which can be acceptable. In contrast, differential misclassification may lead to either overestimation or underestimation, which might cause more complicated or serious consequences [14]. To avoid misclassification of vaccination status, we verified self-reported vaccination status with the individual records of the city vaccination subsidy.

7. Results and interpretation of the results

In our study of the 2003–2004 influenza season [10], a total of 4748 community-dwelling older persons were observed during the 2003–2004 influenza season with "equal intensity" via a monthly telephone survey based on a diary with a symptom checklist. After limiting subjects to those with a fever $\geq$37.8 °C during the influenza epidemic period, 115 cases were defined as ILI. The higher the threshold of the fever, the greater the degree of VE (Fig. 3). VE reached a plateau when fever was $\geq$38.5 °C, indicating that limiting ILI to those with a fever $\geq$38.5 °C adequately minimized the misclassification of influenza. We therefore defined this threshold as "high fever" and set "ILI with high fever" as the primary outcome. Because female sex, vaccination history of influenza, comorbid conditions, day care use, health conscious behavior,

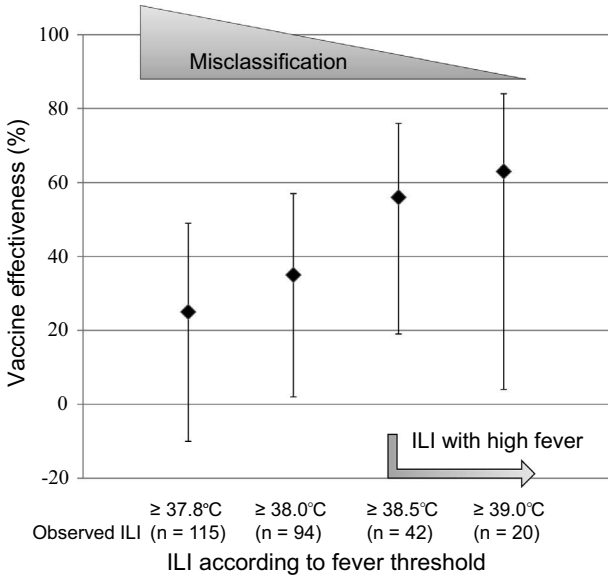

Fig. 3. Minimizing misclassification of influenza by fever threshold. ILI, influenza-like illness.

Table 1
Vaccine effectiveness (VE) according to outcomes and their interpretations.

Outcomes	Influence on VE	Adjusted* RR	95% CI	VE (%)
ILI with high fever		**0.38**	**(0.17–0.85)**	**62**
Clinically diagnosed influenza	Bias	0.76	(0.28–2.06)	24
Hospitalization for all causes	Misclassification	0.72	(0.46–1.13)	28
Hospitalization for IP	Sample size	0.37	(0.09–1.47)	63
Deaths from all causes	Confounding, Misclassification, Sample size	3.68	(0.75–18.12)	−268

CI: confidence interval, ILI: influenza-like illness, IP: influenza or pneumonia, RR: relative risk, VE: vaccine effectiveness.
* Adjusted for age and sex plus the potential confounders at baseline, which were significantly associated with the vaccine uptake. Marked the statistical significance in bold.

and living with children were positively associated with both vaccination status and ILI, these confounding factors were adjusted by multivariate analysis when estimating VE. After follow-up, 42 cases of ILI with high fever, 28 clinically diagnosed influenza, 137 hospitalizations for all causes, 17 hospitalizations for influenza or pneumonia, and 18 deaths were recorded. The VE after adjustment for possible confounding factors, ILI with high fever, clinically diagnosed influenza, hospitalizations for all causes, hospitalizations for influenza or pneumonia, and death were estimated as 62%, 24%, 28%, 63%, and −268%, respectively (Table 1).

Determining which season is suitable for evaluating VE should consider the following points: circulating virus strain and vaccine strain are antigenically well matched or not, and the scale of epidemic is large or not, and the attack rate of influenza is high or not. This season (2003–2004) was not advantageous for evaluating VE, because the influenza epidemic was mild in comparison with the previous 10 seasons, and antigenic similarity between vaccine strain and circulating strain was low. However, we detected VE for ILI with high fever, owing to several reasons as follows: completeness of follow-up (>98%) by setting eligible criteria for participation, sufficient sample size to detect VE for ILI with high fever, ascertainment of all outcomes in equal intensity throughout the epidemic period via telephone interview based on a symptom diary sheet, minimized misclassification of outcomes by setting a fever threshold, minimized misclassification of vaccination status by verification with list of recipients of partially funded vaccination, and controlling confounding factors by multivariate analysis.

In contrast to VE for ILI with high fever, VE against other outcomes were not detected (Table 1). Regarding clinically diagnosed influenza, biased outcome detection at clinical settings might have occurred. Clinically diagnosed influenza was only detected among ILI patients who visited medical institutions. Misclassification might occur, because hospitalization for all causes might include non-influenza virus diseases. Although the specificity of hospitalization for influenza and pneumonia was high and its evaluation was not biased, the sample size was not large enough to detect statistically significant values of VE for this outcome. Regarding death from all causes, several factors, such as confounding by indication, residual confounding, misclassification of outcome, and a small sample size for VE against death, had an influence on the inconclusive result.

As I already mentioned, influenza epidemics differ by season, population, and place; thus, we conducted a study for evaluating VE in the following season in the same people and place. VE against ILI with high fever was estimated at 45% (95% CI: 7–67%) in the 2004–2005 season. Therefore, VE against ILI with high fever in community-dwelling older persons ranged from 45% to 62%, which was consistent with a recent meta-analysis [15,16].

8. Conclusion

The main strategy to evaluate VE is to perform an observational study, because influenza vaccination is recommended worldwide to prevent suffering influenza. This article summarized the basic principles and several potential pitfalls of population-based cohort studies with reference to our previous report [10]. Several points should be emphasized. First, unbiased active surveillance by "equal intensity" for both vaccinated and unvaccinated is essential for cohort studies. Second, minimizing the misclassification of both vaccination status and outcome should be made. Last, careful consideration should be made for confounding factors.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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