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The impact of selection bias on vaccine effectiveness estimates from test-negative studies

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ABSTRACT

Introduction: Estimates of vaccine effectiveness (VE) from test-negative studies may be subject to selection bias. In the context of influenza VE, we used simulations to identify situations in which meaningful selection bias can occur. We also analyzed observational study data for evidence of selection bias.
Methods: For the simulation study, we defined a hypothetical population whose members are at risk for acute respiratory illness (ARI) due to influenza and other pathogens. An unmeasured "healthcare seeking proclivity" affects both probability of vaccination and probability of seeking care for an ARI. We varied the direction and magnitude of these effects and identified situations where meaningful bias occurred. For the observational study, we reanalyzed data from the United States Influenza VE Network, an ongoing test-negative study. We compared "bias-naïve" VE estimates to bias-adjusted estimates, which used data from the source populations to correct for sampling bias.
Results: In the simulation study, an unmeasured care-seeking proclivity could create selection bias if persons with influenza ARI were more (or less) likely to seek care than persons with non-influenza ARI. However, selection bias was only meaningful when rates of care seeking between influenza ARI and non-influenza ARI were very different. In the observational study, the bias-naïve VE estimate of 55% (95% CI, 47-–62%) was trivially different from the bias-adjusted VE estimate of 57% (95% CI, 49-–63%).
Conclusions: In combination, these studies suggest that while selection bias is possible in test-negative VE studies, this bias in unlikely to be meaningful under conditions likely to be encountered in practice. Researchers and public health officials can continue to rely on VE estimates from test-negative studies.

1. Introduction

Observational studies of vaccine effectiveness (VE) are increasingly using the test-negative design [1]. In this design, eligible subjects are any patients who seek care for a defined clinical syndrome; in the case of influenza vaccine, this would be acute respiratory illness (ARI) or influenza-like illness (ILI). All enrolled subjects are tested for the pathogen of interest, and VE is estimated as one minus the ratio of the odds of vaccination among those testing positive to the odds among those testing negative. Although the test-negative design was first introduced in 1980 for estimating pneumococcal vaccine effectiveness [2], it did not see meaningful use until it began to be applied to observational studies of influenza vaccination in 2005 [3]. Since then, this design has become the standard approach for estimating influenza VE [4–6], and has been applied to rotavirus and cholera vaccines as well [7,8].

With the growing popularity of this design, research has increasingly focused on understanding the properties and potential biases of test-negative studies [9]. Recent studies have tested the underlying assumptions of the design [10–12], validated the design against randomized controlled trials [13], and evaluated the impact of information biases such as imperfect test sensitivity [14]. However, the potential impact of selection bias in this context has received little attention. Selection bias occurs when the association between vaccine and disease in the study subjects is different from the association in the full population [15]. For example, selection bias can arise in cohort studies through differential loss to follow-up between exposed and unexposed subjects, or in case-control studies through inappropriate selection of controls. Test-negative studies of influenza vaccines restrict the study population to persons seeking care for an ARI. Seeking care for ARI depends both on having an ARI and on factors that affect

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healthcare seeking behavior, such as socioeconomic status and insurance coverage. As pointed out by Sullivan and colleagues, conditioning (by restriction) on whether one seeks care for an ARI can induce selection bias [16].

While selection bias is theoretically possible in test-negative studies, the magnitude of this bias in practice is unclear. In this paper, we use simulations to quantify the magnitude of selection bias under a wide range of assumptions about the underlying associations between care-seeking behavior, influenza risk, and vaccination. We then look for evidence of selection bias in observational data where the full source population at-risk (from which the test-negative sample is drawn) is available to (1) estimate the probability of selection into a test-negative study using measured covariates and (2) use this information to correct VE estimates for potential selection bias. Specifically, we re-analyze data from Kaiser Permanente Washington (KP WA), one of the five sites in the United States Influenza Vaccine Effectiveness (US Flu VE) Network [5,17,18]. We compared naïve VE estimates using a test-negative design with estimates that account for selection bias using inverse probability of selection weighting (IPSW).

2. Methods

2.1. Simulation study

We simulated a series of test-negative influenza VE studies, with relevant variables defined by a directed acyclic graph (Fig. 1). We simulated a population of individuals who are stratified according to three binary variables: receipt of influenza vaccine prior to the start of influenza season (V); presence of some confounder (C) that can alter the probability of vaccination and the risk of ARI due to influenza and due to other pathogens; and some inherent care-seeking proclivity (X). Care-seeking proclivity may increase the probability of vaccination and the probability of seeking care among individuals who develop an ARI. The log odds of vaccination are:

$$logit(V = 1) = logit(\alpha_V) + \beta C + \gamma X$$

where α_V is the log odds of vaccination when C = 0 and X = 0 (Table 1). We assume that C and X do not have any (multiplicative) interaction on V.

In this population, individuals may experience ARI due to influenza (D) or ARI due to other respiratory viruses (O) at rates λ_D and λ_O, respectively. Rates of ARI due to either cause may be affected by confounder C, and the rate of influenza ARI (but not non-influenza ARI) may be affected by vaccination V. The mean rate of influenza ARI is:

$$log(\lambda_D) = \log(\mu_D) + \delta C + \theta V$$

where μ_D is the mean rate of D when C = 0 and V = 0, δ is the log rate ratio associated with C = 1, and θ is the log rate ratio associated with vaccination (i.e., 1-VE). The corresponding rate of ARI due to other respiratory viruses is:

$$log(\lambda_O) = \log(\mu_O) + \delta C$$

Individuals who develop ARI due to either cause may seek care (S) and be sampled into the test-negative study population; only individuals who develop ARI seek care. Among those with influenza ARI, the log odds of seeking care are:

$$logit(S = 1) = logit(\sigma) + \rho X$$

and the log odds among those with ARI due to other respiratory viruses are:

$$logit(S = 1) = logit(\varphi) + \rho X$$

where ρ is the log odds of seeking care when X = 1, and σ and φ is the probabilities of seeking care when X = 0 for influenza ARI and non-influenza ARI, respectively. Individuals enrolled in the test-negative study are tested for influenza (T).

To focus these simulations on selection bias, we assume there is no information bias (e.g., we assume perfect ascertainment of exposure and outcome in all study subjects). Coupled with the assumption that vaccine does not affect influenza severity among those infected, seeking care for influenza ARI is synonymous with a positive laboratory test for influenza (T), and estimated VE against medically attended influenza is equivalent to VE against influenza disease (D) in our simulations. We also assume that X is not a cause of D or O, other than through V, i.e., that X is not a confounder. Whether this is realistic in practice is uncertain, but this assumption separates the potential for selection bias from confounding due to X.

This simulation involves 12 parameters (Table 1). We fixed values of seven parameters based on prior outpatient studies of influenza VE and prior simulation studies [5,14,18]. For the remaining parameters, we ran separate simulations across combinations of the listed values (Table 1) of: (a) the prevalence of care-seeking proclivity (α_X); (b) the association between care-seeking proclivity and actual care-seeking (ρ); (c) the association between care-seeking proclivity and vaccination (γ); and (d) the probabilities that a person with ARI would seek care (σ for influenza ARI, φ

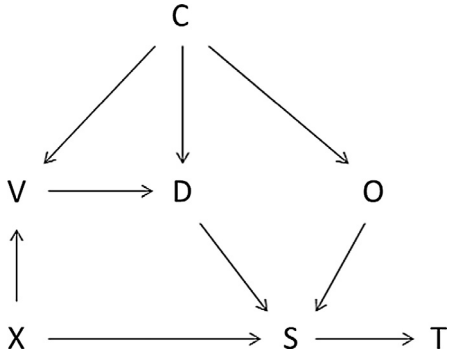

Fig. 1. Directed acyclic graph illustrating associations between variables in simulation models. *Footnote:* C, confounder; V, influenza vaccination; D, acute respiratory illness due to influenza; O, acute respiratory illness due to non-influenza pathogen; X, care-seeking proclivity; S, seeking care for acute respiratory illness; T, testing for influenza.

Table 1
Parameters used in simulation model.

Parameter	Symbol	Value (s)
Prevalence of confounder C	α_C	0.3
Prevalence of care-seeking proclivity X	α_X	0.1, 0.25, 0.333, 0.5, 0.75, 0.9
Prevalence of vaccination V, when C = 0 and X = 0	α_V	0.4
Odds ratio for V from C	exp(β)	2
Odds ratio for V from X	exp(γ)	0.1, 0.25, 0.5, 1, 2, 4, 10
Rate influenza ARI (D), when C = 0 and V = 0	μ_D	0.1522/year (approximate risk, 0.05 per influenza season)
Rate of non-influenza ARI (O), when C = 0 and V = 0	μ_O	0.4566 (approximate risk, 0.15 per influenza season)
Rate ratio for D and O from C	exp(δ)	2
Rate ratio for D from V	exp(θ)	0.5 (i.e., 50% VE)
Probability of sampling S, when O = 1 and X = 0	φ	0.25, 0.3
Probability of sampling S, when D = 1 and X = 0	σ	0.3, 0.33, 0.6
Odds ratio for S from X	exp(ρ)	0.1, 0.25, 0.5, 1, 2, 4, 10

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