Change in covid-19 risk over time following vaccination with CoronaVac: A test-negative case-control study

Supplementary Material

Supplementary Methods

Matching

Matching was performed as follows. Strata defined by unique combinations of the matching factors were formed ("matched sets"), and strata with no cases, or with no controls, were excluded. To improve computational performance of the models while retaining the majority of cases, large strata were reduced in size by dividing into smaller strata. In strata with more controls than cases, each case was matched to up to five controls, and vice versa. For strata with at least five times as many controls as cases, excess controls were discarded, and vice versa. In this way, strata sizes varied from two to six.

Secondary and Sensitivity Analyses

As a secondary analysis, we included time since vaccination as a continuous variable and modelled the association with case status using penalized spline regression. To account for missing race data, we performed multiple imputation of the race variable using 50 imputed data sets with predictive mean matching, using the mice package to perform multiple imputation[1]. Finally, we performed three sensitivity analyses varying aspects of the study design. To better exclude individuals who might have had prior SARS-CoV-2 infection, we excluded any individuals with prior ARI. To control for changing variant distribution during the study period, we restricted the period to August 8th to December 14th, 2020, in which the prevalence of the Delta variant in São Paulo State was >25%[2]. Finally, we estimated vaccine effectiveness in the same time categories by including all individuals regardless of vaccination status, and running the same models with unvaccinated individuals as the reference group. As we only had data on HCW status for vaccinated individuals, this analysis was stratified by age only.

Supplementary Results

Change in odds of covid-19 over time since vaccination

A penalized spline regression showed similar patterns in odds of covid-19 over time by age and HCW status as the primary analysis (Supplementary Figure D).

Change in odds of severe covid-19 outcomes over time since vaccination

The pattern of increased odds over time since vaccination was similar for covid-19 hospitalisation or death, and covid-19 death (Supplementary Figure E).

Sensitivity analyses

Using multiple imputation to account for missing race returned very similar results (Supplementary Figure F), as did excluding individuals with any previous ARI (Supplementary Figure G). Restricting to tests performed during the period of Delta variant dominance, we lacked precision to examine patterns of symptomatic covid-19 odds over time by age and HCW status, but the pattern of changes in odds of covid-19 hospitalisation or death was similar (Supplementary Figure H).

Bibliography

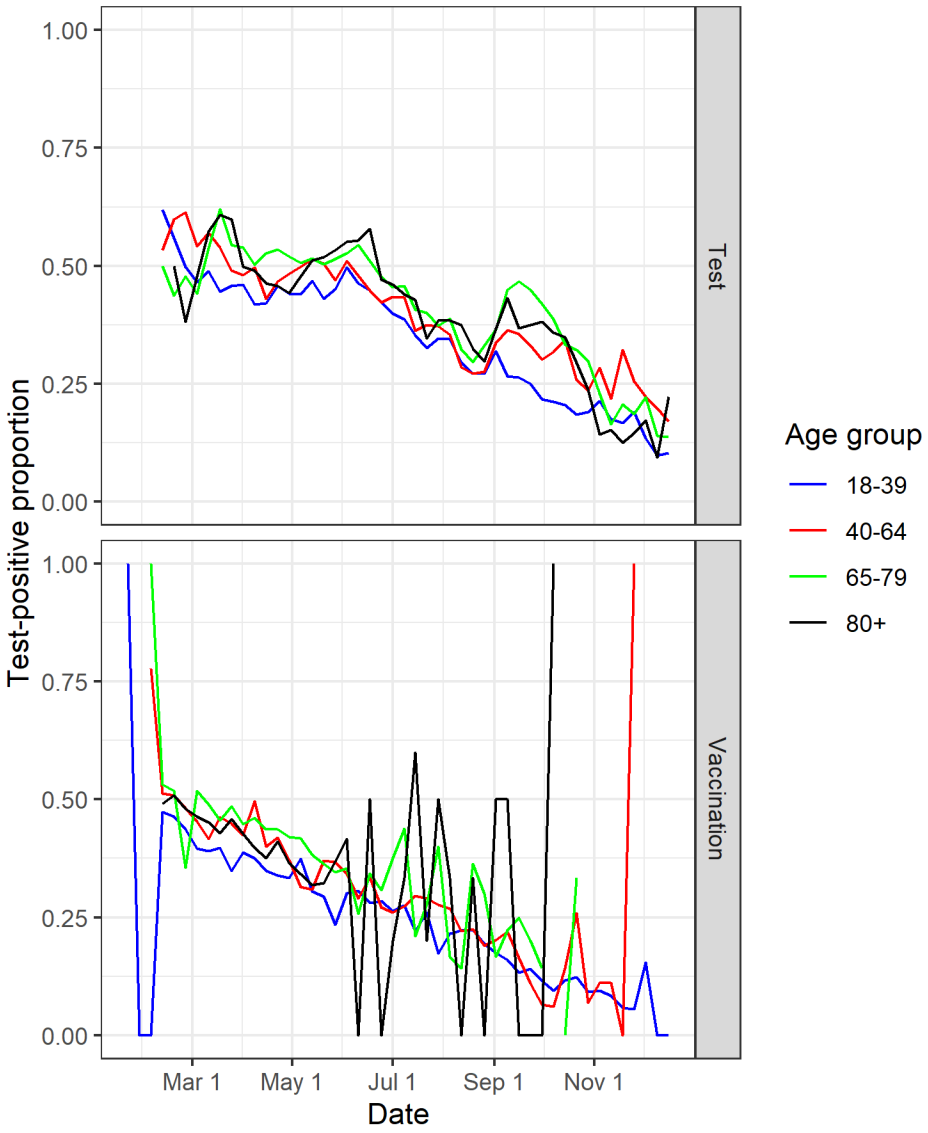
1. Buuren S van, Groothius-Oudshoorn K. mice: Multivariate Imputation by Chained Equations in R. J Stat Softw. **2011**; 45(3):1–67.

2. GISAID. hCoV-19 Variants [Internet]. [cited 2021 Jul 7]. Available from: https://www.gisaid.org/hcov19-variants/

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	5
		(*b*) For matched studies, give matching criteria and the number of controls per case	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4
Bias	9	Describe any efforts to address potential sources of bias	5-7
Study size	10	Explain how the study size was arrived at	8; Fig 1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5-6
		(*b*) Describe any methods used to examine subgroups and interactions	5-6
		(*c*) Explain how missing data were addressed	5-6
		(*d*) If applicable, explain how matching of cases and controls was addressed	6
		(*e*) Describe any sensitivity analyses	6-7
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8; Fig 1, Supp Mat
		(b) Give reasons for non-participation at each stage	Fig 1
		(c) Consider use of a flow diagram	Fig 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8; Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure	Table 1; Supp Mat

Supplementary Table A. STROBE checklist



Supplementary Figure A. Proportion of RT-PCR tests that were positive by week of test performance (top) and by week of completion of primary vaccination series (bottom), by age group, in the study population.

	Case 0-13	Case 14-41	Case 42-69	Case 70-97	Case 98-125	Case 126-153	Case 154-181	Case ≥182
Control 0-13	3009	1495	351	206	69	36	19	12
Control 14-41	1926	6078	1965	630	336	103	41	41
Control 42-69	376	1604	5413	1575	524	206	58	67
Control 70-97	242	452	1396	4667	1431	342	162	73
Control 98-125	63	270	403	1269	4005	1018	289	159
Control 126-153	27	61	191	306	872	2755	798	243
Control 154-181	14	30	44	136	238	703	2164	721
Control ≥182	9	26	36	51	133	212	531	2111

Supplementary Table B. Number of matched sets with discordant cases and controls by time since receipt of second dose (primary analysis)

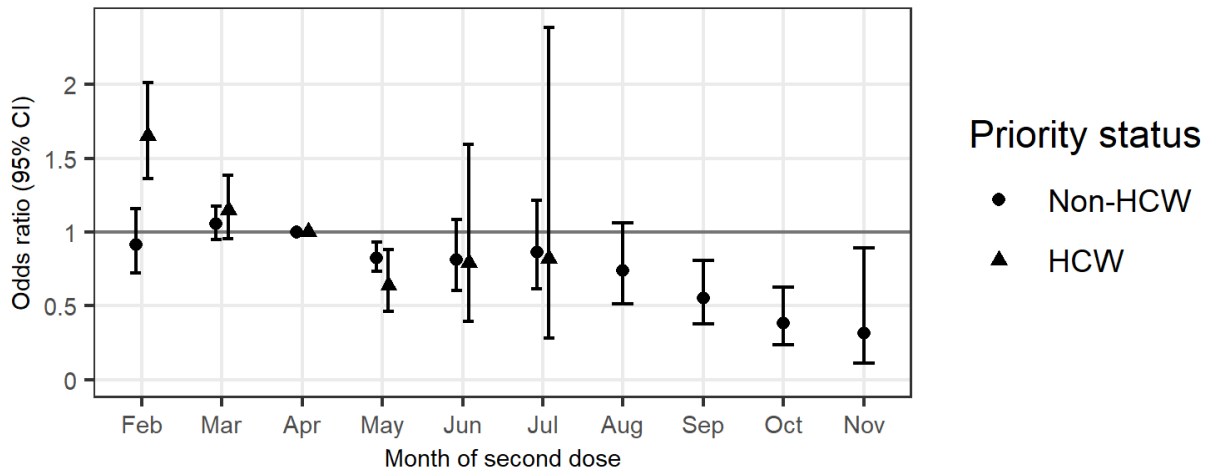
		Non-HCWs	HCWs
Variable	Age subgroup	Odds ratio (95% CI)	
Age	All	1.01 (1.00-1.02)	
Race			
White/Branca		Ref	
Brown/Pardo		0.77 (0.75-0.80)	
Black/Preta		0.78 (0.73-0.83)	
Yellow/Amarela		0.93 (0.82-1.05)	
Indigenous		1.70 (0.63-4.56)	
Missing		1.12 (1.09-1.16)	
Any prior ARI		0.46 (0.42-0.51)	
Female sex		0.82 (0.8-0.85)	
Number comorbidities			
None		Ref	
One-Two		1.30 (1.26-1.35)	
Three or more		1.69 (1.53-1.85)	
Days since second dose (relative to 14-41)			
0-13	18-39	1.41 (1.26-1.57)	1.36 (1.18-1.56)
42-69		1.38 (1.24-1.54)	1.42 (1.24-1.61)
70-97		1.59 (1.38-1.82)	1.81 (1.57-2.09)
98-125		1.63 (1.38-1.94)	2.45 (2.1-2.86)
126-153		1.75 (1.38-2.2)	2.92 (2.43-3.51)
154-181		1.92 (1.43-2.58)	3.38 (2.75-4.15)
≥182		1.67 (1.24-2.26)	4.22 (3.39-5.26)
0-13	40-64	1.52 (1.32-1.76)	1.46 (1.25-1.72)
42-69		1.10 (0.97-1.25)	1.13 (0.98-1.3)
70-97		1.14 (1.00-1.31)	1.31 (1.12-1.53)

98-125		1.04 (0.89-1.21)	1.56 (1.31-1.84)
126-153		1.03 (0.85-1.23)	1.72 (1.4-2.1)
154-181		1.02 (0.81-1.3)	1.8 (1.43-2.26)
≥182		1.04 (0.79-1.37)	2.62 (2.03-3.38)
0-13	65-79	1.49 (1.31-1.7)	-
42-69		1.13 (1.01-1.27)	-
70-97		1.19 (1.02-1.38)	-
98-125		1.17 (0.98-1.4)	-
126-153		1.29 (1.05-1.59)	-
154-181		1.36 (1.07-1.72)	-
≥182		1.40 (1.05-1.86)	-
0-13	80+	1.22 (0.91-1.63)	-
42-69		0.90 (0.70-1.17)	-
70-97		1.08 (0.78-1.48)	-
98-125		1.32 (0.91-1.91)	-
126-153		1.58 (1.04-2.42)	-
154-181		1.56 (0.99-2.48)	-
≥182		1.65 (0.98-2.79)	-

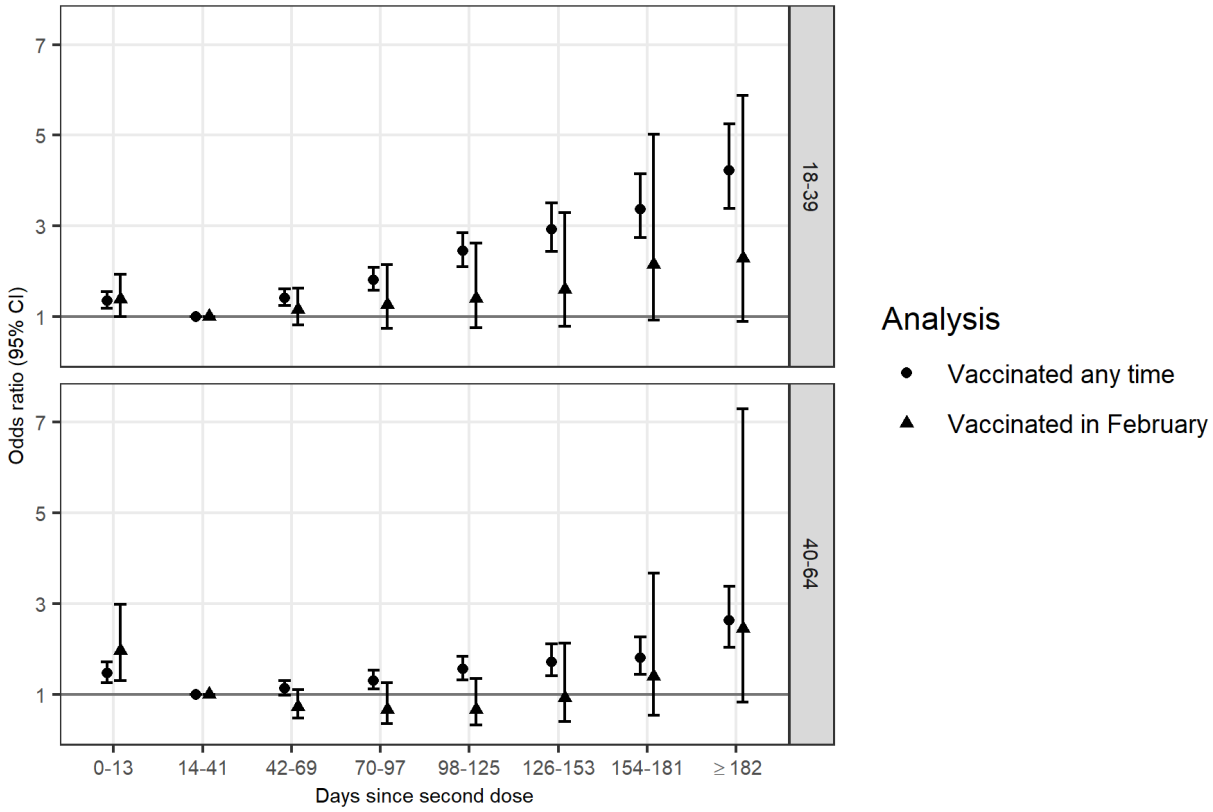
Supplementary Table C. Adjusted odds ratios for covid-19 by demographic characteristics and time since primary vaccination series

Variable	Odds ratio (95% CI)
Age	1.03 (1.01-1.05)
Race	
White/Branca	Ref
Brown/Pardo	0.70 (0.65-0.76)
Black/Preta	0.74 (0.64-0.86)
Yellow/Amarela	0.92 (0.72-1.17)
Indigenous	3.26 (0.43-24.47)
Missing	0.83 (0.77-0.89)
Any prior ARI	0.29 (0.21-0.40)
Female sex	0.65 (0.61-0.68)
Number comorbidities	
None	Ref
One-Two	2.79 (2.63-2.97)
Three or more	4.92 (4.30-5.63)
Days since second dose (relative to 14-41)	
0-13	1.51 (1.28-1.79)
42-69	1.10 (0.95-1.29)
70-97	1.25 (1.04-1.51)
98-125	1.37 (1.10-1.69)
126-153	1.49 (1.16-1.90)
154-181	1.75 (1.33-2.31)
>=182	1.94 (1.41-2.67)

Supplementary Table D. Adjusted odds ratios for covid-19 hospitalisation or death by demographic characteristics and time since primary vaccination series



Supplementary Figure B. Odds ratio of symptomatic covid-19 by month of second dose, among individuals receiving an RT-PCR test within 14-90 days of their second dose, for non-HCWs (circles) and HCWs (triangles)



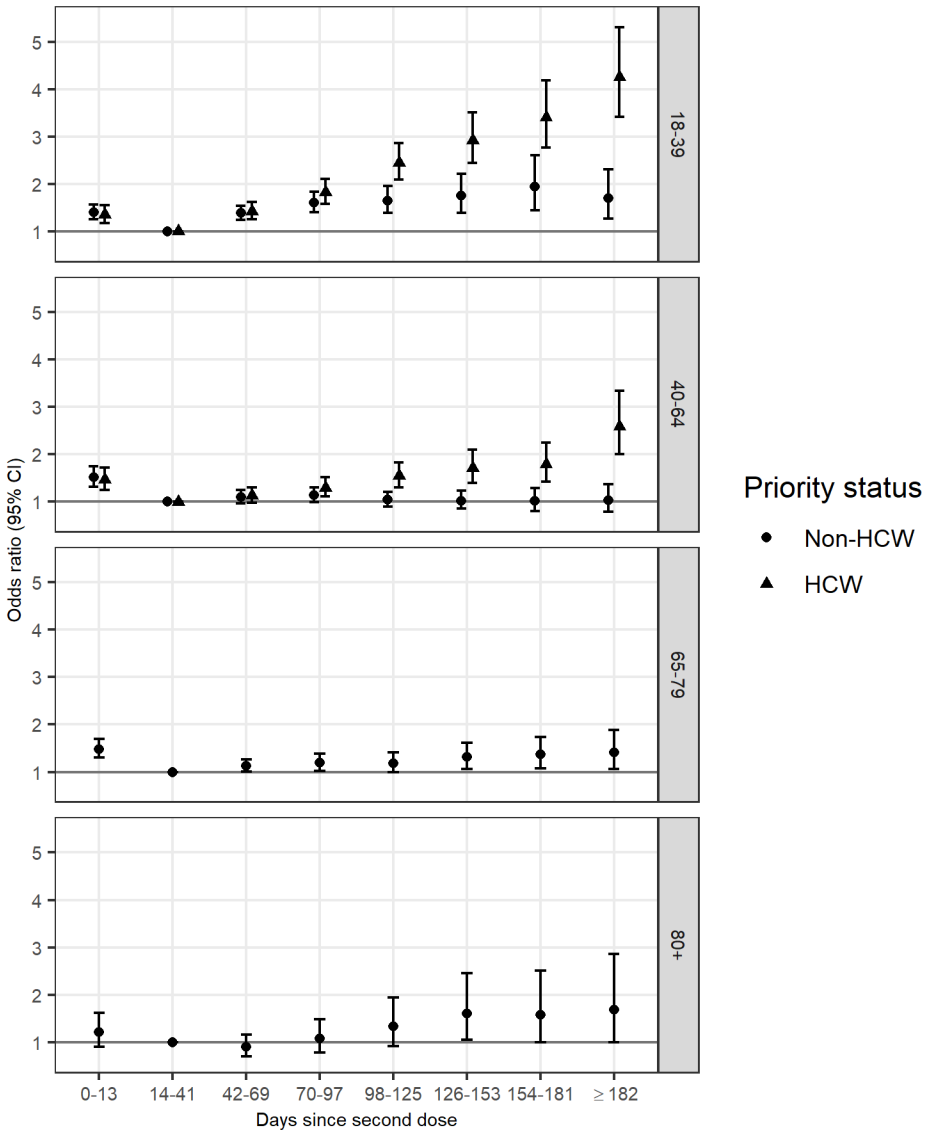
Supplementary Figure C. Odds ratio of symptomatic covid-19 for days since vaccination, relative to 14-41 days following vaccination for HCWs who received their second dose at any time (primary analysis, circles), and for HCWs who received their second dose in February 2021 (triangles), by age group (rows).

	Vaccine effectiveness % (95% CI)			
Vaccination category	18-39 years	40-64 years	65-79 years	≥80 years
Unvaccinated	REF	REF	REF	REF
Dose 1 0-13 days	-19.77 (-24.92--14.83)	-6.51 (-12.67--0.70)	12.40 (5.68-18.65)	45.44 (32.59-55.84)
Dose 1 ≥14 days	-1.00 (-5.18-3.01)	-1.83 (-7.16-3.23)	3.82 (-3.38-10.52)	23.17 (7.13-36.44)
Dose 2 0-13 days	10.45 (5.61-15.04)	12.78 (7.15-18.07)	21.02 (14.25-27.25)	32.25 (17.57-44.31)
Dose 2 14-41 days	36.34 (33.52-39.04)	44.41 (41.79-46.91)	41.72 (37.54-45.61)	41.53 (30.64-50.72)
Dose 2 42-69 days	21.06 (16.99-24.93)	39.85 (36.54-42.99)	36.75 (32.12-41.06)	36.65 (25.07-46.44)
Dose 2 70-97 days	13.71 (9.05-18.13)	29.80 (25.84-33.55)	34.22 (28.92-39.12)	29.39 (16.11-40.57)
Dose 2 98-125 days	10.20 (4.97-15.15)	29.25 (25.12-33.17)	29.84 (23.60-35.56)	30.06 (16.46-41.44)
Dose 2 126-153 days	1.98 (-5.42-8.86)	21.17 (15.37-26.58)	19.61 (11.44-27.02)	23.54 (7.16-37.02)
Dose 2 154-181 days	-10.57 (-20.69--1.30)	3.86 (-5.22-12.14)	9.26 (-1.79-19.11)	23.61 (5.14-38.49)
Dose 2 ≥182 days	-46.68 (-58.54--35.7)	-19.79 (-30.64--9.83)	2.39 (-12.64-15.42)	15.49 (-8.83-34.37)

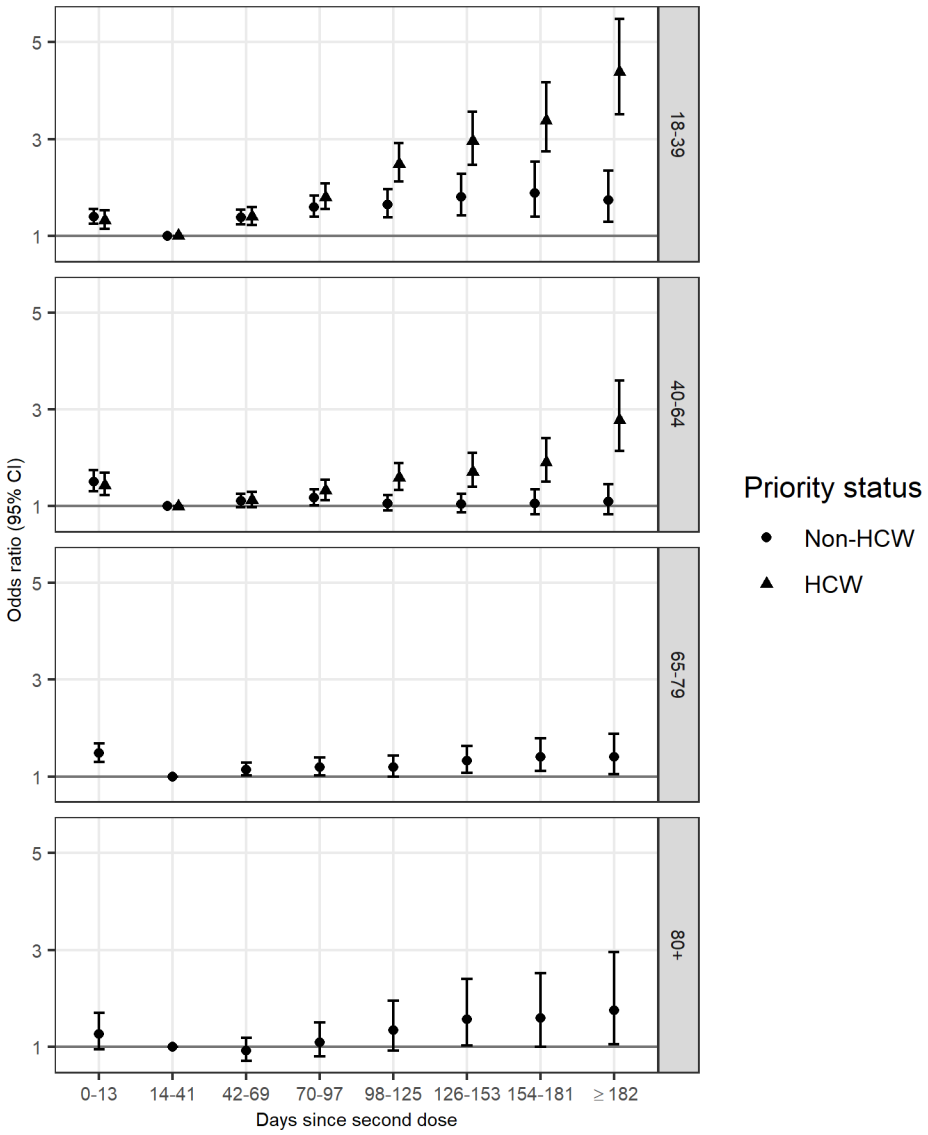
Supplementary Table E. Vaccine effectiveness of one and two doses against symptomatic RT-PCR confirmed covid-19 by time since vaccination, by age categories

	Vaccine effectiveness (95% CI)			
Vaccination category	18-39 years	40-64 years	65-79 years	≥80 years
Unvaccinated	REF	REF	REF	REF
Dose 1 0-13 days	37.26 (22.74-49.05)	24.06 (11.58-34.78)	29.55 (21.23-37.00)	59.51 (45.81-69.74)
Dose 1 ≥14 days	-11.72 (-34.2-6.99)	6.36 (-5.91-17.21)	20.52 (10.94-29.07)	38.52 (21.35-51.94)
Dose 2 0-13 days	50.88 (34.23-63.31)	39.64 (28.37-49.13)	43.29 (35.32-50.29)	49.03 (34.24-60.48)
Dose 2 14-41 days	74.78 (66.95-80.76)	70.10 (66.12-73.61)	61.27 (56.38-65.62)	49.40 (36.95-59.40)
Dose 2 42-69 days	71.25 (61.27-78.66)	71.20 (66.59-75.18)	62.68 (57.64-67.13)	45.38 (32.21-55.99)
Dose 2 70-97 days	56.76 (43.25-67.06)	63.35 (57.47-68.42)	57.52 (51.27-62.96)	40.25 (25.56-52.05)
Dose 2 98-125 days	56.72 (42.69-67.31)	65.10 (59.38-70.02)	58.01 (51.21-63.86)	38.46 (22.86-50.91)
Dose 2 126-153 days	63.35 (46.25-75.00)	67.93 (61.04-73.60)	50.42 (41.24-58.16)	34.42 (16.14-48.71)
Dose 2 154-181 days	49.63 (19.22-68.59)	56.54 (43.21-66.74)	45.25 (33.27-55.09)	31.90 (10.67-48.09)
Dose 2 ≥182 days	28.88 (-9.28-53.71)	26.73 (6.46-42.61)	34.97 (17.59-48.68)	20.24 (-8.05-41.13)

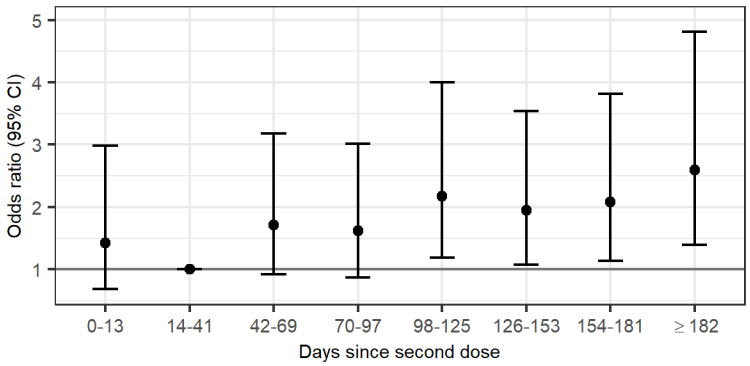
Supplementary Table F. Vaccine effectiveness of one and two doses against RT-PCR confirmed covid-19 hospitalisation or death by time since vaccination, by age categories



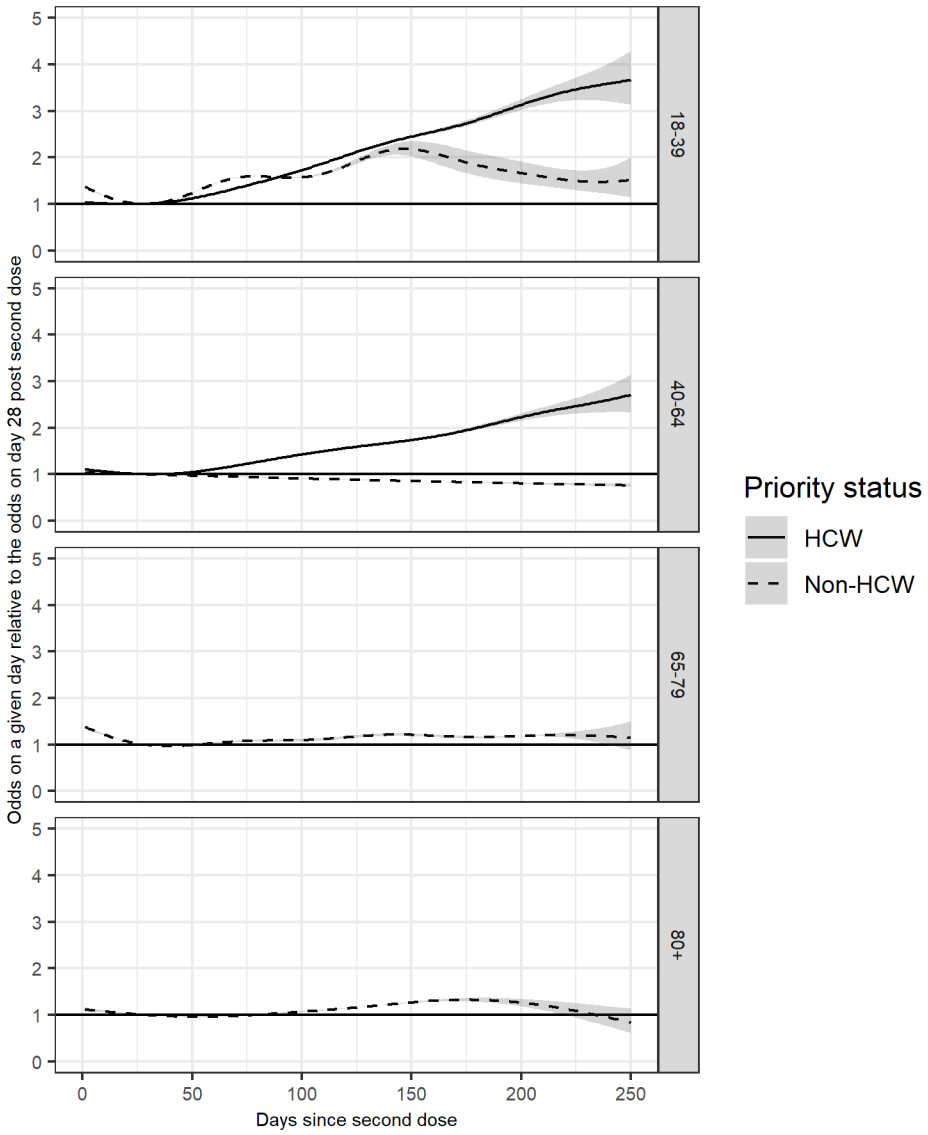
Supplementary Figure D. Odds ratio of symptomatic PCR-confirmed covid-19 disease against days since vaccination, relative to 14-41 days following vaccination, by age group (rows), for non-healthcare workers (circles) and healthcare workers (triangles), using multiple imputation to account for individuals with missing race data



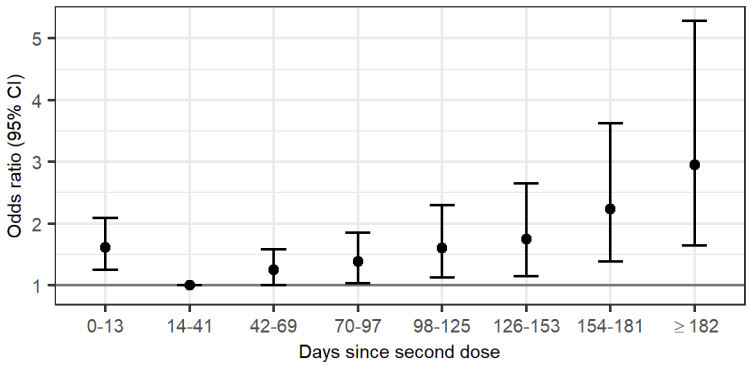
Supplementary Figure E. Odds ratio of symptomatic PCR-confirmed covid-19 disease against days since vaccination, relative to 14-41 days following vaccination, by age group (rows), for non-healthcare workers (circles) and healthcare workers (triangles), excluding individuals with any previous ARI



Supplementary Figure F. Odds ratio of PCR-confirmed covid-19 hospitalisation or death for days since vaccination, relative to 14-41 days following vaccination, restricting to tests that occurred during the period of Delta variant dominance (August 8th, 2020 to December 14th, 2020)



Supplementary Figure G. Odds ratio of symptomatic PCR-confirmed covid-19 over time since second dose receipt, relative to 28 days after second dose receipt, by age group (rows), for non-healthcare workers (dotted line) and healthcare workers (solid line)



Supplementary Figure H. Odds ratio of PCR-confirmed covid-19 death for days since vaccination, relative to 14-41 days following vaccination