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On the bias of estimates of influenza vaccine effectiveness from test–negative studies

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ABSTRACT

Estimates of the effectiveness of influenza vaccines are commonly obtained from a test-negative design (TND) study, where cases and controls are patients seeking care for an acute respiratory illness who test positive and negative, respectively, for influenza infection. Vaccine effectiveness (VE) estimates from TND studies are usually interpreted as vaccine effectiveness against medically-attended influenza (MAI). However, it is also important to estimate VE against *any* influenza illness (symptomatic influenza (SI)) as individuals with SI are still a public health burden even if they do not seek medical care. We present a numerical method to evaluate the bias of TND-based estimates of influenza VE with respect to MAI and SI. We consider two sources of bias: (a) confounding bias due to a (possibly unobserved) covariate that is associated with both vaccination and the probability of the outcome of interest and (b) bias resulting from the effect of vaccination on the probability of seeking care. Our results indicate that (a) VE estimates may suffer from substantial confounding bias when a confounder has a different effect on the probabilities of influenza and non-influenza ARI, and (b) when vaccination reduces the probability of seeking care against influenza ARI, then estimates of VE against MAI may be unbiased while estimates of VE against SI may be have a substantial positive bias.

1. Introduction

The test negative design (TND) has become the most commonly used study design for estimating the effectiveness of vaccines against influenza and other infectious diseases [1–9]. The influenza TND is a prospective study design where patients with symptoms of acute respiratory illness (ARI) seeking medical care are tested for influenza infection. Those who test positive are classified as cases of medically-attended influenza (MAI), while ARI patients testing negative serve as controls. The influenza vaccine effectiveness (VE) is then estimated as one minus the odds ratio (OR) in the 2×2 table cross-classifying vaccination and case/control status. Several publications discuss the bias of VE estimates from TND studies [2,10–15]; however, they do not provide numerical evaluations of the magnitude and direction of the bias under realistic conditions.

We present a simple numerical method to evaluate the bias of a TND-based estimate of influenza VE. This method is based on a probability model [16] where the probabilities of being vaccinated, contracting influenza or non-influenza ARI, and seeking care for ARI depend on a (possibly unobserved) covariate. In our earlier paper [16] we found that in some cases, the bias of the VE estimates depends on the outcome against which the vaccine is supposed to protect. VE estimates from TND studies are usually interpreted as estimates of the effectiveness of the influenza vaccine against *medically-attended influenza* (MAI), defined as influenza illness resulting in medical consultation. We believe that from a broader public health perspective it may be also important to estimate VE against *symptomatic influenza* (SI) i.e., against *any* influenza illness. Evaluating VE against SI is important as influenza patients who do not seek medical care are still capable of infecting others, missing work or school, and developing severe complications. In addition, lay persons may misinterpret the estimated VE against MAI as VE against SI. We will see that under certain circumstances, TND studies may provide unbiased estimates of VE against MAI while substantially overestimating VE against SI.

In this work, we focus on two sources of bias: (a) confounding bias, resulting from the presence of a (possibly unobserved) covariate that is related to both the probability of being vaccinated and the probability of experiencing the outcome of interest, and (b) bias resulting from the fact that the vaccination may modify the probability of seeking medical care against influenza ARI, because

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vaccinated influenza patients may have less severe symptoms compared to unvaccinated patients. We will examine the magnitude and direction of each of these sources of bias.

2. Methods

We assume that every member of the study population is assigned a dichotomous unobserved covariate representing her/his health awareness. In other words, each person is classified as having either a 'higher' or a 'lower' health awareness. Individuals who are more concerned about their health are more likely to be vaccinated and to seek medical care when they develop ARI symptoms. The probabilities of being vaccinated, contracting influenza and non-influenza ARI, and seeking medical care may depend on this covariate. Hence, our method allows us to examine the effects of non-random vaccination where the probability of being vaccinated depends on an unobserved covariate. Since a person's health awareness cannot be easily determined, we assume that it may be difficult to adjust the VE estimate for this potential confounder.

As we want to focus on the two types of bias mentioned in the Introduction we make a few simplifying assumptions to eliminate other potential sources of bias:

- Vaccination does not affect the probability of contracting non-influenza ARI. This is a basic assumption for the validity of the TND [15].
- Every ARI patient seeking medical care is tested for influenza infection.
- The test has perfect sensitivity and specificity, and vaccination status is determined without an error.

Our model [16] allows a person to have an influenza and a non-influenza ARI at the same time, however, we only consider their influenza ARI in this case. The model does not incorporate time, thus a person who has repeated infections may be included more than once. Fig. 1 shows a diagram of our probability model.

First, we present the *baseline scenario* and use it to illustrate the proposed method for calculating bias of VE estimates. In this baseline scenario, the two types of bias mentioned above are absent.

- Without loss of generality we assume that 50% of the population have a higher health awareness.
- The probabilities of being vaccinated are 80% and 40% for persons with higher and lower health awareness, respectively. Hence, the overall vaccination coverage is 60%.
- Based on results from 14 randomized clinical trials [11], the average probability of contracting a non-influenza ARI is 0.084 regardless of vaccination status and health awareness. The average probability of influenza ARI among unvaccinated persons is 0.027.
- We assume that the effectiveness of the vaccine is 50%, hence the probability of influenza ARI among vaccinees is 0.0135.
- Studies found that probabilities of seeking medical care for ARI vary between 0.2 and 0.6. Therefore, we set these probabilities to 0.2 and 0.4 in non-influenza ARI patients with lower and higher health awareness, respectively. We assume that influenza ARI patients are more likely to seek care than non-influenza ARI patients, therefore we set the corresponding probabilities in influenza ARI patients with lower and higher health awareness to 0.3 and 0.6, respectively.

Tables 1 and 2 present our assumptions and the values we assign to various probabilities in general and under the baseline scenario.

The bias of an estimate is defined as the difference between the observed value of the estimate and the true parameter of interest. Therefore, we must determine the true values of VE against SI and MAI. Since the true VE is calculated under the assumption of *random vaccination*, we assume the probability of being vaccinated does not depend on a person's health awareness. The common value of the probability of vaccination is 0.6, as 60% of the population received the vaccine. The risks of SI in non-vaccinees and vaccinees are 0.027 and 0.0135, respectively (as one would expect from probabilities of influenza ARI used in these calculations). The *true* VE against SI is, therefore, $1 - RR = 1 - 0.5 = 0.5$, or 50%. The risks of MAI in non-vaccinees and vaccinees are 0.0243 and 0.01215, respectively. Therefore, the *true* VE against MAI is also $1 - 0.5 = 0.5$, or 50%. We obtain the estimated VE from the proportions of cases of SI and MAI among vaccinated and unvaccinated person within the population. We present the expected number of influenza and non-influenza ARI patients by health awareness and vaccination status in a hypothetical population of size 100,000 under the *baseline scenario* in Appendix.

Table 1
Model assumptions made throughout the entire article and additional assumptions made for the baseline scenario.

Situation	Assumption
Entire article	Every member of the study population is classified as having either high or low health awareness The probabilities of being vaccinated, contracting influenza and non-influenza ARI, and seeking medical care may be associated with health awareness The probability of non-influenza ARI does not depend on vaccination status Every ARI patient seeking medical care is tested for influenza infection The test for influenza infection has perfect sensitivity and specificity. Vaccination status is determined without error The probability of contracting a non-influenza ARI does not depend on vaccination status and health awareness
Additional for baseline scenario	The probability of influenza ARI does not depend on health awareness The probability of seeking medical care does not depend on vaccination status

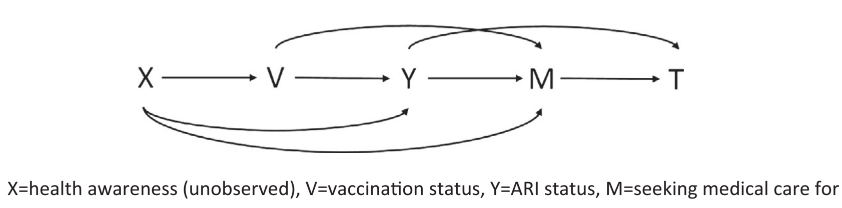

Fig. 1. Directed acyclic graph of influenza vaccine studies with a covariate. X = health awareness (unobserved), V = vaccination status, Y = ARI status, M = seeking medical care for ARI, T = influenza test result.

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