Selection Bias

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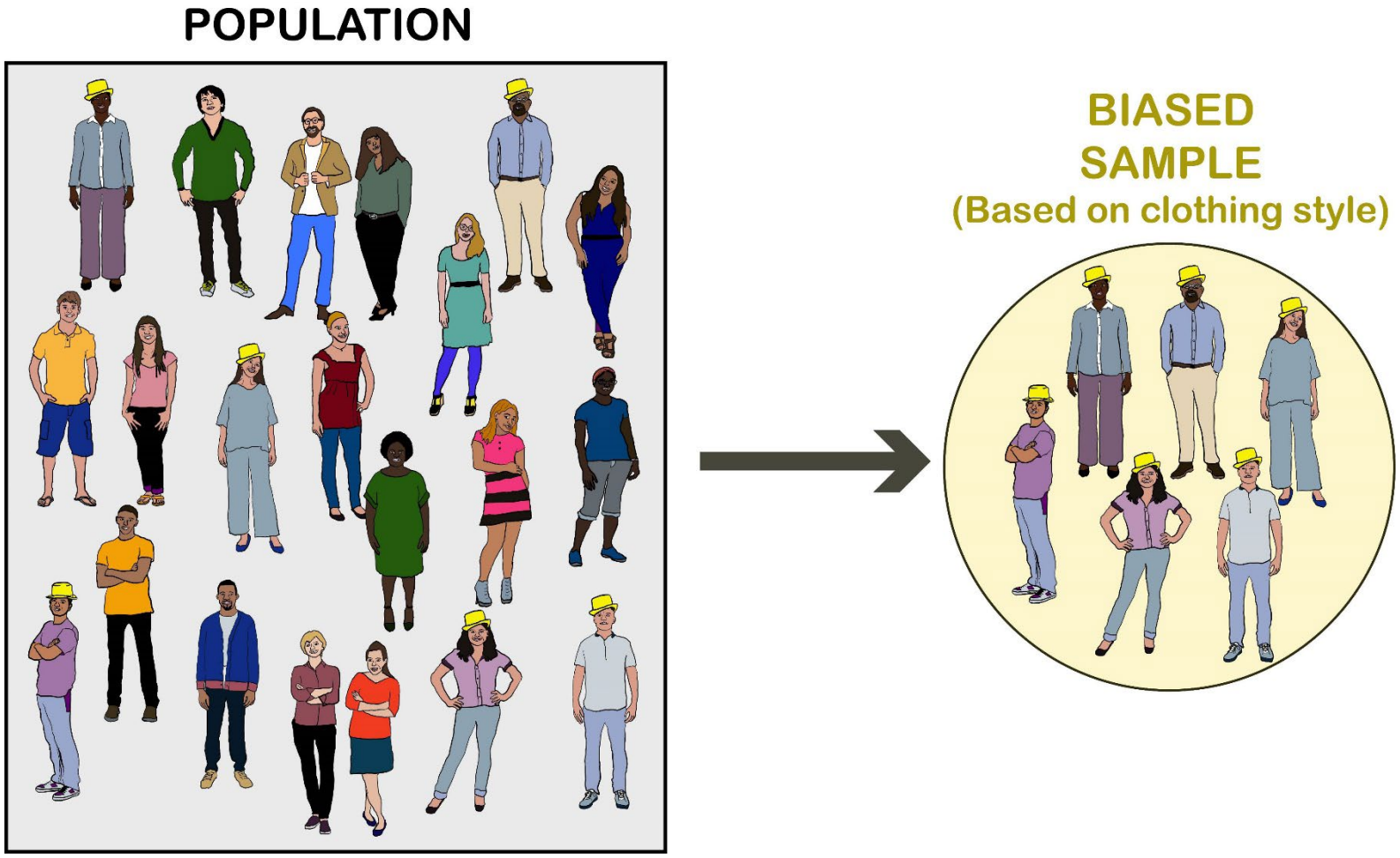
What is selection bias?

- A bias that is introduced when individuals selected into a study do not reflect the target population

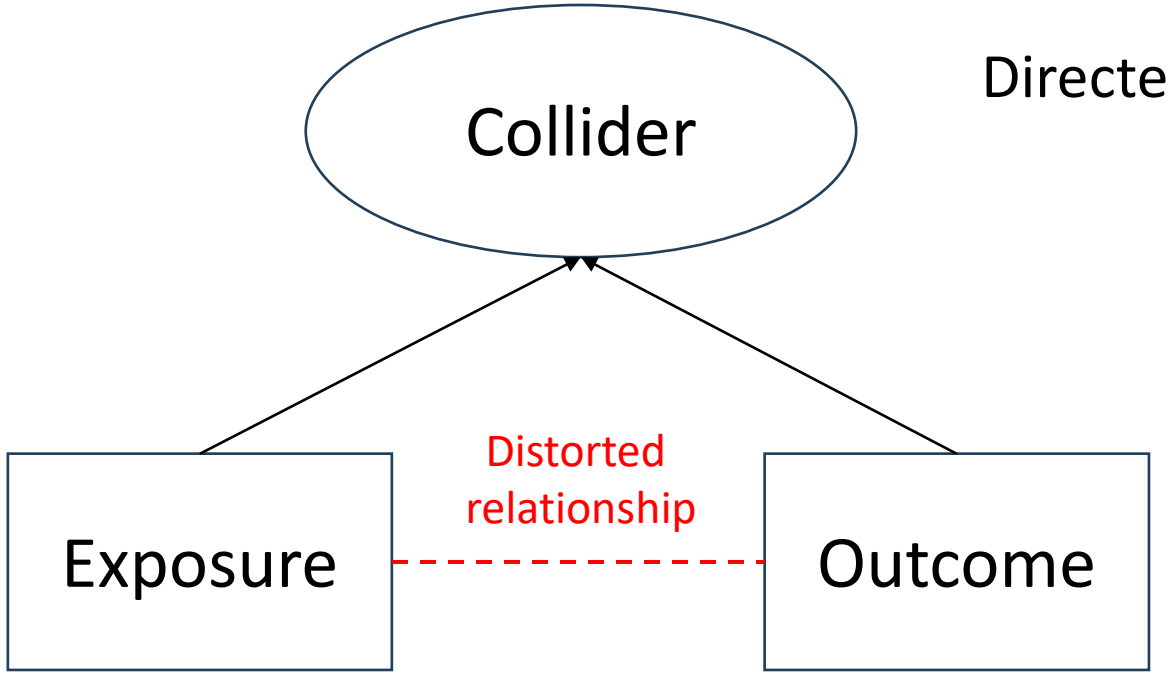


A consequence of selection bias

Can compromise internal validity

- Internal validity is where a study accurately measures the cause-and-effect relationship between an exposure and an outcome

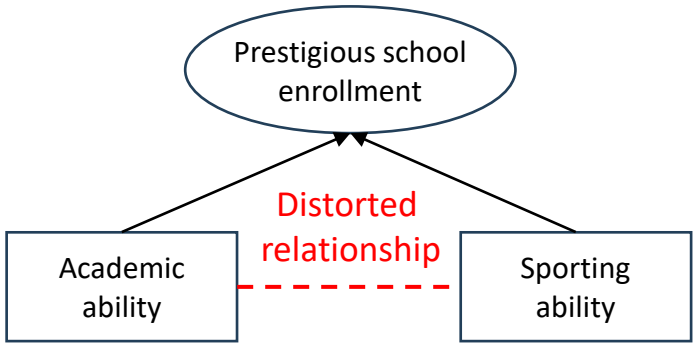
A selection bias can be a collider bias

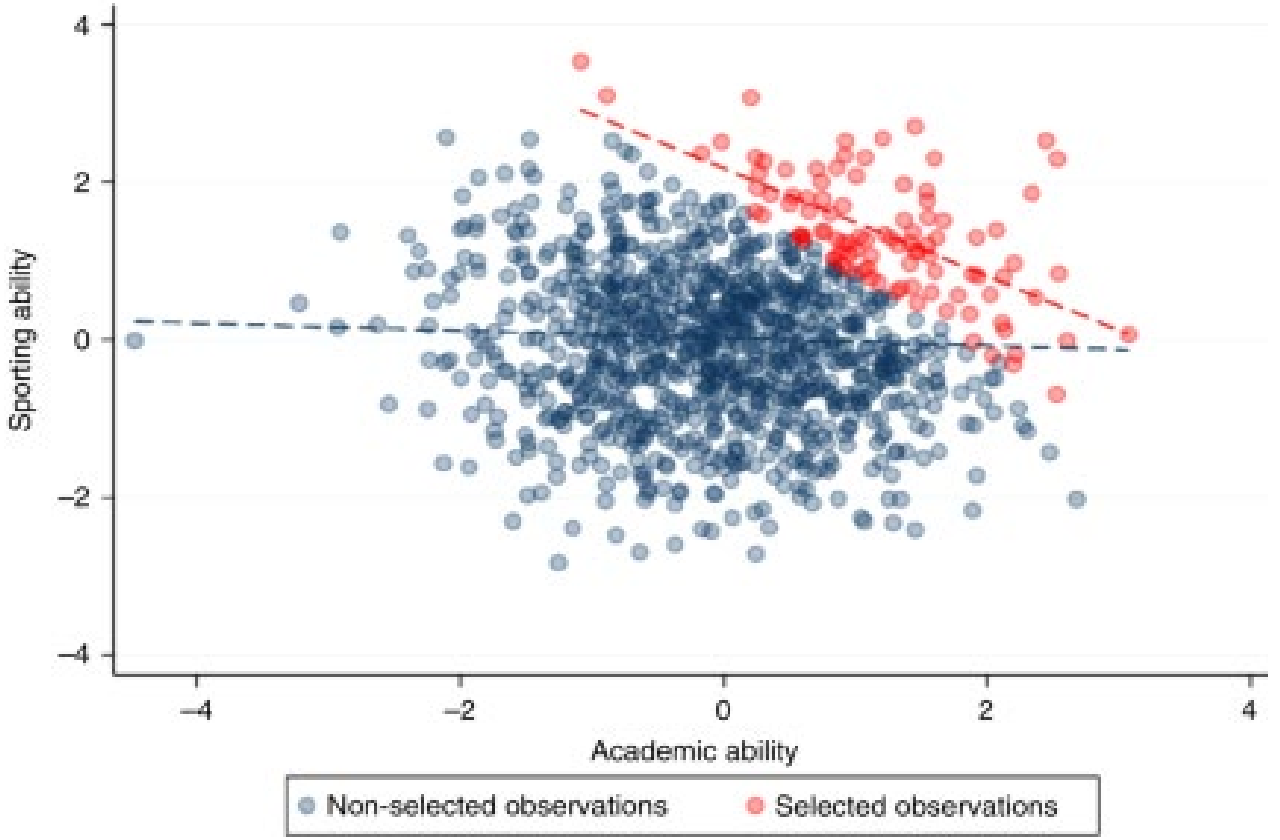


Directed Acyclic Graph (DAG)

Selecting for a collider that induces an association or distorts an association of interest is a selection bias

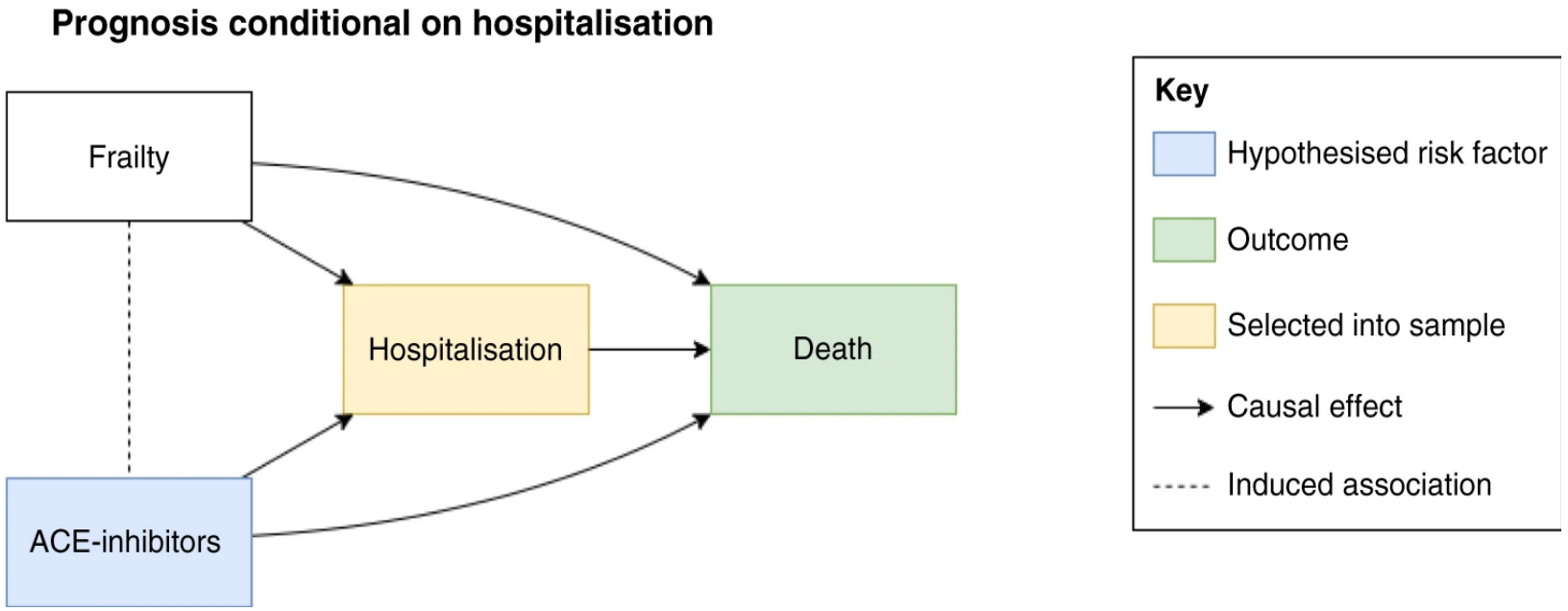
A simple collider bias scenario





Griffith et al. 2020 (Nature Communications)

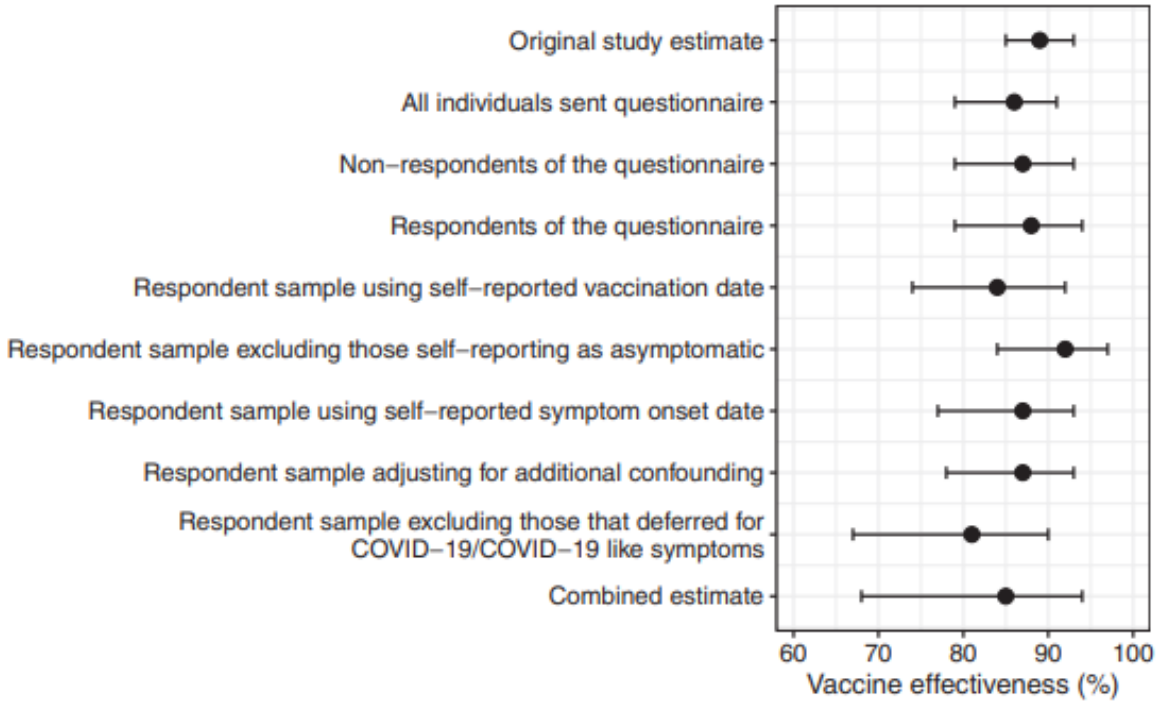
A more complicated collider bias scenario



Directed Acyclic Graphs (DAGs) are useful tools to identify collider and other biases

Griffith et al. 2020 (Nature Communications)

Vaccine effectiveness (VE) study highlighting a potential for collider bias related to testing (Example #1)

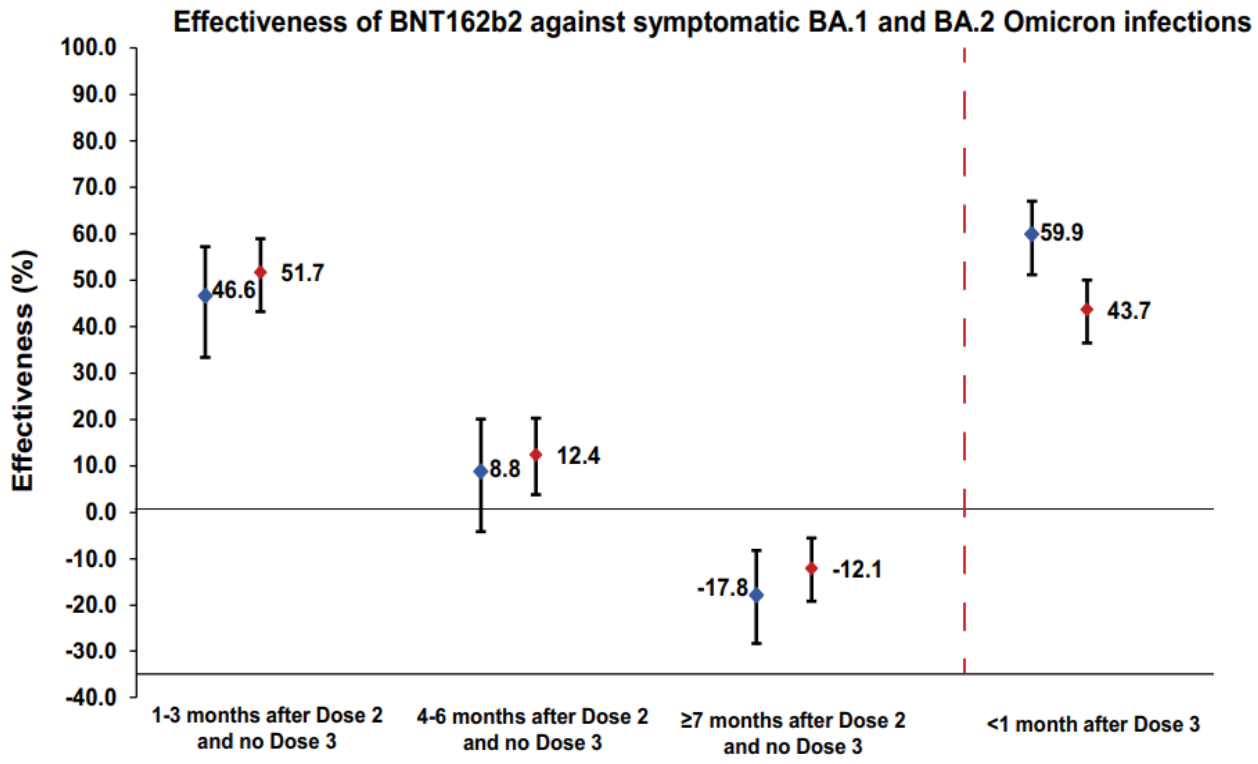


Adopted a test-negative design

"We were unable to assess whether collider bias was present … as the association between health-seeking behaviour and testing could not be assessed"

Graham et al. 2023 (Nature Communications)

Vaccine effectiveness (VE) study highlighting a potential for collider bias related to testing (Example #2)



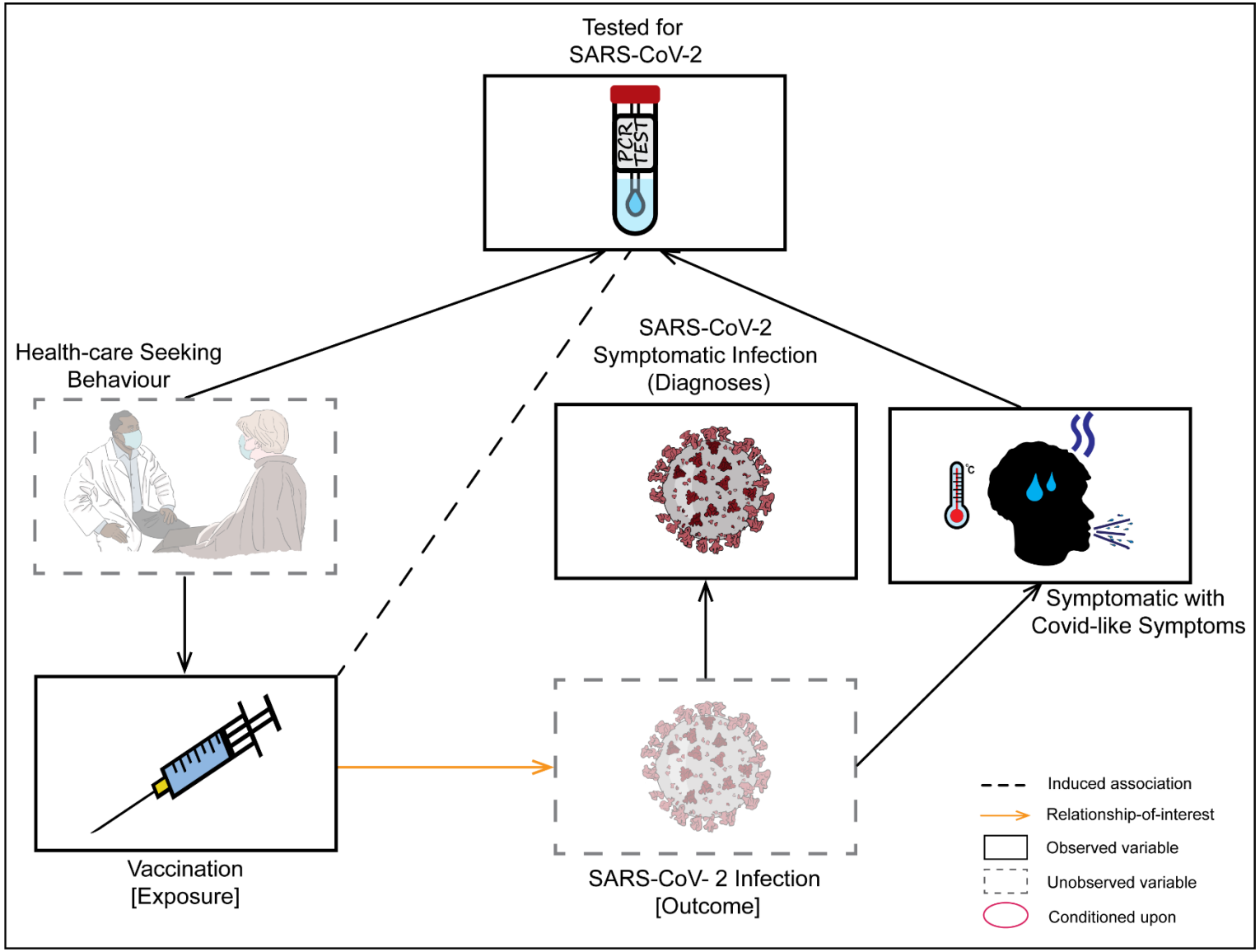
Adopted a test-negative design

"Negative estimated effectiveness likely reflects an effect of bias

...

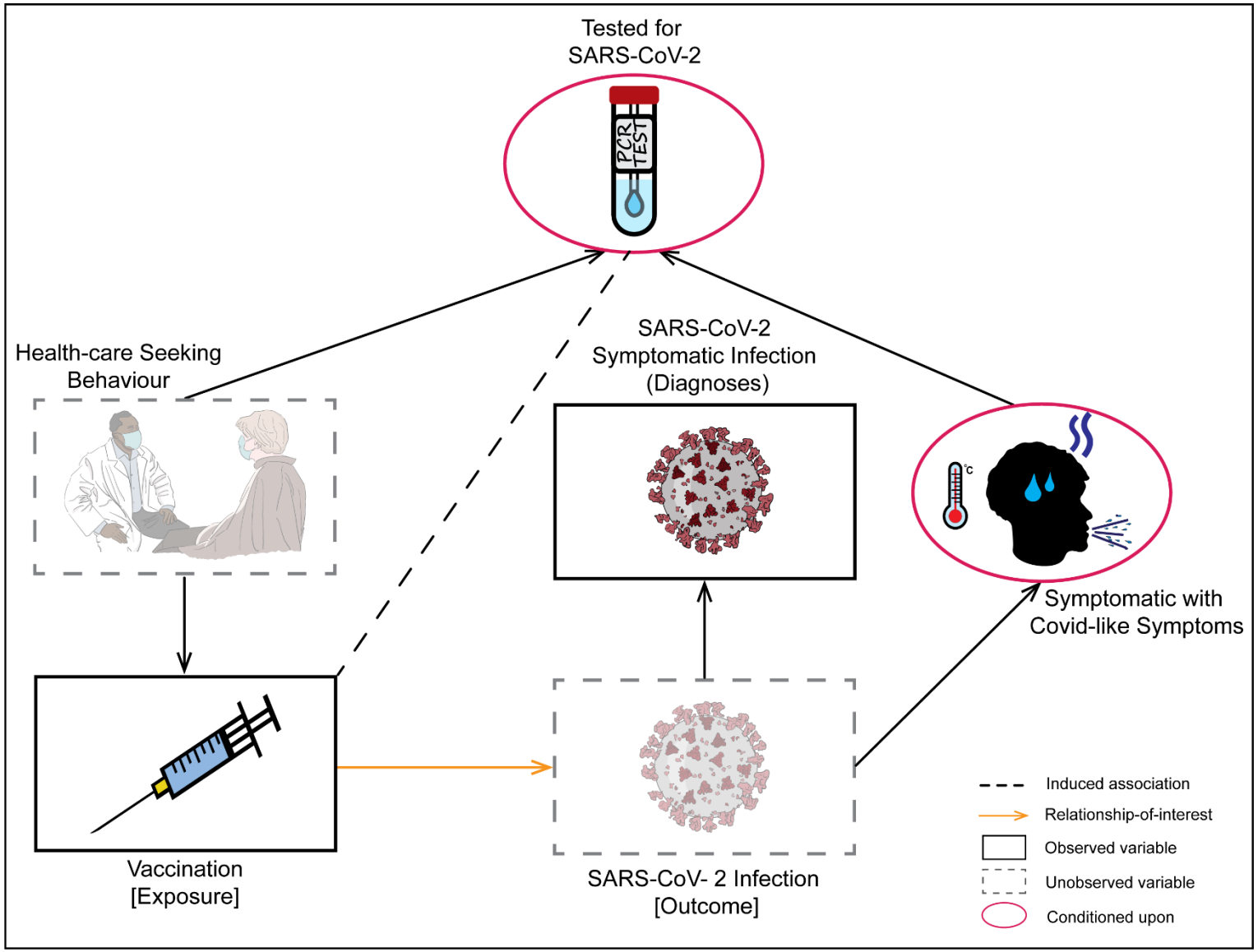
[which could arise due to] **differences in test-seeking behaviour**"

Chemaitelly et al. 2022 (Nature Communications)



Bodner et al. (in prep)

Now using a test-negative study design to estimate symptomatic VE



Bodner et al. (in prep)

Identifying the potential for selection bias in the test-negative design (TND) is not new

ORIGINAL ARTICLE

Epidemiology 2004;15: 615-625

A Structural Approach to Selection Bias

Miguel A. Hernán, Sonia Hernández-Díaz,† and James M. Robins**

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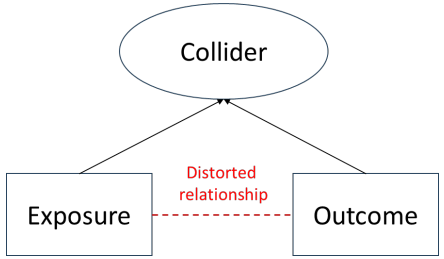
Vol. 184, No. 5
DOI: 10.1093/aje/kww063

Invited Commentary

Invited Commentary: Beware the Test-Negative Design

Daniel Westreich* and Michael G. Hudgens



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Vol. 187, No. 12
DOI: 10.1093/aje/kwy163
Advance Access publication: August 7, 2018

Practice of Epidemiology

Measurement of Vaccine Direct Effects Under the Test-Negative Design

Joseph A. Lewnard*, Christine Tedijanto, Benjamin J. Cowling, and Marc Lipsitch

npj | vaccines
www.nature.com/npjvaccines

BRIEF COMMUNICATION OPEN

Check for updates

The need for a clinical case definition in test-negative design studies estimating vaccine effectiveness

Sheena G. Sullivan[1,2✉], Arseniy Khvorov[1], Xiaotong Huang[3], Can Wang[3], Kylie E. C. Ainslie[3,4], Joshua Nealon[3], Bingyi Yang[3], Benjamin J. Cowling[3,5,6] and Tim K. Tsang[3,6]

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Vol. 184, No. 5
DOI: 10.1093/aje/kww064

Practice of Epidemiology

Theoretical Basis of the Test-Negative Study Design for Assessment of Influenza Vaccine Effectiveness

Sheena G. Sullivan*, Eric J. Tchetgen Tchetgen, and Benjamin J. Cowling

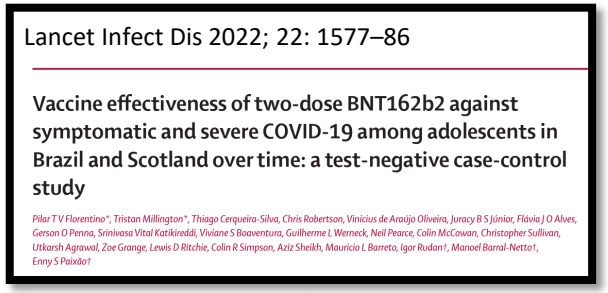
The test-negative design is commonly used when estimating VE


nature COMMUNICATIONS

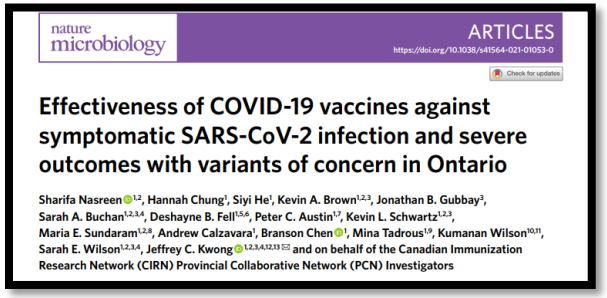
ARTICLE

OPEN

Duration of mRNA vaccine protection against SARS-CoV-2 Omicron BA.1 and BA.2 subvariants in Qatar

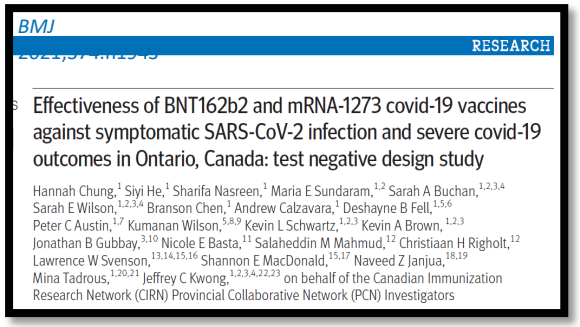

Lancet Infect Dis 2022; 22: 1577–86

Vaccine effectiveness of two-dose BNT162b2 against symptomatic and severe COVID-19 among adolescents in Brazil and Scotland over time: a test-negative case-control study


nature microbiology

ARTICLES

Effectiveness of COVID-19 vaccines against symptomatic SARS-CoV-2 infection and severe outcomes with variants of concern in Ontario


BMJ

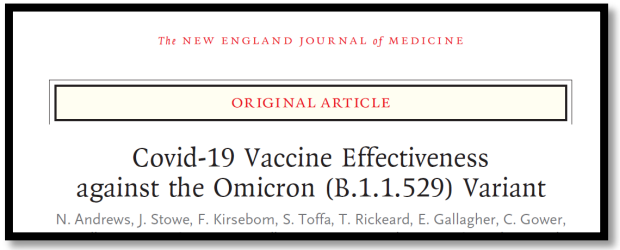
RESEARCH

Effectiveness of BNT162b2 and mRNA-1273 covid-19 vaccines against symptomatic SARS-CoV-2 infection and severe covid-19 outcomes in Ontario, Canada: test negative design study


RESEARCH

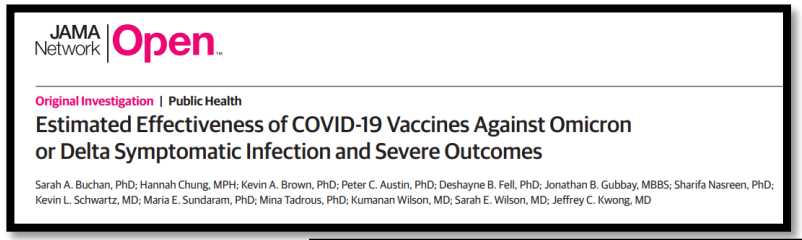
Euro Surveill. 2023;28(26)

COVID-19 vaccine effectiveness against symptomatic infection and hospitalisation in Belgium, July 2021 to May 2022


The NEW ENGLAND JOURNAL of MEDICINE

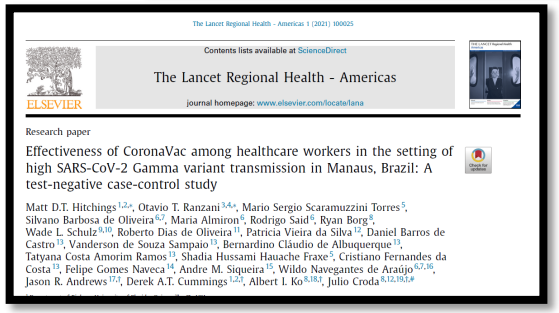
ORIGINAL ARTICLE

Covid-19 Vaccine Effectiveness against the Omicron (B.1.1.529) Variant


JAMA Network Open

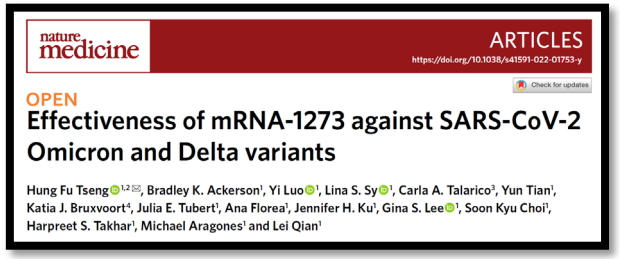
Original Investigation | Public Health

Estimated Effectiveness of COVID-19 Vaccines Against Omicron or Delta Symptomatic Infection and Severe Outcomes


The Lancet Regional Health - Americas

Research paper

Effectiveness of CoronaVac among healthcare workers in the setting of high SARS-CoV-2 Gamma variant transmission in Manaus, Brazil: A test-negative case-control study


nature medicine

ARTICLES

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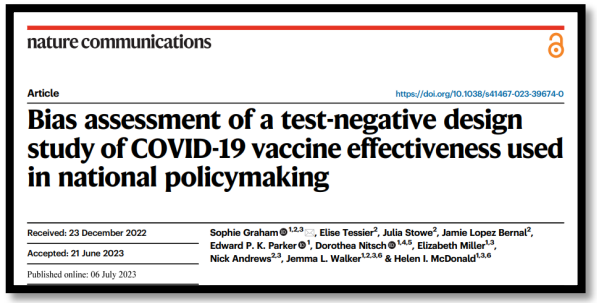
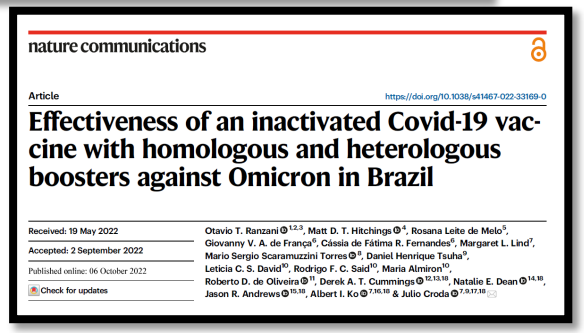
Effectiveness of mRNA-1273 against SARS-CoV-2 Omicron and Delta variants


nature communications

Article

Bias assessment of a test-negative design study of COVID-19 vaccine effectiveness used in national policymaking

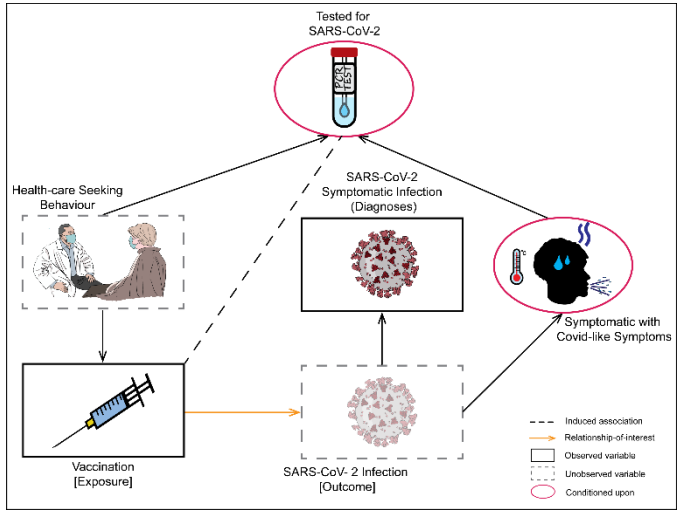

nature communications

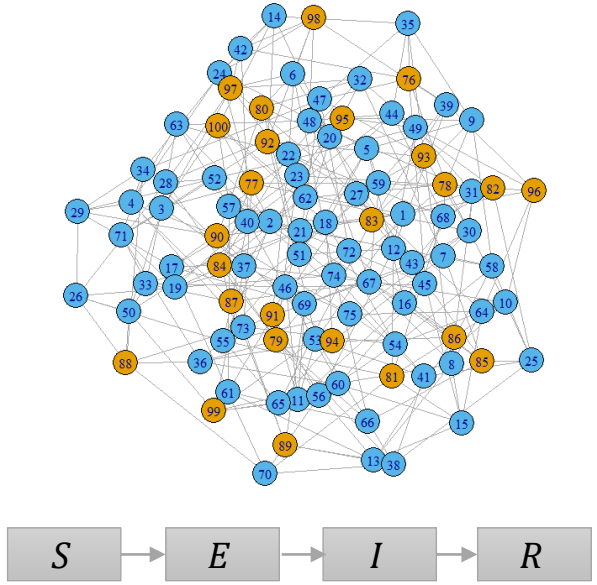
Article

Effectiveness of an inactivated Covid-19 vaccine with homologous and heterologous boosters against Omicron in Brazil

Understanding testing selection bias by combining the test-negative design, DAGs, and transmission models

Test-negative design

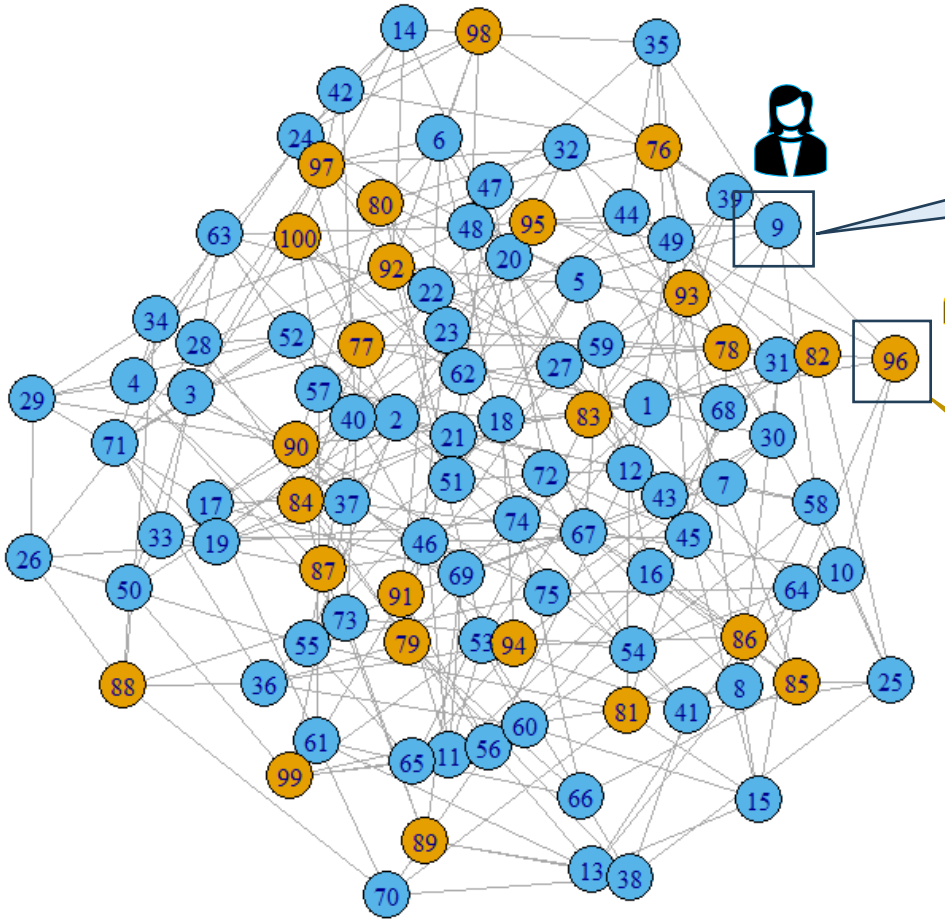




Today I will use this framework to assess:

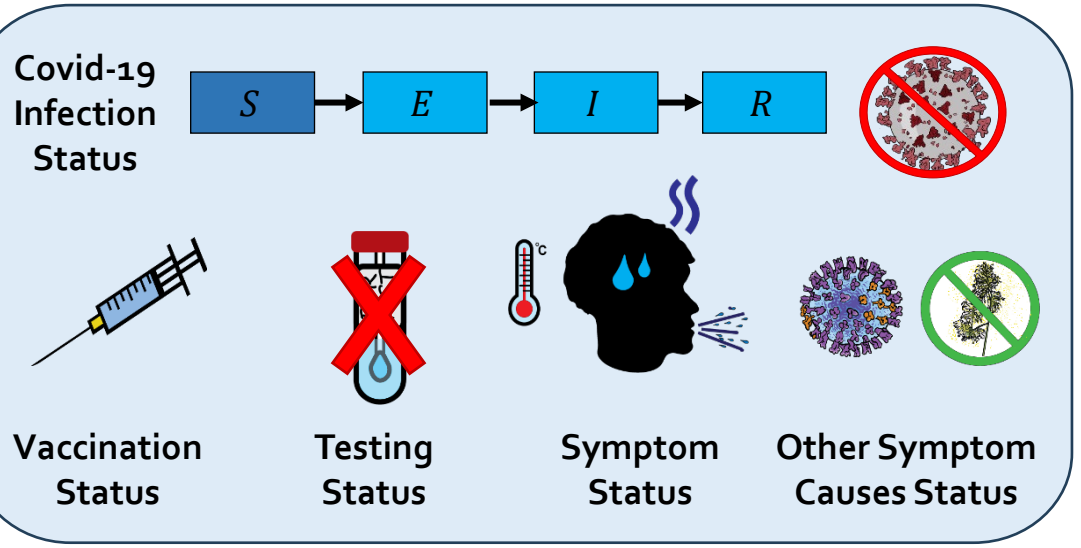
1. How the presence of a testing collider influences estimates of VE
2. Whether other factors influence the effect of this selection bias on VE estimates

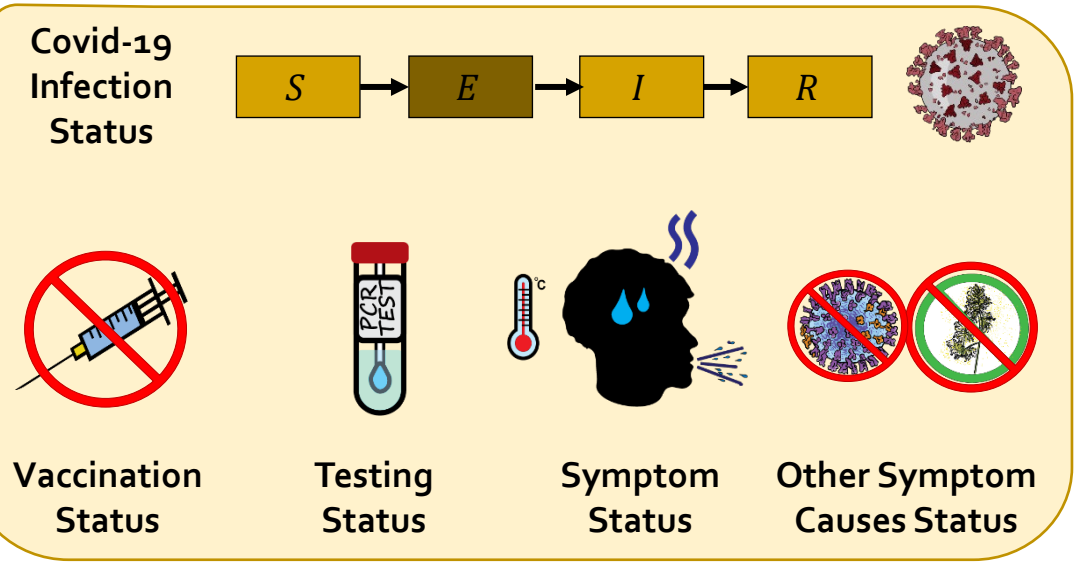
We built an individual-based network model that simulates transmission dynamics

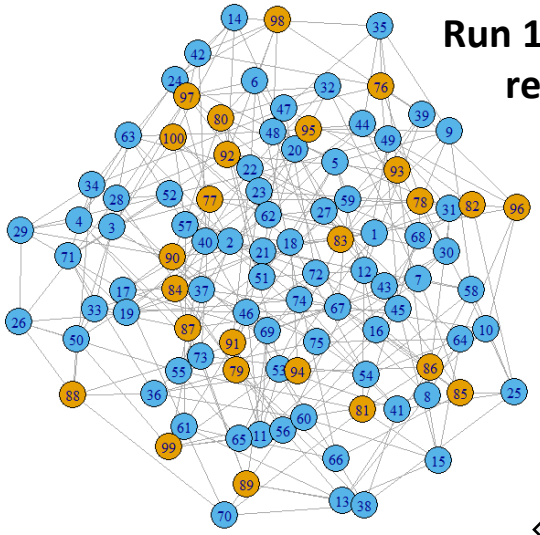


75% vaccinated

25% unvaccinated







Run 100 epidemic realizations

Target VE (VE)

$$\mathrm{VE} = 1 - \text{Odds Ratio}[\mathrm{OR}](t)$$

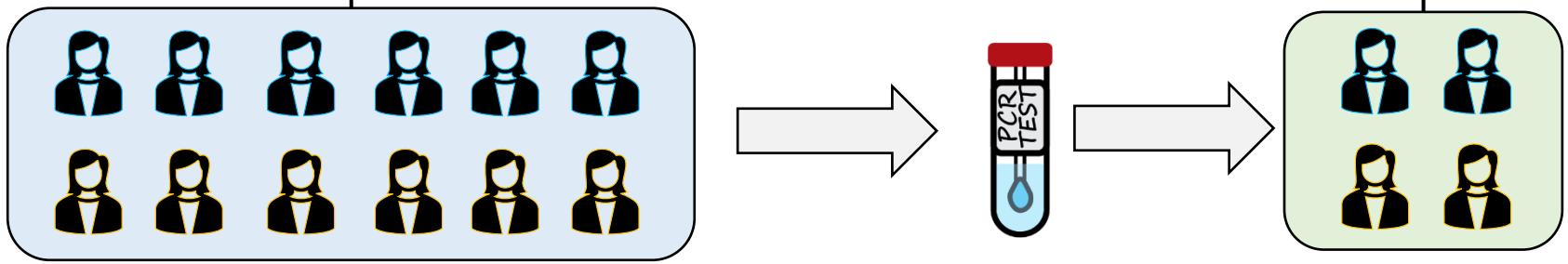
Estimated VE (VE_E)

$$\mathrm{VE_E} = 1 - \text{Odds Ratio}_\mathrm{E}[\mathrm{OR_E}](t)$$

Test-Negative Design

Simulated Full Population

Simulated Sample



Testing Scenarios

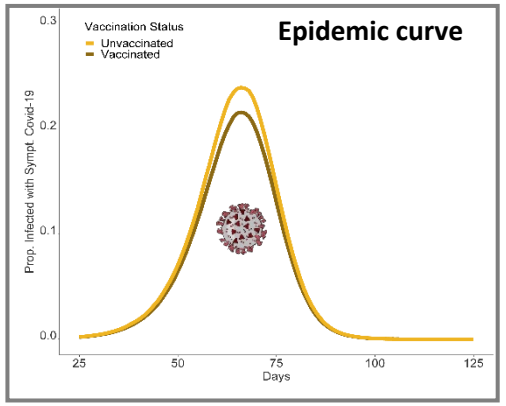
- Equal Testing
- Vac. 50% Higher
- Vac. 100% Higher

Input

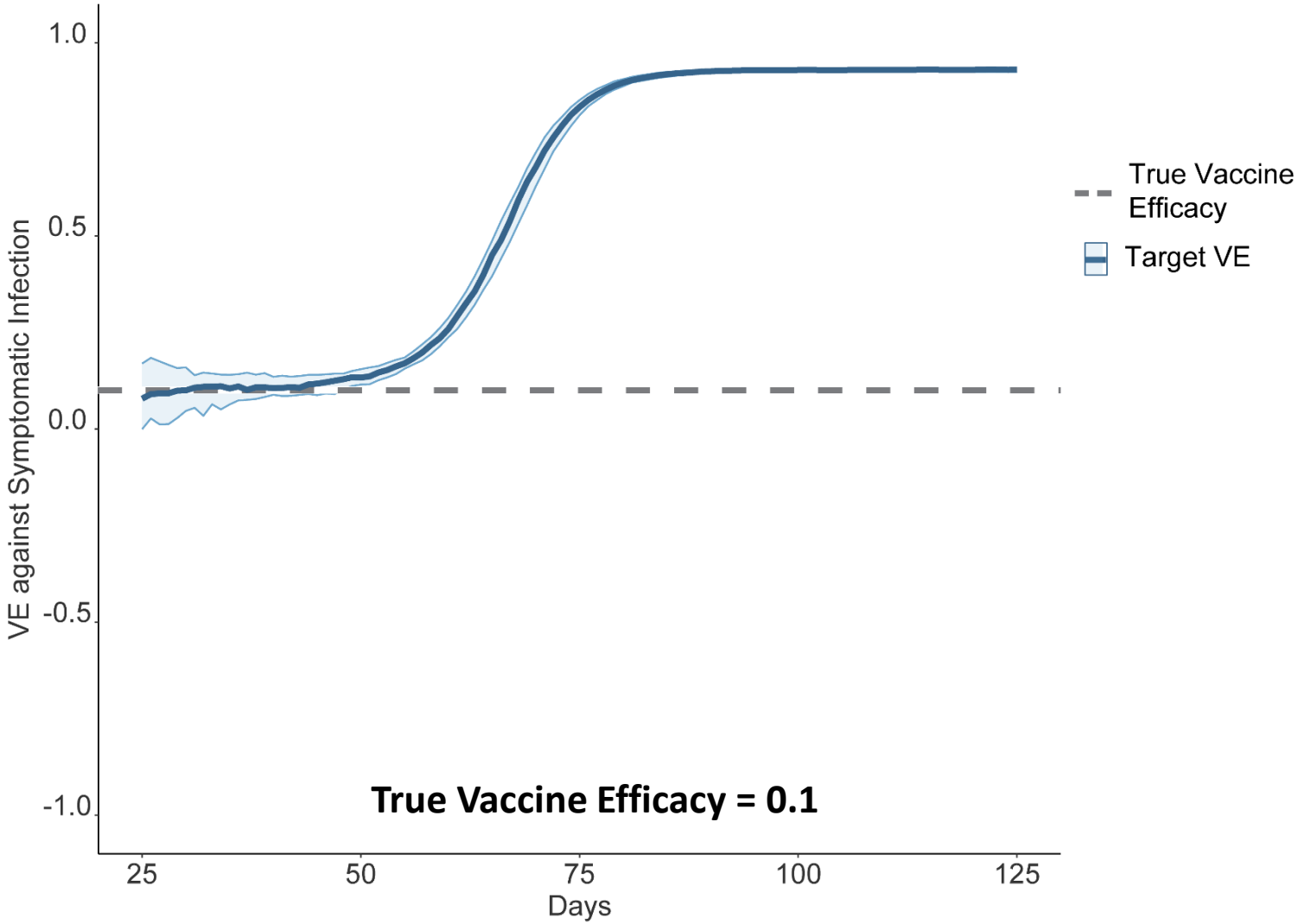
True Vaccine Efficacy

(i.e. Vaccine's true protective effect)

Target VE matches the True Vaccine Efficacy at the beginning of an epidemic

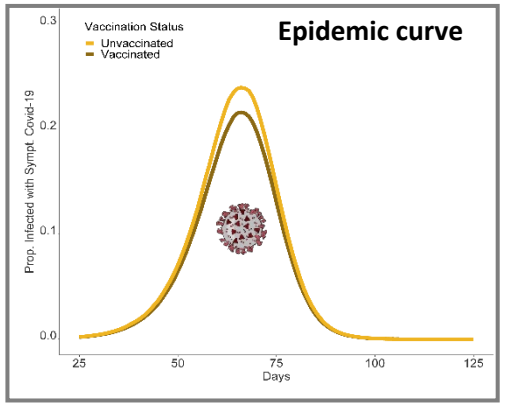


True Vaccine Efficacy = 0.1

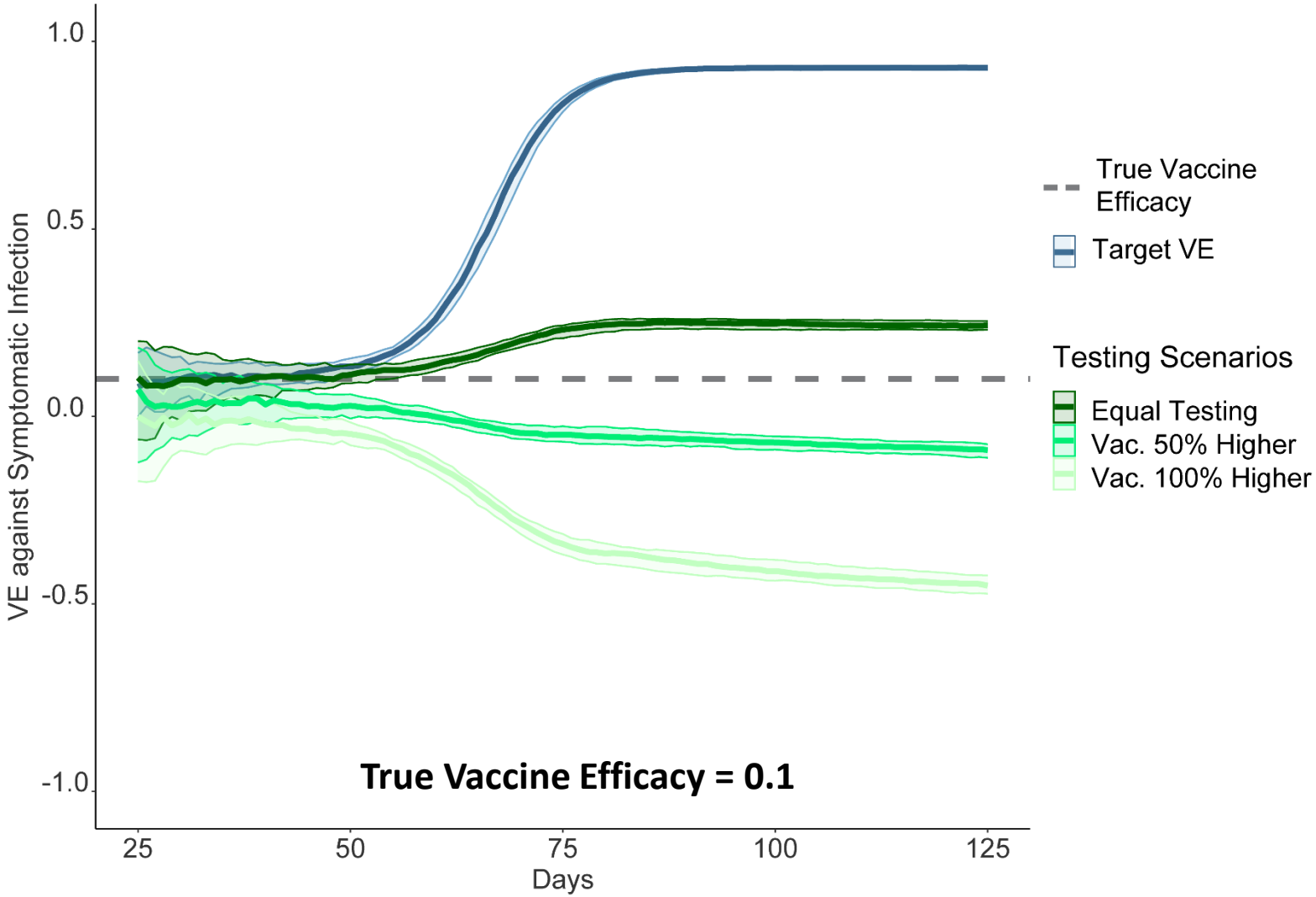


Bodner et al. (in prep)

Higher testing for vaccinated causes VE to be increasingly underestimated over time



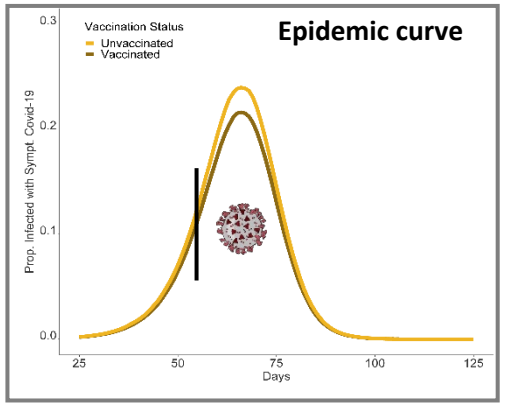
True Vaccine efficacy = 0.1



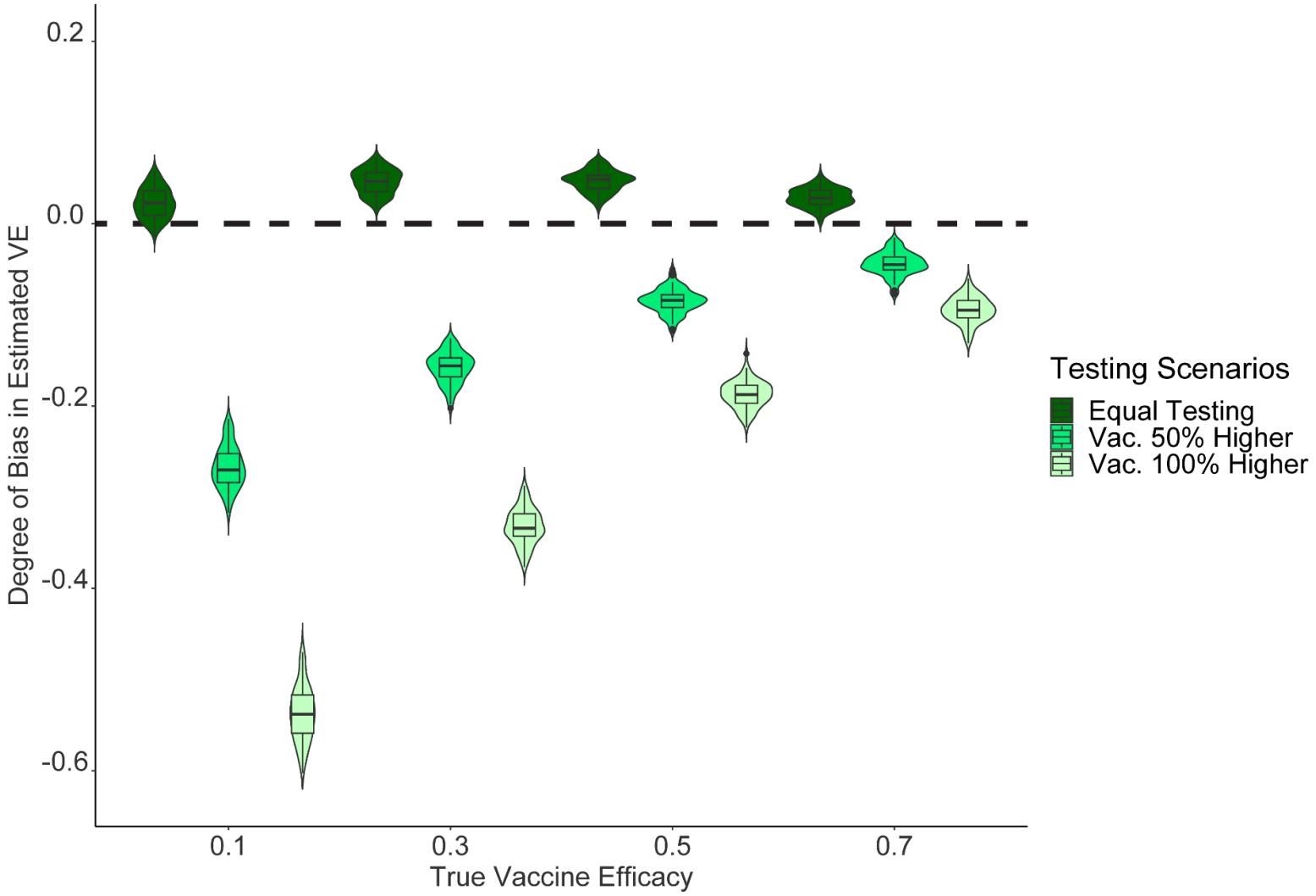
Bodner et al. (in prep)

A higher true protective effect of the vaccine decreases the degree of bias

Measured at inflection point during epidemic growth



True Vaccine efficacy = 0.1



Bodner et al. (in prep)

Final thoughts

- Simulation models can help us to identify under which circumstances biases could have the greatest impact on VE estimates
    - E.g. In our simulations, we found that the amount of bias can change over time and across the true protective effect of a vaccine
- It is important to use DAGs when identifying potential selection biases when estimating VE
- Observational studies can be impacted by various types of selection bias (and colliders) – not only colliders related to testing
    - E.g. Colliders related to prior infection and symptoms

Acknowledgements

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Unity Health Toronto

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NSERC CRSNG