Selection Bias in COVID-19 Test Negative Design Studies

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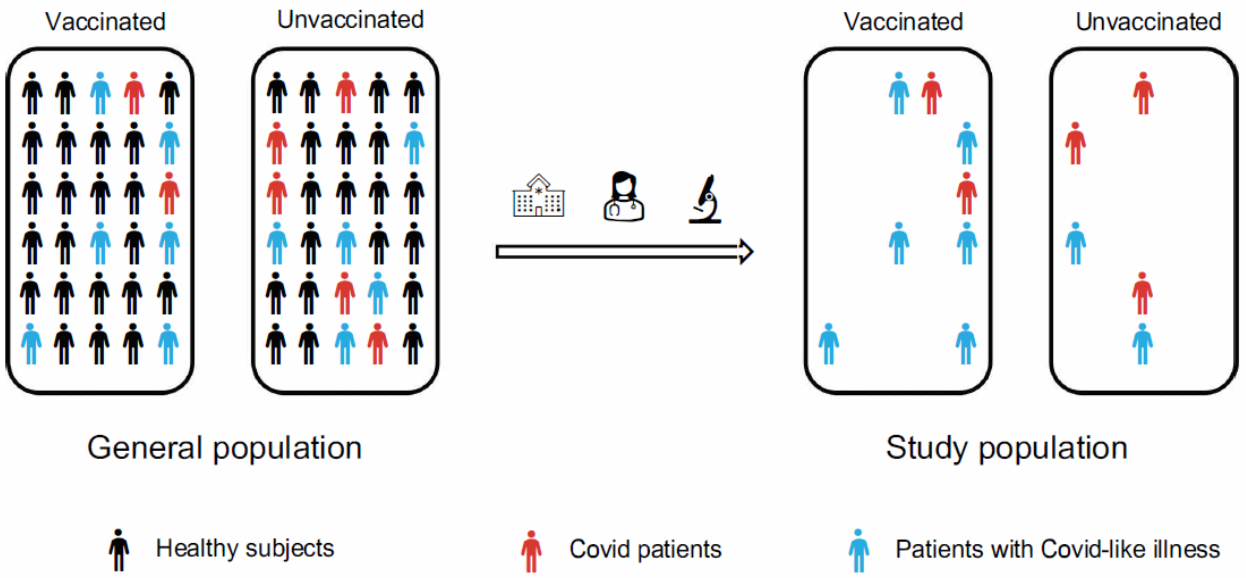
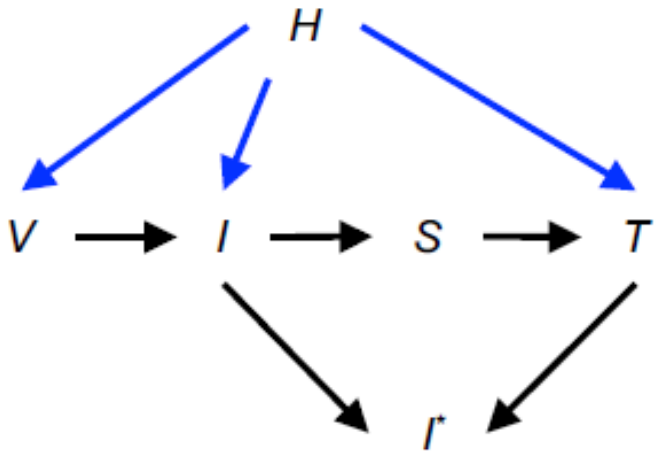
TND Study of vaccine effectiveness (Jackson and Nelson, Vaccine 2013)

- Ideal TND Study Sample : Patients who
  - Have Covid-like symptoms and as a result present at a healthcare facility to get tested.
  - Cases = test-positive, controls = test-negative
  - VE = 1 - risk ratio (risk in vaccinated / risk in unvaccinated) obtained via logistic regression



When does TND work (Jackson and Nelson, Vaccine 2013 Shi et al, AJE, 2023)

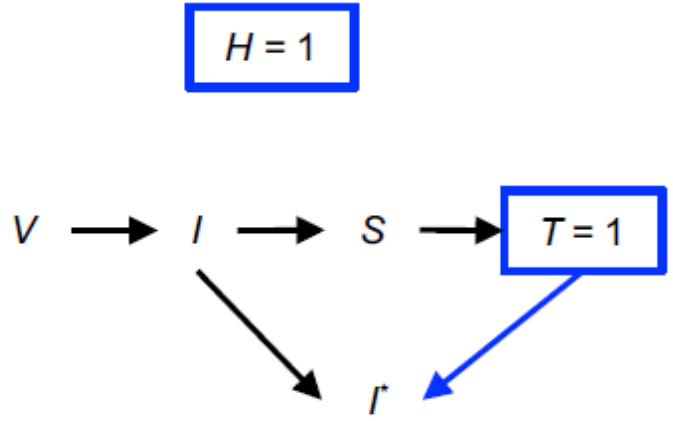
- The Directed Acyclic Graph (DAG) below illustrates the rationale justifying TND and encodes relationships between Vaccination (V), True infection Status (I), Observed infection status (I*), Symptoms (S), Testing (T), and Healthcare-Seeking behavior (H),



- Implicitly conditions on measured confounders: Age, Gender, Socioeconomic status.
- TND works to the extent that it reduces confounding by H by enrolling only individuals who test

When does TND work? (Jackson and Nelson, Vaccine 2013; Shi et al., AJE, 2023)

- More formally, TND makes three key assumptions:
  - Tested patients have the same healthcare-seeking behavior (H=1 if T=1);
  - V does not have a direct effect on testing (no V->T) ;
  - V does not have a direct effect on symptoms in test-positive sample (no V->S);

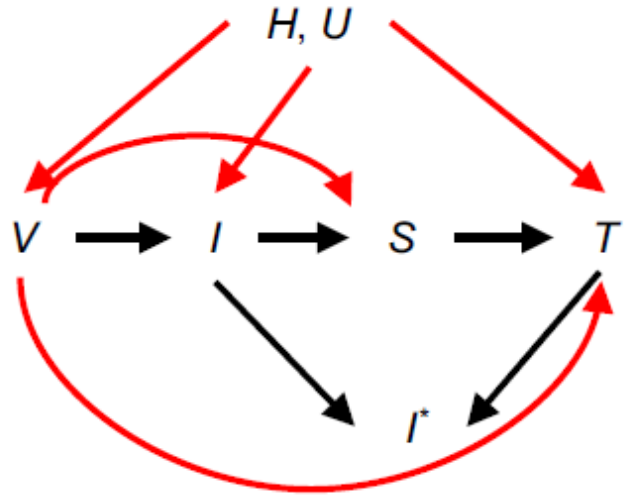


- Under these assumptions, vaccinated vs unvaccinated are comparable wrt H by design, yielding an unbiased VE estimate via logistic regression.

Challenges in TND studies (Shi et al., AJE, 2023; Sullivan et al., AJE, 2016)

- TND is susceptible to several potential sources of bias:
  - Confounding bias: there may be unmeasured common causes U of vaccination, COVID infection and testing, e.g. occupation as healthcare worker, educator, resident of care facility, previous infection, etc.

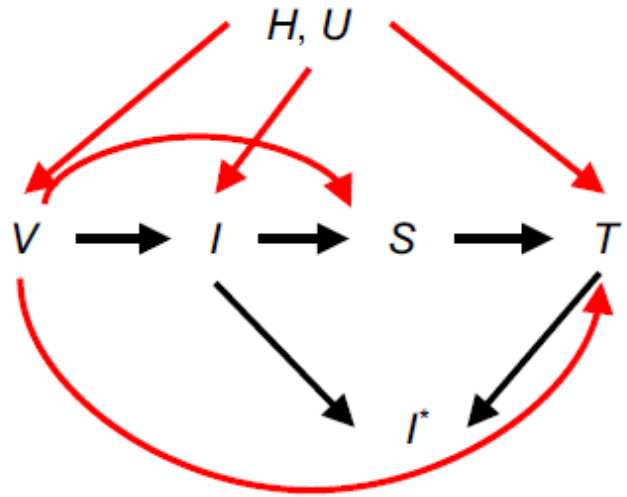
  - Assumption that tested patients have the same healthcare-seeking behavior is seldom realistic. HSB is likely on a spectrum and cannot be accounted for fully by conditioning on testing -> residual confounding by HSB



Challenges in TND studies (Shi et al, AJE, 2023; Sullivan et al, AJE, 2016)

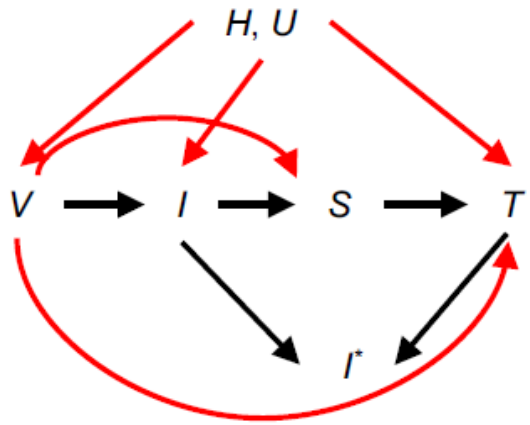
- TND sources of bias continued:
  - More importantly, conditioning on testing may induce a particularly insidious form of selection bias known as collider stratification bias along the pathway V->T<-S->I. Collider bias can be made worse if as likely the case, vaccination has direct effect not only on testing but also on symptoms.

  - Collider bias can render two factors that are independent in the population dependent in the TND sample.



Challenges in TND studies (Sullivan et al, AJE, 2016; Shi et al, AJE, 2023)

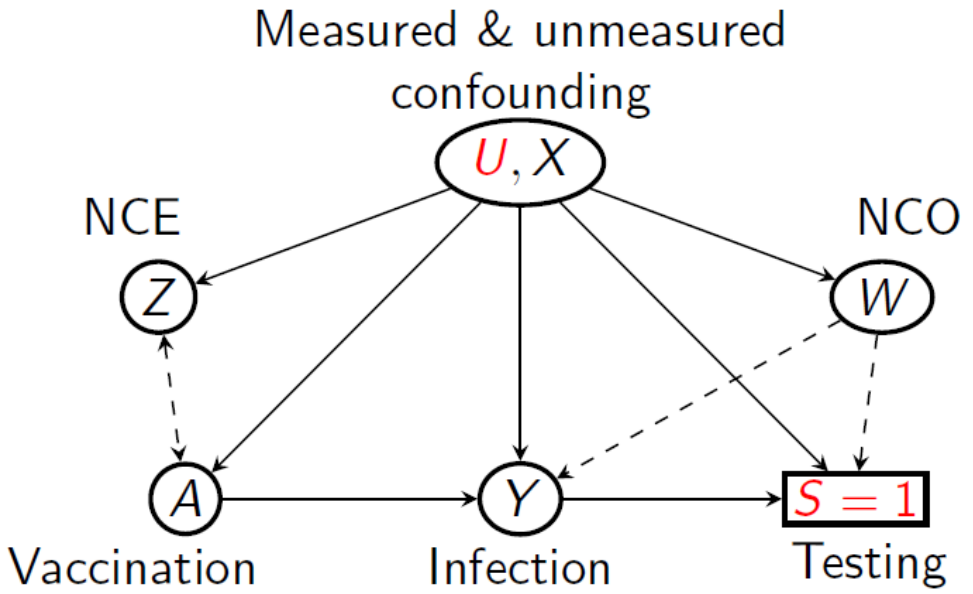
- TND sources of bias continued:
  - In fact, HSB are independent on S in the population, however both are positively associated with testing, then in TND sample HSB and S will be negatively correlated, that is, a person in the TND sample with low HSB is likely in the sample because they experience severe S. This, in turn, creates spurious association between V and I!
  - Furthermore, recent challenges that TND must face include widespread home testing and repeat testing which likely distort selection into TND studies.



Negative Controls for detecting and accounting for hidden selection Bias in TND

COVID-19 VE using data from UMich Health System

	Unvaccinated (N=12,672)	Vaccinated (N=39,591)
Vaccine types		
Pfizer-BioNTech	/	20,312 (51.3%)
Moderna	/	10,831 (27.4%)
J & J	/	1,409 (3.6%)
Other	/	7,039 (17.8%)
COVID-19 Infection	3,074 (24.2%)	2,774 (7.0%)
NCE: Immunization before Dec 2020	3,854 (30.4%)	18,167 (45.9%)
NCO conditions		
Arm/leg cellulitis	39 (0.3%)	161 (0.4%)
Eye/ear disorder	83 (0.6%)	518 (1.3%)
Acid reflux (GERD)	619 (4.9%)	3,188 (8.0%)
Atopic dermatitis	13 (0.1%)	41 (0.1%)
Injuries	1,033 (8.2%)	3,690 (9.3%)
General adult examination	752 (5.9%)	4,687 (11.8%)
No. of NCO conditions ≥ 1	2,258 (17.8%)	10,355 (26.2%)



	Negative control	Logistic regression (OR ≈ RR)
Pfizer-BioNTech	80.2% (78.3%, 81.9%)	74.1% (72.3%, 75.8%)
Moderna	89.7% (88.1%, 91.1%)	78.8% (76.8%, 80.7%)
Janssen (J & J)	65.8% (54.6%, 74.1%)	56.3% (48.4%, 62.9%)

Li, K.Q., Shi, X., Miao, W. and Tchetgen Tchetgen, E., 2023. Double negative control inference in test-negative design studies of vaccine effectiveness. Journal of the American Statistical Association, pp.1-12.

References

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