Hospitalised vaccinated patients during the second wave, update April '21

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ISARIC4C / CO-CIN

Summary

This report investigates hospitalised vaccinated patients during the second wave of the UK COVID19 outbreak using the ISARIC4C / CO-CIN data set with data available up to April 10th 2021.

For patients enrolled to ISARIC4C / CO-CIN:

- 1 in 14 patients admitted to hospital since December 8th 2020 have received at least the first dose of a COVID-19 vaccination (previously 1 in 25).
- The median time between vaccination and symptom onset for these patients was 9 days.
- The median time between vaccination and hospital admission for these patients was 15 days.
- Most vaccinated hospitalised patients were infected shortly before or around the time of vaccination, and others after vaccination but before immunity had developed (immunisation) [high confidence]
- As the period of follow-up observation has increased, there has been a rise in the proportion of SARS-CoV-2 PCR positive people admitted more than 21 days after vaccination (vaccine failure) [moderate confidence]. However, while absolute counts are low and continue to fall as the risk of exposure continues to fall, this will lead to under-representation the signal of vaccine failure.
- In this early descriptive analysis, mortality appears to remain high for people in high-risk vaccination tiers who are admitted to hospital with symptomatic SARS-CoV-2 infection (COVID-19) despite vaccination 21 day or more previously [low confidence].

Important caveats
We do not have all hospitalised patients in our cohort, and vaccinated patients may be over-represented given our recruitment strategy. Absolute numbers of vaccinated patients admitted to hospital are very low. We have not yet performed analyses accounting for other patient characteristics such as sex and ethnicity, so vaccinated patients may be systematically different (and frailer) from vaccinated patients - this is particularly true of "Tier 2" which is likely to contain many Tier 1 patients who we were unable to identify in our dataset.

Admission trends

The period of the second wave of COVID-19 is defined as from September 1st 2020 to present. There have been 99,445 hospital admissions enrolled to ISARIC/CO-CIN in the second wave. There were 3,842 hospitalised vaccinated patients enrolled as of April 10th 2021. This accounts for 7.3% (3,842 /52,280) of enrolled hospital admissions since December 8th 2020, the date when the first people in the UK were vaccinated. Of these patients we have information on date of first vaccination for 3,598 of them and information on date of second vaccination for 140 of them. (Figure 1, Figure 2).
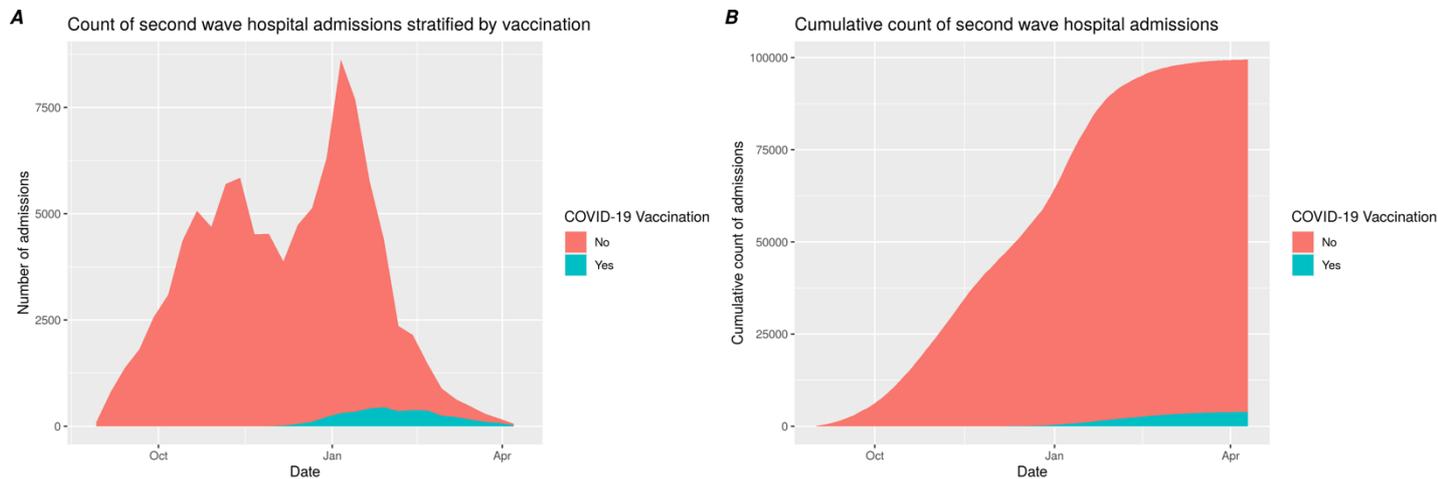

Figure 1: Number of second wave hospital admissions stratified by vaccinated vs non-vaccinated. A: Absolute counts, B: cumulative counts

Time to symptom onset for vaccinated patients

There was information on difference in date of symptom onset and date of vaccination for 2,142 patients (56% of vaccinated population, Figure 2). The difference in date of symptom onset and date of vaccination was filtered to include patients that experienced symptoms 7 days prior to vaccination onwards. The median time between vaccination and symptom onset was 9 days (IQR = [3,24]). Given that the median incubation period is 5 days, the distribution indicates that most vaccinated hospitalised patients were infected around the time of vaccination, and the remainder after vaccination but before immunity had developed (immunisation).
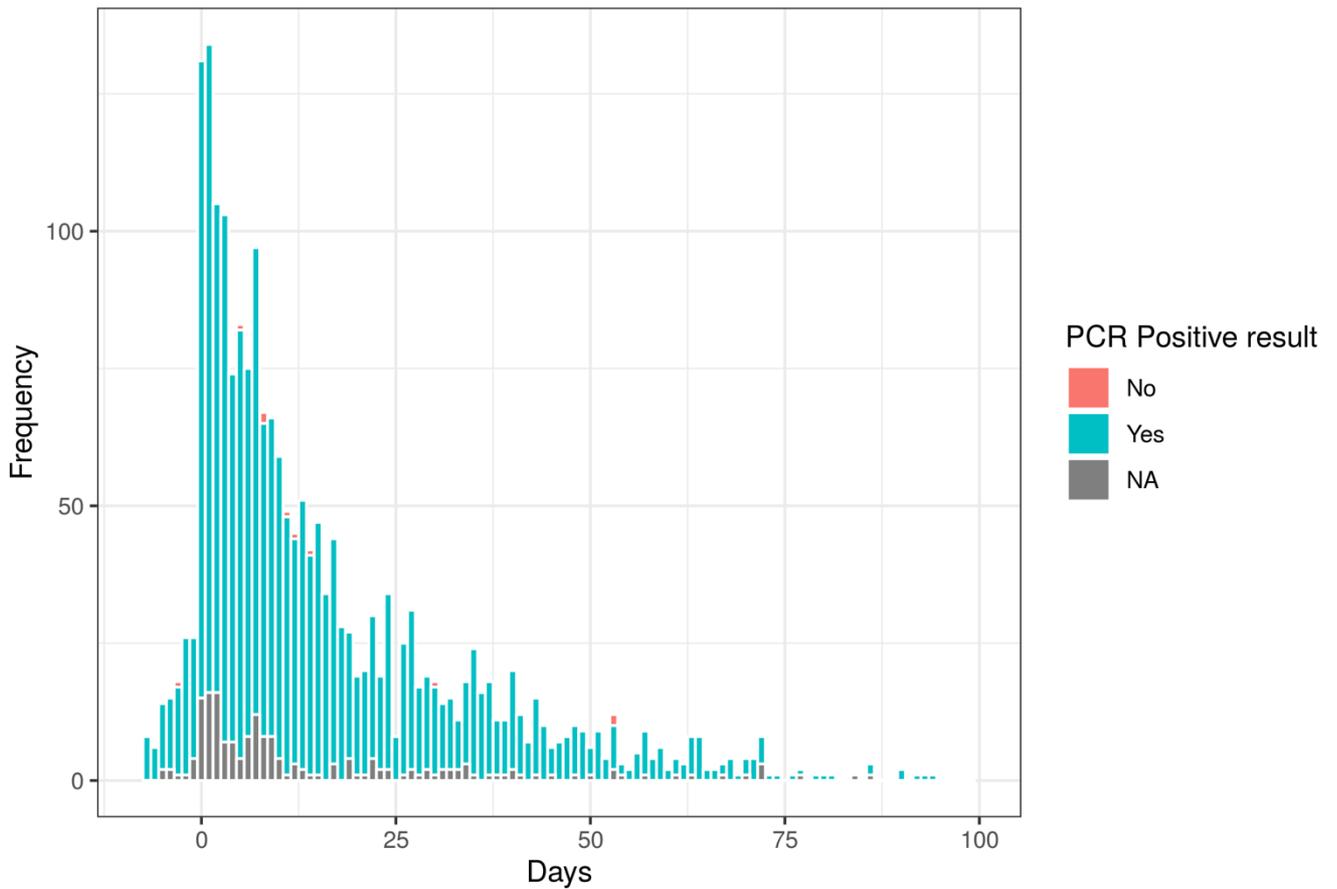
Figure 2: Histogram of count of difference of date in vaccination and symptom onset in hospitalised patients (PCR Positive No, Yes and NA= Not Available).

Time to admission for vaccinated patients

There was information on difference in date of vaccination and date of admission for 2,851 patients (74% of vaccinated population, Figure 3). The difference in date of admission and date of vaccination is filtered to include only patients admitted after vaccination i.e. only positive values. The median time between vaccination and admission to hospital was 15 days (IQR = [9,31]). The data is heavily skewed right.
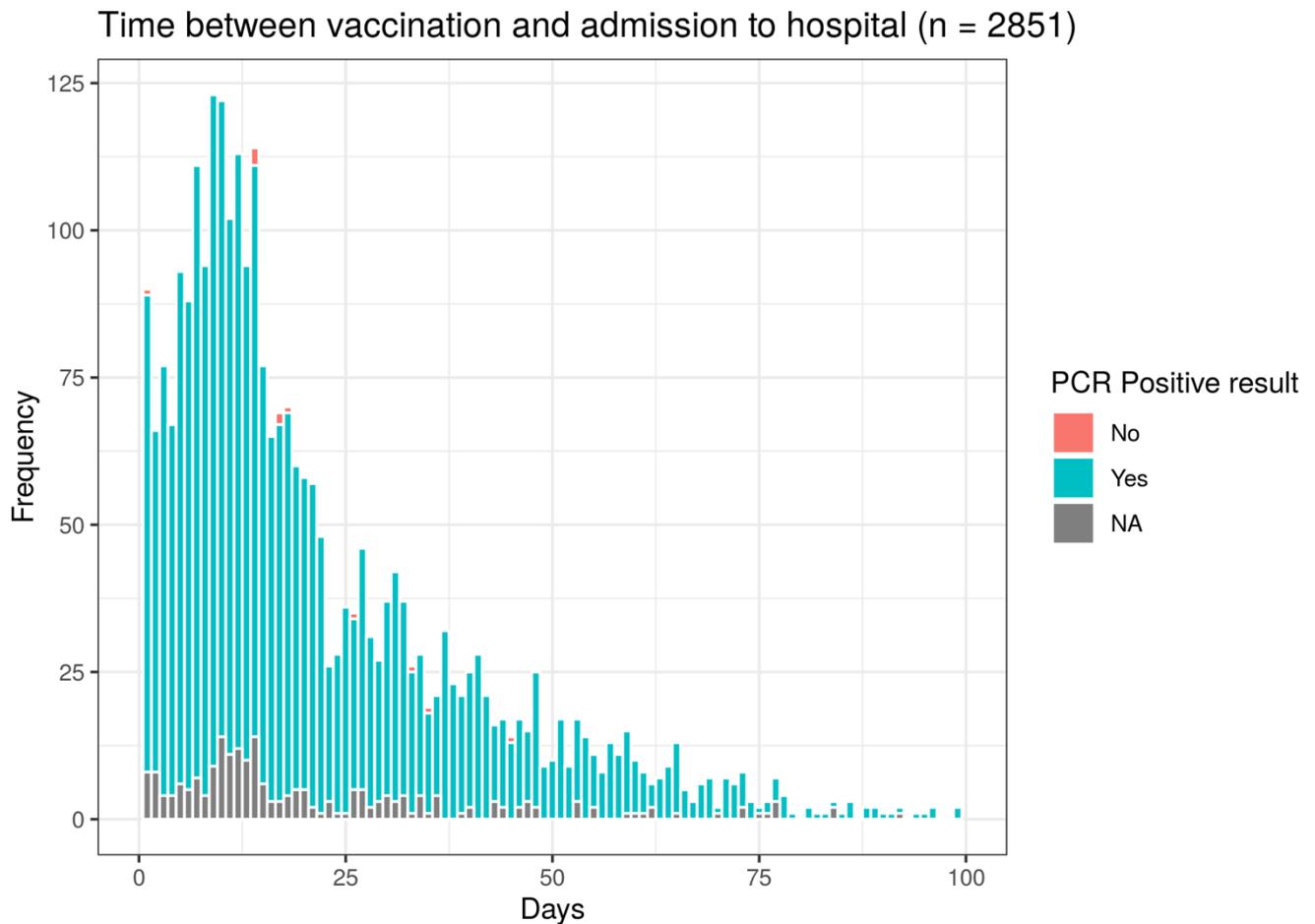
Figure 3: Histogram of count of difference in date of vaccination and date of admission to hospital (PCR Positive No, Yes and NA= Not Available).

Early admissions post-vaccination

We observed an abundance of patients admitted to hospital within 7 days of vaccination (Figure 3). Discussed below are potential reasons for this trend in admissions:

- Most vaccinated hospitalised patients were infected shortly before or around the time of vaccination, and the remainder after vaccination but before immunity had developed (immunisation).
- Elderly and vulnerable people who had been shielding, may have inadvertently been exposed and infected either through the end-to-end process of vaccination, or shortly after vaccination through behavioural changes where they wrongly assume they are immune.
- An additional hypothesis, that we cannot exclude in this analysis, is that some people had recent asymptomatic COVID-19 and vaccination precipitated admission. Previously asymptomatic or pauci-symptomatic PCR positive patients may experience symptoms likened to COVID-19 symptoms including fever due to vaccination. This happens within 48 hours of the vaccination and usually resolves within 48 hours [1].

We have recognised that some vaccinated patients were admitted for non-COVID-19 reasons and were asymptomatic but later identified as PCR positive. Of the 3,842 vaccinated patients admitted to hospital, 3,534 tested PCR positive (92% of vaccinated admissions). Of these patients 817 were asymptomatic (23% of PCR positive vaccinated admissions). Of these asymptomatic patients 120 (15% of asymptomatic PCR positive vaccinated admissions) were admitted within 7 days of vaccination, indicating infection before immunity had opportunity to develop.

Patients with previous COVID-19 infection may test PCR positive for up to 17 days post infection and rarely up to 90 days post-infection. This is because fragments of virus genes can persist in the upper respiratory tract following infection [2].

Sub-populations based on vaccination efficacy

We have stratified our population of vaccinated hospitalised cases based on difference in date of vaccination and date of symptom onset in seven-day intervals (Figure 4, Tables 1, E1, E2):

- 0-7 days (red): Admissions in this population do not correlate with vaccinations. This is too little time for the vaccination to work (immunity to develop) for most people and infection will have occurred before vaccination in many.
- 8-14 days (blue): Admissions in this population remain unlikely due to vaccination failure, as immunity is not expected to have fully developed.
- 14-21 days (yellow): We have defined admissions in this population as vaccination failure only for the purpose of this analysis, as some immunity would be expected to have developed in some people
- >21 days (green): from this period a greater degree of immunity would be expected in more people

Regardless of stratification, visual inspection gives appreciation of decay of frequency of vaccinated hospitalisation of time, or evidence of vaccine immunisation (successful immunity) developing over time. However as the period of follow-up observation has increased, there has been a rise in the proportion of SARS-CoV-2 PCR positive people admitted more than 21 days after vaccination (vaccine failure) (Table 1) [moderate confidence].

Important caveat. The risk of exposure has reduced since early January so the progressively lower number of PCR positive symptomatic cases admitted to hospital after vaccination is likely to under-represent a signal of vaccine failure.

Table 1: Number and proportion of PCR positive vaccinated patients stratified by time between vaccination and symptom onset.

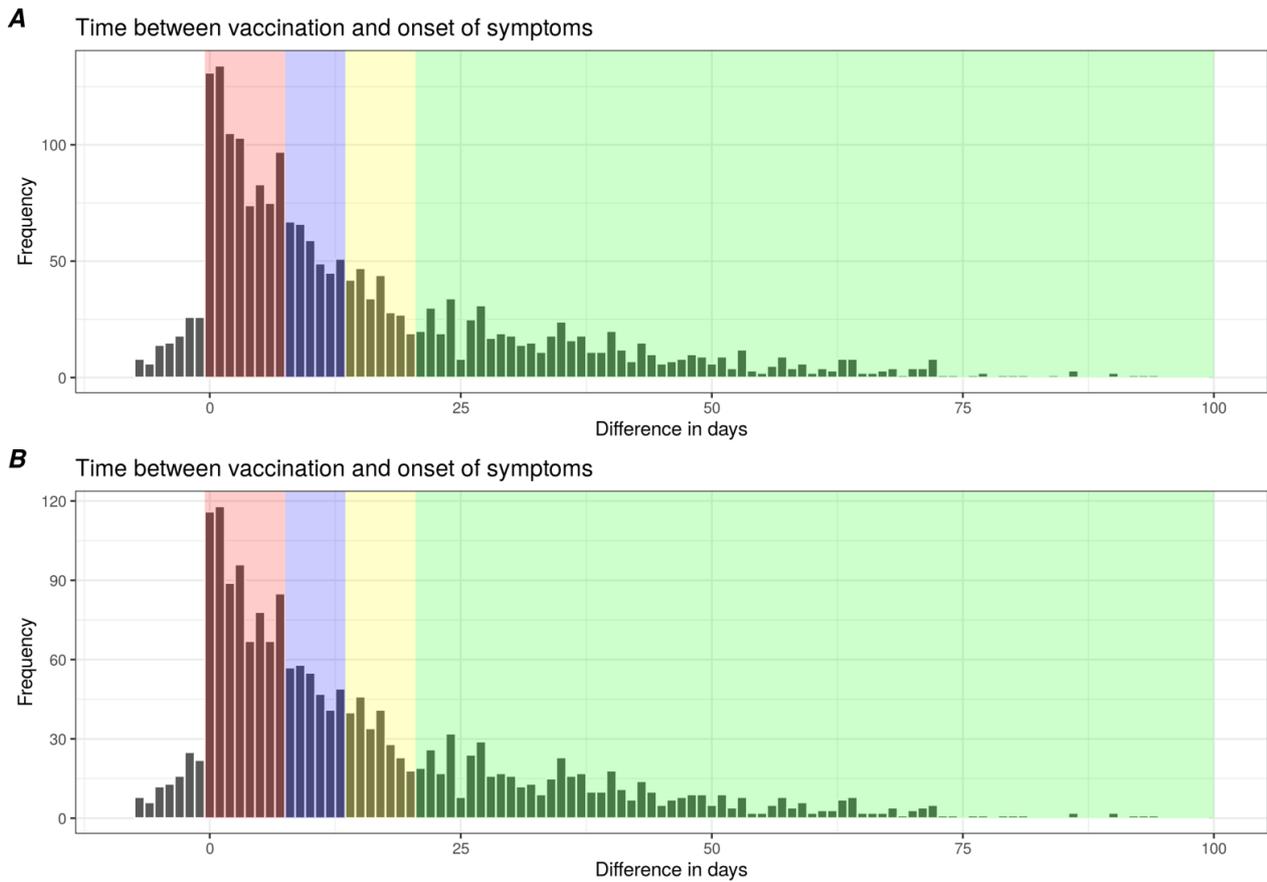| Time between vaccination and onset of symptoms	Number of patients with a PCR positive result	Number of Patients with a PCR negative result	Number of Patients with no available PCR result
0-7 days	729 (40%)	1	85
8-14 days	352 (19%)	5	27
15-21 days	211 (12%)	0	10
> 21 days	526 (29%)	3	51

Figure 4: Histogram of count of difference of date in vaccination and symptom onset in hospitalised patients stratified by period since vaccination. Plot A: all patients, Plot B: PCR +ve patients only
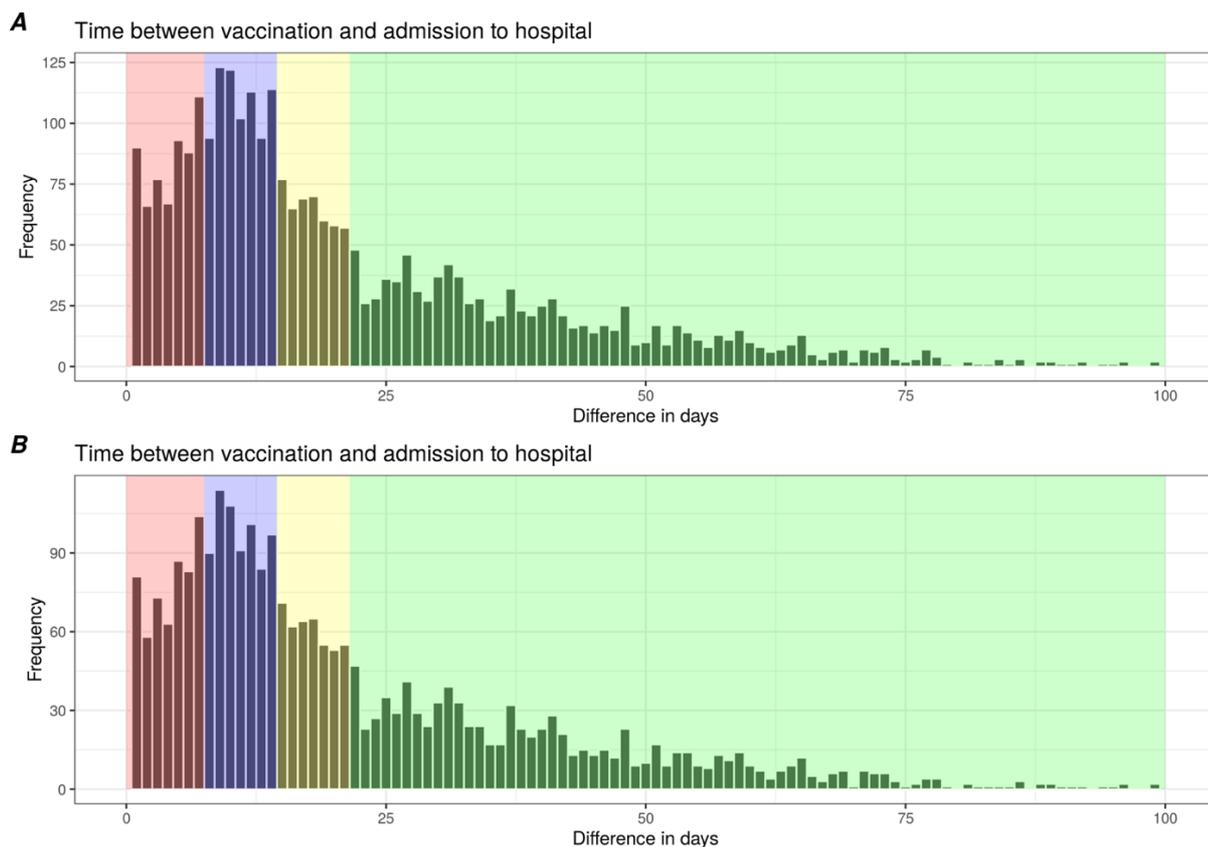
Figure 5: Histogram of count of difference of date in vaccination and admission to hospital in hospitalised patients stratified by period since vaccination. Plot A: all patients, Plot B: PCR +ve patients only

Vaccine and mortality

For this analysis we have restricted to those patients presenting to hospital with symptoms of covid-19, and who are PCR+ve for SARS-CoV-2. All patients have at least 30 days of follow-up (last day of admission March 10th 2021). Figure 6 and Table 2 show the distribution of mortality by vaccination tiers. This is an initial descriptive analysis, and we are currently undertaking a more detailed analysis to look at the effect of the vaccine in patients who meet the threshold to be admitted to hospital with symptoms of covid-19. We cannot identify care home residents in the ISARIC / CO-CIN data set (people in vaccination tier 1), rather we can only assign people to vaccination tier by their age and known co-morbidities. We expect that most care home residents will be assigned (fairly) in this analysis mostly to tier 2.

Outcome based on time since vaccination and onset of symptoms

Patients with outcome stratified by time between vaccination and onset of symptoms
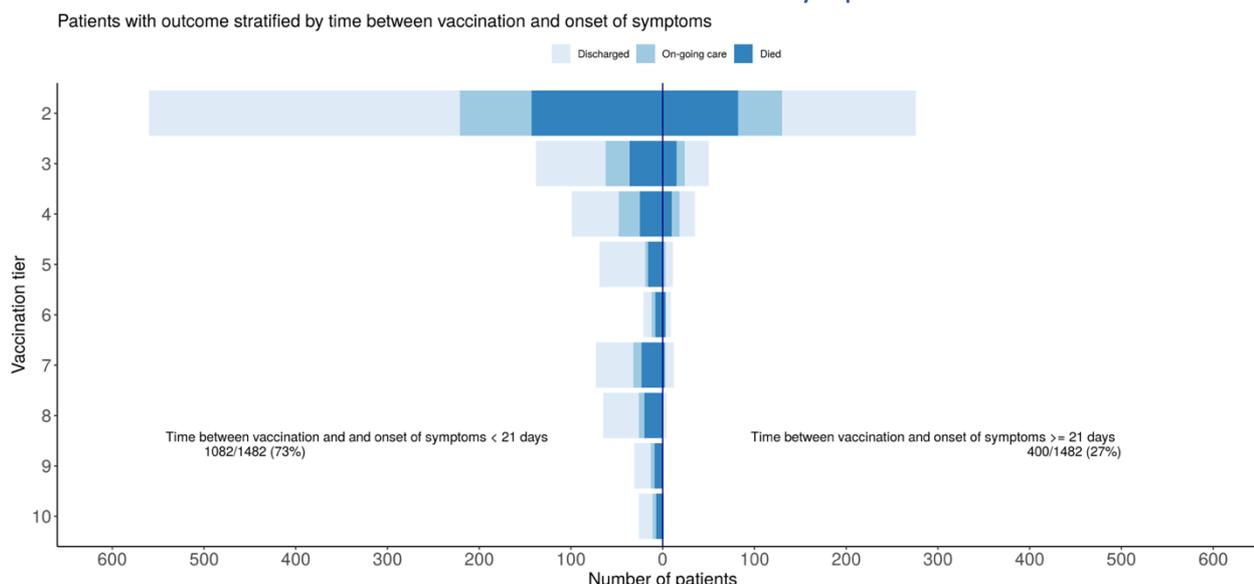

Figure 6: Patient outcome for vaccinated patients stratified by time between vaccination and onset of symptoms. All patients presented a PCR positive result. The population was filtered to remove asymptomatic patients and admissions 30 days prior to April 10th to allow a 30-day follow-up period. Only patients experiencing symptoms post-vaccination were included.

In this early descriptive analysis, mortality appears to remain high for people in high-risk vaccination tiers who are admitted to hospital with SARS-CoV-2 infection despite vaccination 21 day or more previously [low confidence].

Table 2: Patient outcome stratified by vaccination status and vaccination tier.

	Unvaccinated			Time between vaccination and onset of symptoms 0-20 days			Time between vaccination and onset of symptoms 21+ days		
	Died	Discharged	On-going care	Died	Discharged	On-going care	Died	Discharged	On-going care
Tier 2	1606 (19.9%)	4936 (61.1%)	1535 (19%)	143 (25.5%)	339 (60.5%)	78 (14%)	82 (29.7%)	146 (52.9%)	48 (17.4%)
Tier 3	684 (21.2%)	1929 (59.7%)	619 (19.1%)	36 (26.1%)	76 (55.1%)	26 (18.8%)	15 (30%)	26 (52%)	9 (18%)
Tier 4	729 (21.5%)	2037 (60%)	631 (18.5%)	25 (25.3%)	51 (51.5%)	23 (23.2%)	10 (28.6%)	17 (48.6%)	8 (22.8%)
Tier 5	589 (20.8%)	1736 (61.2%)	512 (18%)	16 (23.2%)	50 (72.3%)	3 (4.5%)	1 (9.1%)	8 (72.7%)	2 (18.2%)
Tier 6	479 (22.6%)	1262 (59.6%)	376 (17.8%)	8 (38.1%)	9 (42.9%)	4 (19%)	3 (33.3%)	6 (66.7%)	0 (0%)
Tier 7	691 (21.8%)	1931 (61%)	541 (17.2%)	23 (31.5%)	41 (56.2%)	9 (12.3%)	2 (16.7%)	9 (75%)	1 (8.3%)
Tier 8	661 (22%)	1820 (60.5%)	525 (17.5%)	20 (30.8%)	39 (60%)	6 (9.2%)	0 (0%)	4 (100%)	0 (0%)
Tier 9	534 (20.9%)	1581 (61.9%)	439 (17.2%)	9 (29%)	18 (58.1%)	4 (12.9%)	0 (0%)	1 (100%)	0 (0%)
Tier 10	807 (21.3%)	2353 (62.2%)	622 (16.5%)	7 (26.9%)	15 (57.7%)	4 (15.4%)	0 (0%)	1 (50%)	1 (50%)

Table E1: Baseline characteristics of the vaccinated population stratified by time from vaccine to symptom onset (n=3016).
Stratified unlikely to be vaccine failure (<14 days) and possibly due to vaccine failure (14 to <21 days) and more likely to be vaccine failure (>=21 days). We are unable to identify Tier 1 care home residents from our data – these people are likely to be predominantly allocated to Tier 2. Vaccination tier 10 is comprised of patients aged 16-50 not in a higher vaccination tier [3]. Column three is patients who were asymptomatic (and therefore unable to assign symptom onset group).

	Difference in symptom onset and vaccination < 14 (N=1281)	Difference in symptom onset and vaccination >= 14 & < 21 (N=245)	Difference in symptom onset and vaccination >= 21 (N=616)	No symptoms (N=874)	Overall (N=3016)
Sex					
Female	590 (46.1%)	129 (52.7%)	290 (47.1%)	445 (50.9%)	1454 (48.2%)
Male	691 (53.9%)	116 (47.3%)	325 (52.8%)	428 (49.0%)	1560 (51.7%)
Missing	0 (0%)	0 (0%)	1 (0.2%)	1 (0.1%)	2 (0.1%)
Age					
< 50	94 (7.3%)	10 (4.1%)	19 (3.1%)	32 (3.7%)	155 (5.1%)
50-69	353 (27.6%)	47 (19.2%)	74 (12.0%)	86 (9.8%)	560 (18.6%)
70-79	290 (22.6%)	42 (17.1%)	145 (23.5%)	188 (21.5%)	665 (22.0%)
80+	544 (42.5%)	146 (59.6%)	378 (61.4%)	567 (64.9%)	1635 (54.2%)
Missing	0 (0%)	0 (0%)	0 (0%)	1 (0.1%)	1 (0.0%)
Ethnicity					
Black	15 (1.2%)	4 (1.6%)	1 (0.2%)	7 (0.8%)	27 (0.9%)
Other	89 (6.9%)	8 (3.3%)	26 (4.2%)	39 (4.5%)	162 (5.4%)
White	956 (74.6%)	199 (81.2%)	496 (80.5%)	692 (79.2%)	2343 (77.7%)
Asian	69 (5.4%)	11 (4.5%)	35 (5.7%)	16 (1.8%)	131 (4.3%)
Missing	152 (11.9%)	23 (9.4%)	58 (9.4%)	120 (13.7%)	353 (11.7%)
Vaccination Tier					
2	567 (44.3%)	147 (60.0%)	379 (61.5%)	569 (65.1%)	1662 (55.1%)
3	173 (13.5%)	18 (7.3%)	83 (13.5%)	115 (13.2%)	389 (12.9%)
4	120 (9.4%)	24 (9.8%)	64 (10.4%)	74 (8.5%)	282 (9.4%)
5	101 (7.9%)	13 (5.3%)	28 (4.5%)	30 (3.4%)	172 (5.7%)
6	32 (2.5%)	5 (2.0%)	12 (1.9%)	12 (1.4%)	61 (2.0%)
7	96 (7.5%)	18 (7.3%)	25 (4.1%)	26 (3.0%)	165 (5.5%)
8	97 (7.6%)	12 (4.9%)	13 (2.1%)	19 (2.2%)	141 (4.7%)
9	59 (4.6%)	4 (1.6%)	8 (1.3%)	11 (1.3%)	82 (2.7%)
10	36 (2.8%)	4 (1.6%)	4 (0.6%)	17 (1.9%)	61 (2.0%)
Missing	0 (0%)	0 (0%)	0 (0%)	1 (0.1%)	1 (0.0%)
IMD quantile					
1	281 (21.9%)	44 (18.0%)	138 (22.4%)	144 (16.5%)	607 (20.1%)
2	293 (22.9%)	52 (21.2%)	115 (18.7%)	199 (22.8%)	659 (21.9%)
3	264 (20.6%)	51 (20.8%)	125 (20.3%)	175 (20.0%)	615 (20.4%)
4	245 (19.1%)	62 (25.3%)	120 (19.5%)	186 (21.3%)	613 (20.3%)

	Difference in symptom onset and vaccination < 14 (N=1281)	Difference in symptom onset and vaccination >= 14 & < 21 (N=245)	Difference in symptom onset and vaccination >= 21 (N=616)	No symptoms (N=874)	Overall (N=3016)
5	197 (15.4%)	36 (14.7%)	117 (19.0%)	168 (19.2%)	518 (17.2%)
Missing	1 (0.1%)	0 (0%)	1 (0.2%)	2 (0.2%)	4 (0.1%)
Fever					
YES	657 (51.3%)	97 (39.6%)	237 (38.5%)	33 (3.8%)	1024 (34.0%)
NO	423 (33.0%)	101 (41.2%)	258 (41.9%)	664 (76.0%)	1446 (47.9%)
Unknown	97 (7.6%)	23 (9.4%)	56 (9.1%)	46 (5.3%)	222 (7.4%)
Missing	104 (8.1%)	24 (9.8%)	65 (10.6%)	131 (15.0%)	324 (10.7%)
Cough					
YES	737 (57.5%)	106 (43.3%)	284 (46.1%)	40 (4.6%)	1167 (38.7%)
NO	365 (28.5%)	88 (35.9%)	211 (34.3%)	651 (74.5%)	1315 (43.6%)
Unknown	77 (6.0%)	27 (11.0%)	56 (9.1%)	51 (5.8%)	211 (7.0%)
Missing	102 (8.0%)	24 (9.8%)	65 (10.6%)	132 (15.1%)	323 (10.7%)
Shortness of breath					
YES	872 (68.1%)	137 (55.9%)	345 (56.0%)	58 (6.6%)	1412 (46.8%)
NO	253 (19.8%)	70 (28.6%)	160 (26.0%)	634 (72.5%)	1117 (37.0%)
Unknown	55 (4.3%)	14 (5.7%)	45 (7.3%)	50 (5.7%)	164 (5.4%)
Missing	101 (7.9%)	24 (9.8%)	66 (10.7%)	132 (15.1%)	323 (10.7%)

Table E2: Baseline characteristics stratified by time from vaccine to hospital admission (n=3842)

	Difference in admission and vaccination < 14 (N=1240)	Difference in admission and vaccination >= 14 & < 21 (N=513)	Difference in admission and vaccination >= 21 (N=1098)	Missing (N=244)	Overall (N=3842)
Sex					
Female	569 (45.9%)	266 (51.9%)	532 (48.5%)	113 (46.3%)	1869 (48.6%)
Male	671 (54.1%)	247 (48.1%)	564 (51.4%)	130 (53.3%)	1970 (51.3%)
Missing	0 (0%)	0 (0%)	2 (0.2%)	1 (0.4%)	3 (0.1%)
Age					
< 50	83 (6.7%)	29 (5.7%)	32 (2.9%)	12 (4.9%)	234 (6.1%)
50-69	291 (23.5%)	113 (22.0%)	125 (11.4%)	43 (17.6%)	808 (21.0%)
70-79	273 (22.0%)	111 (21.6%)	232 (21.1%)	62 (25.4%)	875 (22.8%)
80+	593 (47.8%)	260 (50.7%)	708 (64.5%)	126 (51.6%)	1923 (50.1%)
Missing	0 (0%)	0 (0%)	1 (0.1%)	1 (0.4%)	2 (0.1%)

	Difference in admission and vaccination < 14 (N=1240)	Difference in admission and vaccination >= 14 & < 21 (N=513)	Difference in admission and vaccination >= 21 (N=1098)	Missing (N=244)	Overall (N=3842)
Asymptomatic					
Asymptomatic	215 (17.3%)	81 (15.8%)	328 (29.9%)	50 (20.5%)	874 (22.7%)
Symptomatic	1025 (82.7%)	432 (84.2%)	770 (70.1%)	194 (79.5%)	2968 (77.3%)
Ethnicity					
Black	14 (1.1%)	7 (1.4%)	7 (0.6%)	1 (0.4%)	37 (1.0%)
Other	67 (5.4%)	36 (7.0%)	49 (4.5%)	12 (4.9%)	193 (5.0%)
White	954 (76.9%)	388 (75.6%)	872 (79.4%)	185 (75.8%)	2947 (76.7%)
Asian	52 (4.2%)	31 (6.0%)	43 (3.9%)	15 (6.1%)	168 (4.4%)
Missing	153 (12.3%)	51 (9.9%)	127 (11.6%)	31 (12.7%)	497 (12.9%)
Vaccination Tier					
2	613 (49.4%)	265 (51.7%)	709 (64.6%)	128 (52.5%)	1955 (50.9%)
3	168 (13.5%)	59 (11.5%)	132 (12.0%)	40 (16.4%)	503 (13.1%)
4	107 (8.6%)	53 (10.3%)	102 (9.3%)	22 (9.0%)	379 (9.9%)
5	89 (7.2%)	34 (6.6%)	41 (3.7%)	17 (7.0%)	234 (6.1%)
6	29 (2.3%)	9 (1.8%)	20 (1.8%)	7 (2.9%)	84 (2.2%)
7	78 (6.3%)	32 (6.2%)	43 (3.9%)	14 (5.7%)	236 (6.1%)
8	82 (6.6%)	26 (5.1%)	26 (2.4%)	5 (2.0%)	199 (5.2%)
9	42 (3.4%)	21 (4.1%)	15 (1.4%)	7 (2.9%)	139 (3.6%)
10	32 (2.6%)	14 (2.7%)	9 (0.8%)	2 (0.8%)	110 (2.9%)
Missing	0 (0%)	0 (0%)	1 (0.1%)	2 (0.8%)	3 (0.1%)
IMD quantile					
1	261 (21.0%)	108 (21.1%)	222 (20.2%)	56 (23.0%)	762 (19.8%)
2	292 (23.5%)	110 (21.4%)	214 (19.5%)	50 (20.5%)	897 (23.3%)
3	243 (19.6%)	107 (20.9%)	238 (21.7%)	47 (19.3%)	785 (20.4%)
4	239 (19.3%)	105 (20.5%)	214 (19.5%)	58 (23.8%)	763 (19.9%)
5	204 (16.5%)	83 (16.2%)	207 (18.9%)	33 (13.5%)	631 (16.4%)
Missing	1 (0.1%)	0 (0%)	3 (0.3%)	0 (0%)	4 (0.1%)
Fever					
YES	523 (42.2%)	194 (37.8%)	297 (27.0%)	85 (34.8%)	1327 (34.5%)
NO	526 (42.4%)	220 (42.9%)	550 (50.1%)	108 (44.3%)	1689 (44.0%)
Unknown	88 (7.1%)	46 (9.0%)	85 (7.7%)	14 (5.7%)	261 (6.8%)
Missing	103 (8.3%)	53 (10.3%)	166 (15.1%)	37 (15.2%)	565 (14.7%)
Cough					
YES	571 (46.0%)	238 (46.4%)	367 (33.4%)	104 (42.6%)	1540 (40.1%)
NO	488 (39.4%)	183 (35.7%)	480 (43.7%)	91 (37.3%)	1496 (38.9%)

	Difference in admission and vaccination < 14 (N=1240)	Difference in admission and vaccination >= 14 & < 21 (N=513)	Difference in admission and vaccination >= 21 (N=1098)	Missing (N=244)	Overall (N=3842)
Unknown	80 (6.5%)	38 (7.4%)	85 (7.7%)	12 (4.9%)	242 (6.3%)
Missing	101 (8.1%)	54 (10.5%)	166 (15.1%)	37 (15.2%)	564 (14.7%)
Shortness of breath					
YES	694 (56.0%)	289 (56.3%)	442 (40.3%)	128 (52.5%)	1838 (47.8%)
NO	387 (31.2%)	148 (28.8%)	415 (37.8%)	73 (29.9%)	1253 (32.6%)
Unknown	59 (4.8%)	23 (4.5%)	74 (6.7%)	7 (2.9%)	188 (4.9%)
Missing	100 (8.1%)	53 (10.3%)	167 (15.2%)	36 (14.8%)	563 (14.7%)

References
1. *Side effects of the coronavirus vaccines.* Available at: https://www.nhsinform.scot/covid-19vaccine/the-vaccines/side-effects-of-the-coronavirus-vaccines (Accessed: 10 March 2021).
2. *COVID-19: management of staff and exposed patients or residents in health and social care settings.* Available at: https://www.gov.uk/government/publications/covid-19-managementof-exposed-healthcare-workers-and-patients-in-hospital-settings/covid-19-management-ofexposed-healthcare-workers-and-patients-in-hospitalsettings#:~:text=If%20a%20person%20is%20re,contacts%20should%20be%20traced. (Accessed: 10 March 2021).
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