Identifying vaccine effectiveness in a TND under an equi-confounding assumption

Christopher B. Boyer

Department of Epidemiology
Harvard TH Chan School of Public Health

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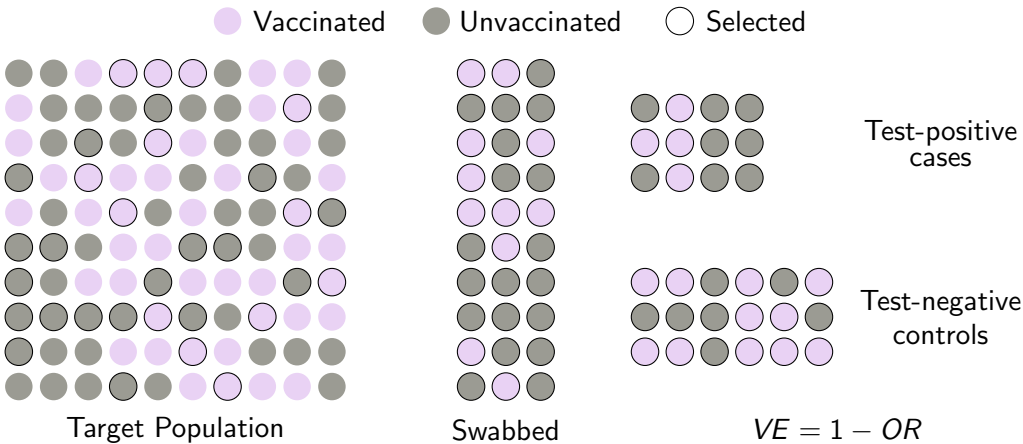
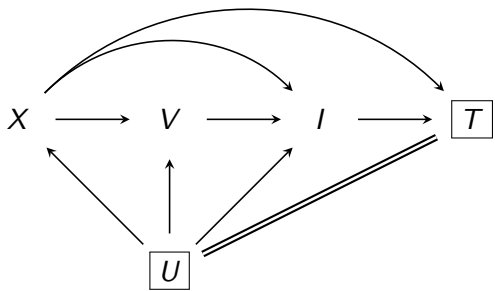
The test-negative design

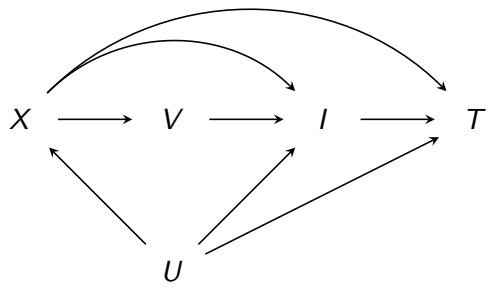
The test-negative design (TND) is frequently used to monitor the effectiveness of vaccines under real-world conditions.



Prior work



(a) Jackson and Nelson (2013) and Sullivan, Tchetgen Tchetgen, and Cowling (2016)



(b) Schnitzer (2022)

Setup

We define the following:

- X is vector of pre-vaccine covariates,
- V is vaccination status $(0/1)$,
- I is symptomatic illness where[1]

$$I := \begin{cases} I = 2 & \text{when symptomatic illness is caused by the pathogen of interest} \\ I = 1 & \text{when symptomatic illness is caused by something else} \\ I = 0 & \text{when no symptomatic illness} \end{cases}$$

- T is an indicator of receiving a test for the pathogen of interest $(0/1)$,
- I^* is the result of the test (assume perfect for now).

[1] This implies mutually exclusivity of test positive and test negative illnesses and was first suggested in Schnitzer (2022)

Estimand: causal risk ratio among the vaccinated

In a TND study, the causal estimand is the **marginal risk ratio**[2], i.e.

$$\Psi_{RR} := \frac{\Pr[I^1 = 2, T^1 = 1]}{\Pr[I^0 = 2, T^0 = 1]},$$

with $VE = 1 - RR$.

Here, we focus instead on the **risk ratio among the vaccinated**[3], i.e.

$$\Psi_{RRV} := \frac{\Pr[I^1 = 2, T^1 = 1 | V = 1]}{\Pr[I^0 = 2, T^0 = 1 | V = 1]}.$$

[2]The outcome $\mathbb{1}(I = 2, T = 1)$ is referred to as "medically-attended illness" in TND literature, e.g. Jackson and Nelson (2013).

[3]This parameter is similar to the average treatment effect on the treated (ATT) in the causal inference literature.

Identifiability conditions

(A1) **Consistency**. For all individuals i, we have $I_i^v = I_i$ and $T_i^v = T_i$ when $V_i = v$.

(A2) **No effect of vaccination on the test-negative outcome or selection among the vaccinated**. That is, $\Pr[I^0 = 1, T^0 = 1 | V = 1, X] = \Pr[I^1 = 1, T^1 = 1 | V = 1, X]$.

(A3) **Odds ratio equi-confounding**. That is,

$$OR_2(X) = OR_1(X),$$

$$\text{where } OR_i(X) := \frac{\Pr[I^0 = i, T^0 = 1 | V = 1, X] \Pr[I^0 = 0, T^0 = 1 | V = 0, X]}{\Pr[I^0 = 0, T^0 = 1 | V = 1, X] \Pr[I^0 = i, T^0 = 1 | V = 0, X]}.$$

(A4) **Overlap of vaccination among test-positives and test-negatives**. Define $\mathcal{S}_i(v)$ as the support of the law of $(I^v = i, T^v = 1, V = v, X)$ for $v \in \{0, 1\}$, then

$$\mathcal{S}_2(1) \subseteq \mathcal{S}_2(0) \text{ and } \mathcal{S}_2(v) \subseteq \mathcal{S}_1(v).$$

More on equi-confounding

By simple factorization, we can split A3 into[4]:

(A3a) **Odds ratio equi-confounding**.

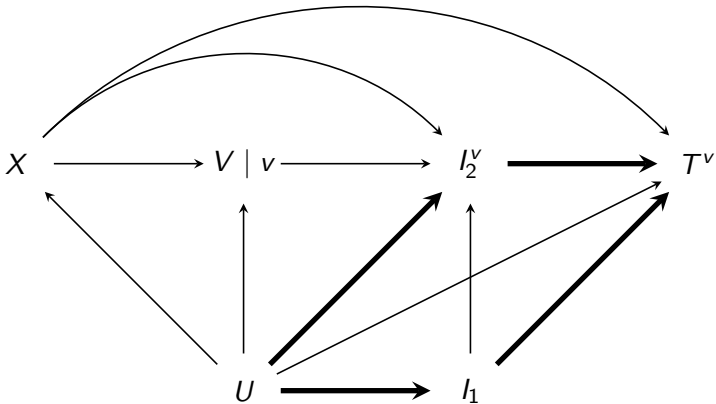
$$\frac{\Pr[I^0 = 2|V = 1, X]}{\Pr[I^0 = 2|V = 0, X]} = \frac{\Pr[I^0 = 1|V = 1, X]}{\Pr[I^0 = 1|V = 0, X]}.$$

(A3b) **Odds ratio equi-selection**.

$$\frac{\Pr[T^0 = 1|I^0 = 2, V = 1, X]}{\Pr[T^0 = 1|I^0 = 2, V = 0, X]} = \frac{\Pr[T^0 = 1|I^0 = 1, V = 1, X]}{\Pr[T^0 = 1|I^0 = 1, V = 0, X]}.$$

[4] A similar condition was discussed in Lewnard et al. (2018) for TND and Park and Tchetgen (2023) and Tchetgen, Park, and Richardson (2023b) for difference-in-differences designs.

Causal model



Result 1

Theorem

Under A1 - A4, $\Psi(X)$ is identified by

$$\Psi_{om}(X) := \frac{\Pr[I = 2, T = 1 | V = 1, X] / \Pr[I = 1, T = 1 | V = 1, X]}{\Pr[I = 2, T = 1 | V = 0, X] / \Pr[I = 1, T = 1 | V = 0, X]}$$

which is equivalent to the **difference-in-difference** operator for the outcomes $\mathbb{1}(I = 2, T = 1)$ and $\mathbb{1}(I = 1, T = 1)$ on the multiplicative scale.

Sketch of proof

Start with

$$\Psi_{RRV}(X) := \frac{\Pr[I^1 = 2,\, T^1 = 1 | V = 1, X]}{\Pr[I^0 = 2,\, T^0 = 1 | V = 1, X]}.$$

Multiply by $\frac{\Pr[I^0=2, T^0=1|V=0,X]}{\Pr[I^0=2, T^0=1|V=0,X]} = 1$. Under A1, we have that

$$\Psi_{RRV}(X) = \underbrace{\frac{\Pr[I = 2,\, T = 1 | V = 1, X]}{\Pr[I = 2,\, T = 1 | V = 0, X]}}_{\text{observed risk ratio}} \times \underbrace{\frac{\Pr[I^0 = 2,\, T^0 = 1 | V = 0, X]}{\Pr[I^0 = 2,\, T^0 = 1 | V = 1, X]}}_{\text{de-biasing term}}.$$

Sketch of proof (cont.)

Under A2 and A3, the de-biasing term is equivalent to

$$\frac{\Pr[I^0 = 2, T^0 = 1 | V = 0, X]}{\Pr[I^0 = 2, T^0 = 1 | V = 1, X]} = \frac{\Pr[I = 1, T = 1 | V = 0, X]}{\Pr[I = 1, T = 1 | V = 1, X]}$$

Therefore, we have that

$$\Psi_{RRV}(X) = \frac{\Pr[I = 2, T = 1 | V = 1, X] / \Pr[I = 1, T = 1 | V = 1, X]}{\Pr[I = 2, T = 1 | V = 0, X] / \Pr[I = 1, T = 1 | V = 0, X]}$$

Result 2

Theorem

Under selection $S = \mathbb{1}(I \neq 0, T = 1)$, $\Psi_{om}(X)$ is equivalent to

$$\Psi^*_{om}(X) = \frac{\Pr[I^* = 1 | S = 1, V = 1, X] / \Pr[I^* = 0 | S = 1, V = 1, X]}{\Pr[I^* = 1 | S = 1, V = 0, X] / \Pr[I^* = 0 | S = 1, V = 0, X]}$$

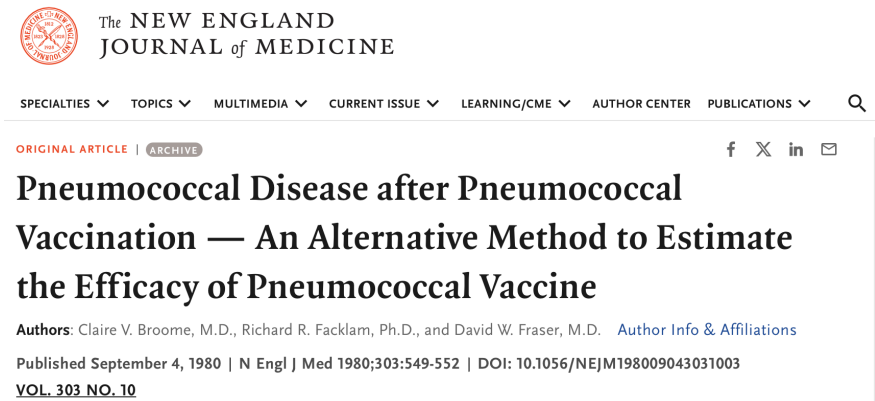
which is also equal to the conventional odds ratio estimated in a **logistic regression** of I^* on V and X.

Additional results

In the preprint, we additionally

- Derive estimators for Ψ_{RRV} based on outcome-modeling and inverse probability weighting.
- Derive estimator for Ψ_{RRV} based on efficient influence function that can be used with more flexible machine-learning estimators.
- Assess robustness to model misspecification and statistical properties of our estimators.
- Investigate finite sample performance of our estimators via simulation.
- Discuss violations of our assumptions.

What is the ideal test-negative illness?



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ORIGINAL ARTICLE | ARCHIVE

Pneumococcal Disease after Pneumococcal Vaccination — An Alternative Method to Estimate the Efficacy of Pneumococcal Vaccine

Authors: Claire V. Broome, M.D., Richard R. Facklam, Ph.D., and David W. Fraser, M.D. Author Info & Affiliations

Published September 4, 1980 | N Engl J Med 1980;303:549-552 | DOI: 10.1056/NEJM198009043031003

VOL. 303 NO. 10

Broome, Facklam, and Fraser (1980)

Other papers

- Schnitzer (2022)
- Jiang et al. (2023)
- Park and Tchetgen (2023)
- Tchetgen, Park, and Richardson (2023b)
- Tchetgen, Park, and Richardson (2023a)
- Li et al. (2023)

Collaborators
Kendrick (Qijun) Li

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Slide deck
`https://github.com/boyercb/presentations`

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