Challenges and successes in estimating vaccine effectiveness from observational data

Jonathan Sterne
University of Bristol, UK

University of BRISTOL OpenSAFELY NUFFIELD DEPARTMENT OF PRIMARY CARE HEALTH SCIENCES Medical Sciences Division DataLab

Declarations

I do not have any financial interests with any firms/entities that are related to the meeting topic

I am co-lead of the Longitudinal Health and Wellbeing COVID-19 UK National Core Study (see https://www.ucl.ac.uk/covid-19-longitudinal-health-wellbeing/national-core-study-0).

> This study aims to understand the health, social and economic impacts of the COVID-19 pandemic by uniting established population cohorts and national anonymised electronic health records to inform policy

COVID-19 LONGITUDINAL HEALTH & WELLBEING NATIONAL CORE STUDY

UKRI Medical Research Council

UCL · London School of Hygiene & Tropical Medicine · University of York · Bradford Institute for Health Research – Making Research Real · University of Essex · University of Oxford Nuffield Department of Primary Care Health Sciences · UWE University of the West of England · University of Bristol · The University of Edinburgh · University of Glasgow · University of Cambridge · King's College London · Swansea University Prifysgol Abertawe · NICE National Institute for Health and Care Excellence

Randomized trials of COVID-19 vaccines

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Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine

Fernando P. Polack, M.D., Stephen J. Thomas, M.D., Nicholas Kitchin, M.D., Judith Absalon, M.D., Alejandra Gurtman, M.D., Stephen Lockhart, D.M., John L. Perez, M.D., Gonzalo Pérez Marc, M.D., Edson D. Moreira, M.D., Cristiano Zerbini, M.D., Ruth Bailey, B.Sc., Kena A. Swanson, Ph.D., Satrajit Roychoudhury, Ph.D., Kenneth Koury, Ph.D., Ping Li, Ph.D., Warren V. Kalina, Ph.D., David Cooper, Ph.D., Robert W. Frenck, Jr., M.D., Laura L. Hammitt, M.D., Özlem Türeci, M.D., Haylene Nell, M.D., Axel Schaefer, M.D., Serhat Ünal, M.D., Dina B. Tresnan, D.V.M., Ph.D., Susan Mather, M.D., Philip R. Dormitzer, M.D., Ph.D., Uğur Şahin, M.D., Kathrin U. Jansen, Ph.D., and William C. Gruber, M.D., for the C4591001 Clinical Trial Group*

ABSTRACT

BACKGROUND

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and the resulting coronavirus disease 2019 (Covid-19) have afflicted tens of millions of people in a worldwide pandemic. Safe and effective vaccines are needed urgently.

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Absalon at Pfizer, 401 N. Middletown Rd., Pearl River, NY 10965, or at judith.absalon@pfizer.com.

Among 10 cases of severe Covid-19 with onset after the first dose, 9 occurred in placebo recipients and 1 in a BNT162b2 recipient

Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK

Merryn Voysey, Sue Ann Costa Clemens*, Shabir A Madhi*, Lily Y Weckx*, Pedro M Folegatti*, Parvinder K Aley, Brian Angus, Vicky L Baillie, Shaun L Barnabas, Qasim E Bhorat, Sagida Bibi, Carmen Briner, Paola Cicconi, Andrea M Collins, Rachel Colin-Jones, Clare L Cutland, Thomas C Darton, Keertan Dheda, Christopher J A Duncan, Katherine R W Emary, Katie J Ewer, Lee Fairlie, Saul N Faust, Shuo Feng, Daniela M Ferreira, Adam Finn, Anna L Goodman, Catherine M Green, Christopher A Green, Paul T Heath, Catherine Hill, Helen Hill, Ian Hirsch, Susanne H C Hodgson, Alane Izu, Susan Jackson, Daniel Jenkin, Carina C D Joe, Simon Kerridge, Anthonet Koen, Gaurav Kwatra, Rajeka Lazarus, Alison M Lawrie, Alice Lelliott, Vincenzo Libri, Patrick J Lillie, Raburn Mallory, Ana V A Mendes, Eveline P Milan, Angela M Minassian, Alastair McGregor, Hazel Morrison, Yama F Mujadidi, Anusha Nana, Peter J O'Reilly, Sherman D Padayachee, Ana Pittella, Emma Plested, Katrina M Pollock, Maheshi N Ramasamy, Sarah Rhead, Alexandre V Schwarzbold, Nisha Singh, Andrew Smith, Rinn Song, Matthew D Snape, Eduardo Sprinz, Rebecca K Sutherland, Richard Tarrant, Emma C Thomson, M Estée Török, Mark Toshner, David P J Turner, Johan Vekemans, Tonya L Villafana, Marion E E Watson, Christopher J Williams, Alexander D Douglas*, Adrian V S Hill*, Teresa Lambe*, Sarah C Gilbert*, Andrew J Pollard* on behalf of the Oxford COVID Vaccine Trial Group†*

Summary

Background A safe and efficacious vaccine against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), if deployed with high coverage, could contribute to the control of the COVID-19 pandemic. We evaluated the safety and efficacy of the ChAdOx1 nCoV-19 vaccine in a pooled interim analysis of four trials.

Methods This analysis includes data from four ongoing blinded, randomised, controlled trials done across the UK,

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From 21 days after first dose, there were ten cases hospitalised for COVID-19, all in the control arm; two classified as severe COVID-19, including one death.

Most studies of effectiveness of COVID-19 vaccines are observational studies using routine data assembled during the rollout

- Randomized trials provide the best estimates of effectiveness in the real world, but…
  - A host of urgent questions could not be addressed in randomized trials
  - Far reaching policy decisions have been made using observational studies
  - Such studies aim to make *causal inferences* about the effects, and comparative effects, of vaccines and vaccination strategies
- To make causal inferences from observational data, think about the randomized trial whose result you would like to estimate

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Practice of Epidemiology

Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available

Miguel A. Hernán* and James M. Robins

* Correspondence to Dr. Miguel A. Hernán, Department of Epidemiology, 677 Huntington Avenue, Boston, MA 02115 (e-mail: miguel_hernan@post.harvard.edu).

Initially submitted December 9, 2014; accepted for publication September 8, 2015.

Ideally, questions about comparative effectiveness or safety would be answered using an appropriately designed and conducted randomized experiment. When we cannot conduct a randomized experiment, we analyze observational data. Causal inference from large observational databases (big data) can be viewed as an attempt to emulate a randomized experiment—the target experiment or target trial—that would answer the question of interest. When the goal is to guide decisions among several strategies, causal analyses of observational data need to be evaluated with respect to how well they emulate a particular target trial. We outline a framework for comparative effectiveness research using big data that makes the target trial explicit. This framework channels counterfactual theory for comparing the effects of sustained treatment strategies, organizes analytic approaches, provides a structured process for the criticism of observational studies, and helps avoid common methodologic pitfalls.

big data; causal inference; comparative effectiveness research; target trial

Features of randomized trials of vaccine effectiveness

- Define eligible participants
- Define intervention (vaccination) and comparator (no vaccination / vaccination against a different infection)
- Random assignment to vaccine or comparator
- Follow up for vaccine and comparator group starts on the day of assignment
  - The calendar date of assignment is comparable for the two groups
- Follow up continues for the same time, regardless of intervention group

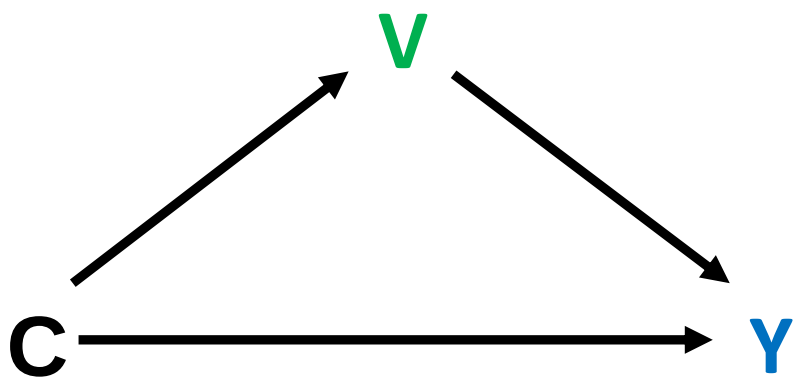
Confounding

Confounding occurs when there is a common cause (C) of both

vaccination (V)

and

the outcome event (Y)



“Sequential” specification of a target trial

ORIGINAL ARTICLE

BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting

Noa Dagan, M.D., Noam Barda, M.D., Eldad Kepten, Ph.D., Oren Miron, M.A., Shay Perchik, M.A., Mark A. Katz, M.D., Miguel A. Hernán, M.D., Marc Lipsitch, D.Phil., Ben Reis, Ph.D., and Ran D. Balicer, M.D.

From the Clalit Research Institute, Innovation Division, Clalit Health Services, Tel Aviv (N.D., N.B., E.K., O.M., S.P., M.A.K., R.D.B.), and the School of Public Health, Faculty of Health Sciences, Ben Gurion University of the Negev, Be'er Sheva (O.M., M.A.K., R.D.B.) — both in Israel; University of Michigan School of Public Health, Ann Arbor (M.A.K.); and the Department of Biomedical Informatics (N.D., N.B.), Harvard Medical School (B.R.), the Departments of Epidemiology and Biostatistics (M.A.H.), and the Cen-

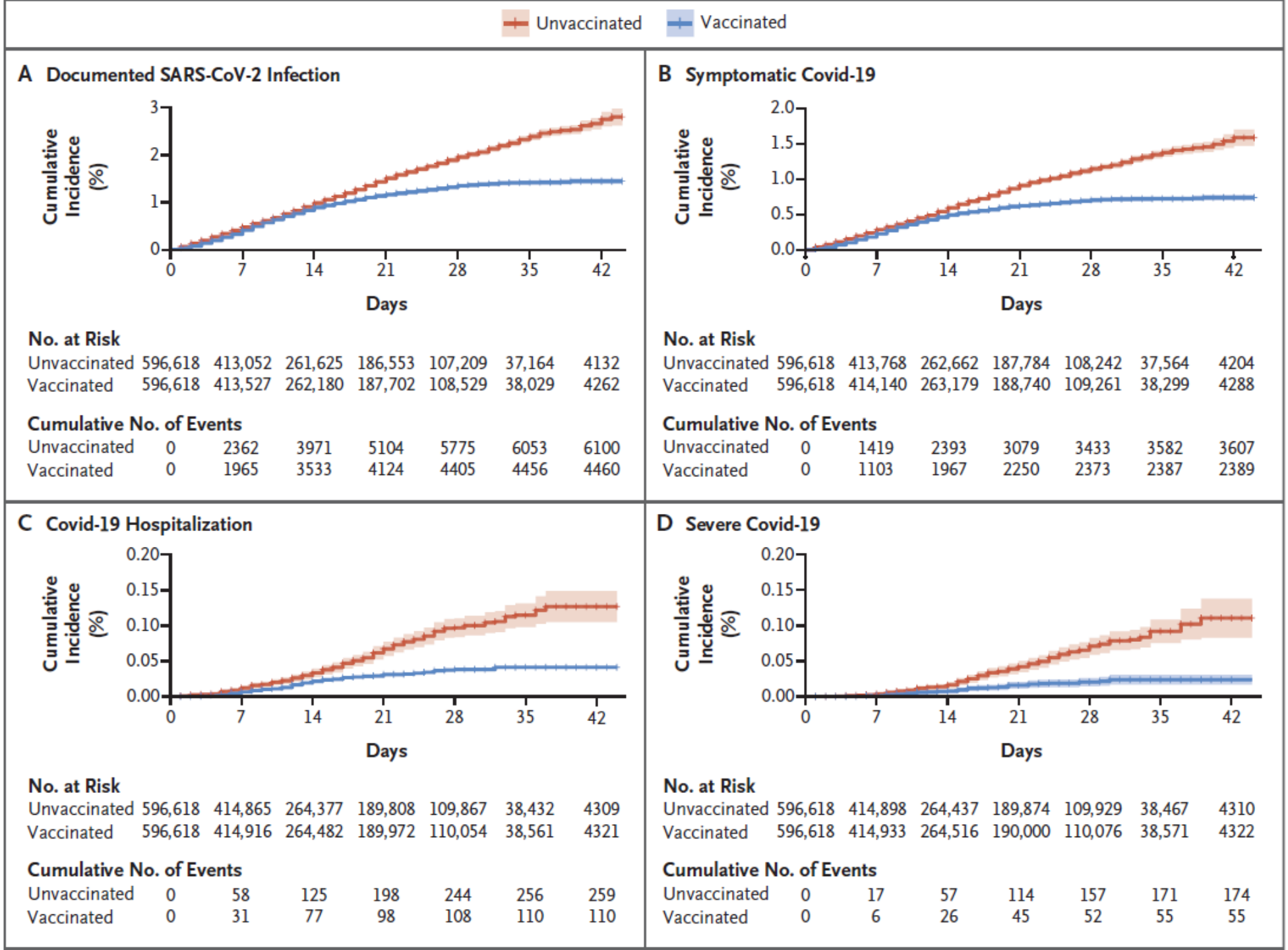
ABSTRACT

BACKGROUND

As mass vaccination campaigns against coronavirus disease 2019 (Covid-19) commence worldwide, vaccine effectiveness needs to be assessed for a range of outcomes across diverse populations in a noncontrolled setting. In this study, data from Israel's largest health care organization were used to evaluate the effectiveness of the BNT162b2 mRNA vaccine.

METHODS

All persons who were newly vaccinated during the period from December 20, 2020, to February 1, 2021, were matched to unvaccinated controls in a 1:1 ratio according to demographic and clinical characteristics. Study outcomes included documented


Unvaccinated
Vaccinated
A Documented SARS-CoV-2 Infection
Cumulative Incidence (%)
0
1
2
3
0
7
14
21
28
35
42
Days
No. at Risk
Unvaccinated 596,618 413,052 261,625 186,553 107,209 37,164 4132
Vaccinated 596,618 413,527 262,180 187,702 108,529 38,029 4262
Cumulative No. of Events
Unvaccinated 0 2362 3971 5104 5775 6053 6100
Vaccinated 0 1965 3533 4124 4405 4456 4460
B Symptomatic Covid-19
Cumulative Incidence (%)
0.0
0.5
1.0
1.5
2.0
0
7
14
21
28
35
42
Days
No. at Risk
Unvaccinated 596,618 413,768 262,662 187,784 108,242 37,564 4204
Vaccinated 596,618 414,140 263,179 188,740 109,261 38,299 4288
Cumulative No. of Events
Unvaccinated 0 1419 2393 3079 3433 3582 3607
Vaccinated 0 1103 1967 2250 2373 2387 2389
C Covid-19 Hospitalization
Cumulative Incidence (%)
0.00
0.05
0.10
0.15
0.20
0
7
14
21
28
35
42
Days
No. at Risk
Unvaccinated 596,618 414,865 264,377 189,808 109,867 38,432 4309
Vaccinated 596,618 414,916 264,482 189,972 110,054 38,561 4321
Cumulative No. of Events
Unvaccinated 0 58 125 198 244 256 259
Vaccinated 0 31 77 98 108 110 110
D Severe Covid-19
Cumulative Incidence (%)
0.00
0.05
0.10
0.15
0.20
0
7
14
21
28
35
42
Days
No. at Risk
Unvaccinated 596,618 414,898 264,437 189,874 109,929 38,467 4310
Vaccinated 596,618 414,933 264,516 190,000 110,076 38,571 4322
Cumulative No. of Events
Unvaccinated 0 17 57 114 157 171 174
Vaccinated 0 6 26 45 52 55 55

“Sequential” specification of a target trial

- On each day, a vaccinated individual is closely matched to an unvaccinated (control) individual
  - Covariates (matching factors) are measured up to the day of vaccination
  - Follow up continues until the control individual is vaccinated, *at which time follow up for both individuals is censored*.
    - Can conduct sensitivity analyses extending follow up (eg for a week) subsequent to vaccination of the control individual
  - Control individuals can subsequently be included as a vaccinated individual in a new pair
  - Can directly compare cumulative incidence in the two groups, or can adjust for additional covariates beyond those used for matching.
  - We waste a lot of data (matching failures, censoring follow up of vaccinated individuals) but we compare similar individuals over the same time periods

In a public health emergency, we need to balance the need for rapid estimates of VE with the need to address potential biases

ORIGINAL ARTICLE

Covid-19 Vaccine Effectivene
against the Omicron (B.1.1.529) V

N. Andrews, J. Stowe, F. Kirsebom, S. Toffa, T. Rickeard, E. Galla
M. Kall, N. Groves, A.-M. O'Connell, D. Simons, P.B. Blomquist, A
N. Iwani Binti Abdul Aziz, S. Thelwall, G. Dabrera, R. Myers, G. A
S. Gharbia, J.C. Barrett, R. Elson, S.N. Ladhani, N. Ferguson, I
C.N.J. Campbell, K. Brown, S. Hopkins, M. Chand, M. Ramsay, and

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Lopez Bernal can be contacted at jamie.lopezbernal2@phe.gov.uk or at the U.K. Health Security Agency, 61 Colindale Ave., London, NW9 5EQ, United Kingdom.

Drs. Andrews and Stowe contributed equally to this article.

This article was published on March 2, 2022, at NEJM.org.

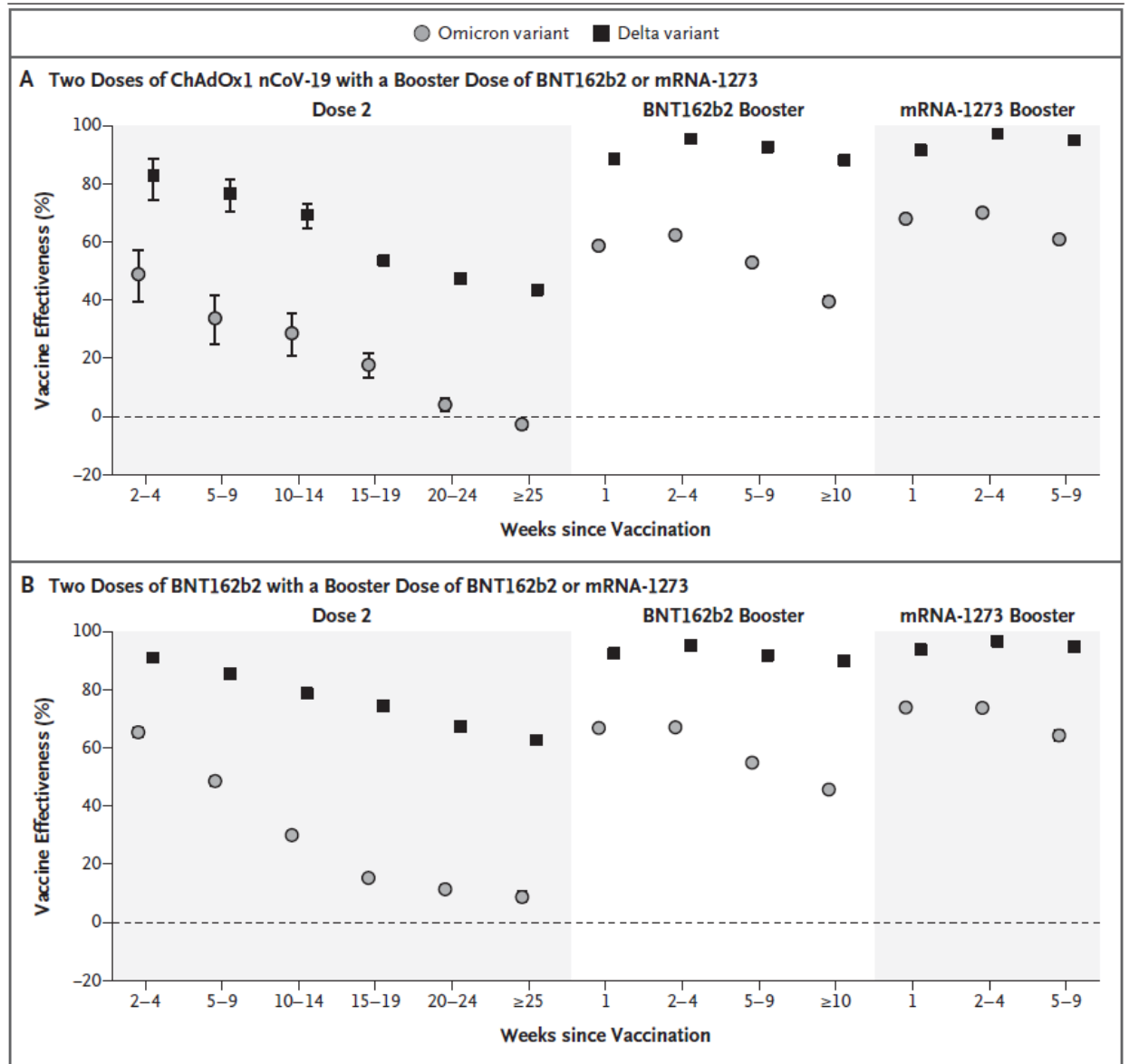
ABSTRACT

BACKGROUND

A rapid increase in coronavirus disease 2019 (Covid-19) cases due
(B.1.1.529) variant of severe acute respiratory syndrome coronavirus
cinated populations has aroused concerns about the effectiveness of

METHODS

We used a test-negative case–control design to estimate vaccine effe
symptomatic disease caused by the omicron and delta (B.1.617.2) var
Vaccine effectiveness was calculated after primary immunization w
BNT162b2 (Pfizer–BioNTech), ChAdOx1 nCoV-19 (AstraZeneca), or r
derna) vaccine and after a booster dose of BNT162b2, ChAdOx1 nCoV-1



Test negative designs

Compare individuals with symptoms who test positive (cases) with those who test negative (controls)

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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

* Correspondence to Dr. Sheena G. Sullivan, WHO Collaborating Centre for Reference and Research on Influenza, Peter Doherty Institute for Infection and Immunity, Locked Bag 815, Carlton South, VIC 3053, Australia (e-mail: sgsullivan@ucla.edu).

Initially submitted April 22, 2015; accepted for publication January 14, 2016.

Influenza viruses undergo frequent antigenic changes. As a result, the viruses circulating change within and between seasons, and the composition of the influenza vaccine is updated annually. Thus, estimation of the vaccine's effectiveness is not constant across seasons. In order to provide annual estimates of the influenza vaccine's effectiveness, health departments have increasingly adopted the "test-negative design," using enhanced data from routine surveillance systems. In this design, patients presenting to participating general practitioners with influenza-like illness are swabbed for laboratory testing; those testing positive for influenza virus are defined as cases, and those testing negative form the comparison group. Data on patients' vaccination histories and confounder profiles are also collected. Vaccine effectiveness is estimated from the odds ratio comparing the odds of testing positive for influenza among vaccinated patients and unvaccinated patients, adjusting for confounders. The test-negative design is purported to reduce bias associated with confounding by health-care-seeking behavior and misclassification of cases. In this paper, we use directed acyclic graphs to characterize potential biases in studies of influenza vaccine effectiveness using the test-negative design. We show how studies using this design can avoid or minimize bias and where bias may be introduced with particular study design variations.

causal inference; directed acyclic graphs; epidemiologic methods; influenza; observational studies; test-negative study design; vaccine effectiveness

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Invited Commentary

Invited Commentary: Beware the Test-Negative Design

Daniel Westreich* and Michael G. Hudgens

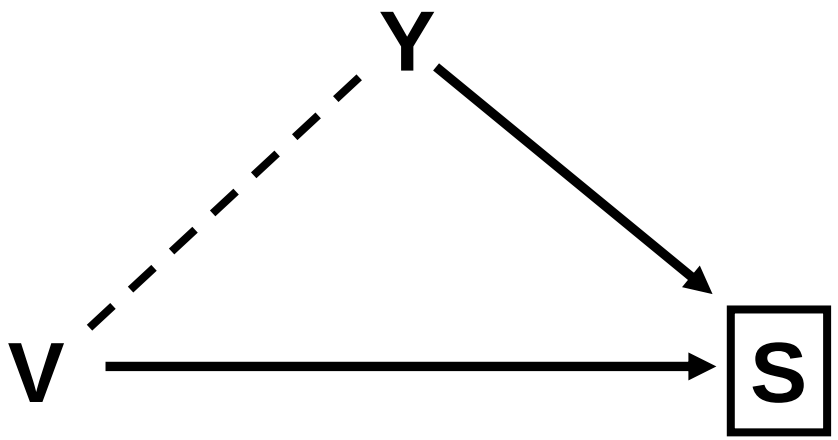
* Correspondence to Dr. Daniel Westreich, Department of Epidemiology, CB #7435, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599 (e-mail: djw@unc.edu).

Initially submitted February 26, 2016; accepted for publication April 8, 2016.

In this issue of the *Journal*, Sullivan et al. (*Am J Epidemiol*. 2016;184(5):345–353) carefully examine the theoretical justification for use of the test-negative design, a common observational study design, in assessing the effectiveness of influenza vaccination. Using modern causal inference methods (in particular, directed acyclic graphs), they describe different threats to the validity of inferences drawn about the effect of vaccination from test-negative design studies. These threats include confounding, selection bias, and measurement error in either the exposure or the outcome. While confounding and measurement error are common in observational studies, the potential for selection bias inherent in the test-negative design brings into question the validity of inferences drawn from such studies.

confounding; epidemiologic methods; influenza vaccine; selection bias; test-negative study design

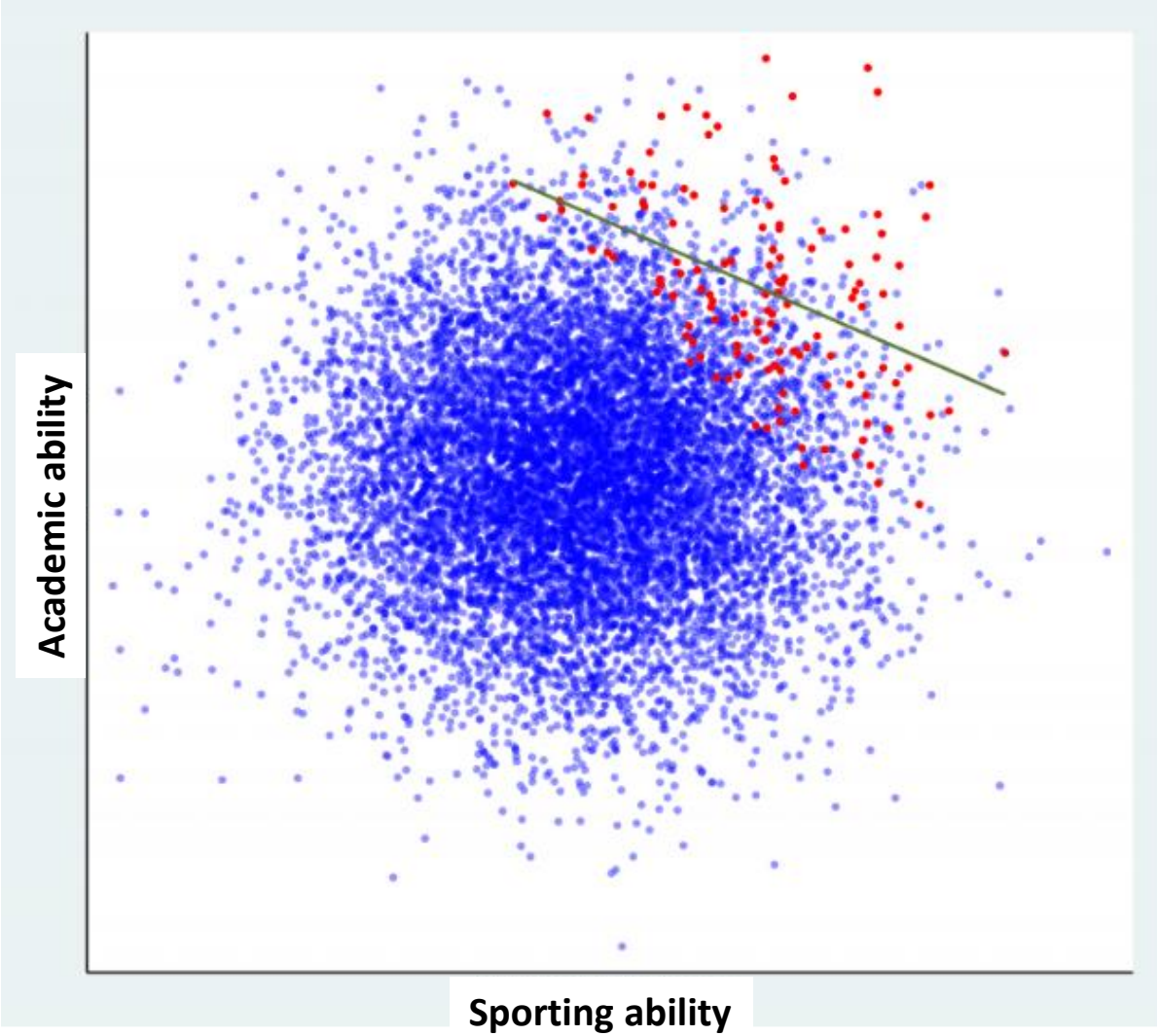
Conditioning on common effects induces associations



Selection bias (‘collider bias’)

Academic ability and sporting ability

- In the general population, academic ability and sporting ability are unrelated
- However, expensive private schools in England recruit on the basis of both academic and sporting ability:
- Among children at expensive private schools, the two characteristics are inversely associated



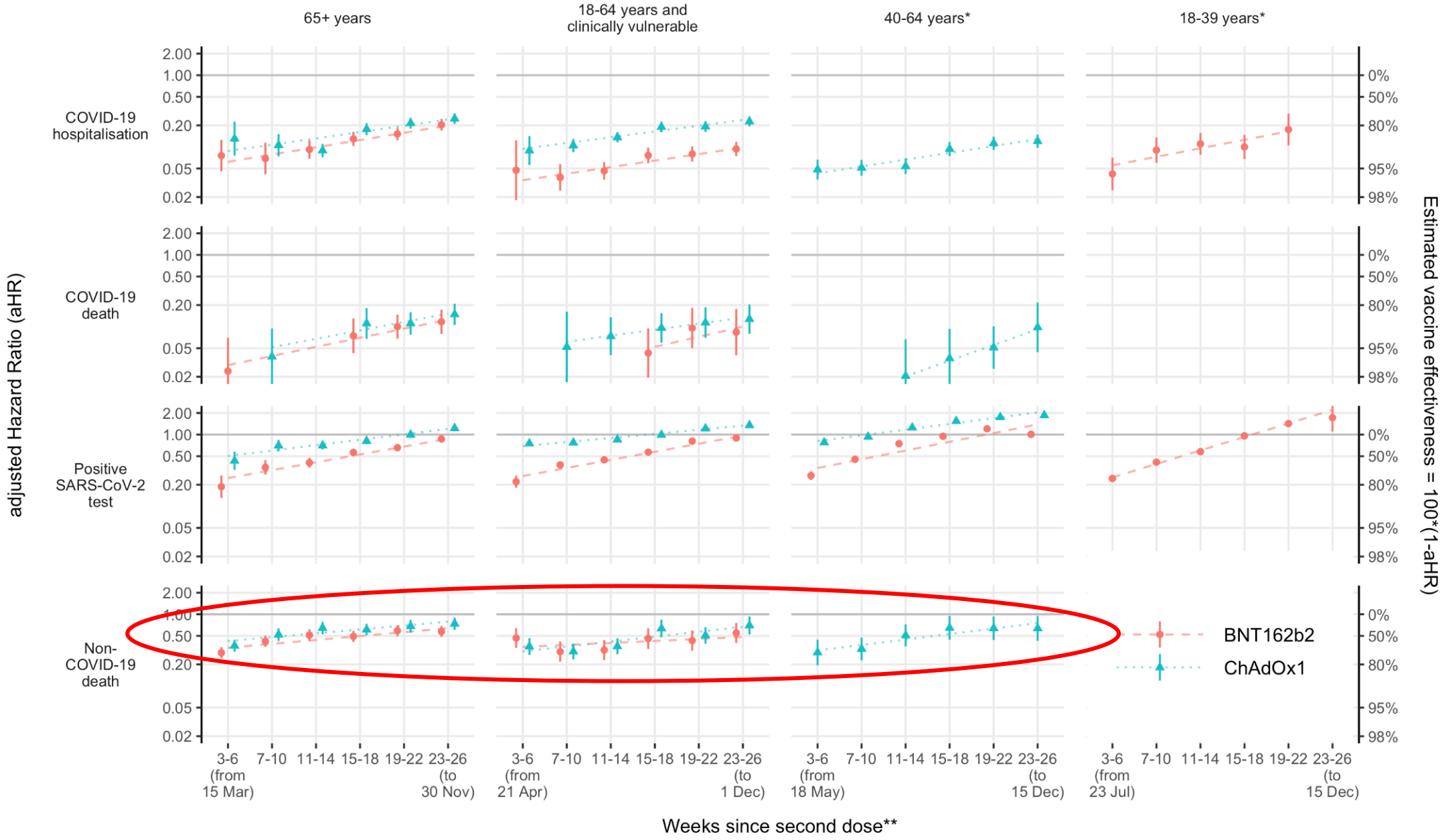
Using selected populations for VE research

- Suppose that perceived risk of infection and attitudes to vaccination each influence use of a health monitoring app
  - Associations between causes of vaccination and risk factors for the target infection may be distorted among app users
- To correct for this, we would need to measure and adjust for influences on use of the app

Case-control studies

- Useful to think of a cohort study in relation to its target randomized trial
- Useful to think of a case-control study in relation to its target cohort
  - For example, in the target cohort, potential confounders are measured at the start of follow up, not when the outcome occurs
- Do we need to sample controls?
  - Modern computers can handle analyses based on many millions of individuals
  - If the whole population is defined, we can sample based on any characteristic, and use inverse sampling probability weighting to recreate the result from the whole cohort
  - For example, if vaccination is rare we could include all outcome events *and* all vaccinated individuals, together with a random sample of other individuals
- Main justification for case-control studies may be when the population is not well-defined, and we sample controls on the basis of geographical or social proximity to cases.

Include “negative control” outcomes



*and not clinically vulnerable; **all dates are in 2021

BMJ 2022; 377:e071249

Thank you for your attention