Supplementary material S1: VE cohort exclusions

Initial cohort: 7,217,929, population excluded and reasons:

- Not registered at GP before study start, required to ensure we captured data about whether they were in a risk group or the shielding category, n = 351,645
- Practices for which <10% 65+ year olds have a record of COVID-19 vaccination, n = 81
- Practices for which <10% adults in risk groups have a record of COVID-19 vaccination, n = 0
- Practices for which <0.01% of the whole practice population have a record of a positive test, n = 0
- Both first vaccination dose before 8 December 2020 and no corresponding second dose within 28 days, n = 832
- Second vaccination dose <19 days after first vaccination dose, n = 476
- AstraZeneca vaccination recorded between 7 December 2020 and 29 December 2020, n = 234
- Females above age 112 and males above age 108, n = 14
- Individuals with outcomes < 90 days following COVID-19 diagnosis without a PCR test, n = 48
- Aged < 16 years, n = 1,221,912

Final cohort: 5,642,687

Box S1.1: Exclusions from the PHE COVID-19 VE cohort

Supplementary material S2: descriptive statistics and deaths

Some basic patient characteristics for members of the eligible cohort, including median age, the proportion aged 65 and over, the proportion male and the proportion of non-white ethnic origin (where known).

The percentage of deaths within 28 days of a new positive test within the study period (from 7 December up to 28 days before the study end) is given as an approximate case fatality ratio, this was calculated regardless of vaccination status. A 'new' positive test was defined as for the cohort study: positive tests must be both at least 42-days apart and beyond 90 days of the first in a series. The death rate per 1000 person years in individuals with no record of a positive test over the study period is also given, to give a general indication of frailty. Patients who had a positive test in the 8 weeks before the start of the study period were excluded from death statistics.

Table S2.1: descriptive demographic statistics, death rates and approximate case fatality ratio

	median age	% age ≥ 65	% male	% non-white	death rate per 1000 person-years in non-cases	% deaths within 28 days of a new positive test
age < 65	40		51	18	2.2	0.15
age < 65, non-risk	38		51	18	0.9	0.07
age < 65, risk	52		54	19	10.1	0.66
age <65, shielding	49		42	29	18.3	0.79
age >= 65	74		46	6	40.4	10.3
age >= 65, non-risk	72		49	5	15.6	6.12
age >= 65, risk	76		51	7	63.2	12.85
age >= 65, shielding	79		51	9	101.1	9.36
CHD	73	72	59	8	60.7	8.73
diabetes	66	55	56	20	36.4	4.66
neurological	74	68	48	8	81.6	12.71
chronic kidney	78	84	43	8	72.4	12.88
morbid obesity	52	23	31	10	14.1	1.7
chronic respiratory	71	69	50	7	72.5	8.82
immunocompromised	64	48	45	10	40.7	5.28
chronic liver	58	33	55	16	29.6	1.98

Supplementary material S3: vaccine coverage

Table S3.1: coverage by vaccination brand and month vaccinated within specific PRIMIS risk groups

group	total	% unvacc	Vaccination brand			Month vaccinated					
			% AZ	% Pf	% n/k	% Dec	% Jan	% Feb	% Mar	% Apr	% May -Jun
16-64 (from Feb), all	4039042	45	28	13	14			13	23	5	14
16-64, non-risk	3561576	49	26	12	13			8	22	6	15
16-64, risk	415338	18	43	22	16			49	29	2	3
16-64, shielding	160401	18	45	18	19			60	17	2	2
65+, all	1276517	7	37	33	24	7	43	39	3	1	0
65+, non-risk	645166	8	36	28	27	5	37	46	3	1	0
65+, risk	584752	6	37	37	19	9	50	32	2	1	0
65+, shielding	211341	6	38	40	16	11	55	25	2	0	0
CHD	369832	9	37	36	18	8	40	33	9	1	1
diabetes	328211	9	40	33	18	5	29	43	12	1	1
neuro	221411	11	39	33	17	8	40	30	10	1	1
chronic kidney	193393	7	36	41	16	11	50	27	5	1	0
morbid obesity	170947	15	42	24	19	2	16	37	24	2	3
chronic respiratory	157685	9	39	33	18	6	39	37	7	1	1
immuno	91559	8	40	32	20	5	34	42	9	1	1
chronic liver	89428	15	41	26	17	2	19	39	20	2	2

AZ = AstraZeneca, Pf = Pfizer Bio-Ntech, n/k = other brand or unknown

Supplementary material S4: Seropositivity and Post-vaccination antibody responses in RCGP patients

Blood samples were collected opportunistically alongside routine blood tests from a geographically representative sample of GP practices throughout England. Patients that are older and in risk groups are over-represented in this serological surveillance collection. Here we consider post-vaccination antibody responses in 3,905 vaccinated individuals aged 18+ who had received 1 or 2 doses of COVID-19 vaccination with results available using the Roche S (spike) and N (nucleoprotein) assays.

Modelled and adjusted N-assay based seropositivity is given in Supplementary Figure S4.1. For individuals not belonging to a risk group seropositivity was 9.0% (95% CI 8.1 to 9.9%). Seropositivity was lower for individuals in risk groups and shielding, though not significantly. For the specific risk groups seropositivity was only significantly lower for the immune-compromised group, although the chronic respiratory and chronic liver disease groups also showed relatively low seropositivity of around 6%.

Figure S4.1: Modelled, age and region weighted, seropositivity based on the Roche neucleoprotein (N) assay, January to May 2021

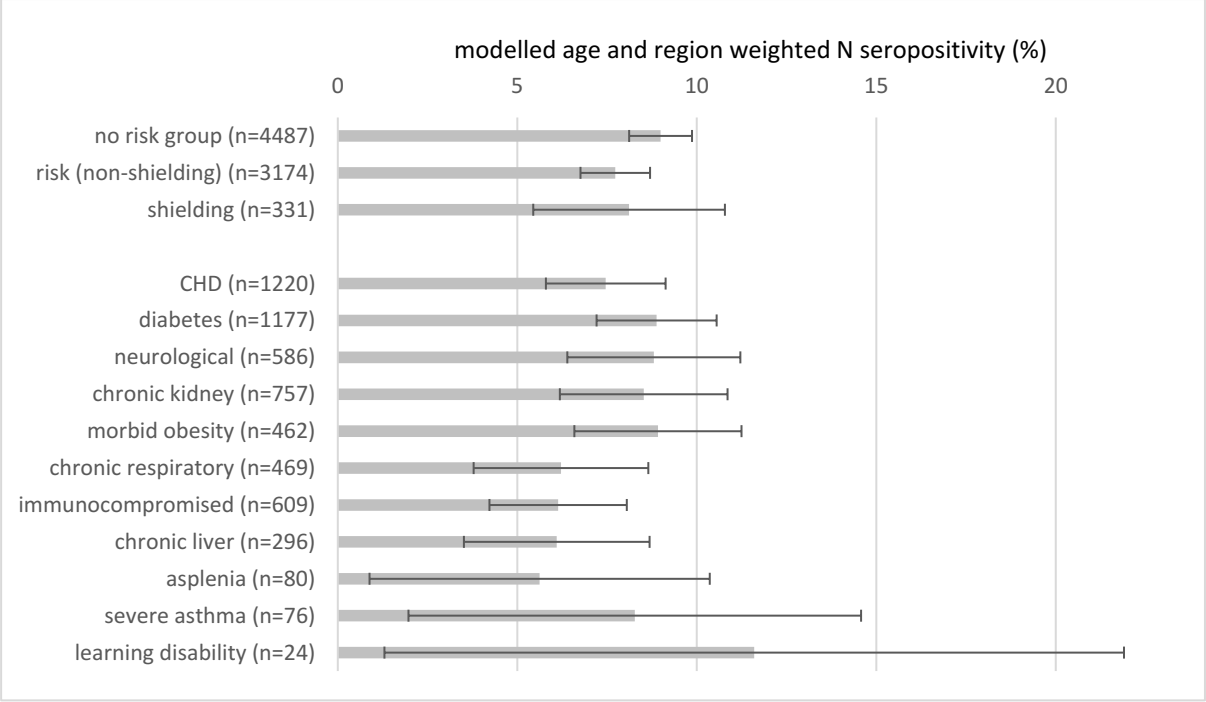


Figure S4.2 shows the Roche S antibody level plotted against time since vaccination, with points coloured by vaccine manufacturer and Roche N outcome. Note the caveat that quantitative Roche S outcomes were capped at 2,500 before testing at greater dilutions commenced, hence some results

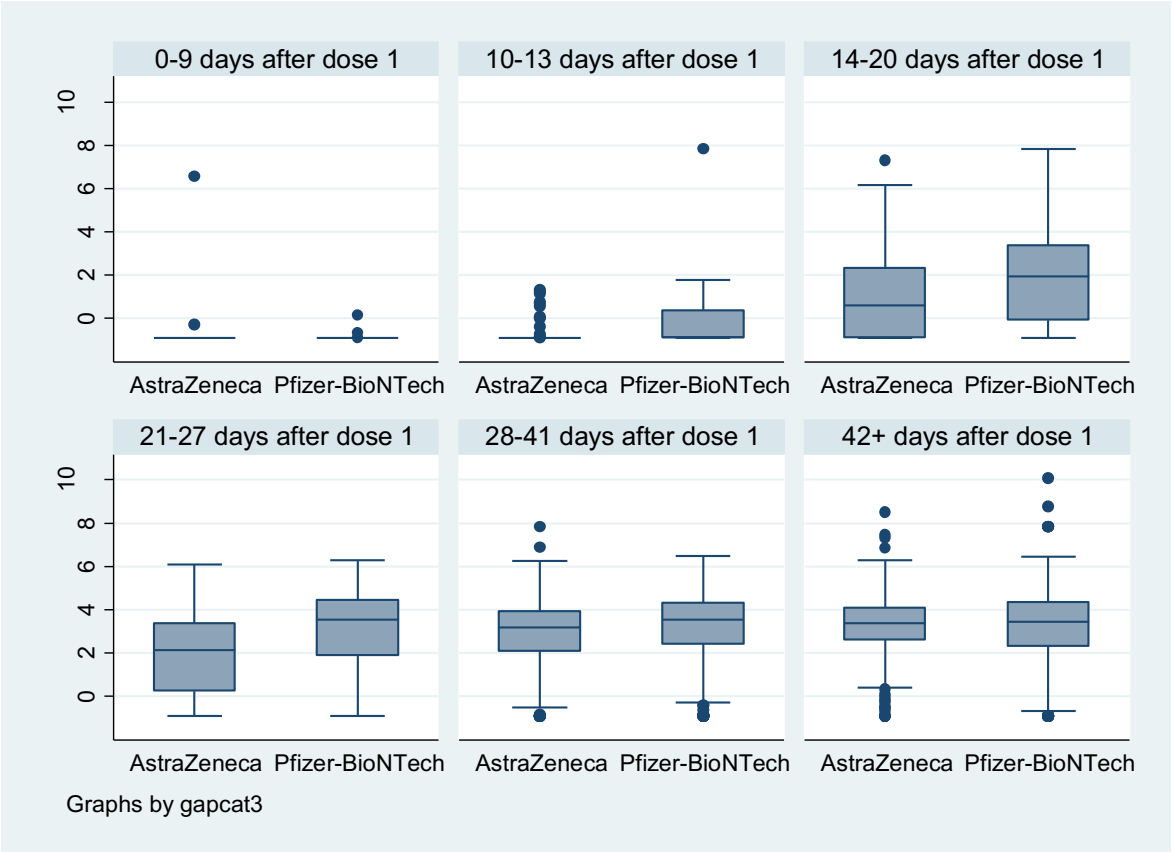
can only be given as >2500. Roche S levels 2500+ should be considered very high responses, well beyond that typically seen following infection.

Figure S4.2: Roche S antibody titre following dose 1 vaccination, coloured by vaccine manufacturer and N antibody status

Given the high specificity of the Roche N assay (99.8%), we assume that individuals with a positive Roche N outcome have experienced a past infection and developed antibodies to the S protein. These antibodies appear to be boosted by vaccination, and most Roche N positive individuals reach very high Roche S antibody levels within 7 to 10 days of vaccination with 100% Roche S positive 7+ days after dose 1. We do not consider these individuals further in analyses and instead focus on Roche N negative individuals only.

Figure S4.3 gives boxplots of Roche S antibody levels by vaccine manufacturer in N negative samples following dose 1. Note that for many samples this is unknown, we plot only where known. This shows that antibody response to Pfizer tends to occur quicker than AstraZeneca, but that by 28-days post vaccination responses are similar between vaccines.

Figure S4.3: Boxplots of log Roche S level following dose 1 by vaccine manufacturer and time since vaccination, Roche N negative individuals only



Similar to the analysis of seropositivity presented in the main paper (Table 1), we fit regression models to (log) Roche S titres 28 to 90 days post dose 1 vaccination and 10+ days post dose 2 vaccination in Roche N negative individuals to explore the effects of age, sex, vaccine manufacturer with time since vaccination and risk status affect titres, and for dose 2 the effect of schedule. Since many levels were capped at 2500, regression models that allowed for this censoring (generalised Tobit models) were fitted.

Table S4.1: Median responses, and geometric mean ratios given by multivariable regression of (log) Roche S antibody concentrations, 28 to 90 days post dose 1

	N	median (IQR)	geometric mean ratio (95% CI)	p-value
age group				
18-49	166	47.6 (20 - 106)	1 (ref)	
50-59	189	30.1 (12.1 - 70.3)	0.63 (0.45 - 0.89)	0.009
60-69	330	34.1 (13.7 - 70.8)	0.61 (0.45 - 0.83)	0.002
70-74	293	28.9 (7.3 - 66.5)	0.51 (0.37 - 0.71)	**<0.001**
75-79	252	24.7 (8.2 - 54.8)	0.41 (0.29 - 0.57)	**<0.001**
80-84	184	16.7 (5.2 - 43.1)	0.3 (0.21 - 0.44)	**<0.001**
85+	125	15.4 (3.8 - 48.6)	0.28 (0.18 - 0.42)	**<0.001**
sex				
F	829	33.4 (12.8 - 76)	1 (ref)	
M	710	21.5 (6.9 - 52.7)	0.69 (0.59 - 0.82)	**<0.001**
days after dose X manufacturer interaction				
28-41, AZ	183	23.7 (8.2 - 50.9)	0.57 (0.4 - 0.81)	**0.002**
28-41, Pfizer	154	34.2 (11.4 - 75.8)	1 (ref)	
28-41, unknown	195	16.4 (4.7 - 57.6)	0.45 (0.32 - 0.64)	**<0.001**
42+, AZ	294	28.3 (13.1 - 58.4)	0.77 (0.56 - 1.07)	0.115
42+, Pfizer	328	30.8 (10 - 75.4)	0.96 (0.7 - 1.32)	0.807
42+, unknown	385	29.4 (9.3 - 65)	0.88 (0.65 - 1.2)	0.431
risk group status				
CHD: no	1201	30.1 (10.3 - 70.4)	1 (ref)	
CHD: yes	338	20.4 (5.7 - 48.2)	0.78 (0.63 - 0.96)	**0.022**
diabetes: no	1286	29 (9.8 - 68.7)	1 (ref)	
diabetes: yes	253	19.1 (5.3 - 50.6)	0.71 (0.56 - 0.89)	**0.003**
neurological: no	1386	28.7 (9.7 - 68.7)	1 (ref)	
neurological: yes	153	18.3 (5.6 - 42.2)	0.81 (0.61 - 1.07)	0.138
chronic kidney: no	1317	28.3 (9.4 - 67.8)	1 (ref)	
chronic kidney: yes	222	22.5 (7.2 - 52.7)	1.03 (0.8 - 1.32)	0.832
morbid obesity: no	1450	27.6 (9.1 - 66.5)	1 (ref)	
morbid obesity: yes	89	27.9 (9.4 - 53.4)	0.61 (0.42 - 0.87)	**0.007**
chronic respiratory: no	1413	27.9 (9.4 - 65.8)	1 (ref)	
chronic respiratory: yes	126	21 (5.9 - 65.6)	1.04 (0.76 - 1.42)	0.799
immuno: no	1407	29.5 (11.3 - 69)	1 (ref)	
immuno: yes	132	6.4 (0.5 - 30.9)	0.17 (0.13 - 0.23)	**<0.001**
chronic liver: no	1465	27.8 (9.3 - 65.7)	1 (ref)	
chronic liver: yes	74	24.8 (8.3 - 65.8)	0.93 (0.63 - 1.39)	0.736

The dose 1 model (Table S4.1) suggests that the vaccine-induced antibody response diminishes with advancing age, but this was not found in the dose 2 model (Table 2 of main paper). There is a significant sex effect both post dose 1 and post dose 2, males have lower antibody concentrations than females. Post dose 1 Pfizer levels were a little higher at 28 to 41 days, but there was no difference in levels by manufacturer at 42 to 90 days. Pfizer dose 2 responses were significantly higher than Astra Zeneca. Effects of schedule post dose 2 were also strongly significant, with greater responses following extended schedules.

Within the risk groups, responses were lower among the immunocompromised group, both post dose 1 and dose 2, median responses were considerably lower and effects strongly significant. Post dose 1 only responses were significantly lower in the CHD, diabetes and morbid obesity groups, and post dose 2 only responses were significantly lower in the chronic respiratory group.

It should be noted that a caveat with these analyses is that some patients may have multiple comorbidities hence the geometric mean ratio may be affected by joint effects.

These analyses were repeated without the specific risk groups, but instead with a single categorical variable for non-risk / risk (non-shielding) / shielding (Tables S4.2, S4.3).

Table S4.2: Median responses, and geometric mean ratios given by multivariable regression of (log) Roche S antibody concentrations, 28 to 90 days post dose 1

	N	median (IQR)	adjusted GM ratio (95% CI)	p-value
risk status				
no risk group	699	36.9 (14.8 - 74.4)		
any risk group (non-shielding)	780	20.4 (6.6 - 53.2)	0.59 (0.49 - 0.71)	<0.001
Shielding	60	16.8 (2.4 - 58.2)	0.39 (0.24 - 0.62)	<0.001

Table S4.3: Median responses, and geometric mean ratios given by multivariable regression of (log) Roche S antibody concentrations, 10+ days post dose 2

	N	median (IQR)	adjusted GM ratio (95% CI)	p-value
risk status				
no risk group	240	1948.5 (702 - 4204)		
any risk group (non-shielding)	258	1434.5 (428 - 2500)	0.59 (0.43 - 0.82)	0.002
shielding	34	1793.5 (581 - 3189)	0.97 (0.5 - 1.91)	0.937

The effect of risk-group membership was significant in all models, and for shielding post dose 1. Shielding numbers post dose 2 were fairly small, but responses appeared to be typically good.

Supplementary material S5: TNCC estimates

Table S5.1: Vaccine effectiveness 28 to 90 days post dose 1 and 14+ days post dose 2, for any vaccine, Pfizer and AstraZeneca (TNCC analysis)

		Unvaccinated		Dose 1			Dose 2		
Vaccine	group	controls	cases	controls	cases	aVE	controls	cases	aVE
Any vaccine									
	all, ages 16-64	9222	4198	2480	245	66.2% (59.5% - 71.8%)	749	56	86.5% (81.2% - 90.4%)
	non-risk, ages 16-64	7929	3541	1613	175	66.8% (59.1% - 73.1%)	382	35	84.4% (76.4% - 89.7%)
	risk group, ages 16-64	1132	564	742	58	66.2% (52.9% - 75.8%)	308	18	88.7% (80.4% - 93.5%)
	shielding, ages 16-64	455	233	390	38	57.6% (35.4% - 72.1%)	179	7	92.9% (82.9% - 97.0%)
	all, ages 65+	5263	4896	3081	344	59.1% (50.0% - 66.4%)	3001	67	82.8% (74.2% - 88.5%)
	non-risk, ages 65+	1380	1414	590	60	61.8% (45.7% - 73.1%)	541	19	75.0% (54.1% - 86.4%)
	risk group, ages 65+	3542	3220	2244	264	56.9% (46.6% - 65.2%)	2174	44	84.8% (76.2% - 90.2%)
	shielding, ages 65+	2001	1511	1525	175	54.9% (42.6% - 64.6%)	1637	28	83.5% (72.7% - 90.0%)
	CHD	2622	2452	1364	153	62.0% (52.3% - 69.7%)	1256	27	90.0% (83.8% - 93.8%)
	diabetes	2023	2523	908	119	58.5% (46.9% - 67.6%)	767	28	87.0% (79.1% - 91.9%)
	neurological	2252	1810	1258	148	59.4% (48.6% - 67.9%)	1282	13	94.3% (89.2% - 97.0%)
	chronic kidney	1299	1276	747	105	53.4% (39.1% - 64.3%)	740	23	85.5% (76.2% - 91.2%)
	morbid obesity	1681	1555	478	54	56.3% (38.3% - 69.0%)	395	7	90.1% (78.1% - 95.5%)
	chronic respiratory	1953	1122	924	59	61.5% (47.5% - 71.7%)	798	11	90.3% (81.1% - 95.0%)
	immuno-compromised	700	601	278	50	18.3% (-18.4% - 43.7%)	233	9	77.9% (54.4% - 89.3%)
	chronic liver	859	725	248	27	40.2% (6.2% - 61.9%)	152	5	84.7% (56.6% - 94.6%)
Pfizer									
	all, ages 16-64	9222	4198	470	41	62.9% (46.3% - 74.4%)	232	8	94.5% (87.8% - 97.5%)
	non-risk, ages 16-64	7929	3541	240	20	69.1% (47.4% - 81.9%)	115	7	88.6% (73.9% - 95.0%)
	risk group, ages 16-64	1132	564	203	19	55.6% (24.3% - 74.0%)	100	1	90.2% (77.7% - 95.7%)
	shielding, ages 16-64	455	233	100	7	64.2% (19.5% - 84.1%)	47	1	
	all, ages 65+	5263	4896	1128	198	56.1% (45.1% - 65.0%)	1309	33	84.2% (75.2% - 89.9%)
	non-risk, ages 65+	1380	1414	220	41	52.4% (27.3% - 68.8%)	224	11	66.5% (32.4% - 83.3%)
	risk group, ages 65+	3542	3220	812	148	54.4% (41.5% - 64.5%)	954	22	86.3% (76.9% - 91.9%)
	shielding, ages 65+	2001	1511	561	101	49.7% (32.8% - 62.3%)	735	16	81.7% (67.4% - 89.7%)
	CHD	2622	2452	502	80	59.5% (45.8% - 69.7%)	591	15	89.3% (80.7% - 94.1%)
	diabetes	2023	2523	331	56	55.2% (37.2% - 68.0%)	354	12	89.3% (79.2% - 94.5%)
	neurological	2252	1810	434	76	55.1% (38.7% - 67.1%)	495	7	91.8% (82.0% - 96.2%)
	chronic kidney	1299	1276	291	58	50.6% (29.8% - 65.2%)	353	10	88.5% (76.9% - 94.2%)
	morbid obesity	1681	1555	152	24	46.0% (11.1% - 67.1%)	186	2	94.7% (77.9% - 98.7%)
	chronic respiratory	1953	1122	300	30	59.5% (38.3% - 73.5%)	388	5	91.8% (79.6% - 96.7%)
	immuno-compromised	700	601	98	22	26.0% (-26.9% - 56.9%)	124	5	79.6% (47.6% - 92.1%)
	chronic liver	859	725	80	14	17.9% (-55.8% - 56.8%)	57	1	91.2% (34.4% - 98.8%)
AZ									
	all, ages 16-64	9222	4198	1591	184	64.7% (56.6% - 71.2%)	423	47	81.4% (73.0% - 87.2%)
	non-risk, ages 16-64	7929	3541	1112	140	65.1% (56.0% - 72.4%)	216	27	81.6% (70.2% - 88.6%)
	risk group, ages 16-64	1132	564	410	37	63.1% (44.6% - 75.4%)	173	17	79.8% (64.0% - 88.7%)
	shielding, ages 16-64	455	233	216	26	51.1% (19.3% - 70.4%)	110	6	89.4% (73.9% - 95.7%)
	all, ages 65+	5263	4896	1343	99	64.0% (51.7% - 73.1%)	1226	30	81.7% (66.9% - 89.8%)
	non-risk, ages 65+	1380	1414	230	15	62.5% (31.8% - 79.3%)	196	8	79.9% (48.0% - 92.2%)
	risk group, ages 65+	3542	3220	1002	78	63.5% (49.7% - 73.5%)	912	19	83.5% (67.9% - 91.5%)
	shielding, ages 65+	2001	1511	770	55	65.9% (50.9% - 76.3%)	771	10	87.3% (71.4% - 94.4%)
	CHD	2622	2452	607	54	63.8% (48.7% - 74.4%)	492	10	91.2% (80.5% - 96.1%)
	diabetes	2023	2523	416	47	60.9% (43.6% - 72.9%)	318	15	82.8% (67.6% - 90.9%)
	neurological	2252	1810	589	51	63.8% (48.1% - 74.8%)	626	5	96.6% (89.1% - 98.9%)
	chronic kidney	1299	1276	331	34	55.0% (32.4% - 70.1%)	307	11	82.0% (62.7% - 91.3%)
	morbid obesity	1681	1555	246	24	61.3% (36.5% - 76.4%)	153	5	81.8% (53.3% - 92.9%)
	chronic respiratory	1953	1122	427	16	69.8% (48.8% - 82.2%)	310	5	88.2% (67.1% - 95.8%)
	immuno-compromised	700	601	130	26	-7.7% (-76.0% - 34.1%)	83	3	79.5% (31.3% - 93.9%)
	chronic liver	859	725	126	10	52.3% (5.3% - 76.0%)	72	4	75.8% (17.9% - 92.9%)

Figure S5.1a: TNCC odds ratios 28 to 90 days after dose 1 of any COVID-19 vaccine

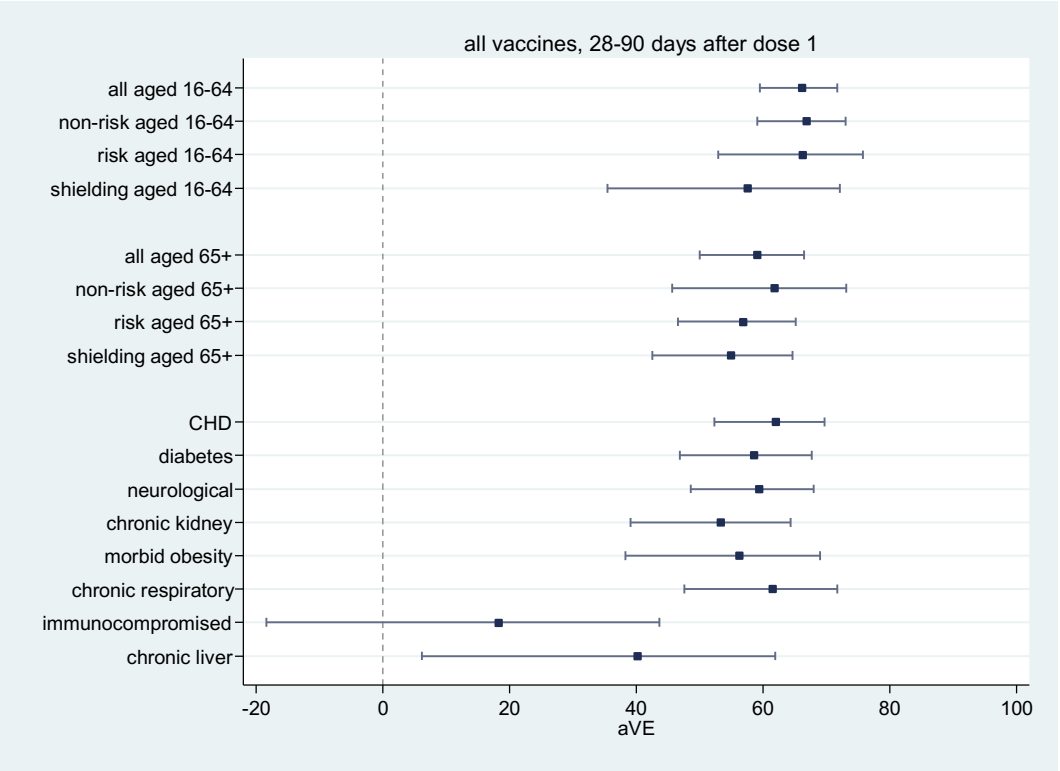


Figure S5.1b: TNCC odds ratios 14+ days after dose 2 of any COVID-19 vaccine