Vaccines and Related Biological Products Advisory Committee September 17, 2021 Meeting Presentation

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Real-world effectiveness of COVID-19 vaccines

Jonathan Sterne
University of Bristol, UK

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

Declarations

I do not have any financial interests with any of the 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

Acknowledgements

- Isabelle Boutron, Ana-Maria Henao-Restrepo, Nicholas Henschke, Julian Higgins, Fatema Kazi, Philip Krause, Hongchao Pan, Richard Peto, Gemma Villanueva

“Real-world” effectiveness of vaccines

- Randomized trials provide the best estimates of effectiveness in the real world, but…
  - A host of urgent questions have not been addressed in randomized trials
  - The ongoing emergency, and amazing success of the vaccines, mean that we have to make far reaching policy decisions using observational studies

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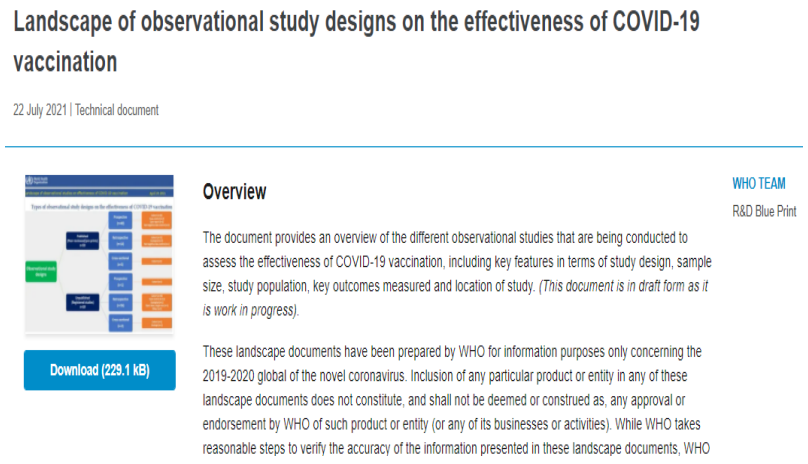
  - The ongoing emergency, and amazing success of the vaccines, mean that we have to make far reaching policy decisions using observational studies
- ~~Estimated effectiveness of vaccines in observational studies~~
- Estimated effectiveness of vaccines that is biased, by an unknown amount

Monitoring/tracking published observational studies on vaccine effectiveness

- WHO & Cochrane run a systematic screening/data extraction process on published studies
- 100s of studies are screened per week



Landscape of observational study designs on the effectiveness of COVID-19 vaccination

22 July 2021 | Technical document

Download (229.1 kB)

Overview

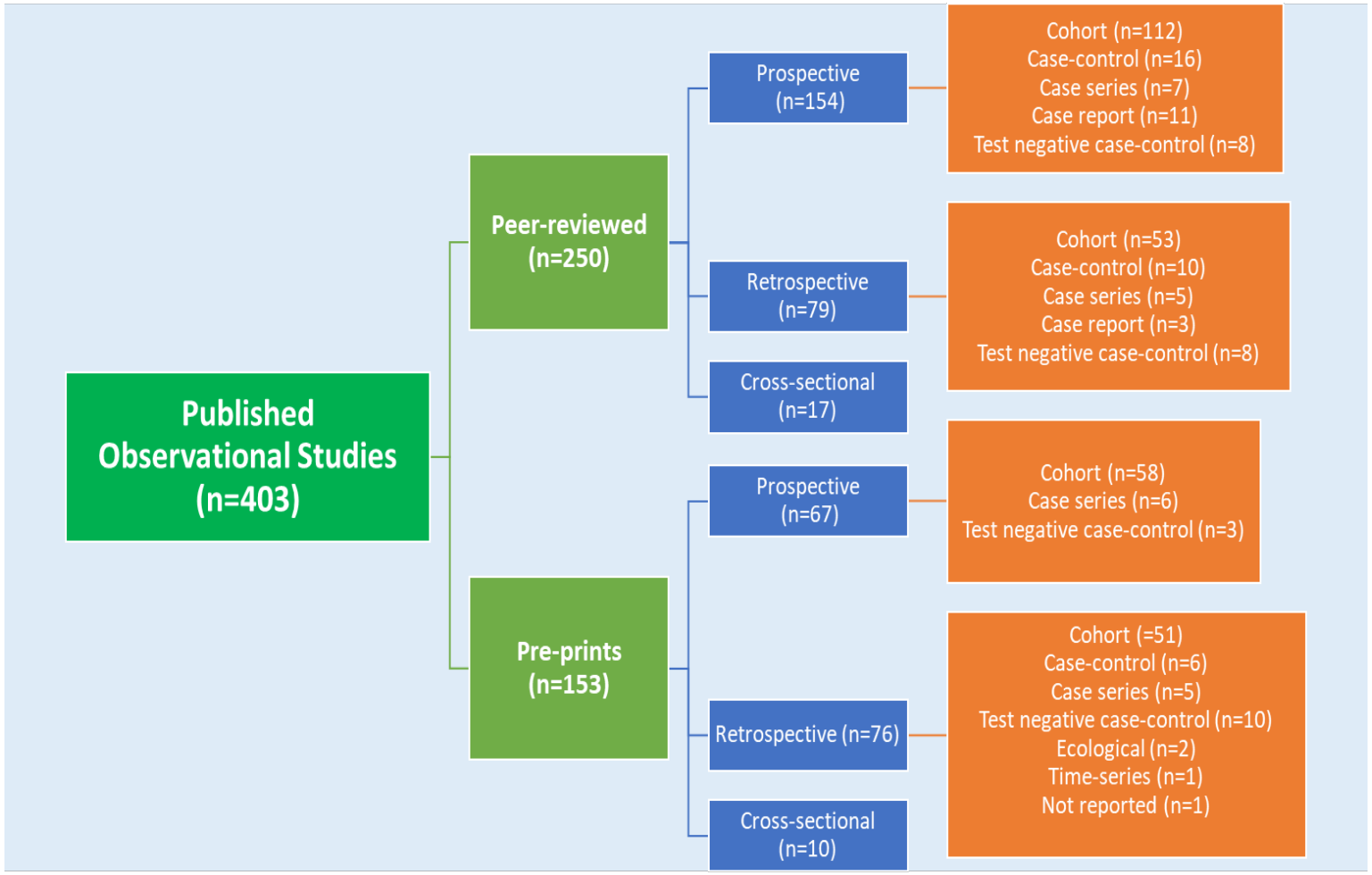
WHO TEAM

R&D Blue Print

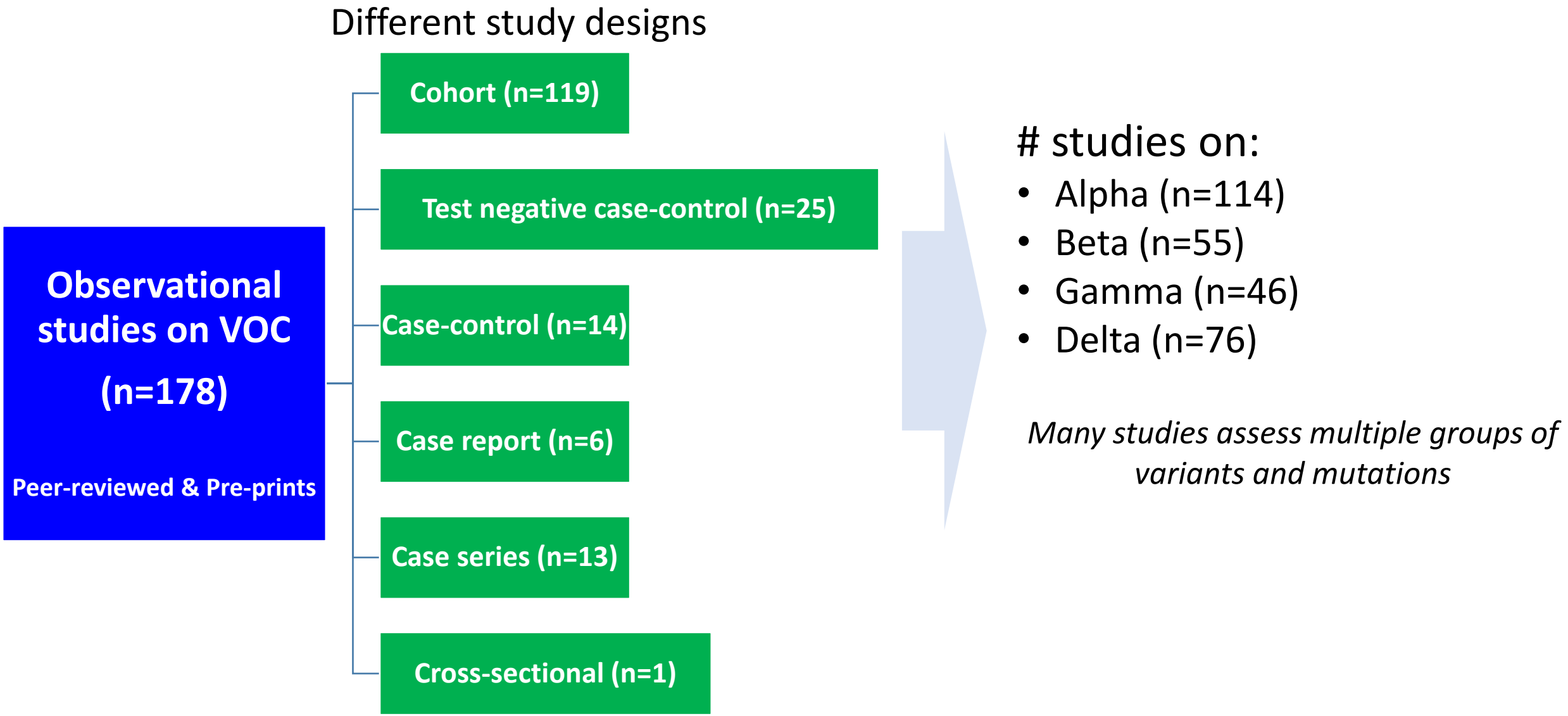
The document provides an overview of the different observational studies that are being conducted to assess the effectiveness of COVID-19 vaccination, including key features in terms of study design, sample size, study population, key outcomes measured and location of study. *(This document is in draft form as it is work in progress).*

These landscape documents have been prepared by WHO for information purposes only concerning the 2019-2020 global of the novel coronavirus. Inclusion of any particular product or entity in any of these landscape documents does not constitute, and shall not be deemed or construed as, any approval or endorsement by WHO of such product or entity (or any of its businesses or activities). While WHO takes reasonable steps to verify the accuracy of the information presented in these landscape documents, WHO

https://www.who.int/publications/m/item/draft-landscape-of-observational-study-designs-on-the-effectiveness-of-covid-19-vaccination

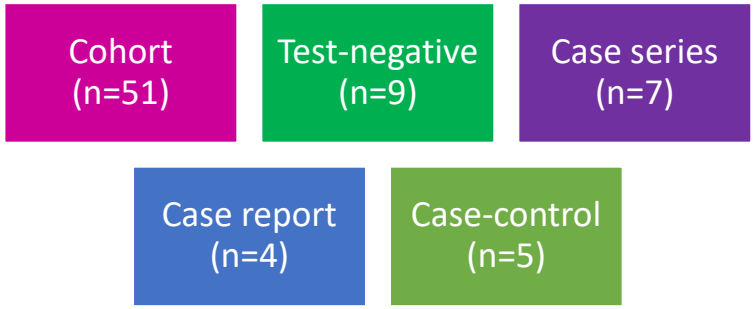


Observational studies on vaccine effectiveness against variants of concern (VOC)



Monitoring/tracking published observational studies on Delta variant

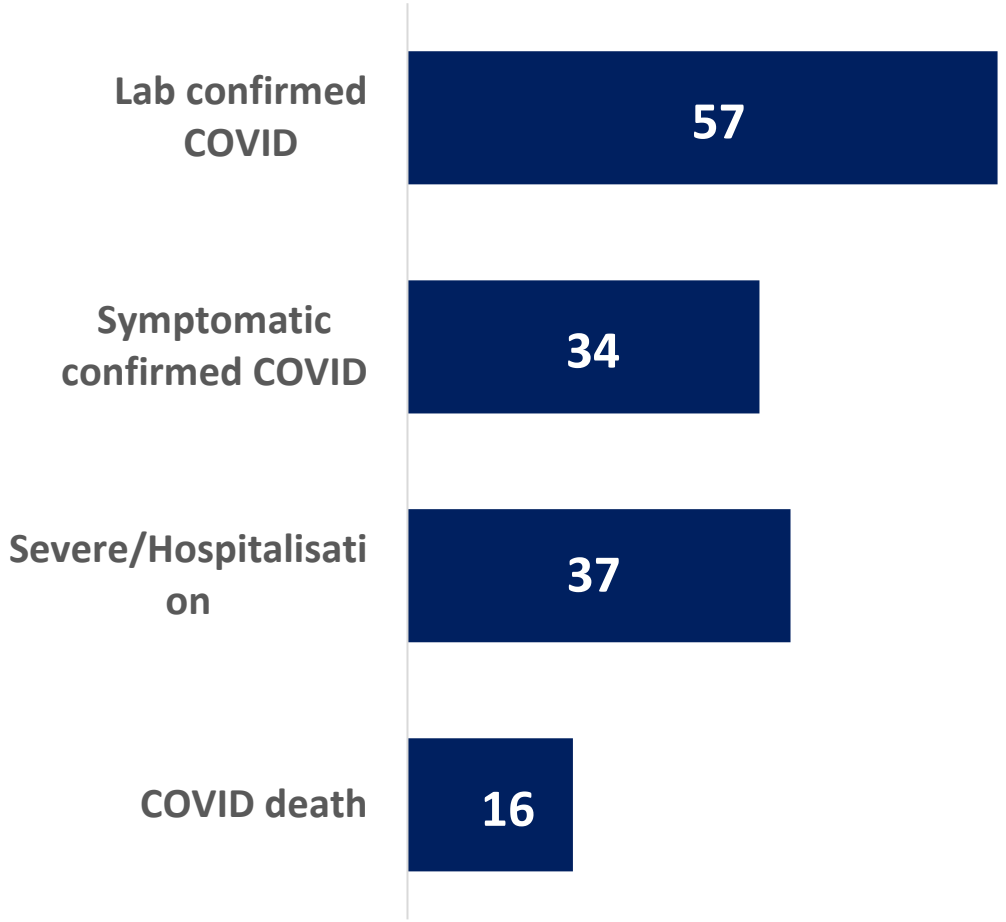
- 76 studies on Delta variant assess immunogenicity and/or vaccine effectiveness (number of studies are increasing weekly)



- Study populations:
  - General community, healthcare workers, elderly, immunocompromised

- Majority of studies assess the mRNA vaccines:
  - 49 studies with mRNA vaccines
  - 34 studies with viral vector vaccines
  - 13 studies with inactivated vaccine

76 studies on Delta variant assess vaccine effectiveness endpoints:



Considerations in boosting COVID-19 vaccine immune responses

Philip R Krause, Thomas R Fleming, Richard Peto, Ira M Longini, J Peter Figueroa, Jonathan A C Sterne, Alejandro Cravioto, Helen Rees, Julian P T Higgins, Isabelle Boutron, Hongchao Pan, Marion F Gruber, Narendra Arora, Fatema Kazi, Rogerio Gaspar, Soumya Swaminathan, Michael J Ryan, Ana-Maria Henao-Restrepo

A new wave of COVID-19 cases caused by the highly transmissible delta variant is exacerbating the worldwide public health crisis, and has led to consideration of the potential need for, and optimal timing of, booster doses for vaccinated populations.[1] Although the idea of further be implications for vaccine acceptance that go beyond COVID-19 vaccines. Thus, widespread boosting should be undertaken only if there is clear evidence that it is appropriate.

Findings from randomised trials have reliably shown

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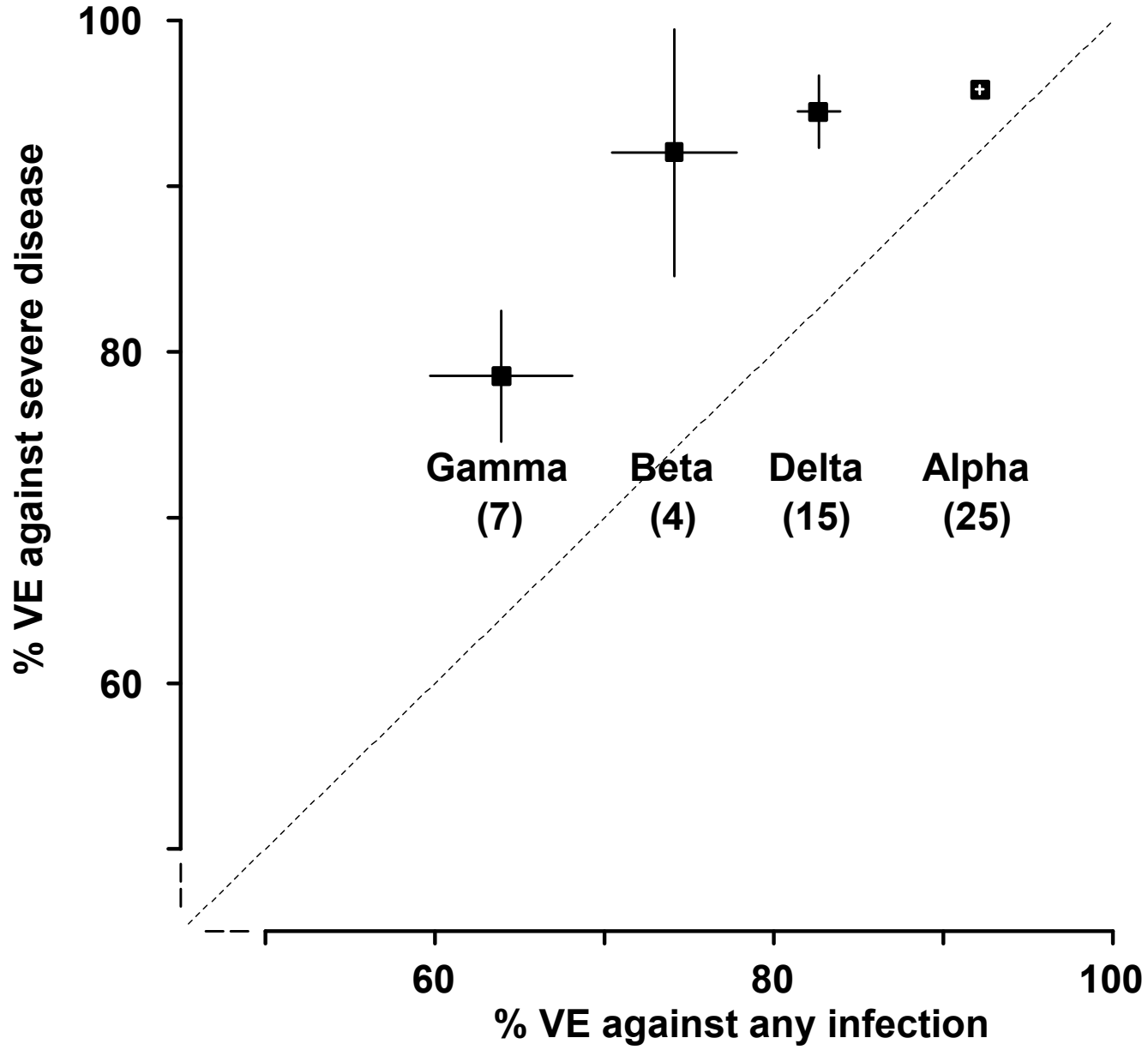
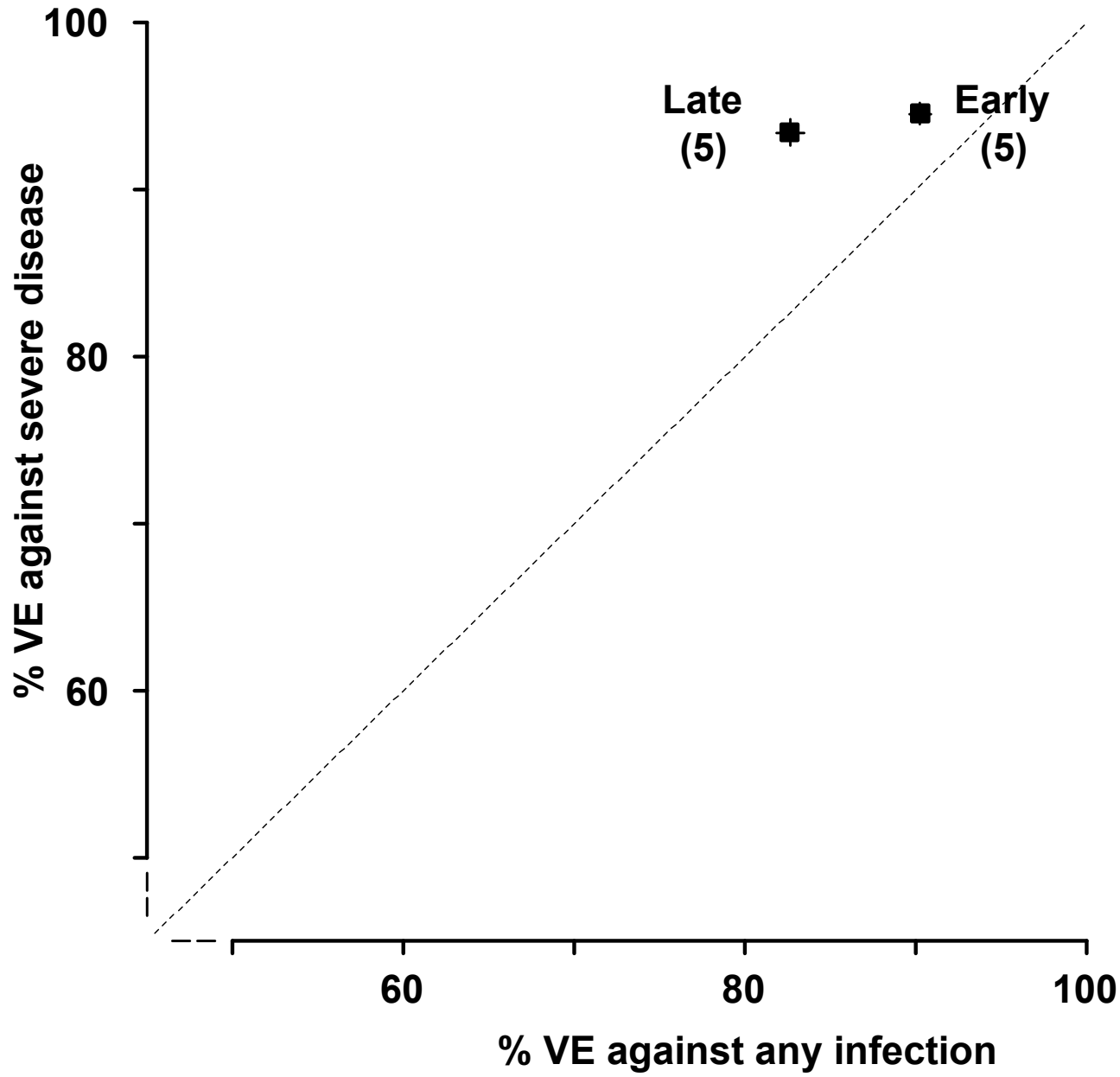
S0140-6736(21)02046-8

Office of Vaccines Research and Review, Food and Drug

Efficacy by viral variant



Efficacy for early versus later follow up of same study



Efficacy of mRNA vaccines against severe disease in settings where Delta variant is circulating, Sept 2021

Study Location (reference)	Vaccine	Effectiveness vs. severe disease or hospitalization	Lower limit of 95% CI	Upper limit of 95% CI
USA, Southern California KPSC (1)	BNT162b2 or mRNA-1273	93	84	96
USA, Minnesota (2)	BNT162b2	75	24	94
	mRNA-1273	81	33	96
USA, New York (3)	BNT162b2; mRNA-1273; Ad26.COV2.S	94.4	92.7	95.7
USA 13 jurisdictions (5)	BNT162b2; mRNA-1273; Ad26.COV2.S	90.4	87.7	92.5
USA, 7 locations VISION network (7)	BNT162b2	87	85	90
	mRNA-1273	91	83	93
USA, 9 States VISION network (8)	BNT162b2	80	73	85
	mRNA-1273	95	92	97
USA, 5 VA Medical Centers (9)	mRNA-1273	89	80	94
USA (14)	mRNA-1273	96	91	98
Israel, (4)	BNT162b2	88	94	91
Qatar (10)	BNT162b2	89.7	61	98.1
Qatar (11)	mRNA-1273	100	41.2	100
Singapore (12)	BNT162b2 or mRNA-1273	93	66	98
UK (13)	BNT162b2	96	86	99

(1) Tartof SY, Slezak JM, Fischer H, et al. Six-Month Effectiveness of BNT162B2 mRNA COVID-19 Vaccine in a Large US Integrated Health System: A Retrospective Cohort Study. SSRN Electron J 2021. DOI:10.2139/ssrn.3909743.

(2) Puranik A, Lenehan P, Silvert E, et al. Comparison of Two Highly-Effective mRNA Vaccines for COVID-19 During Periods of Alpha and Delta Variant Prevalence. SSRN Electron J 2021. DOI:10.2139/ssrn.3902782.

(3) Rosenberg ES, Holtgrave DR, Dorabawila V, et al. New COVID-19 Cases and Hospitalizations Among Adults, by Vaccination Status — New York, May 3–July 25, 2021. MMWR Morb Mortal Wkly Rep 2021; 70. DOI:10.15585/mmwr.mm7034e1.

(4) Goldberg Y, Mandel M, Woodbridge Y, et al. Protection of previous SARS-CoV-2 infection is similar to that of BNT162b2 vaccine protection: A three-month nationwide experience from Israel. medRxiv 2021.

(5) Scoobie HM, Johnson PAG, Suthar AB, et al. Monitoring Incidence of COVID-19 Cases, Hospitalizations, and Deaths, by Vaccination Status
13 U.S. Jurisdictions, April 4–July 17, 2021. MMWR Morb Mortal Wkly Rep 2021. DOI: http://dx.doi.org/10.15585/mmwr.mm7037

(7) Thompson MG, Stenehjem E, Grannis S, et al. Effectiveness of Covid-19 Vaccines in Ambulatory and Inpatient Care Settings. New Engl J Med 2021. DOI:10.1056/NEJMoa2110362.

(8) Grannis SJ, Rowley EA, . Ong TC,et al. Interim Estimates of COVID-19 Vaccine Effectiveness Against COVID-19–Associated Emergency Department or Urgent Care Clinic Encounters and Hospitalizations Among Adults During SARS- CoV-2 B.1.617.2 (Delta) Variant Predominance — Nine States, June–August 202. MMWR Morb Mortal Wkly Rep 2021. DOI:DOI: http://dx.doi.org/10.15585/mmwr.mm7037e2.

(9) Bajema KL, . Dahl RM, Prill MM, et al. Effectiveness of COVID-19 mRNA Vaccines Against COVID-19–Associated Hospitalization — Five Veterans Affairs Medical Centers, United States, February 1–August 6, 2021. MMWR Morb Mortal Wkly Rep DOI:DOI: http://dx.doi.org/10.15585/mmwr.mm7037e3.

(10) Abu-Raddad LJ, Chemaitelly H, Butt AA. Effectiveness of the BNT162b2 Covid-19 Vaccine against the B.1.1.7 and B.1.351 Variants. N Engl J Med 2021; 385. DOI:10.1056/nejmc2104974.

(11) Tang P, Hasan MR, Chemaitelly H, et al. BNT162b2 and mRNA-1273 COVID-19 vaccine effectiveness against the Delta (B.1.617.2) variant in Qatar. medRxiv 2021.

(12) Chia PY, Xiang Ong SW, Chiew CJ, et al. Virological and serological kinetics of SARS-CoV-2 Delta variant vaccine-breakthrough infections: a multi-center cohort study. medRxiv 2021.

(13)Stowe J, Andrews N, Gower C, et al. Effectiveness of COVID-19 vaccines against hospital admission with the Delta (B.1.617.2) variant. Public Heal Engl 2021; 37.

(14) Bruxvoort K, Sy L, Qian L, et al . Real-World Effectiveness of the mRNA-1273 Vaccine Against COVID-19: Interim Results from a Prospective Observational Cohort Study. SSRN Electron J 2021.

Methodological issues in estimating vaccine efficacy during the rollout

Vaccine effectiveness in people aged over 70 years

- The OpenSAFELY Collaborative: William J Hulme, Elizabeth Williamson, Amelia Green, Helen I McDonald, Alex J Walker, Helen J Curtis, Caroline E Morton, Brian MacKenna, Richard Croker, Jessica Morley, Amir Mehrkar, Seb Bacon, David Evans, Peter Inglesby, George Hickman, Tom Ward, Simon Davy, Krishnan Bhaskaran, Anna Schultze, Daniel Grint, Christopher T Rentsch, Anna Rowan, Louis Fisher, Laurie Tomlinson, Rohini Mathur, John Tazare, Richard Grieve, Rosalind M Eggo, Kevin Wing, Angel YS Wong, Harriet Forbes, Chris Bates, Jonathan Cockburn, John Parry, Frank Hester, Sam Harper, Ian J Douglas, Stephen JW Evans, Liam Smeeth, Tom Palmer, Miguel Hernan, Jonathan A C Sterne, Ben Goldacre
- 667,024 people aged 80+ years, 1,418,760 people aged 70-79 years

https://www.opensafely.org

My examples are from analyses of UK (English) data but they illustrate general issues in trying to estimate vaccine effectiveness from observational data

Methodological issues in estimating COVID-19 vaccine effectiveness

1. Baseline confounding (presence of characteristics predicting both vaccination and outcome)
2. Defining the comparison group
   - Very rapid rollout of vaccination, so unvaccinated people rapidly become vaccinated
   - Solution: split follow up time for each individual into unvaccinated and post-vaccination
3. Time-varying confounding
4. Unmeasured confounding
5. Accounting for pandemic waves
6. Characterising persistently unvaccinated individuals

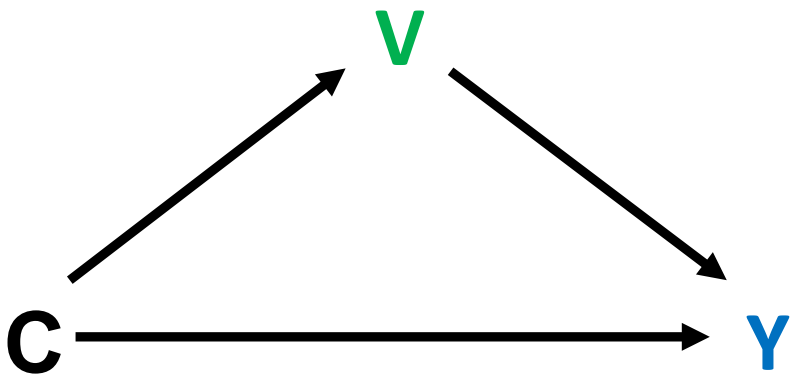
Confounding

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

vaccination (V)

and

the outcome event (Y)



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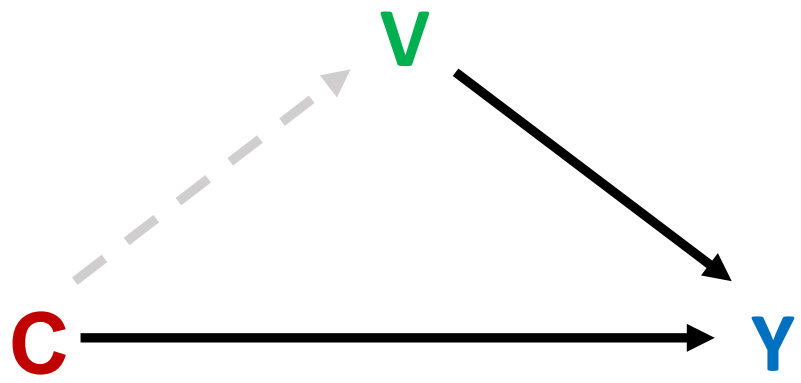
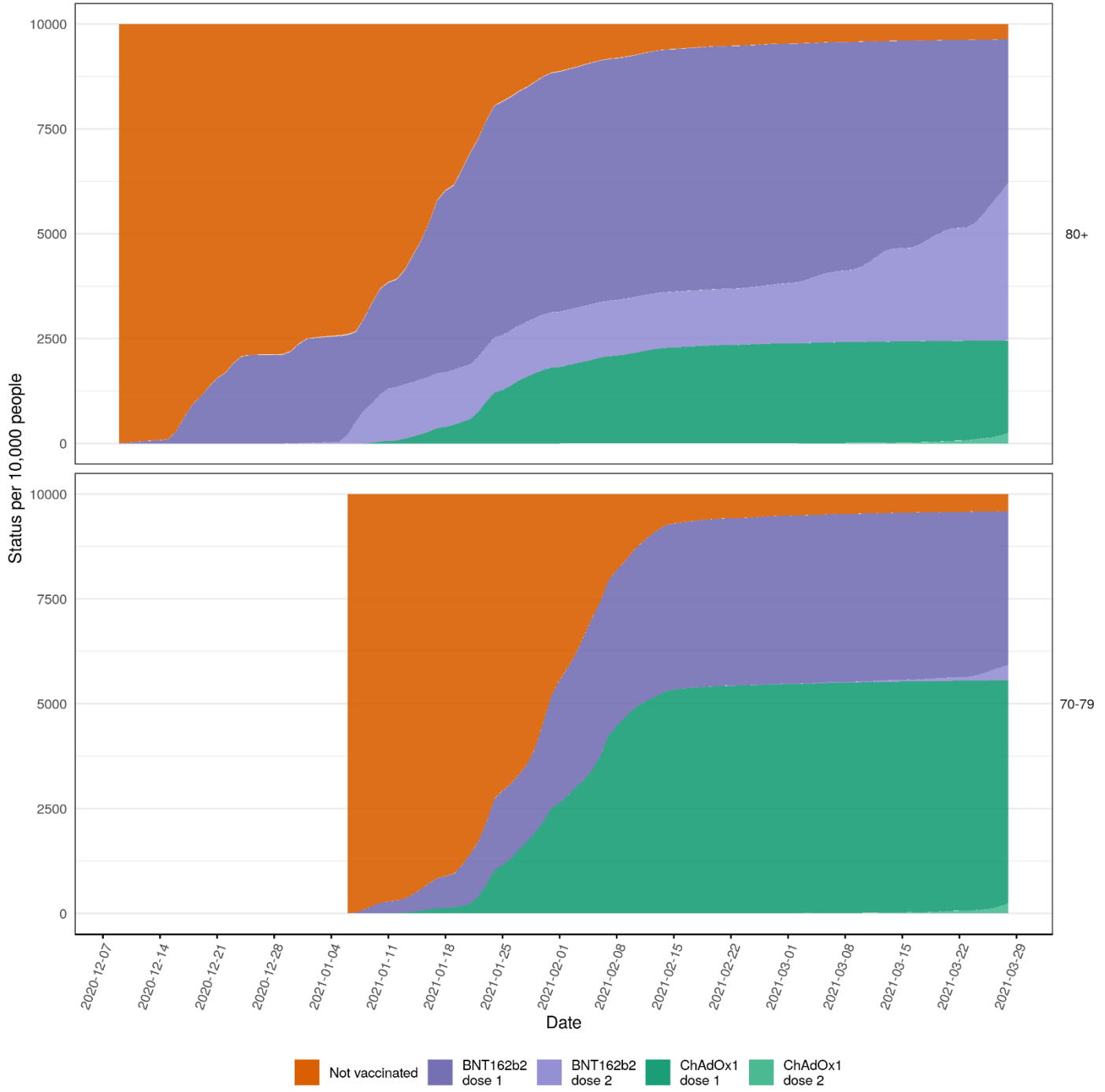
Randomization removes these links by ensuring that only chance determines whether someone is vaccinated



Vaccination status over time



COVID-19 LONGITUDINAL HEALTH & WELLBEING NATIONAL CORE STUDY

OpenSAFELY

NUFFIELD DEPARTMENT OF PRIMARY CARE HEALTH SCIENCES Medical Sciences Division

DataLab

Characteristics predicting vaccination

		People aged 80 years and over		People aged 70-79 years	
		BNT162b2	ChAdOx1	BNT162b2	ChAdOx1
Age per 5 years		1.64 (1.52-1.77)	0.96 (0.87-1.06)	0.57 (0.43-0.74)	1.65 (1.30-2.11)
IMD	2	1.14 (1.10-1.17)	1.09 (1.05-1.14)	1.14 (1.10-1.19)	1.14 (1.11-1.18)
ref: 1, most deprived	3	1.18 (1.15-1.22)	1.20 (1.15-1.25)	1.11 (1.07-1.15)	1.22 (1.18-1.26)
	4	1.28 (1.24-1.31)	1.31 (1.25-1.37)	1.19 (1.15-1.24)	1.22 (1.18-1.26)
	5	1.38 (1.34-1.42)	1.31 (1.25-1.38)	1.41 (1.36-1.46)	1.25 (1.21-1.29)
Ethnicity	Black	0.46 (0.41-0.52)	0.47 (0.40-0.55)	0.50 (0.40-0.61)	0.45 (0.38-0.54)
ref: White	South Asian	0.47 (0.44-0.50)	0.45 (0.42-0.49)	0.60 (0.56-0.65)	0.61 (0.58-0.65)
	Mixed	0.71 (0.60-0.85)	0.78 (0.62-0.98)	0.51 (0.37-0.69)	0.64 (0.51-0.80)
	Other	0.81 (0.70-0.93)	0.67 (0.54-0.83)	0.70 (0.58-0.85)	0.75 (0.64-0.87)
Body Mass Index (kg/m2)	30-34.9	1.01 (0.99-1.04)	0.97 (0.93-1.01)	1.07 (1.03-1.10)	1.02 (1.00-1.05)
Ref: <30 or not recorded	35-39.9	0.87 (0.82-0.92)	1.05 (0.96-1.15)	0.98 (0.90-1.06)	1.01 (0.95-1.09)
	40+	0.71 (0.65-0.77)	1.04 (0.92-1.17)	0.93 (0.84-1.03)	0.96 (0.89-1.04)
Heart failure		0.92 (0.89-0.95)	1.01 (0.96-1.06)	0.96 (0.90-1.02)	0.92 (0.87-0.97)
Other heart disease		1.02 (0.98-1.06)	1.08 (1.02-1.14)	1.03 (0.96-1.11)	0.99 (0.93-1.05)
COPD		0.94 (0.90-0.98)	0.97 (0.90-1.03)	0.94 (0.87-1.01)	0.95 (0.89-1.01)
Other respiratory conditions		0.94 (0.90-0.99)	1.01 (0.95-1.08)	0.94 (0.88-1.02)	0.94 (0.89-1.00)
Dementia		0.71 (0.67-0.74)	1.02 (0.95-1.09)	0.86 (0.78-0.96)	0.86 (0.79-0.94)
Other neurological conditions		0.75 (0.70-0.80)	1.02 (0.94-1.11)	0.87 (0.78-0.97)	0.98 (0.90-1.07)
Learning disabilities		0.57 (0.38-0.85)	0.94 (0.61-1.44)	0.60 (0.44-0.80)	0.64 (0.52-0.79)
Serious mental illness		0.65 (0.58-0.73)	0.93 (0.80-1.07)	0.68 (0.59-0.79)	0.82 (0.73-0.91)
Morbidity count ref: 0	1	1.05 (1.00-1.09)	0.93 (0.87-1.00)	1.01 (0.94-1.09)	1.02 (0.96-1.08)
	2	1.10 (1.02-1.20)	0.87 (0.78-0.98)	1.04 (0.91-1.20)	1.02 (0.91-1.15)
	3	1.18 (1.05-1.33)	0.85 (0.71-1.01)	1.10 (0.89-1.35)	1.07 (0.90-1.27)
	4+	1.23 (1.04-1.46)	0.77 (0.60-0.98)	1.09 (0.81-1.47)	0.99 (0.77-1.26)
Shielding criteria met		1.01 (0.99-1.04)	1.08 (1.04-1.13)	1.07 (1.03-1.12)	1.08 (1.04-1.12)
Flu vaccine in previous 5 years		1.87 (1.82-1.93)	2.02 (1.94-2.11)	1.59 (1.53-1.64)	1.73 (1.69-1.78)
Frailty	Mild	1.09 (1.05-1.13)	1.36 (1.27-1.47)	1.06 (1.03-1.09)	1.07 (1.05-1.10)
ref: None	Moderate	1.03 (0.99-1.06)	1.39 (1.29-1.50)	1.00 (0.96-1.04)	1.07 (1.03-1.10)
	Severe	0.88 (0.85-0.92)	1.42 (1.31-1.53)	0.91 (0.85-0.97)	1.02 (0.96-1.07)

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Frailty	Mild	1.09 (1.05-1.13)	1.36 (1.27-1.47)	1.06 (1.03-1.09)	1.07 (1.05-1.10)
ref: None	Moderate	1.03 (0.99-1.06)	1.39 (1.29-1.50)	1.00 (0.96-1.04)	1.07 (1.03-1.10)
	Severe	0.88 (0.85-0.92)	1.42 (1.31-1.53)	0.91 (0.85-0.97)	1.02 (0.96-1.07)

Characteristics predicting vaccination

		People aged 80 years and over		People aged 70-79 years	
		BNT162b2	ChAdOx1	BNT162b2	ChAdOx1
Age per 5 years		1.64 (1.52-1.77)	0.96 (0.87-1.06)	0.57 (0.43-0.74)	1.65 (1.30-2.11)
IMD	2	1.14 (1.10-1.17)	1.09 (1.05-1.14)	1.14 (1.10-1.19)	1.14 (1.11-1.18)
ref: 1, most deprived	3	1.18 (1.15-1.22)	1.20 (1.15-1.25)	1.11 (1.07-1.15)	1.22 (1.18-1.26)
	4	1.28 (1.24-1.31)	1.31 (1.25-1.37)	1.19 (1.15-1.24)	1.22 (1.18-1.26)
	5	1.38 (1.34-1.42)	1.31 (1.25-1.38)	1.41 (1.36-1.46)	1.25 (1.21-1.29)
Ethnicity	Black	0.46 (0.41-0.52)	0.47 (0.40-0.55)	0.50 (0.40-0.61)	0.45 (0.38-0.54)
ref: White	South Asian	0.47 (0.44-0.50)	0.45 (0.42-0.49)	0.60 (0.56-0.65)	0.61 (0.58-0.65)
	Mixed	0.71 (0.60-0.85)	0.78 (0.62-0.98)	0.51 (0.37-0.69)	0.64 (0.51-0.80)
	Other	0.81 (0.70-0.93)	0.67 (0.54-0.83)	0.70 (0.58-0.85)	0.75 (0.64-0.87)
Body Mass Index (kg/m2)	30-34.9	1.01 (0.99-1.04)	0.97 (0.93-1.01)	1.07 (1.03-1.10)	1.02 (1.00-1.05)
Ref: <30 or not recorded	35-39.9	0.87 (0.82-0.92)	1.05 (0.96-1.15)	0.98 (0.90-1.06)	1.01 (0.95-1.09)
	40+	0.71 (0.65-0.77)	1.04 (0.92-1.17)	0.93 (0.84-1.03)	0.96 (0.89-1.04)
Heart failure		0.92 (0.89-0.95)	1.01 (0.96-1.06)	0.96 (0.90-1.02)	0.92 (0.87-0.97)
Other heart disease		1.02 (0.98-1.06)	1.08 (1.02-1.14)	1.03 (0.96-1.11)	0.99 (0.93-1.05)
COPD		0.94 (0.90-0.98)	0.97 (0.90-1.03)	0.94 (0.87-1.01)	0.95 (0.89-1.01)
Other respiratory conditions		0.94 (0.90-0.99)	1.01 (0.95-1.08)	0.94 (0.88-1.02)	0.94 (0.89-1.00)
Dementia		0.71 (0.67-0.74)	1.02 (0.95-1.09)	0.86 (0.78-0.96)	0.86 (0.79-0.94)
Other neurological conditions		0.75 (0.70-0.80)	1.02 (0.94-1.11)	0.87 (0.78-0.97)	0.98 (0.90-1.07)
Learning disabilities		0.57 (0.38-0.85)	0.94 (0.61-1.44)	0.60 (0.44-0.80)	0.64 (0.52-0.79)
Serious mental illness		0.65 (0.58-0.73)	0.93 (0.80-1.07)	0.68 (0.59-0.79)	0.82 (0.73-0.91)
Morbidity count ref: 0	1	1.05 (1.00-1.09)	0.93 (0.87-1.00)	1.01 (0.94-1.09)	1.02 (0.96-1.08)
	2	1.10 (1.02-1.20)	0.87 (0.78-0.98)	1.04 (0.91-1.20)	1.02 (0.91-1.15)
	3	1.18 (1.05-1.33)	0.85 (0.71-1.01)	1.10 (0.89-1.35)	1.07 (0.90-1.27)
	4+	1.23 (1.04-1.46)	0.77 (0.60-0.98)	1.09 (0.81-1.47)	0.99 (0.77-1.26)
Shielding criteria met		1.01 (0.99-1.04)	1.08 (1.04-1.13)	1.07 (1.03-1.12)	1.08 (1.04-1.12)
Flu vaccine in previous 5 years		1.87 (1.82-1.93)	2.02 (1.94-2.11)	1.59 (1.53-1.64)	1.73 (1.69-1.78)
Frailty	Mild	1.09 (1.05-1.13)	1.36 (1.27-1.47)	1.06 (1.03-1.09)	1.07 (1.05-1.10)
ref: None	Moderate	1.03 (0.99-1.06)	1.39 (1.29-1.50)	1.00 (0.96-1.04)	1.07 (1.03-1.10)
	Severe	0.88 (0.85-0.92)	1.42 (1.31-1.53)	0.91 (0.85-0.97)	1.02 (0.96-1.07)

Characteristics predicting vaccination

		People aged 80 years and over		People aged 70-79 years	
		BNT162b2	ChAdOx1	BNT162b2	ChAdOx1
Age per 5 years		1.64 (1.52-1.77)	0.96 (0.87-1.06)	0.57 (0.43-0.74)	1.65 (1.30-2.11)
IMD	2	1.14 (1.10-1.17)	1.09 (1.05-1.14)	1.14 (1.10-1.19)	1.14 (1.11-1.18)
ref: 1, most deprived	3	1.18 (1.15-1.22)	1.20 (1.15-1.25)	1.11 (1.07-1.15)	1.22 (1.18-1.26)
	4	1.28 (1.24-1.31)	1.31 (1.25-1.37)	1.19 (1.15-1.24)	1.22 (1.18-1.26)
	5	1.38 (1.34-1.42)	1.31 (1.25-1.38)	1.41 (1.36-1.46)	1.25 (1.21-1.29)
Ethnicity	Black	0.46 (0.41-0.52)	0.47 (0.40-0.55)	0.50 (0.40-0.61)	0.45 (0.38-0.54)
ref: White	South Asian	0.47 (0.44-0.50)	0.45 (0.42-0.49)	0.60 (0.56-0.65)	0.61 (0.58-0.65)
	Mixed	0.71 (0.60-0.85)	0.78 (0.62-0.98)	0.51 (0.37-0.69)	0.64 (0.51-0.80)
	Other	0.81 (0.70-0.93)	0.67 (0.54-0.83)	0.70 (0.58-0.85)	0.75 (0.64-0.87)
Body Mass Index (kg/m2)	30-34.9	1.01 (0.99-1.04)	0.97 (0.93-1.01)	1.07 (1.03-1.10)	1.02 (1.00-1.05)
Ref: <30 or not recorded	35-39.9	0.87 (0.82-0.92)	1.05 (0.96-1.15)	0.98 (0.90-1.06)	1.01 (0.95-1.09)
	40+	0.71 (0.65-0.77)	1.04 (0.92-1.17)	0.93 (0.84-1.03)	0.96 (0.89-1.04)
Heart failure		0.92 (0.89-0.95)	1.01 (0.96-1.06)	0.96 (0.90-1.02)	0.92 (0.87-0.97)
Other heart disease		1.02 (0.98-1.06)	1.08 (1.02-1.14)	1.03 (0.96-1.11)	0.99 (0.93-1.05)
COPD		0.94 (0.90-0.98)	0.97 (0.90-1.03)	0.94 (0.87-1.01)	0.95 (0.89-1.01)
Other respiratory conditions		0.94 (0.90-0.99)	1.01 (0.95-1.08)	0.94 (0.88-1.02)	0.94 (0.89-1.00)
Dementia		0.71 (0.67-0.74)	1.02 (0.95-1.09)	0.86 (0.78-0.96)	0.86 (0.79-0.94)
Other neurological conditions		0.75 (0.70-0.80)	1.02 (0.94-1.11)	0.87 (0.78-0.97)	0.98 (0.90-1.07)
Learning disabilities		0.57 (0.38-0.85)	0.94 (0.61-1.44)	0.60 (0.44-0.80)	0.64 (0.52-0.79)
Serious mental illness		0.65 (0.58-0.73)	0.93 (0.80-1.07)	0.68 (0.59-0.79)	0.82 (0.73-0.91)
Morbidity count ref: 0	1	1.05 (1.00-1.09)	0.93 (0.87-1.00)	1.01 (0.94-1.09)	1.02 (0.96-1.08)
	2	1.10 (1.02-1.20)	0.87 (0.78-0.98)	1.04 (0.91-1.20)	1.02 (0.91-1.15)
	3	1.18 (1.05-1.33)	0.85 (0.71-1.01)	1.10 (0.89-1.35)	1.07 (0.90-1.27)
	4+	1.23 (1.04-1.46)	0.77 (0.60-0.98)	1.09 (0.81-1.47)	0.99 (0.77-1.26)
Shielding criteria met		1.01 (0.99-1.04)	1.08 (1.04-1.13)	1.07 (1.03-1.12)	1.08 (1.04-1.12)
Flu vaccine in previous 5 years		1.87 (1.82-1.93)	2.02 (1.94-2.11)	1.59 (1.53-1.64)	1.73 (1.69-1.78)
Frailty	Mild	1.09 (1.05-1.13)	1.36 (1.27-1.47)	1.06 (1.03-1.09)	1.07 (1.05-1.10)
ref: None	Moderate	1.03 (0.99-1.06)	1.39 (1.29-1.50)	1.00 (0.96-1.04)	1.07 (1.03-1.10)
	Severe	0.88 (0.85-0.92)	1.42 (1.31-1.53)	0.91 (0.85-0.97)	1.02 (0.96-1.07)

Characteristics predicting vaccination

		People aged 80 years and over		People aged 70-79 years	
		BNT162b2	ChAdOx1	BNT162b2	ChAdOx1
Age per 5 years		1.64 (1.52-1.77)	0.96 (0.87-1.06)	0.57 (0.43-0.74)	1.65 (1.30-2.11)
IMD	2	1.14 (1.10-1.17)	1.09 (1.05-1.14)	1.14 (1.10-1.19)	1.14 (1.11-1.18)
ref: 1, most deprived	3	1.18 (1.15-1.22)	1.20 (1.15-1.25)	1.11 (1.07-1.15)	1.22 (1.18-1.26)
	4	1.28 (1.24-1.31)	1.31 (1.25-1.37)	1.19 (1.15-1.24)	1.22 (1.18-1.26)
	5	1.38 (1.34-1.42)	1.31 (1.25-1.38)	1.41 (1.36-1.46)	1.25 (1.21-1.29)
Ethnicity	Black	0.46 (0.41-0.52)	0.47 (0.40-0.55)	0.50 (0.40-0.61)	0.45 (0.38-0.54)
ref: White	South Asian	0.47 (0.44-0.50)	0.45 (0.42-0.49)	0.60 (0.56-0.65)	0.61 (0.58-0.65)
	Mixed	0.71 (0.60-0.85)	0.78 (0.62-0.98)	0.51 (0.37-0.69)	0.64 (0.51-0.80)
	Other	0.81 (0.70-0.93)	0.67 (0.54-0.83)	0.70 (0.58-0.85)	0.75 (0.64-0.87)
Body Mass Index (kg/m2)	30-34.9	1.01 (0.99-1.04)	0.97 (0.93-1.01)	1.07 (1.03-1.10)	1.02 (1.00-1.05)
Ref: <30 or not recorded	35-39.9	0.87 (0.82-0.92)	1.05 (0.96-1.15)	0.98 (0.90-1.06)	1.01 (0.95-1.09)
	40+	0.71 (0.65-0.77)	1.04 (0.92-1.17)	0.93 (0.84-1.03)	0.96 (0.89-1.04)
Heart failure		0.92 (0.89-0.95)	1.01 (0.96-1.06)	0.96 (0.90-1.02)	0.92 (0.87-0.97)
Other heart disease		1.02 (0.98-1.06)	1.08 (1.02-1.14)	1.03 (0.96-1.11)	0.99 (0.93-1.05)
COPD		0.94 (0.90-0.98)	0.97 (0.90-1.03)	0.94 (0.87-1.01)	0.95 (0.89-1.01)
Other respiratory conditions		0.94 (0.90-0.99)	1.01 (0.95-1.08)	0.94 (0.88-1.02)	0.94 (0.89-1.00)
Dementia		0.71 (0.67-0.74)	1.02 (0.95-1.09)	0.86 (0.78-0.96)	0.86 (0.79-0.94)
Other neurological conditions		0.75 (0.70-0.80)	1.02 (0.94-1.11)	0.87 (0.78-0.97)	0.98 (0.90-1.07)
Learning disabilities		0.57 (0.38-0.85)	0.94 (0.61-1.44)	0.60 (0.44-0.80)	0.64 (0.52-0.79)
Serious mental illness		0.65 (0.58-0.73)	0.93 (0.80-1.07)	0.68 (0.59-0.79)	0.82 (0.73-0.91)
Morbidity count ref: 0	1	1.05 (1.00-1.09)	0.93 (0.87-1.00)	1.01 (0.94-1.09)	1.02 (0.96-1.08)
	2	1.10 (1.02-1.20)	0.87 (0.78-0.98)	1.04 (0.91-1.20)	1.02 (0.91-1.15)
	3	1.18 (1.05-1.33)	0.85 (0.71-1.01)	1.10 (0.89-1.35)	1.07 (0.90-1.27)
	4+	1.23 (1.04-1.46)	0.77 (0.60-0.98)	1.09 (0.81-1.47)	0.99 (0.77-1.26)
Shielding criteria met		1.01 (0.99-1.04)	1.08 (1.04-1.13)	1.07 (1.03-1.12)	1.08 (1.04-1.12)
Flu vaccine in previous 5 years		1.87 (1.82-1.93)	2.02 (1.94-2.11)	1.59 (1.53-1.64)	1.73 (1.69-1.78)
Frailty	Mild	1.09 (1.05-1.13)	1.36 (1.27-1.47)	1.06 (1.03-1.09)	1.07 (1.05-1.10)
ref: None	Moderate	1.03 (0.99-1.06)	1.39 (1.29-1.50)	1.00 (0.96-1.04)	1.07 (1.03-1.10)
	Severe	0.88 (0.85-0.92)	1.42 (1.31-1.53)	0.91 (0.85-0.97)	1.02 (0.96-1.07)

Characteristics predicting vaccination

		People aged 80 years and over		People aged 70-79 years	
		BNT162b2	ChAdOx1	BNT162b2	ChAdOx1
Age per 5 years		1.64 (1.52-1.77)	0.96 (0.87-1.06)	0.57 (0.43-0.74)	1.65 (1.30-2.11)
IMD	2	1.14 (1.10-1.17)	1.09 (1.05-1.14)	1.14 (1.10-1.19)	1.14 (1.11-1.18)
ref: 1, most deprived	3	1.18 (1.15-1.22)	1.20 (1.15-1.25)	1.11 (1.07-1.15)	1.22 (1.18-1.26)
	4	1.28 (1.24-1.31)	1.31 (1.25-1.37)	1.19 (1.15-1.24)	1.22 (1.18-1.26)
	5	1.38 (1.34-1.42)	1.31 (1.25-1.38)	1.41 (1.36-1.46)	1.25 (1.21-1.29)
Ethnicity	Black	0.46 (0.41-0.52)	0.47 (0.40-0.55)	0.50 (0.40-0.61)	0.45 (0.38-0.54)
ref: White	South Asian	0.47 (0.44-0.50)	0.45 (0.42-0.49)	0.60 (0.56-0.65)	0.61 (0.58-0.65)
	Mixed	0.71 (0.60-0.85)	0.78 (0.62-0.98)	0.51 (0.37-0.69)	0.64 (0.51-0.80)
	Other	0.81 (0.70-0.93)	0.67 (0.54-0.83)	0.70 (0.58-0.85)	0.75 (0.64-0.87)
Body Mass Index (kg/m2)	30-34.9	1.01 (0.99-1.04)	0.97 (0.93-1.01)	1.07 (1.03-1.10)	1.02 (1.00-1.05)
Ref: <30 or not recorded	35-39.9	0.87 (0.82-0.92)	1.05 (0.96-1.15)	0.98 (0.90-1.06)	1.01 (0.95-1.09)
	40+	0.71 (0.65-0.77)	1.04 (0.92-1.17)	0.93 (0.84-1.03)	0.96 (0.89-1.04)
Heart failure		0.92 (0.89-0.95)	1.01 (0.96-1.06)	0.96 (0.90-1.02)	0.92 (0.87-0.97)
Other heart disease		1.02 (0.98-1.06)	1.08 (1.02-1.14)	1.03 (0.96-1.11)	0.99 (0.93-1.05)
COPD		0.94 (0.90-0.98)	0.97 (0.90-1.03)	0.94 (0.87-1.01)	0.95 (0.89-1.01)
Other respiratory conditions		0.94 (0.90-0.99)	1.01 (0.95-1.08)	0.94 (0.88-1.02)	0.94 (0.89-1.00)
Dementia		0.71 (0.67-0.74)	1.02 (0.95-1.09)	0.86 (0.78-0.96)	0.86 (0.79-0.94)
Other neurological conditions		0.75 (0.70-0.80)	1.02 (0.94-1.11)	0.87 (0.78-0.97)	0.98 (0.90-1.07)
Learning disabilities		0.57 (0.38-0.85)	0.94 (0.61-1.44)	0.60 (0.44-0.80)	0.64 (0.52-0.79)
Serious mental illness		0.65 (0.58-0.73)	0.93 (0.80-1.07)	0.68 (0.59-0.79)	0.82 (0.73-0.91)
Morbidity count ref: 0	1	1.05 (1.00-1.09)	0.93 (0.87-1.00)	1.01 (0.94-1.09)	1.02 (0.96-1.08)
	2	1.10 (1.02-1.20)	0.87 (0.78-0.98)	1.04 (0.91-1.20)	1.02 (0.91-1.15)
	3	1.18 (1.05-1.33)	0.85 (0.71-1.01)	1.10 (0.89-1.35)	1.07 (0.90-1.27)
	4+	1.23 (1.04-1.46)	0.77 (0.60-0.98)	1.09 (0.81-1.47)	0.99 (0.77-1.26)
Shielding criteria met		1.01 (0.99-1.04)	1.08 (1.04-1.13)	1.07 (1.03-1.12)	1.08 (1.04-1.12)
Flu vaccine in previous 5 years		1.87 (1.82-1.93)	2.02 (1.94-2.11)	1.59 (1.53-1.64)	1.73 (1.69-1.78)
Frailty	Mild	1.09 (1.05-1.13)	1.36 (1.27-1.47)	1.06 (1.03-1.09)	1.07 (1.05-1.10)
ref: None	Moderate	1.03 (0.99-1.06)	1.39 (1.29-1.50)	1.00 (0.96-1.04)	1.07 (1.03-1.10)
	Severe	0.88 (0.85-0.92)	1.42 (1.31-1.53)	0.91 (0.85-0.97)	1.02 (0.96-1.07)

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).

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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).

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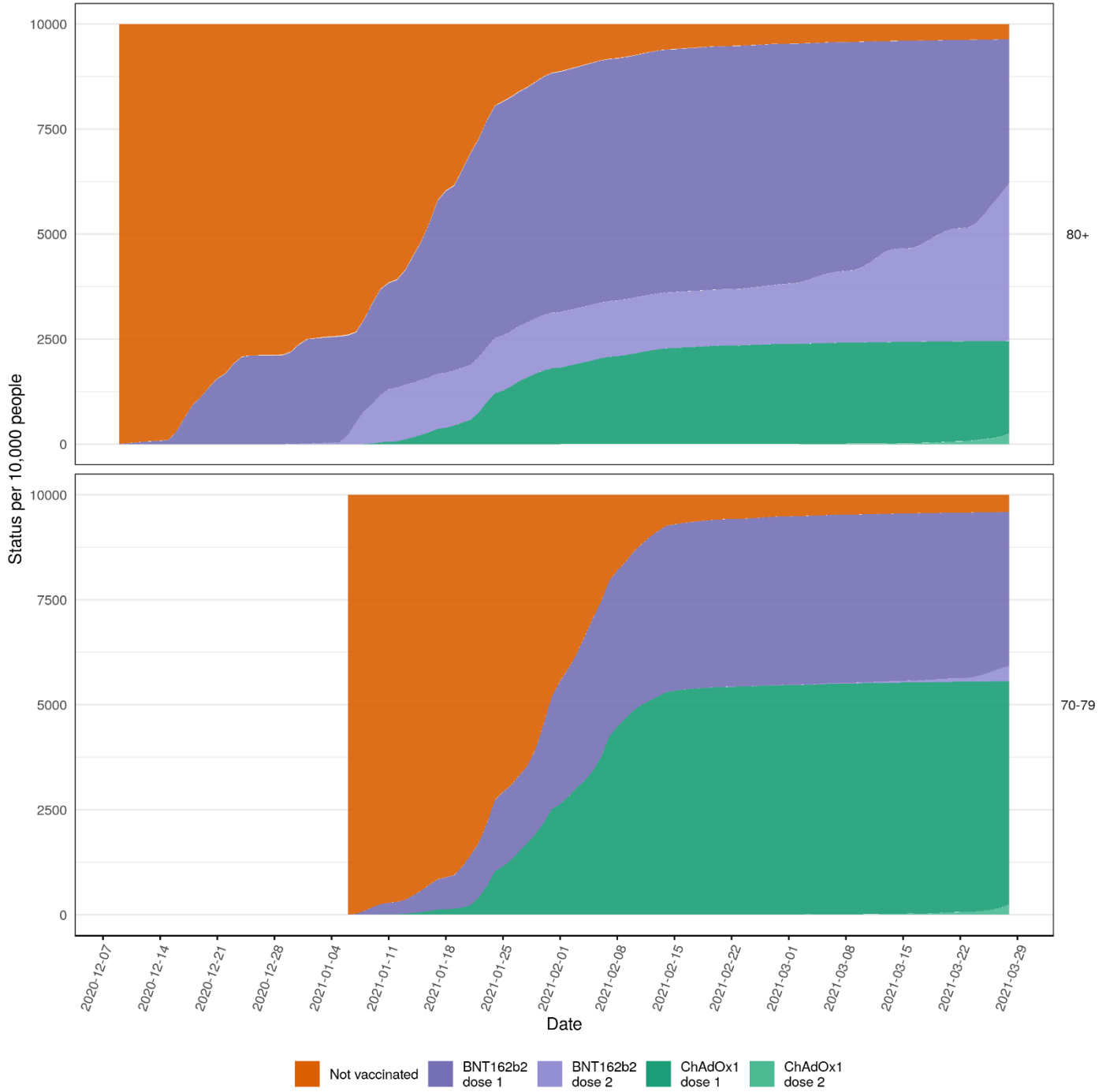
In this issue of the *Journal*, Sullivan et al. (*Am J Epidemiol*. 2016;184(5):345–353) carefully examine the theoretical justification for use of the test-negative design, a common observational study design, in assessing the effectiveness of influenza vaccination. Using modern causal inference methods (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

Careful evaluation of the potential for bias in estimates of VE from test negative designs seems warranted

Vaccination status over time

Unvaccinated people are rapidly vaccinated



COVID-19 LONGITUDINAL HEALTH & WELLBEING NATIONAL CORE STUDY

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UNIVERSITY OF OXFORD

NUFFIELD DEPARTMENT OF PRIMARY CARE HEALTH SCIENCES Medical Sciences Division

DataLab

Methodological issues in estimating COVID-19 vaccine effectiveness

1. Baseline confounding (presence of characteristics predicting both vaccination and outcome)
2. Defining the comparison group
   - Very rapid rollout of vaccination, so unvaccinated people rapidly become vaccinated
   - Solution: split follow up time for each individual into unvaccinated and post-vaccination
3. Time-varying confounding
4. Unmeasured confounding
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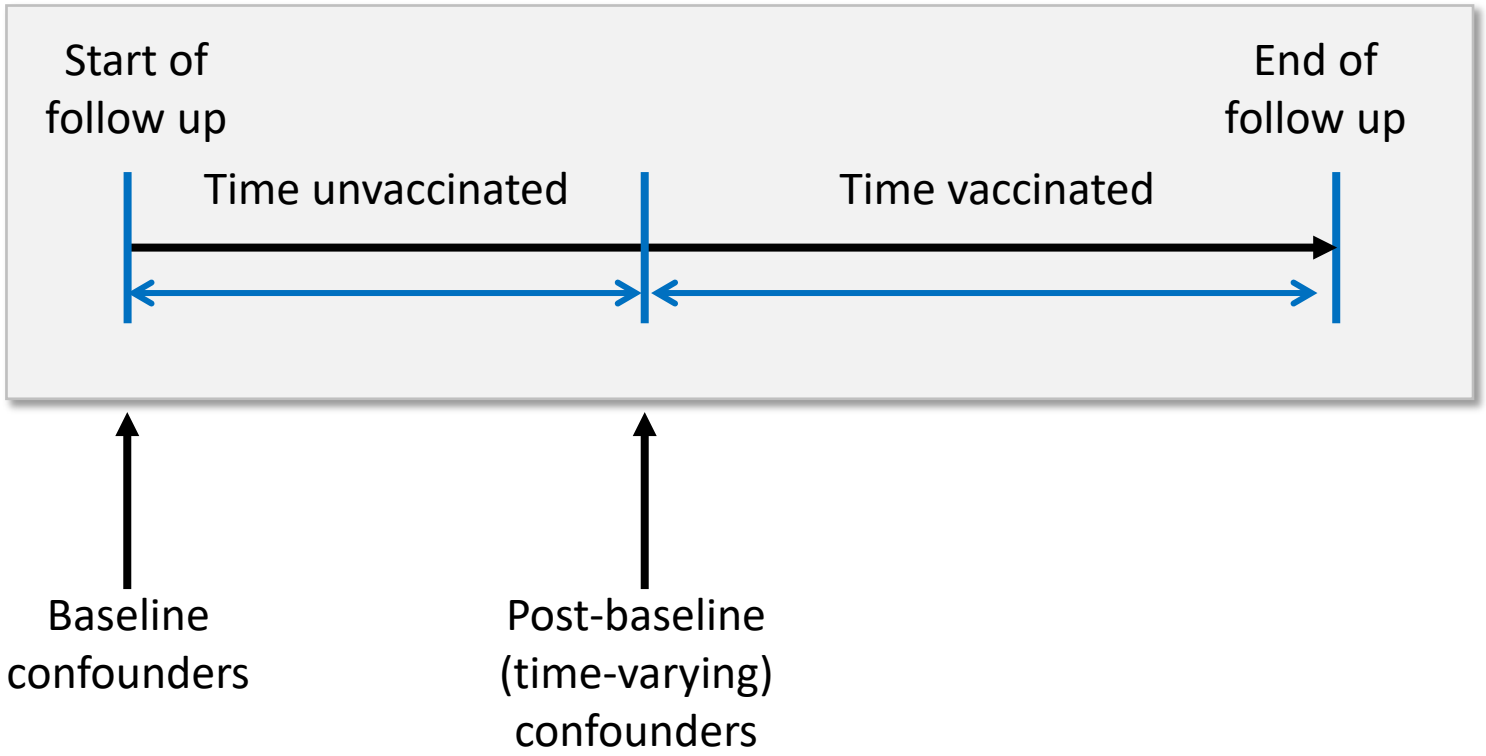
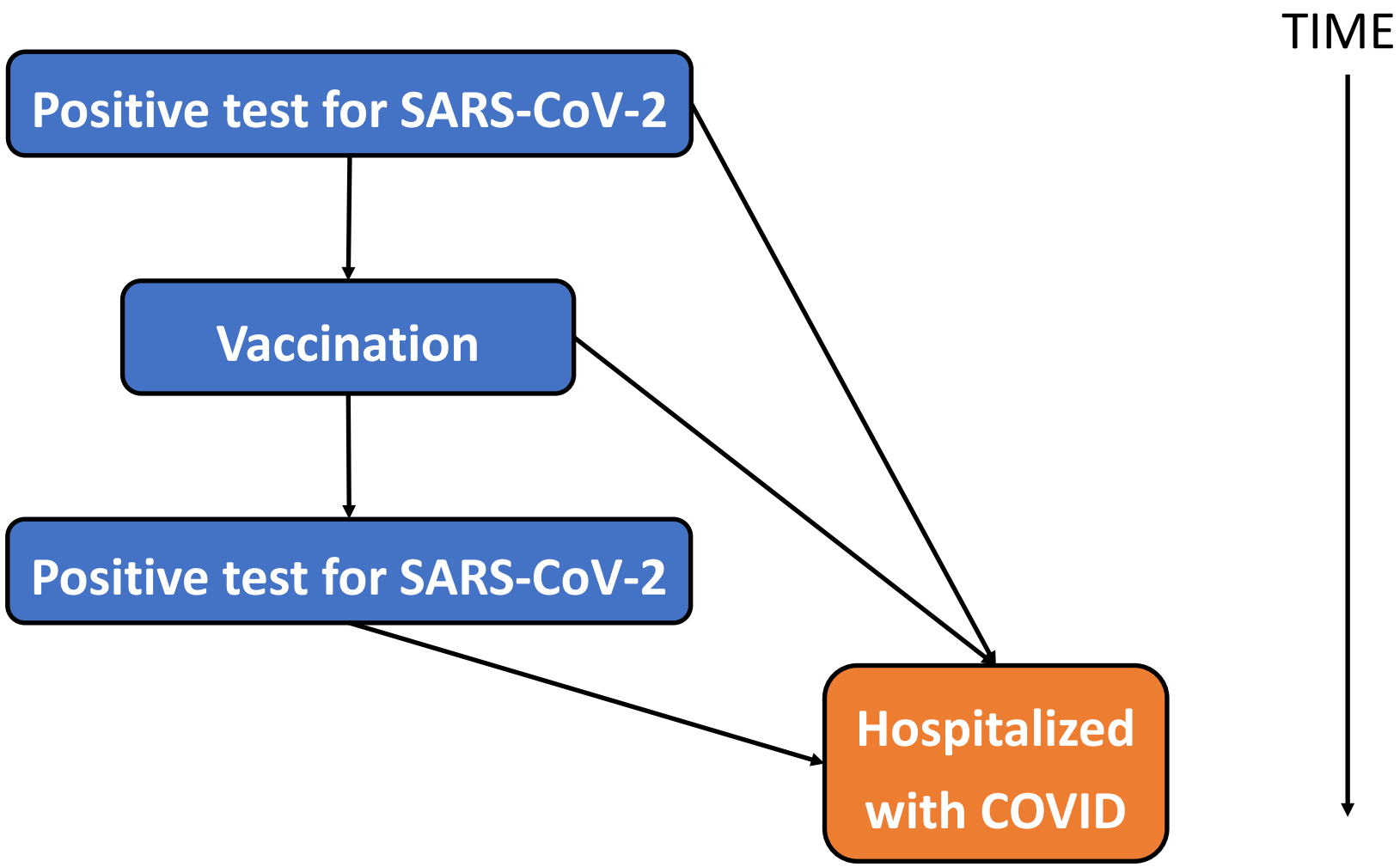


Special methods (such as marginal structural models) are likely to be needed when there are time-varying confounders

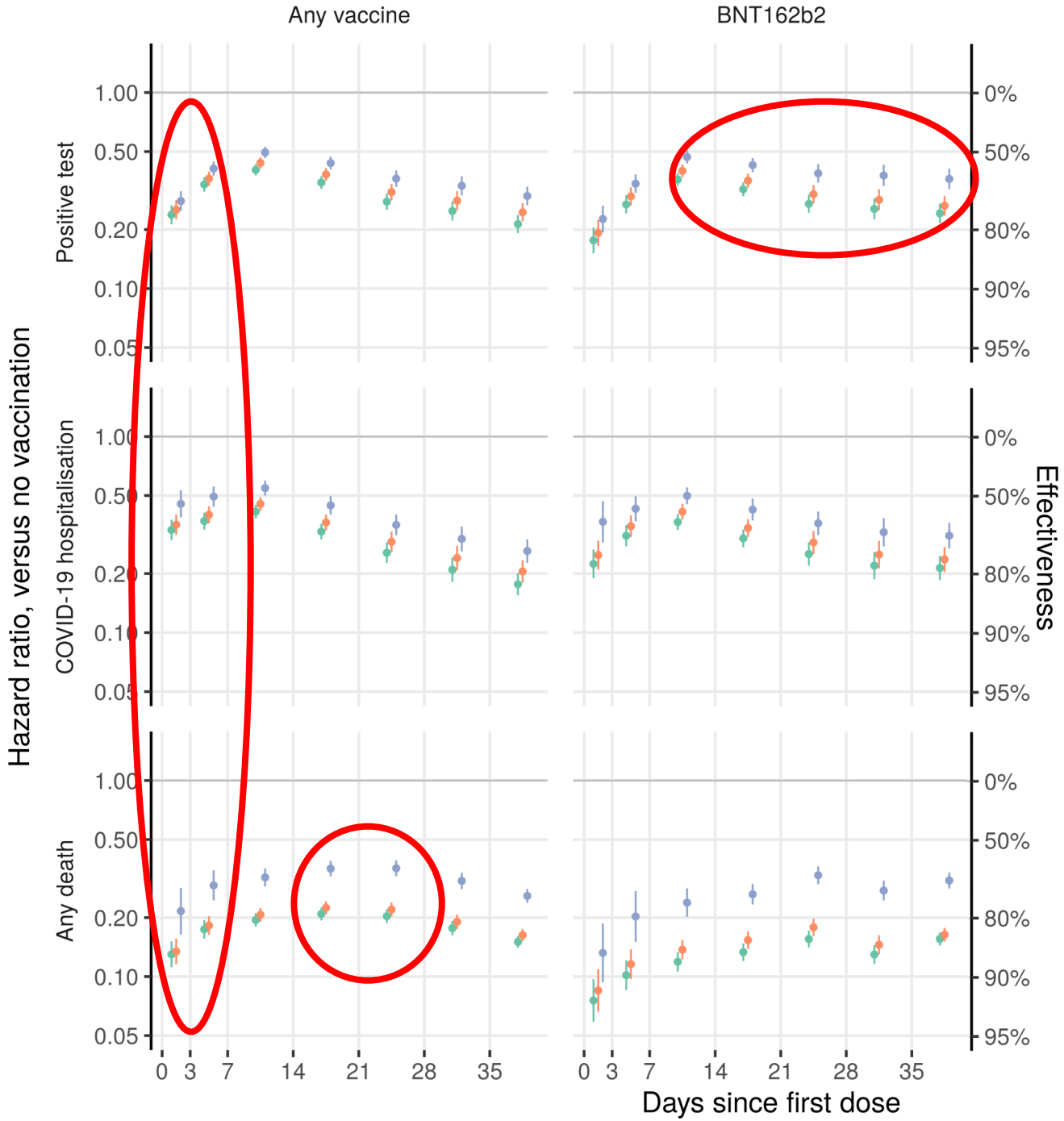
Time-varying characteristics predicting vaccination

		People aged 80 years and over		People aged 70-79 years	
Time-varying confounders		**BNT162b2**	**ChAdOx1**	**BNT162b2**	**ChAdOx1**
Time since positive SARS-CoV-2 test ref: no positive test	1-21	0.06 (0.04-0.08)	0.11 (0.08-0.15)	0.04 (0.02-0.07)	0.08 (0.05-0.11)
	22-28	0.23 (0.16-0.34)	0.32 (0.25-0.42)	0.21 (0.13-0.34)	0.22 (0.16-0.30)
	29+	0.69 (0.56-0.84)	1.31 (1.20-1.43)	1.31 (0.97-1.76)	1.34 (1.16-1.54)
Time since suspected COVID ref: not suspected	1-21	1.33 (1.15-1.55)	1.32 (1.04-1.68)	1.09 (0.84-1.42)	1.44 (1.18-1.76)
	22-28	0.98 (0.67-1.44)	1.44 (0.90-2.28)	0.56 (0.25-1.23)	0.81 (0.49-1.32)
	29+	1.30 (0.95-1.77)	1.03 (0.78-1.36)	1.05 (0.54-2.03)	1.16 (0.79-1.71)
Time since discharge from infectious hospital admission ref: not in hospital	In-hospital	0.84 (0.82-0.87)	0.09 (0.07-0.11)	0.90 (0.87-0.92)	0.94 (0.92-0.97)
	1-21	0.47 (0.43-0.51)	0.71 (0.65-0.77)	0.48 (0.39-0.57)	0.60 (0.54-0.68)
	22-28	0.70 (0.59-0.82)	1.04 (0.91-1.19)	0.79 (0.50-1.23)	0.86 (0.66-1.13)
Time since discharge from non-infectious hosp admission ref: in hospital	In hospital	0.90 (0.86-0.94)	0.44 (0.31-0.63)	0.95 (0.91-0.99)	0.97 (0.94-1.01)
	1-21	0.58 (0.44-0.76)	1.01 (0.77-1.33)	0.41 (0.26-0.65)	0.71 (0.57-0.90)
	22-28	0.90 (0.59-1.37)	1.16 (0.78-1.71)	0.52 (0.18-1.54)	0.79 (0.46-1.35)

Time-varying confounding



Estimated vaccine effectiveness following at least one dose of any vaccine, cohort aged 80 years and over



Region-stratified Cox model, with no further adjustment
Region-stratified Cox model, with adjustment for baseline confounders
Region-stratified marginal structural Cox model, with adjustment for baseline and time-varying confounders

COVID-19 LONGITUDINAL HEALTH & WELLBEING NATIONAL CORE STUDY

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Medical Sciences Division
DataLab

Estimated vaccine effectiveness following at least one dose of any vaccine, cohort aged 70-79 years

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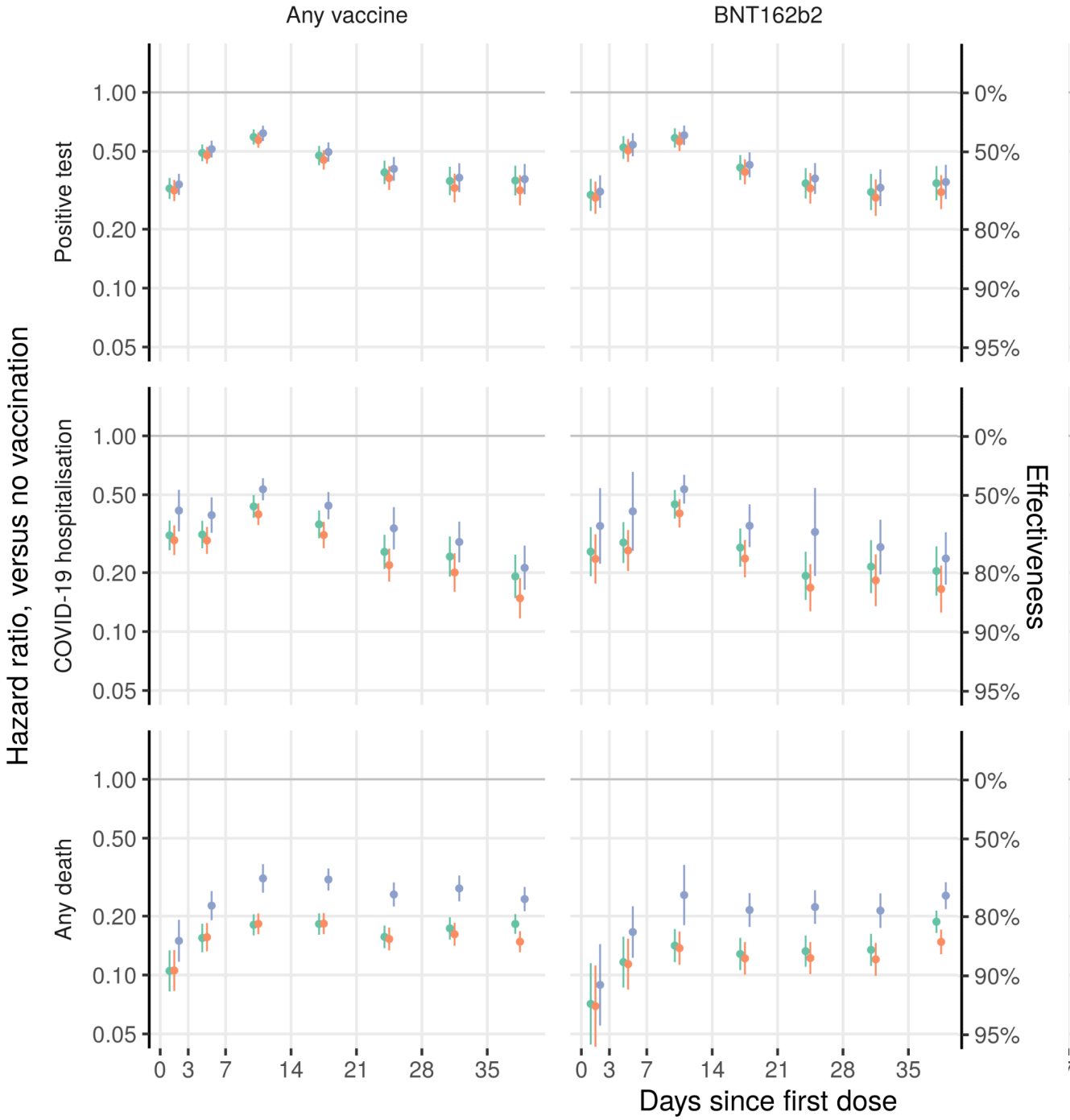

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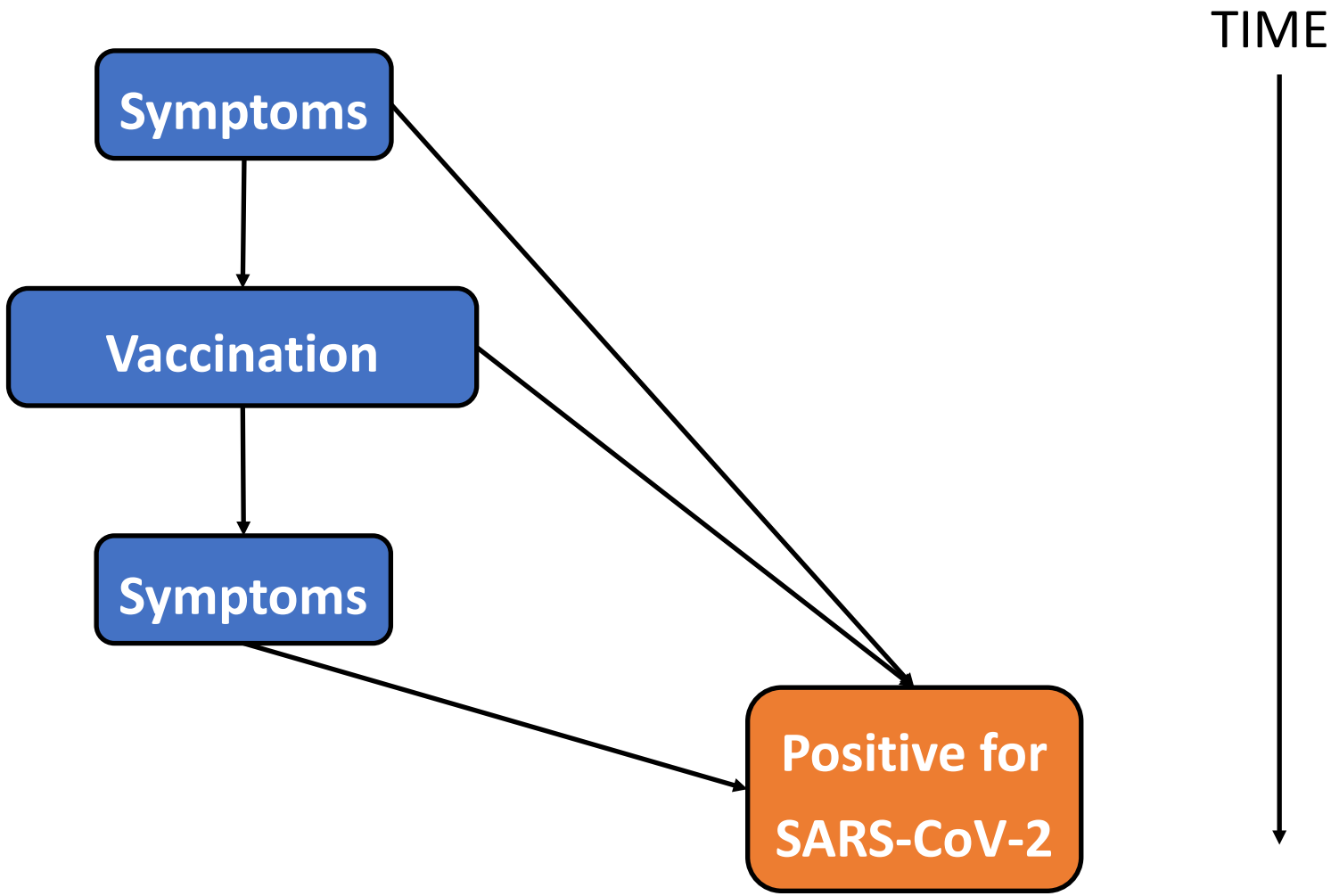
Unmeasured (time-varying) confounding



Biases because recent symptoms predict postponement of vaccination may wane with time, but it seems particularly hard to estimate short-term effects of vaccination

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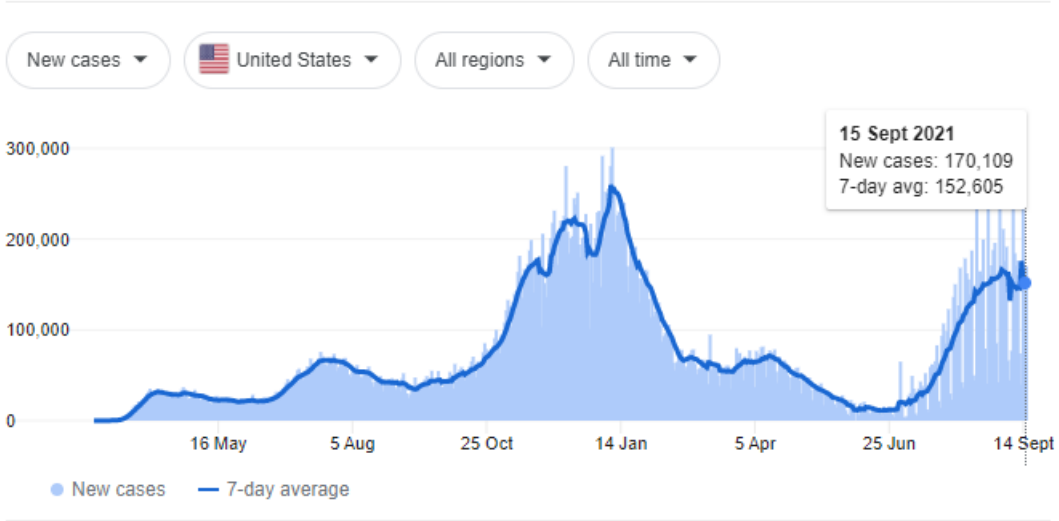
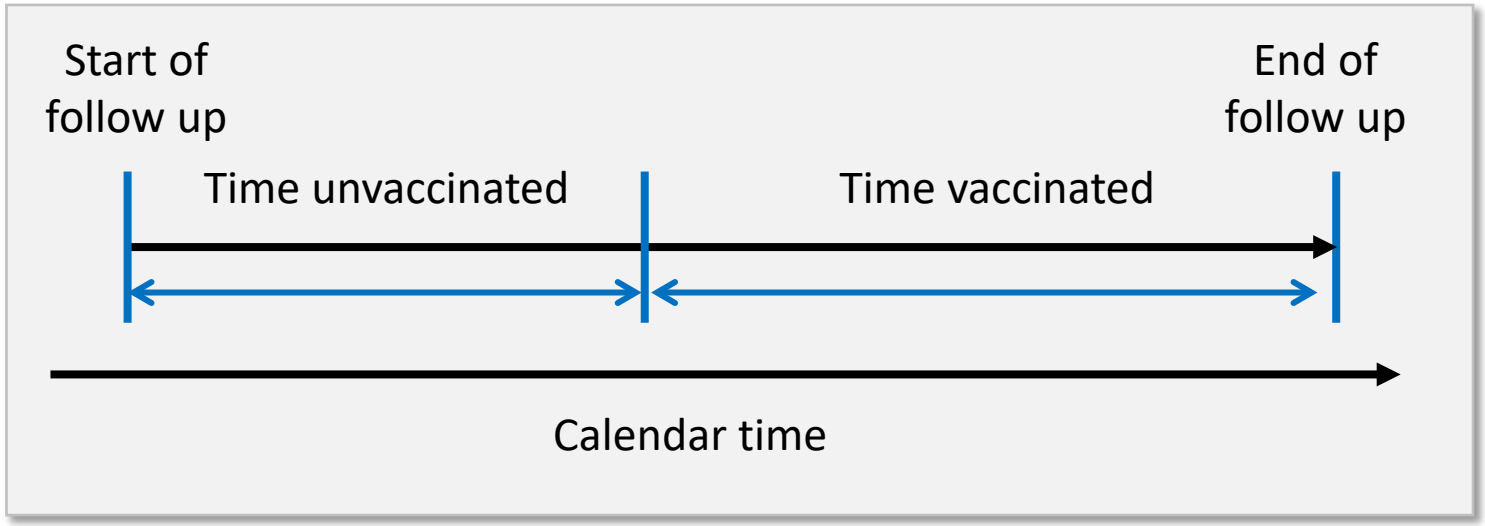
Accounting for pandemic waves





It will usually be important to allow for *both* calendar time *and* time since vaccination in analyses

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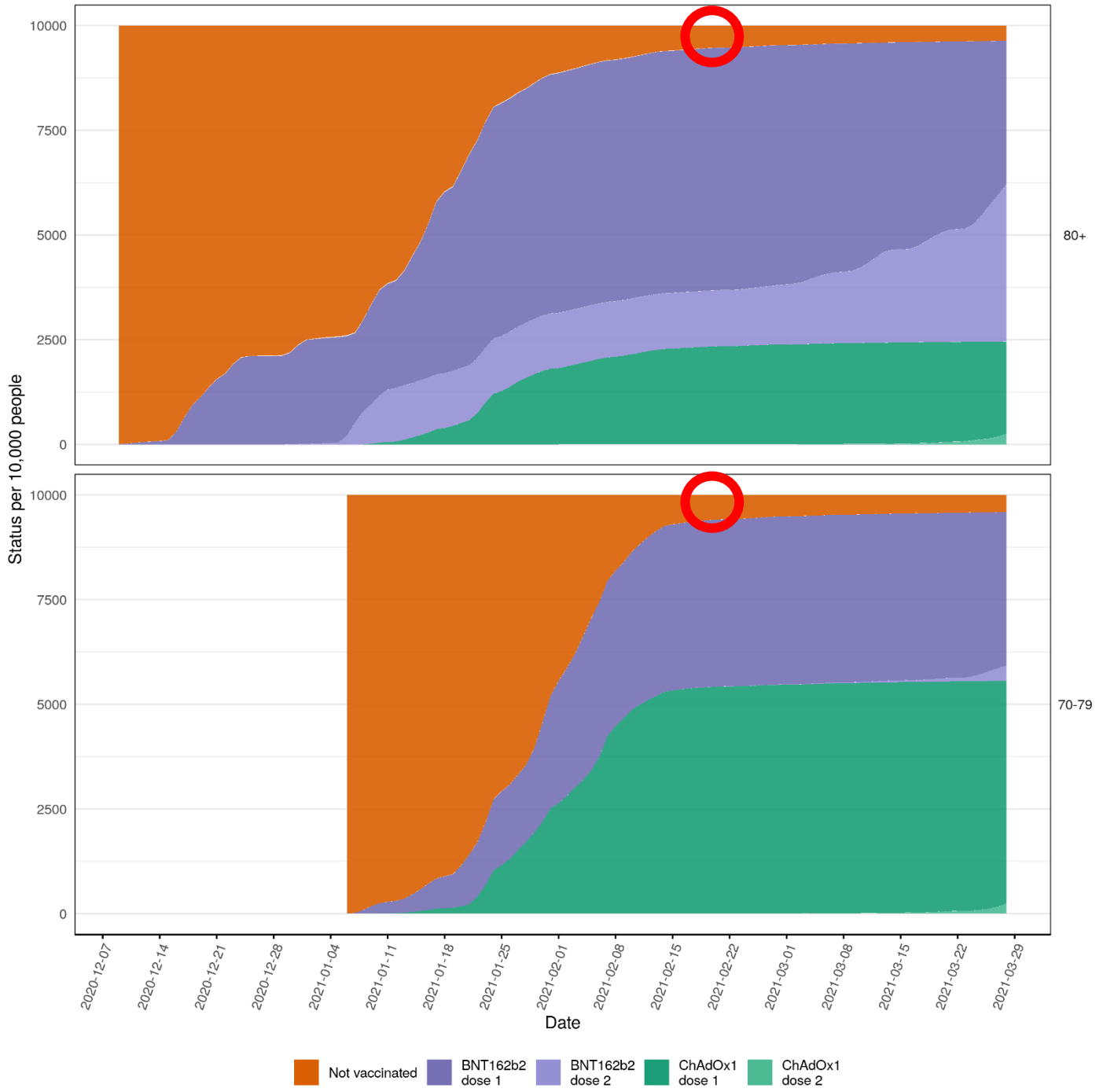
Characteristing the persistently unvaccinated

We're mainly interested in vaccine efficacy some weeks after receipt of the second dose.

In highly vaccinated populations, we need to understand the characteristics of the small proportion of people remaining unvaccinated

Did they remain unvaccinated because of recent infection that conferred protection?



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The vaccines work brilliantly.
But how should we use observational data to guide policy?

- It's very hard to estimate vaccine effectiveness using data assembled during the rollout
- We need careful and critical evaluations of designs and analysis strategies
  - Compare estimates from different approaches
  - Consider effects on negative control outcomes (eg non-COVID mortality)

Addressing potential bias in studies of COVID-19 vaccination

- Confounding by characteristics predicting both vaccination and outcome
  - Rollout was in stages, depending on age and whether at particular risk (eg a health care worker)
    - Conduct analyses stratified by risk groups and accounting for when vaccination became available
  - Control for a wide range of predictors of vaccination using linked electronic health records
    - In studies of longer term effects of vaccination, what were the characteristics of the comparison (unvaccinated) group, and **what proportion of the unvaccinated were protected because of previous COVID?**
  - Omit those very unlikely to be vaccinated (eg on an end of life care pathway)
  - Critically appraise "test-negative" designs
    - Check the potential for unmeasured or induced confounding
  - **Be very cautious of apparent short-term benefits of vaccination, because of the potential for unmeasured confounding (eg by symptoms of COVID)**
- Deal with the rapidly changing incidence of outcome events
  - Allow for calendar time, ensuring that all comparisons are among individuals at risk on the same day
- Consider the possibility of 'cherry picking'
  - Was there an analysis plan? Was it published before outcome data were available?

Thank you for your attention