

Vaccines and variants

Methodological issues in using non-randomized studies to estimate vaccine effectiveness

Jonathan Sterne
University of Bristol, UK



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Monitoring/tracking published observational studies on vaccine effectiveness against variants of concern (VOC)

- 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



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).

Download (229.1 kB)

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

Observational study designs on VOC (n=55)

Peer-reviewed & Pre-prints

- Alpha (n=44)
- Beta (n=30)
- Gamma (n=22)
- Delta (n=14)
- Many studies assess multiple groups of variants and mutations

Cohort (n=38)

Test negative case-control (n=8)

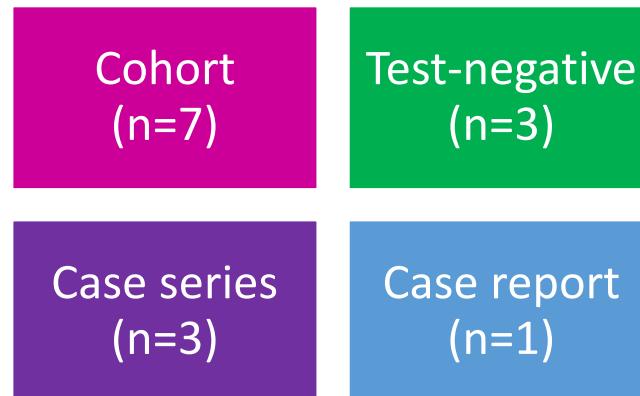
Case-control (n=4)

Case report (n=1)

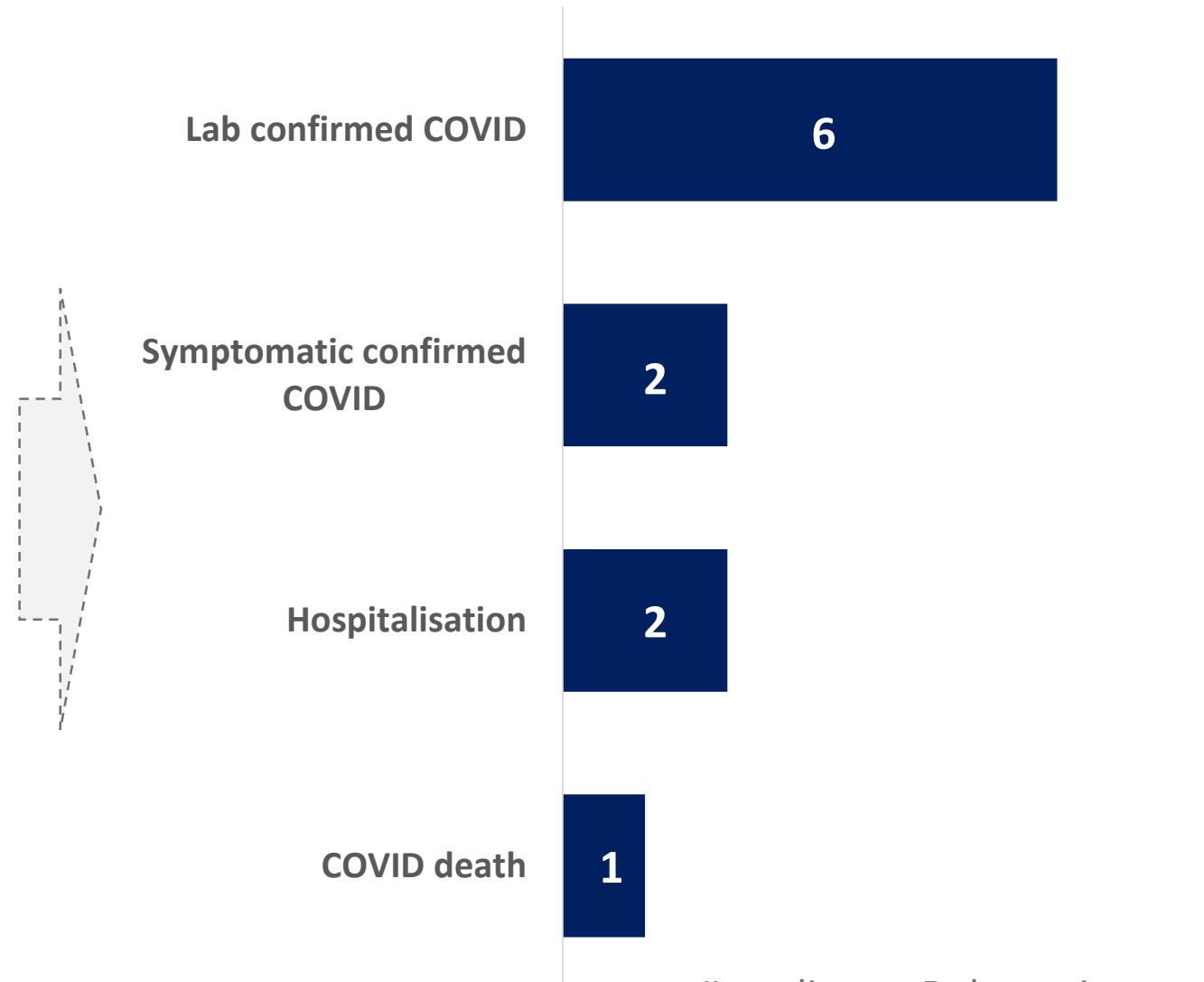
Case series (n=4)

Monitoring/tracking published observational studies on Delta variant

- 14 studies on Delta variant assess immunogenicity and/or vaccine effectiveness



- Study populations: General community (n=8), healthcare workers (n=4), elderly (n=1), immunocompromised (n=1)
- Majority of studies assess the mRNA vaccines:
 - 12 studies with mRNA vaccines
 - 5 studies with viral vector vaccines
 - 1 study with inactivated vaccine
- 6 studies on Delta variant assess vaccine effectiveness



studies on Delta variant assessing specific VE endpoints

“Real-world” studies to inform VE against VOC

- Examples of “real-world” data on VOC – Alpha, Beta, Gamma and Delta
- VE outcomes measured against one or more of the following endpoints: ***RT-PCR/NAAT confirmed infection, symptomatic Covid-19 disease, Covid-19 related hospitalization and deaths***
- **Test-negative case control models** control for biases such as health seeking behavior, access to testing and case ascertainment

Study	Country	Study design	Vaccine	RT-PCR confirmed symptomatic SARS-CoV-2 infection Fully vaccinated, Adjusted VE (95% CI)		
				Alpha	Beta/Gamma	Delta
Jamie Lopez Bernal et al <i>Effectiveness of Covid-19 Vaccines against the B.1.617.2 (Delta) Variant</i>	England	Test negative case-control	BNT162b2	94% (92,95)	*	88% (85,90)
			ChAdOx1	75% (68–79)	*	67% (61,72)
Sharifa Nasreen et al <i>Effectiveness of COVID-19 vaccines against variants of concern, Canada</i>	Canada	Test negative case-control	BNT162b2	89% (86, 91)	84% (69, 92)	87% (64, 95)
			ChAdOx1	64% (60, 68)	48% (28, 63)	67% (44, 80)
			mRNA-1273	92% (86, 96)	*	*
Aziz Sheikh et al <i>SARS-CoV-2 Delta VOC in Scotland: demographics, risk of hospital admission, and vaccine effectiveness</i>	Scotland	Test negative case-control	BNT162b2	*	*	83% (78,87)
			ChAdOx1	*	*	61% (51,70)

Emerging evidence from observational studies on effectiveness by boosters

Vaccination strategy	Study designs	Country	Vaccines	Study populations	Outcome
Heterologous prime-boost vaccination	6 observational cohort studies 1 case report	Europe	ChAdOx1 BNT162b2	Adult volunteers Healthcare workers Immunocompromised patients	Immunogenicity
	1 observational cohort study	Canada	ChAdOx1 BNT162b2 mRNA-1273	Immunocompromised patients	Immunogenicity
	1 observational retrospective cohort study	Denmark	ChAdOx1 BNT162b2	General population	Effectiveness*
Providing 3 rd COVID-19 vaccine dose	1 case report	USA	BNT162b2 mRNA-1273 J&J/Janssen	Transplant patients	Immunogenicity
	1 observational cohort study	France	BNT162b2	Immunocompromised patients	Immunogenicity

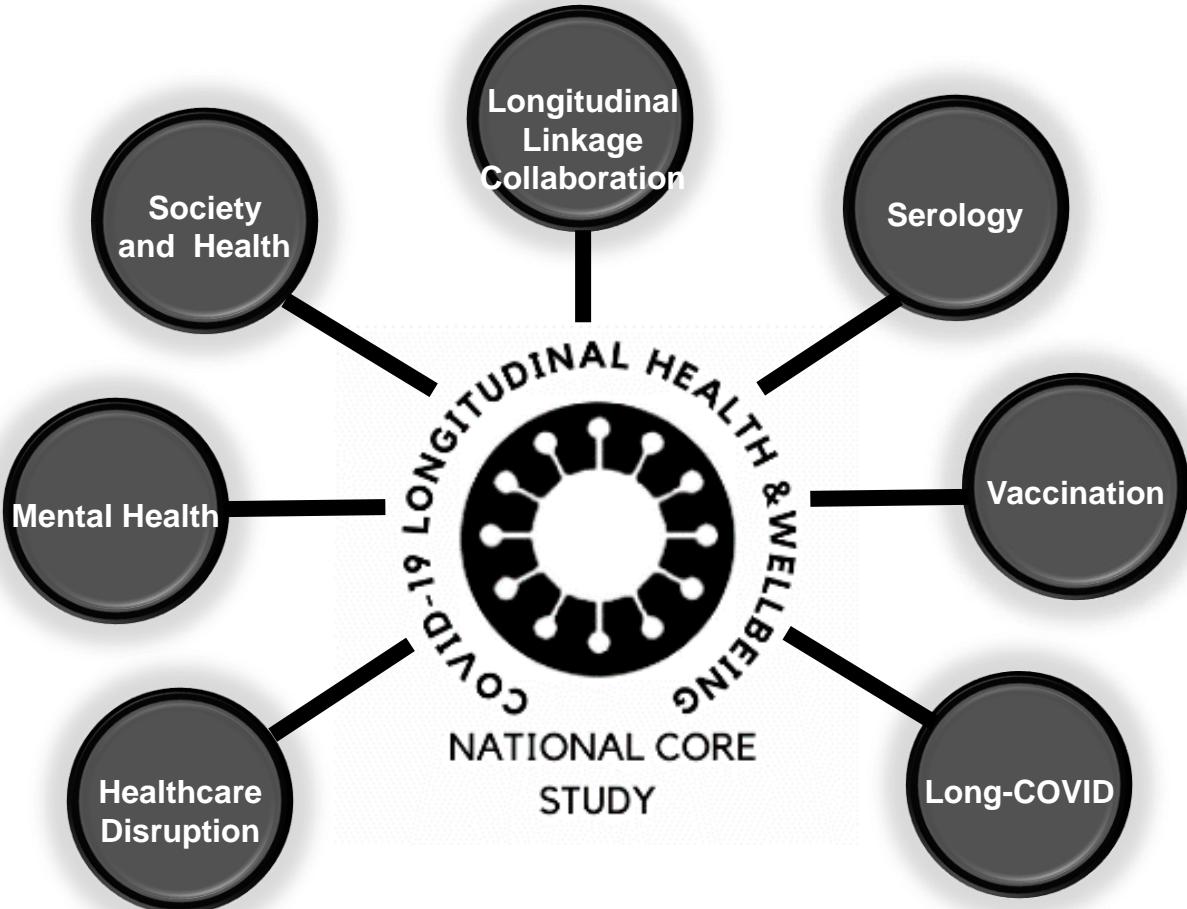
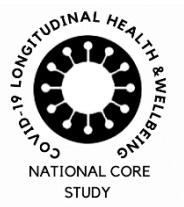
* Only 1 observational study on VE:

- Outcomes assessed in study are RT-PCR confirmed infection and all-cause deaths or COVID-19 related hospitalization/death, after receiving the ChAdOx1 vaccine as the first dose followed by mRNA vaccine as the second dose.
- **Alpha variant** was pre-dominant and a small proportion of the delta variant was observed during the study period, based on sequencing data.

An apology

This talk is very UK focussed, because that is the setting in which I've been working

COVID-19 Longitudinal Health and Wellbeing National Core Study



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OpenSAFELY delivers research across over 58 million people's health records, always respecting patient confidentiality

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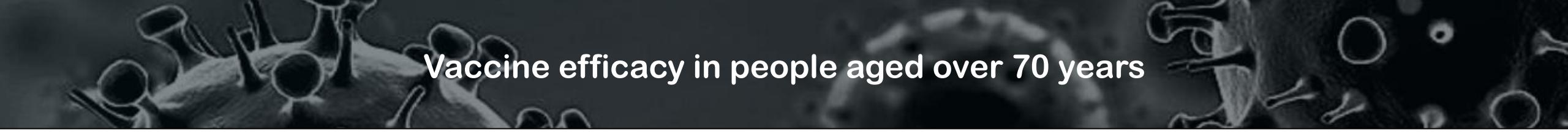
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EMIS
connecting healthcare

<https://www.opensafely.org/>



Vaccine efficacy in people aged over 70 years

- Working with OpenSAFELY to estimate the effect of vaccination (overall and separately for Pfizer (BNT162b2)and Ox/AZ (ChAdOx1)) in over 80s and those aged 70-79 in England
 - 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

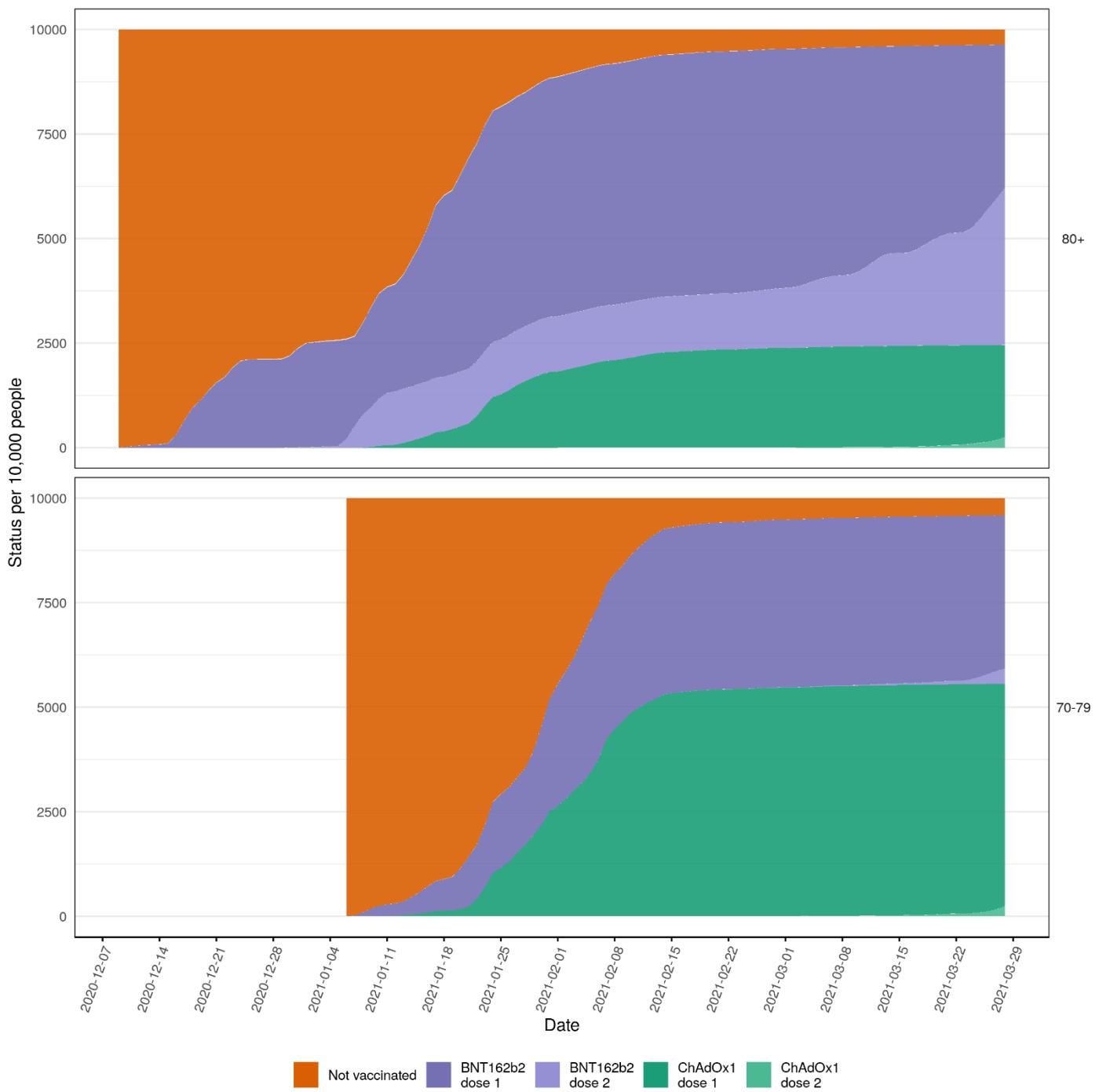
Vaccination status over time



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Methodological issues

- Defining the comparison group
 - Very rapid rollout vaccination, so unvaccinated people (controls) rapidly become vaccinated
- Confounding (presence of characteristics predicting both vaccination and outcome)
 - Baseline confounding
 - Time-varying confounding
 - Unmeasured confounding

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/m ²)	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 ref: 1, most deprived	2 3 4 5	1.14 (1.10-1.17) 1.18 (1.15-1.22) 1.28 (1.24-1.31) 1.38 (1.34-1.42)	1.09 (1.05-1.14) 1.20 (1.15-1.25) 1.31 (1.25-1.37) 1.31 (1.25-1.38)	1.14 (1.10-1.19) 1.11 (1.07-1.15) 1.19 (1.15-1.24) 1.41 (1.36-1.46)	1.14 (1.11-1.18) 1.22 (1.18-1.26) 1.22 (1.18-1.26) 1.25 (1.21-1.29)
Ethnicity ref: White	Black South Asian Mixed Other	0.46 (0.41-0.52) 0.47 (0.44-0.50) 0.71 (0.60-0.85) 0.81 (0.70-0.93)	0.47 (0.40-0.55) 0.45 (0.42-0.49) 0.78 (0.62-0.98) 0.67 (0.54-0.83)	0.50 (0.40-0.61) 0.60 (0.56-0.65) 0.51 (0.37-0.69) 0.70 (0.58-0.85)	0.45 (0.38-0.54) 0.61 (0.58-0.65) 0.64 (0.51-0.80) 0.75 (0.64-0.87)
Body Mass Index (kg/m ²) Ref: <30 or not recorded	30-34.9 35-39.9 40+	1.01 (0.99-1.04) 0.87 (0.82-0.92) 0.71 (0.65-0.77)	0.97 (0.93-1.01) 1.05 (0.96-1.15) 1.04 (0.92-1.17)	1.07 (1.03-1.10) 0.98 (0.90-1.06) 0.93 (0.84-1.03)	1.02 (1.00-1.05) 1.01 (0.95-1.09) 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 2 3 4+	1.05 (1.00-1.09) 1.10 (1.02-1.20) 1.18 (1.05-1.33) 1.23 (1.04-1.46)	0.93 (0.87-1.00) 0.87 (0.78-0.98) 0.85 (0.71-1.01) 0.77 (0.60-0.98)	1.01 (0.94-1.09) 1.04 (0.91-1.20) 1.10 (0.89-1.35) 1.09 (0.81-1.47)	1.02 (0.96-1.08) 1.02 (0.91-1.15) 1.07 (0.90-1.27) 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 ref: None	Mild Moderate Severe	1.09 (1.05-1.13) 1.03 (0.99-1.06) 0.88 (0.85-0.92)	1.36 (1.27-1.47) 1.39 (1.29-1.50) 1.42 (1.31-1.53)	1.06 (1.03-1.09) 1.00 (0.96-1.04) 0.91 (0.85-0.97)	1.07 (1.05-1.10) 1.07 (1.03-1.10) 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/m ²)	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/m ²)	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/m ²)	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 ref: 1, most deprived	2 3 4 5	1.14 (1.10-1.17) 1.18 (1.15-1.22) 1.28 (1.24-1.31) 1.38 (1.34-1.42)	1.09 (1.05-1.14) 1.20 (1.15-1.25) 1.31 (1.25-1.37) 1.31 (1.25-1.38)	1.14 (1.10-1.19) 1.11 (1.07-1.15) 1.19 (1.15-1.24) 1.41 (1.36-1.46)	1.14 (1.11-1.18) 1.22 (1.18-1.26) 1.22 (1.18-1.26) 1.25 (1.21-1.29)
Ethnicity ref: White	Black South Asian Mixed Other	0.46 (0.41-0.52) 0.47 (0.44-0.50) 0.71 (0.60-0.85) 0.81 (0.70-0.93)	0.47 (0.40-0.55) 0.45 (0.42-0.49) 0.78 (0.62-0.98) 0.67 (0.54-0.83)	0.50 (0.40-0.61) 0.60 (0.56-0.65) 0.51 (0.37-0.69) 0.70 (0.58-0.85)	0.45 (0.38-0.54) 0.61 (0.58-0.65) 0.64 (0.51-0.80) 0.75 (0.64-0.87)
Body Mass Index (kg/m ²) Ref: <30 or not recorded	30-34.9 35-39.9 40+	1.01 (0.99-1.04) 0.87 (0.82-0.92) 0.71 (0.65-0.77)	0.97 (0.93-1.01) 1.05 (0.96-1.15) 1.04 (0.92-1.17)	1.07 (1.03-1.10) 0.98 (0.90-1.06) 0.93 (0.84-1.03)	1.02 (1.00-1.05) 1.01 (0.95-1.09) 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 2 3 4+	1.05 (1.00-1.09) 1.10 (1.02-1.20) 1.18 (1.05-1.33) 1.23 (1.04-1.46)	0.93 (0.87-1.00) 0.87 (0.78-0.98) 0.85 (0.71-1.01) 0.77 (0.60-0.98)	1.01 (0.94-1.09) 1.04 (0.91-1.20) 1.10 (0.89-1.35) 1.09 (0.81-1.47)	1.02 (0.96-1.08) 1.02 (0.91-1.15) 1.07 (0.90-1.27) 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 ref: None	Mild Moderate Severe	1.09 (1.05-1.13) 1.03 (0.99-1.06) 0.88 (0.85-0.92)	1.36 (1.27-1.47) 1.39 (1.29-1.50) 1.42 (1.31-1.53)	1.06 (1.03-1.09) 1.00 (0.96-1.04) 0.91 (0.85-0.97)	1.07 (1.05-1.10) 1.07 (1.03-1.10) 1.02 (0.96-1.07)

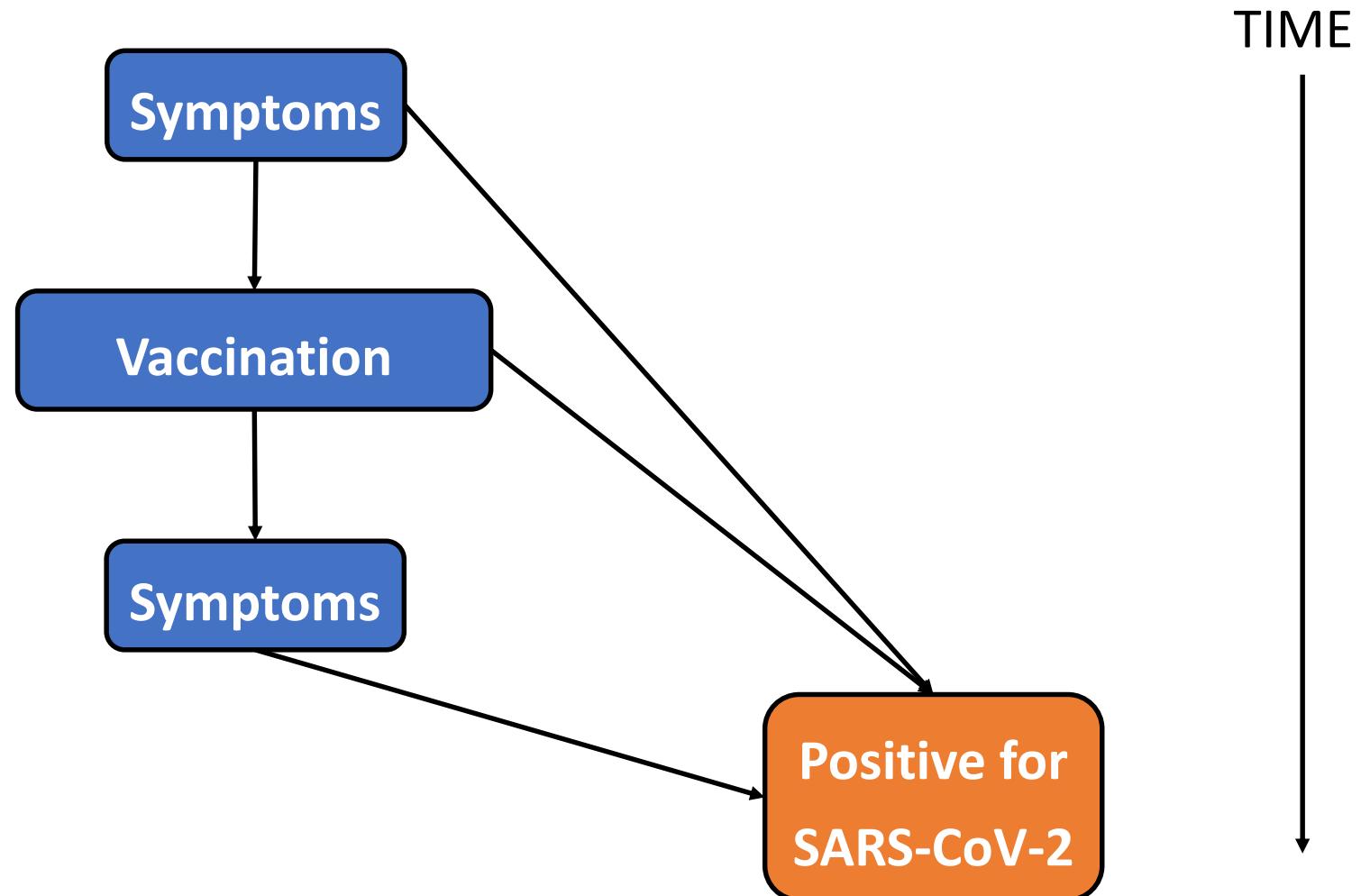
Time-varying confounding

A covariate is a ***time-varying confounder*** for the effect of treatment on outcome if:

1. past covariate values predict current treatment
2. current covariate value predicts outcome

If, in addition, past treatment predicts current covariate value then standard survival analyses with time-updated treatment effects will give biased treatment effect estimates

Time-varying confounding



Time-varying characteristics predicting vaccination

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

In the UK, the only feasible comparison is vaccination in the absence of a recent positive test with no vaccination
(with those vaccinated after a recent positive test coded as unvaccinated)

What comparison can we make?

- Almost nobody is vaccinated soon after a positive SARS-CoV-2 test
- A more meaningful comparison is of vaccination vs no vaccination *in individuals with no recent positive test*
- The small number of individuals vaccinated after a positive test are coded as unvaccinated

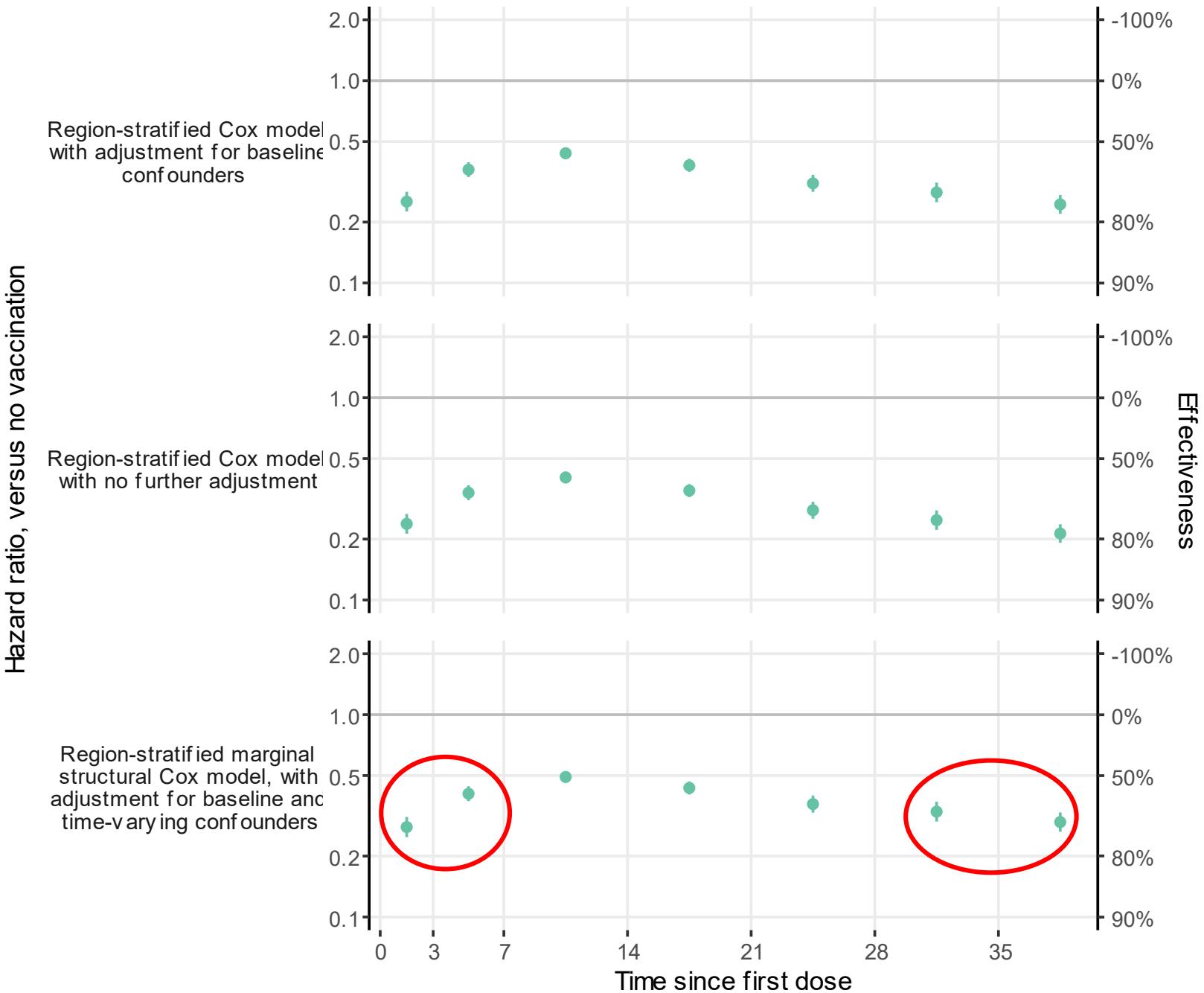
Estimated vaccine effectiveness against a positive test following at least one dose of any vaccine, cohort aged 80 years and over



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



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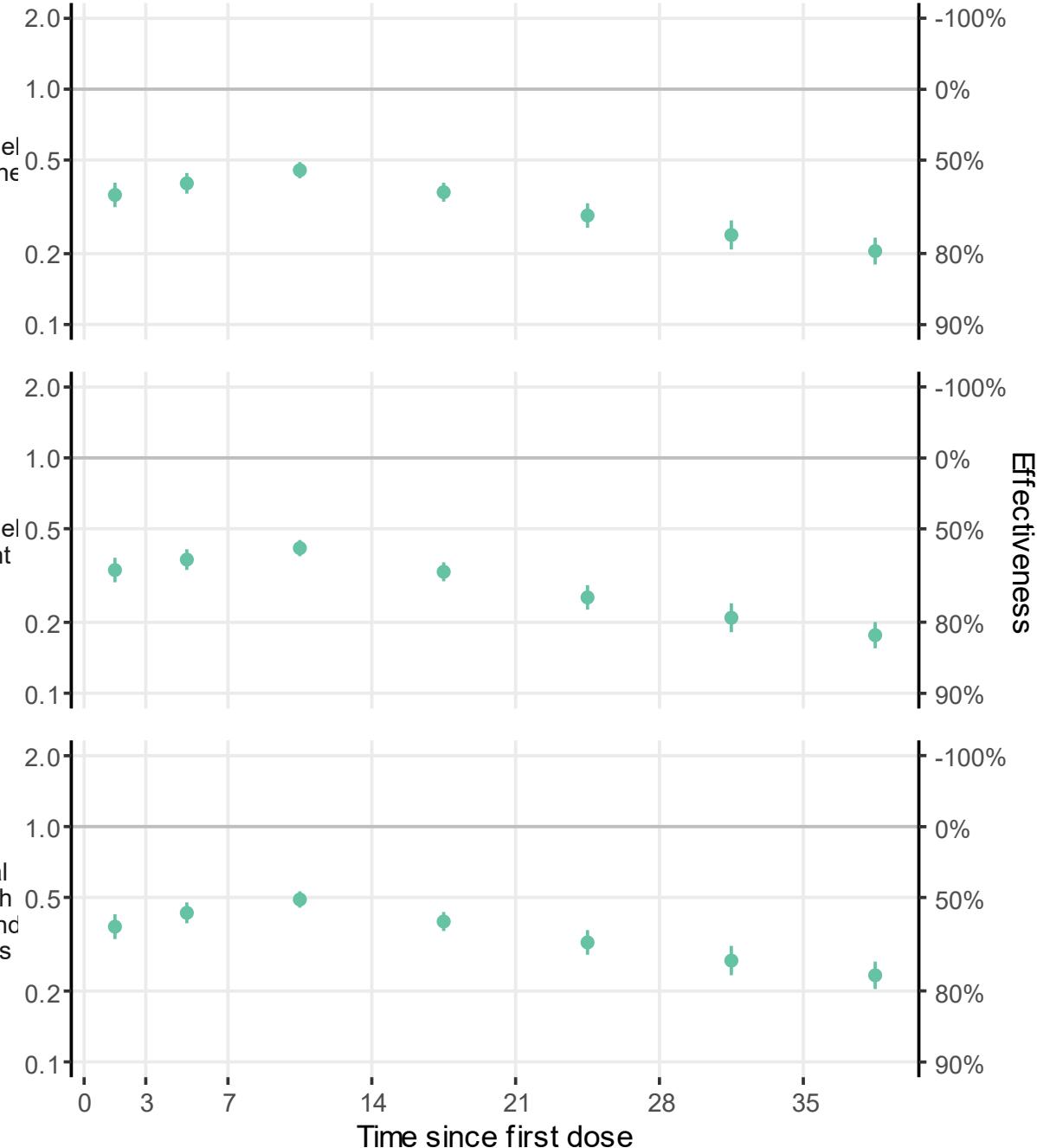


Hazard ratio, versus no vaccination

Region-stratified Cox model
with adjustment for baseline
confounders

Region-stratified Cox model
with no further adjustment

Region-stratified marginal
structural Cox model, with
adjustment for baseline and
time-varying confounders



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



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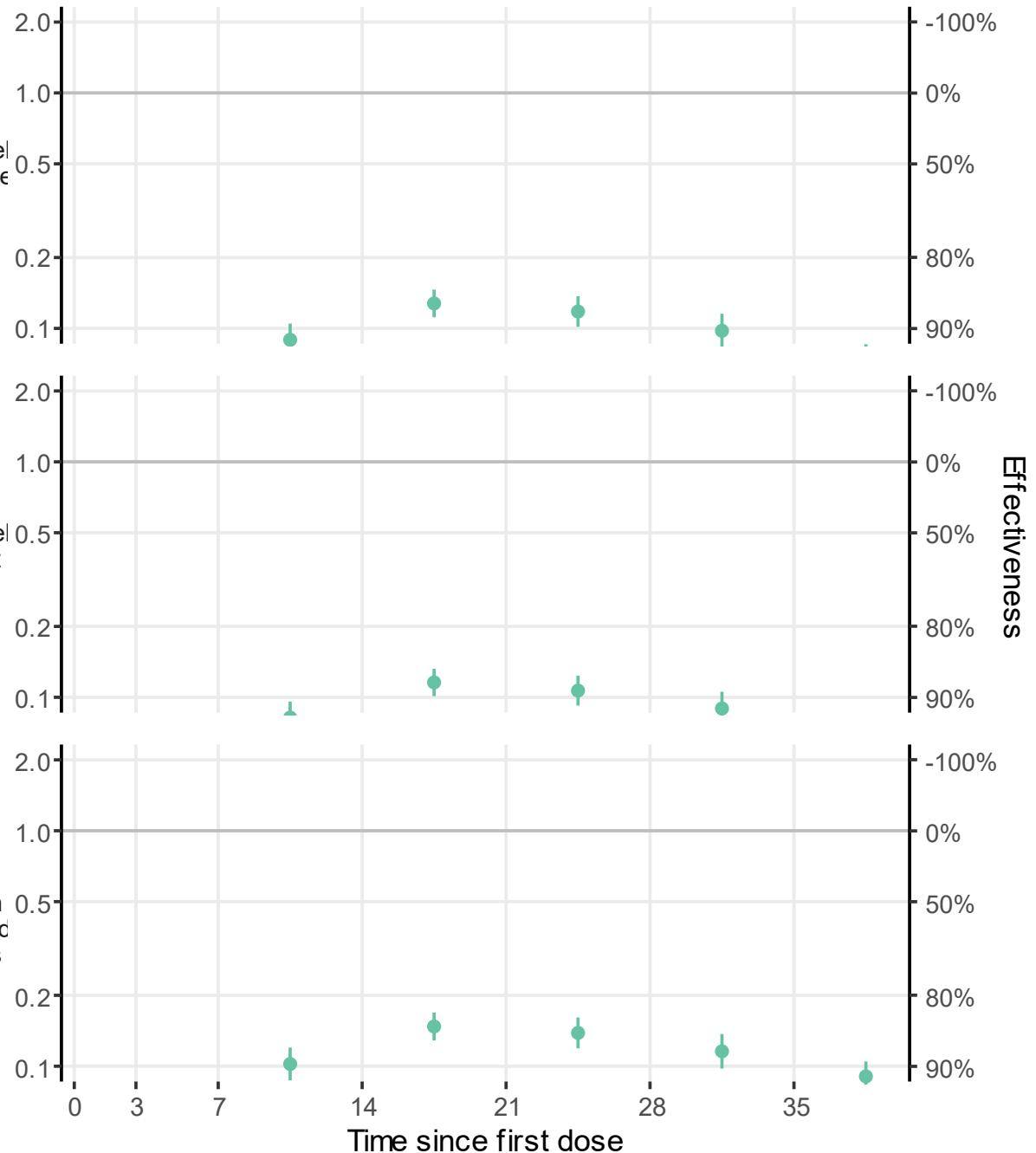


Hazard ratio, versus no vaccination

Region-stratified Cox model
with adjustment for baseline
confounders

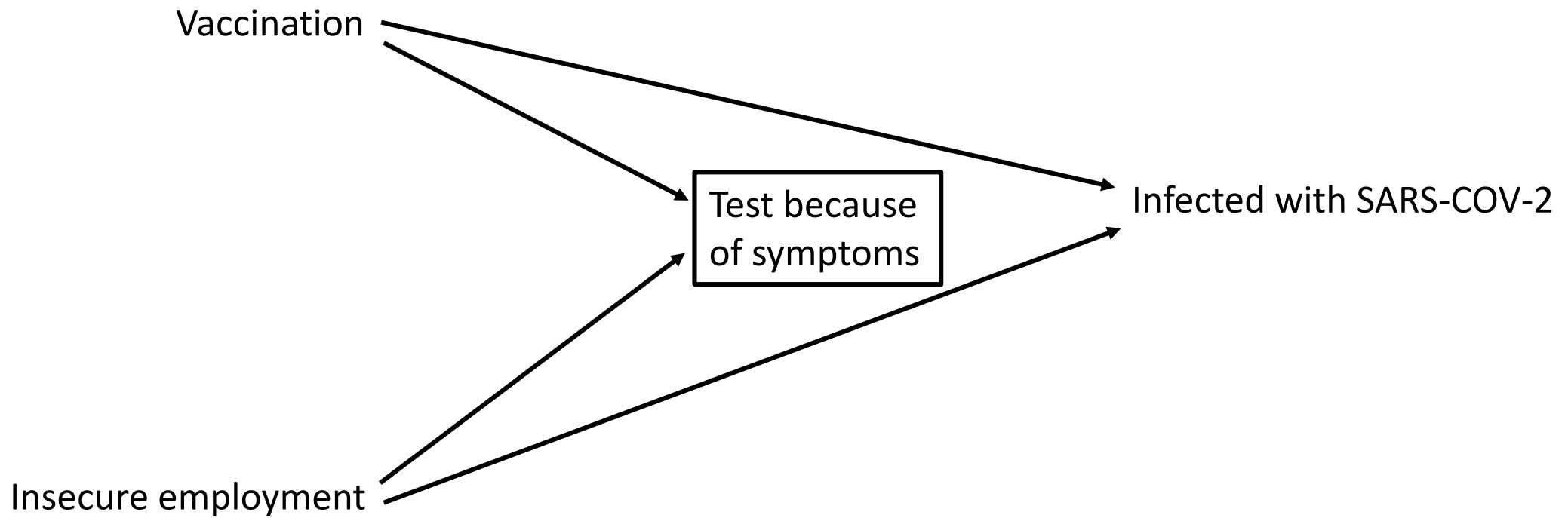
Region-stratified Cox model
with no further adjustment

Region-stratified marginal
structural Cox model, with
adjustment for baseline and
time-varying confounders



Test negative designs

Conditioning on a common effect of two variables (a ‘collider’) induces associations between them



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

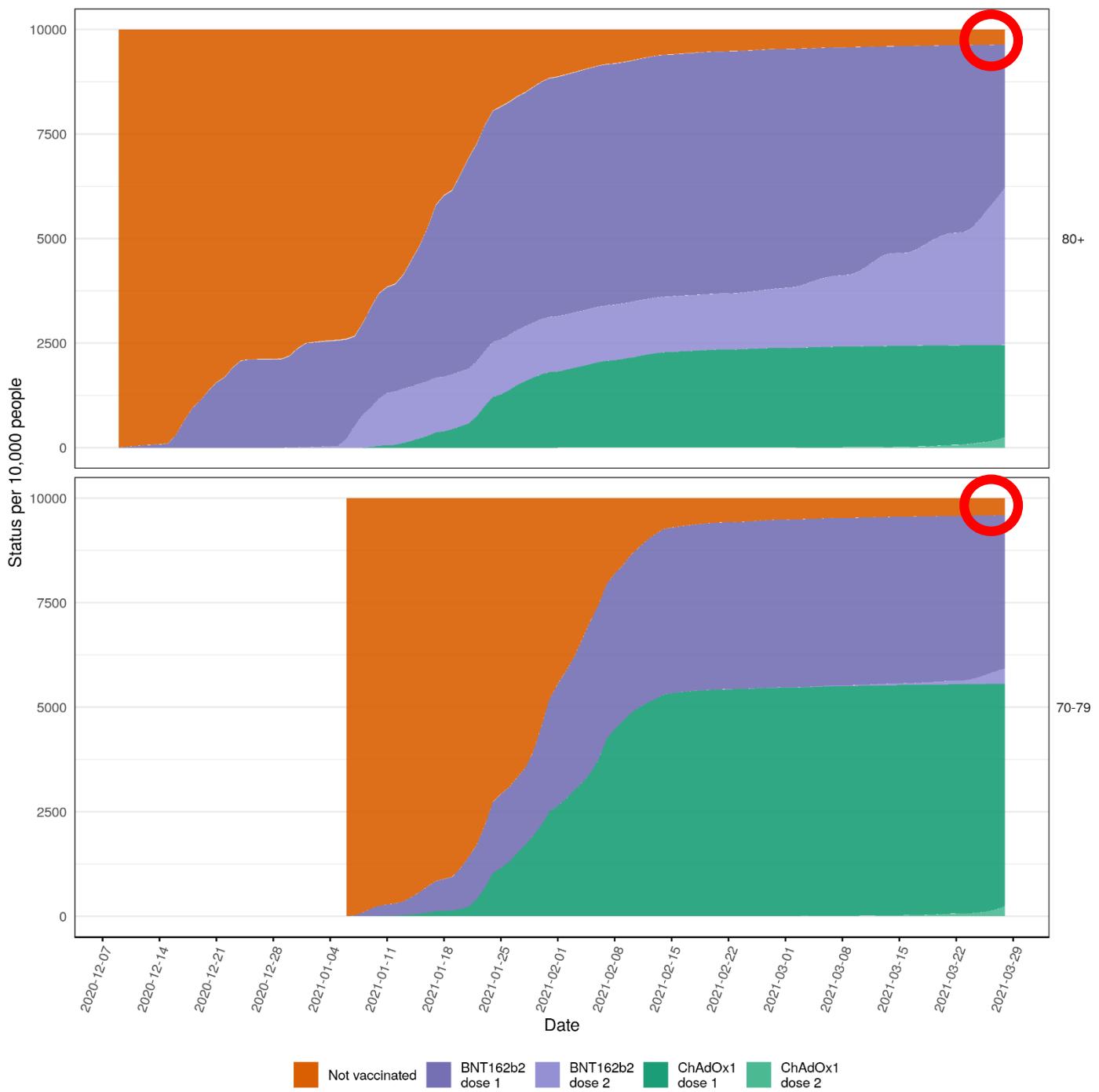
Vaccination status over time



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The vaccines work brilliantly. But what can we learn from observational data?

- 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
 - Effects on negative control outcomes (eg non-COVID mortality)
 - What are the characteristics of the persistently unvaccinated?