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Basic principles of test-negative design in evaluating influenza vaccine effectiveness

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ABSTRACT

Based on the unique characteristics of influenza, the concept of "monitoring" influenza vaccine effectiveness (VE) across the seasons using the same observational study design has been developed. In recent years, there has been a growing number of influenza VE reports using the test-negative design, which can minimize both misclassification of diseases and confounding by health care-seeking behavior. Although the test-negative designs offer considerable advantages, there are some concerns that widespread use of the test-negative design without knowledge of the basic principles of epidemiology could produce invalid findings. In this article, we briefly review the basic concepts of the test-negative design with respect to classic study design such as cohort studies or case-control studies. We also mention selection bias, which may be of concern in some countries where rapid diagnostic testing is frequently used in routine clinical practices, as in Japan.

1. Introduction

It is widely accepted that the best study design for obtaining conclusive findings on prophylactic or therapeutic effects in human population is the randomized controlled trial (RCT). Such a concept can be also applied in assessing efficacy/effectiveness for almost all vaccines. With regard to the influenza vaccines, however, even a large and well-conducted RCT would simply provide a time-, place-, and subject-specific observation because: (1) epidemic strains of influenza differ by time and place; (2) the proportion of those having pre-existing antibody titers differ by time, place and age group; (3) vaccine strains differ by time (i.e., season) [1]. Together with the ethical consideration that influenza vaccination is recommended for wide-ranging high risk groups [2], the concept of "monitoring" the influenza vaccine effectiveness (VE) across the seasons using the same observational study design has been developed.

During the last decade, a test-negative design, which is a modified case-control study, has been introduced to assess VE against influenza. The design enables us to estimate VE in the early, mid, and end of the influenza season in a timely manner. Several countries including the US [3], Canada [4], Europe [5], Australia [6] and New Zealand [7] have applied the method for monitoring the annual VE. Because the test-negative design is practically easier to conduct than other study designs, a growing number of reports have been recently published. However, there are some concerns that widespread use of the test-negative design without knowledge of the basic principles of epidemiology would introduce invalid findings. In this article, we briefly review the basic concepts of the test-negative design with respect to classic study design such as cohort studies or case-control studies. We also discuss selection bias, which may be introduced when results from clinician-ordered laboratory testing is used as an outcome measure. This may be particularly of concern in some countries, including Japan, where rapid diagnostic testing for influenza is frequently used in routine clinical practice.

2. Rationale for applying the test-negative design in evaluating influenza VE

At present, the test-negative design seems to be very useful in evaluating VE against influenza. Using laboratory-confirmed influenza as an outcome measure, we can reduce disease misclassification. Furthermore, the design enable us to minimize confounding due to health care-seeking behavior. For a better understanding

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of the latter advantage, the basic principles in cohort studies should be referred.

In cohort studies, both vaccinees and non-vaccinees should be followed-up with "equal intensity" to identify the occurrence of the outcome [8,9]. If influenza-like illness (ILI) is used as an outcome measure, equal intensity of follow-up would be achieved via telephone or questionnaire survey for all subjects on a weekly or monthly basis to obtain information on onset of the disease (i.e., active surveillance) [10–12]. In contrast, when using outcome of laboratory-confirmed influenza, a more strictly defined outcome, there is a concern that bias due to health care-seeking behavior becomes an issue because: (1) the outcome is usually confirmed only after the subjects visit medical institutions due to symptoms (i.e., passive surveillance); (2) vaccinees and non-vaccinees are inherently different in the likelihood of a medical visit (Fig. 1). Given these issues relating to health care-seeking behavior, the basic principle of following the vaccinees and non-vaccinees with equal intensity is difficult to satisfy when laboratory-confirmed influenza is used as an outcome measure in cohort studies. It is still possible to comply with the principle, as noted in a previous RCT among children [13]. In that study, the investigators contacted all subjects on a weekly basis to obtain the information on ILI onset, and once they confirmed that a subject had developed ILI, they attempted to collect his/her respiratory specimens within a couple of days. Obviously, such procedures require significant efforts and costs. Other exceptions may include a VE study based on antibody efficacy, in which all subjects received vaccine and medical visits for respiratory illnesses were compared between those with and without protective level of hemagglutination inhibition titer [14]. As subjects were not aware of their post-vaccination antibody level, the distortion due to health care-seeking behavior would be non-differential. Although antibody efficacy is expected to be an accurate index of VE [15], the estimates are strain-specific and interpretation of the results is sometimes complicated. Thus, it is considered a reasonable alternative for researchers to accept ILI as an outcome measure in cohort studies, which ensures achievement of equal intensity of follow-up resulting in higher feasibility and validity [10–12].

The test-negative design has a notable strength in controlling for afore-mentioned health care-seeking behavior (Fig. 2). Typically, study subjects are patients who visit medical institutions due to ILI during the influenza season. Subjects with positive test results for influenza are classified into cases, while subjects with negative results are classified as controls, and then vaccination status during the season can be compared between cases and controls. As the subjects are likely to visit a medical institution soon after ILI onset, both cases and controls are considered to be similar in their health care-seeking behavior. Therefore, the test-negative design can minimize confounding by health care-seeking behavior in evaluating influenza VE even though the outcome measure is laboratory-confirmed influenza, which is expected to resolve the dilemma in cohort studies.

Some articles have discussed the theoretical issues of the test-negative design [16–19]. VE against influenza is supposed to be the same in those who do seek care for ILI and who do not [17], although the test-negative design is limited by visitor attendance at the medical institution. An important factor relating to seeking of care may be the disease severity because disease severity is also expected to be associated with vaccination status. For example, it is possible that non-vaccinees are likely to develop severe ILI once

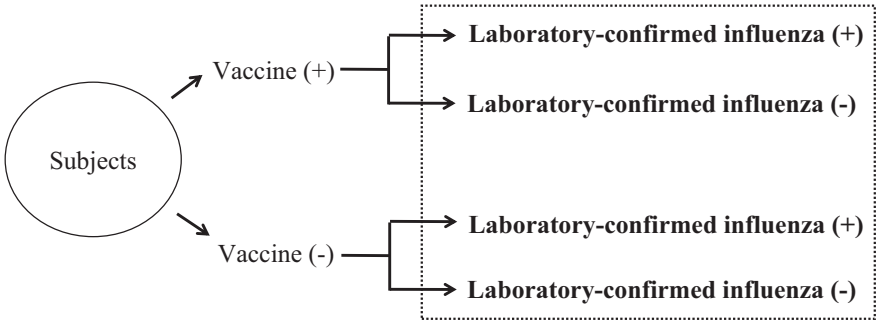

Fig. 1. Design of a cohort study to evaluate influenza vaccine effectiveness against laboratory-confirmed influenza. "Health care-seeking behavior" can introduce bias because (1) the outcome is usually confirmed only after the subjects visit medical institutions and (2) vaccinees and non-vaccinees are inherently different in the likelihood of their medical visit.

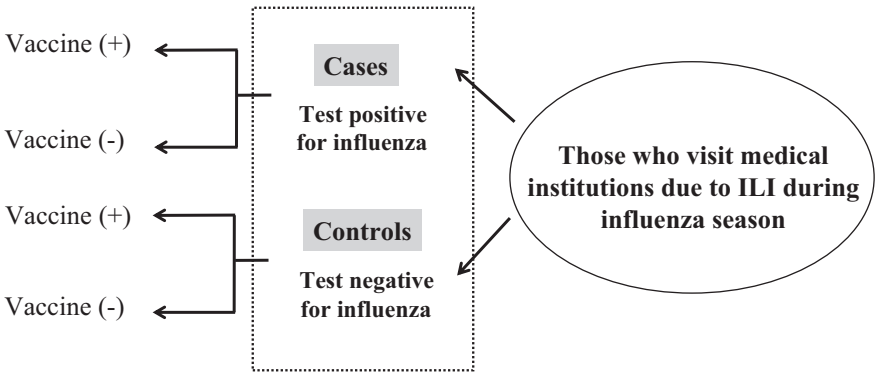

Fig. 2. A test-negative design to evaluate influenza vaccine effectiveness against laboratory-confirmed influenza. ILI denotes influenza-like illness. The test-negative design can minimize confounding by health care-seeking behavior even though the outcome measure is laboratory-confirmed influenza because "health care-seeking behavior" is likely to be similar between cases and controls.