Bias of Influenza Vaccine Effectiveness Estimates from Case-Control Studies

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Introduction

- Influenza vaccination is required each year due to
  - Changes in the influenza virus (antigenic drift)
  - Waning immunity from vaccination
- A new influenza vaccine is produced and vaccine effectiveness (VE) must be estimated annually.
- Placebo-controlled randomized clinical trials (RCT) can no longer be used to assess influenza VE in the USA and many other populations.
- Observational studies are used to obtain annual VE estimates.

Objective

Compare bias of influenza VE estimates from test-negative (TN) and traditional case-control (TCC) studies.

- TN cases/controls are individuals with acute respiratory illness (ARI) who seek medical care and test positive/negative for influenza.
- TCC cases are the same as in a TN study, while controls are individuals who never developed an ARI.

Outcomes of Interest

- ***Symptomatic influenza (SI)*** **– influenza infection resulting in an ARI**
- ***Medically-attended influenza (MAI)*** **– influenza infection resulting in an ARI for which a person seeks medical care**

- TN and TCC studies provide estimates of VE against MAI.
- We also evaluate the bias of VE estimates against SI as the public may interpret VE against MAI as VE against *any* influenza illness, i.e., against SI.

Abbreviations

ARI	Acute respiratory illness	**SI**	Symptomatic influenza
FARI	Influenza ARI	**TN**	Test-negative
MAI	Medically-attended influenza	**TCC**	Traditional case-control
NFARI	Non-influenza ARI	**VE**	Vaccine effectiveness

Aims

1. Develop a dynamic probability model that incorporates:
   - Two covariates (health status and health awareness)
   - A time component (measured in weeks) to allow the
     - intensities of FARI and NFARI to change over time
     - possibility of developing more than one ARI during the study
2. Use the model to compare bias of VE estimates against two outcomes of interest from two case-control study designs

Assumptions

a) A person may only be vaccinated prior to the study and vaccination is determined without error.
b) A person can only have one FARI during the season.
c) A person can have at most one NFARI per week.
d) The probabilities of FARI and NFARI do not depend on a person's health awareness given his/her health status.
e) Every person who seeks medical care for ARI is tested for influenza infection. Test has 100% sensitivity and specificity.

Model

The model consists of five steps

Step 1: Covariates

We assume people within the study population can be classified with respect to

- *health status* (X) of "healthy" (X=1) or "frail" (X=0)
- *health awareness* (U) of "high" (U=1) or "low" (U=0)

Step 2: Vaccination

We consider the vaccination scenario where everyone who is vaccinated (V=1) becomes effectively vaccinated prior to the study.

Step 3: Influenza and non-influenza ARI

During the study,

- A person may become infected with influenza and develop FARI and/or develop one or more NFARIs.
- Y_j is the illness/infection status in week j, where

$$Y_j = \begin{cases} 0, & \text{no ARI in week j} \\ 1, & \text{NFARI in week j} \\ 2, & \text{FARI in week j} \end{cases}$$

Step 4: Seeking medical care for ARI

A person with ARI in week j may seek care (M_j):

- M_j =1 for a person who sought care for ARI in week j.

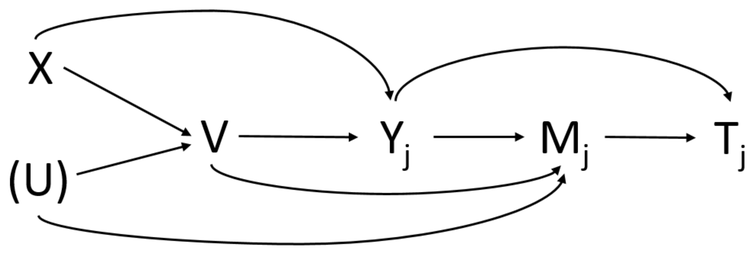
Step 5: Testing for influenza infection

A person who seeks medical care for ARI in week j is tested for influenza infection (T_j):

- T_j =1 for an influenza positive test result.

Model (continued)

Figure 1. Directed acyclic graph (DAG) of our model



X=health status, (U)=health awareness (unobserved), V=vaccination status, Y_j = ARI status in week j, M_j = seeking medical care for ARI in week j, and T_j = influenza test result in week j.

True VE

True VE against SI

$$VE_{TSI} = 1 - RR_{TSI}, \text{ where } RR_{TSI} = \frac{P(\text{classified as SI} \mid V=1)}{P(\text{classified as SI} \mid V=0)}$$

- True VE is calculated under random vaccination (i.e., vaccination does not depend on health status or health awareness.
- A person is considered a true case of SI if s/he develops an ARI as a result of influenza infection.

True VE against MAI

$$VE_{TMAI} = 1 - RR_{TMAI}, \text{ where } RR_{TMAI} = \frac{P(\text{classified as MAI} \mid V=1)}{P(\text{classified as } MAI \mid V=0)}$$

- A person is considered a true case of MAI in week j if s/he develops an ARI as a result of influenza infection and seeks medical care for her/his ARI in that week.
- A person is classified as MAI if s/he is considered a true case of MAI in at least one week of the study.

Estimated VE

- The same case definition is used in both study designs.
- A person is considered a case in week j if they:
  - did not seek medical care for ARI prior to week j ($M_{(j-1)} = 0$)
  - seek medical care for their ARI in week j ($M_j = 1$)
  - test positive for influenza infection in week j ($T_j = 1$)
- A person is considered a TN control in week j if they:
  - did not seek medical care for ARI prior to week j ($M_{(j-1)} = 0$)
  - seek medical care for their ARI in week j ($M_j = 1$)
  - test negative for influenza infection in week j ($T_j = 0$)
- A person is considered a TCC control if they did not have an ARI during the entire study ($Y_J = 0$)

- VE is estimated as

$$\widehat{VE} = 1 - OR,$$

where OR is the odds ratio in the 2x2 table cross-classifying case/control by vaccination status.

- Estimated VE is the same regardless of the outcome of interest.

Calculations and Simulations

- Bias was calculated as the difference between estimated and true VE using the expressions derived from our model.
- We used a simulation study to validate our calculated results.
  - 1000 simulations, N=30,000, and the same parameter values used in the calculations.

Sources of Bias

Source of Bias	Description
A	Vaccination affects probability of non-influenza ARI
B1	Healthy persons have a lower probability of non-influenza ARI
B2	Healthy persons have a lower probability of influenza ARI
BS	Healthy persons have lower probabilities of influenza and non-influenza ARI. Health status has the same effect on the probabilities of both types of ARI
C	Vaccination lowers the probability of seeking medical care in influenza ARI patients (because of reduced symptoms' severity)
D	ARI patients with high health awareness have a higher probability of seeking medical care

Probability Ratios Corresponding to Sources of Bias

PR	Definition	Range	Bias
PR_A	P(NFARI | Vacc) / P(NFARI | Unvacc)	0.5 – 2.0	A
PR_B1	P(NFARI | Frail) / P(NFARI | Healthy)	1.0 – 2.0	B1
PR_B2	P(FARI | Frail) / P(FARI | Healthy)	1.0 – 2.0	B2
PR_BS	Common value of PR_B1 and PR_B2	1.0 – 2.0	BS
PR_C	P(SMC | FARI, Vacc) / P(SMC | FARI,Unvacc)	0.5 – 1.0	C
PR_D	P(SMC| Low HA) / P(SMC | High HA)	0.5 – 1.0	D

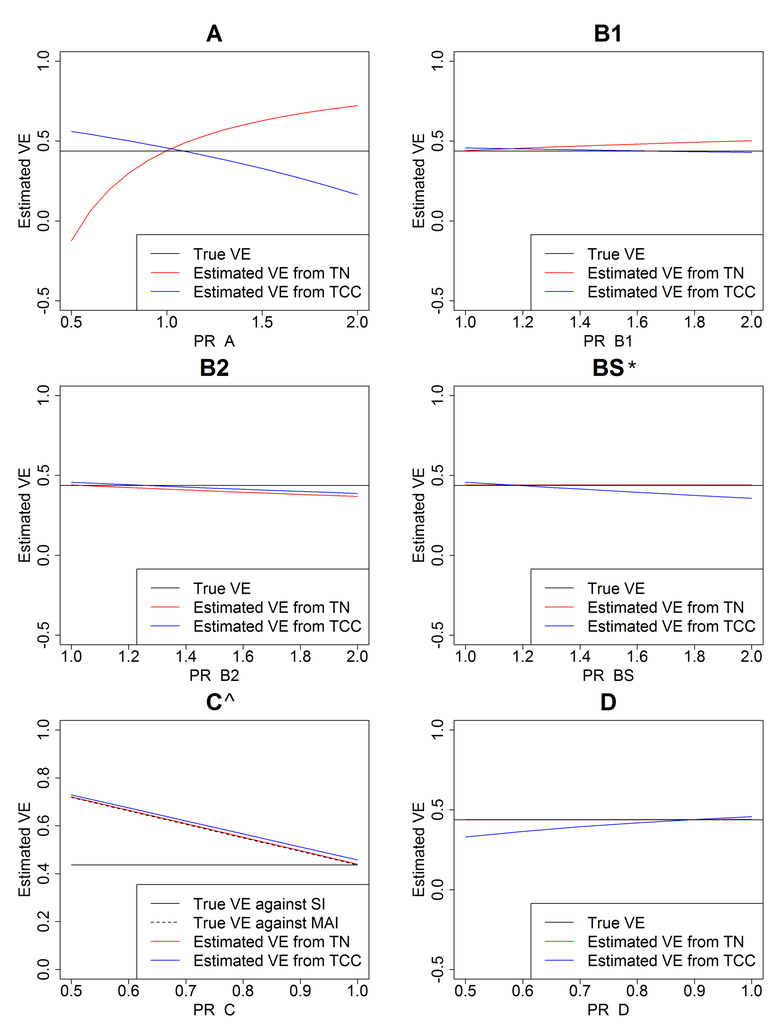
P = Probability, PR = Probability ratio, Vacc = Vaccinated, Unvacc = Unvaccinated, FARI = Influenza ARI, NFARI = Non-influenza ARI, HA = Health awareness, SMC = Seeking medical care

Results

Source of Bias	Test-Negative Range of Bias	Traditional Case-Control Range of Bias
None	(0.00, 0.00)	(0.02, 0.02)
A	(-0.56, 0.29)	(-0.27, 0.12)
B1	(0.00, 0.07)	(-0.01, 0.02)
B2	(-0.07, 0.00)	(-0.05, 0.02)
BS	(0.00, 0.00)	(-0.08, 0.02)
C (VE against SI)	(0.00, 0.28)	(0.02, 0.29)
C (VE against MAI)	(0.00, 0.00)	(0.01, 0.02)
D	(0.00, 0.00)	(-0.11, 0.02)

- Little or no bias (maximum absolute bias less than 0.05)
- Moderate bias (maximum absolute bias greater than or equal to 0.05 and less than 0.10)
- Substantial bias (maximum absolute bias greater than or equal to 0.10 and less than 0.20)
- Severe bias (maximum absolute bias 0.20 or more)

Figure 2. Plot of VE estimates from TN and TCC studies compared to true VE for each source of bias



* Under source of bias BS, the TN-based estimate is equal to the true VE.
^ Under source of bias C, the TN-based estimate is equal to the true VE against MAI.

Interpretation

- A: VE estimates from both studies may be severely biased.
- B1: The TCC-based estimate has very little bias.
- B2: The VE estimates from both study designs have similarly small bias.
- BS: The TN-based estimate has very little bias.
- C: Estimates of VE against MAI have little or no bias, but estimates of VE against SI may suffer from severe bias. True VE and bias depend on outcome of interest.
- D: TN-based estimate is less biased than TCC-based estimate.

Conclusions

- Estimates of influenza VE from case-control studies may suffer from severe bias, especially when the outcome of interest is SI.
- Bias of estimates may depend on the outcome of interest.
- When the outcome of interest is MAI then the TN study provides valid estimates of VE if:
  a) Vaccination does not affect the probability of NFARI
  b) Confounding variables have the same effect on the probabilities of FARI and NFARI
- When the outcome of interest is SI then the TN study provides valid estimates of VE if (a), (b), and the additional assumption (c) hold:
  c) Vaccination does not affect the probability of seeking care for NFARI
- If vaccination affects the probability of NFARI then the TCC may be preferred over the TN.

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Conflicts of Interest

The authors report no conflicts of interest.