Hospital Admission for COVID-19 and impact of vaccination: analysis of linked data from the National Immunisation Management Service (NIMS) and the Coronavirus Clinical Information Network (CO-CIN)

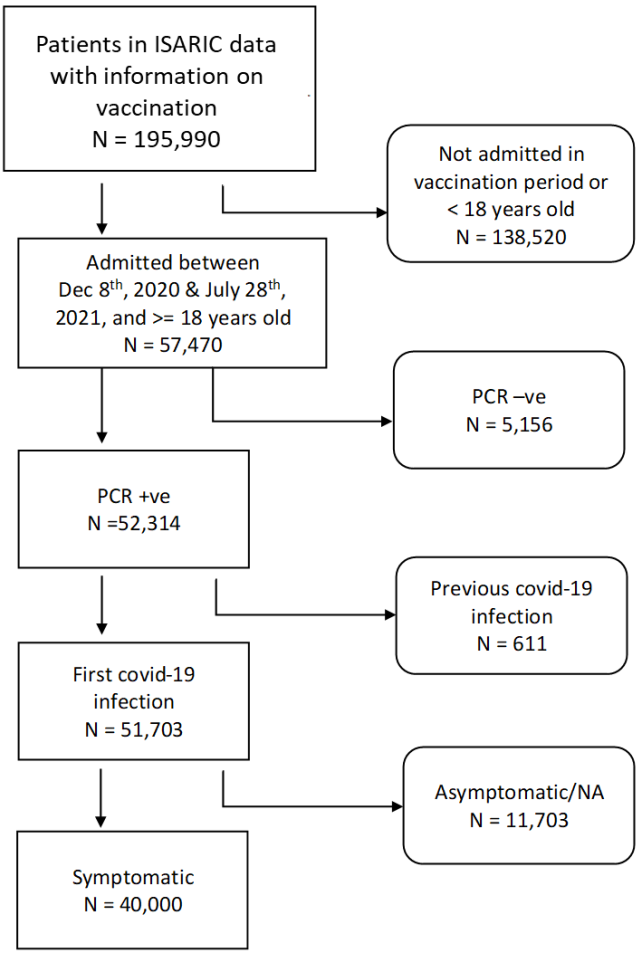
Conor Egan, Mathew Thorpe, Stephen Knight, Catherine Shaw, Kenneth McLean, Kenny Baillie, Lance Turtle, Ewen Harrison, Calum Semple, Annemarie Docherty

Background

- Vaccination data from the National Immunisation Management Service (NIMS), which gives information on patient's vaccinations, has recently been shared with the ISARIC Coronavirus Clinical Characterisation Consortium (ISARIC4C.net).
- There are 194,103 patients in the NIMS vaccine data as of June 15th, 2021.
- This has been linked with the Coronavirus Clinical Information Network (CO-CIN) data on people in UK hospitals with SARS-CoV-2 infection and COVID-19.
- There are 228,968 patients in the CO-CIN data as August 25th, 2021.
- Of these 194,103 patients in NIMS there are 193,416 patients that have matching subject IDs in the latest CO-CIN data. There are a further 2,574 patients in the CO-CIN data with information on vaccination status not contained in the NIMS data.

Study population restrictions

- The study population was restricted to admissions that occurred between the December 8th, 2020, when vaccination started and July 28th, 2021, to allow for at least 28 days of follow-up from most recent data pull.
- In order to identify patients admitted "because of COVID-19" i.e. with severe disease, rather than merely "with SARS-CoV-2 infection" (admitted for another reason, and found positive on screening), asymptomatic patients were excluded. Thus all patients considered as presenting with vaccine failure in this cohort were symptomatic (see table A.1)
- The remaining patients were only included if they presented with at least one of the symptoms in the paper "Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study". Note: patients with uncommon COVID-19 symptoms could potentially be misclassified as asymptomatic based on the above definition, however this conservative case definition permits robust definition of severe COVID-19 cases.
- At the time of admission, of the 40,000 patients included in this analysis, 33,496 (83.7%) were unvaccinated, 5,198 (13.0%) had received their first vaccination and 1,274 (3.3%) had received their second vaccination.
- Patients with previous COVID-19 (re-infection) have been removed from this analysis (n=611).



Vaccination failure

Vaccine failure is defined by patients admitted to hospital with COVID-19 who have received one or two vaccine doses, plus adequate time to mount an immune response. The term 'failure' does not imply no vaccine protection, only failure to protect from admission to hospital with COVID-19.

Types of vaccination failures were categorized to evaluate effectiveness of dosages and time to symptom onset. A variable for failure status was created as follows:

- No information on date of symptom onset.
- No virus immunity: no presumption of immunity in unvaccinated patients and patients experiencing onset of COVID-19 symptoms $\leq$ 20 days after first vaccination dose.
- First dose failure: Patients experiencing COVID-19 symptoms 21 days or more after first vaccination dose or patients experiencing symptoms $\leq$ 13 days after second vaccination dose.
- Second dose failure: Patients experiencing COVID-19 symptoms 14 days or more after second vaccination dose.

Using these conservative categories, of the 40,000 patients 83 (0.2%) had no information on date of symptom onset, 36,956 (92.4%) had no virus immunity, 1,859 (4.6%) had first dose failure and 1,071 (2.8%) had second dose failure. Of the 36,956 patients with no virus immunity 33,496 were unvaccinated and 3,460 had received their first vaccination $\leq$21 days previously.

Admission trends

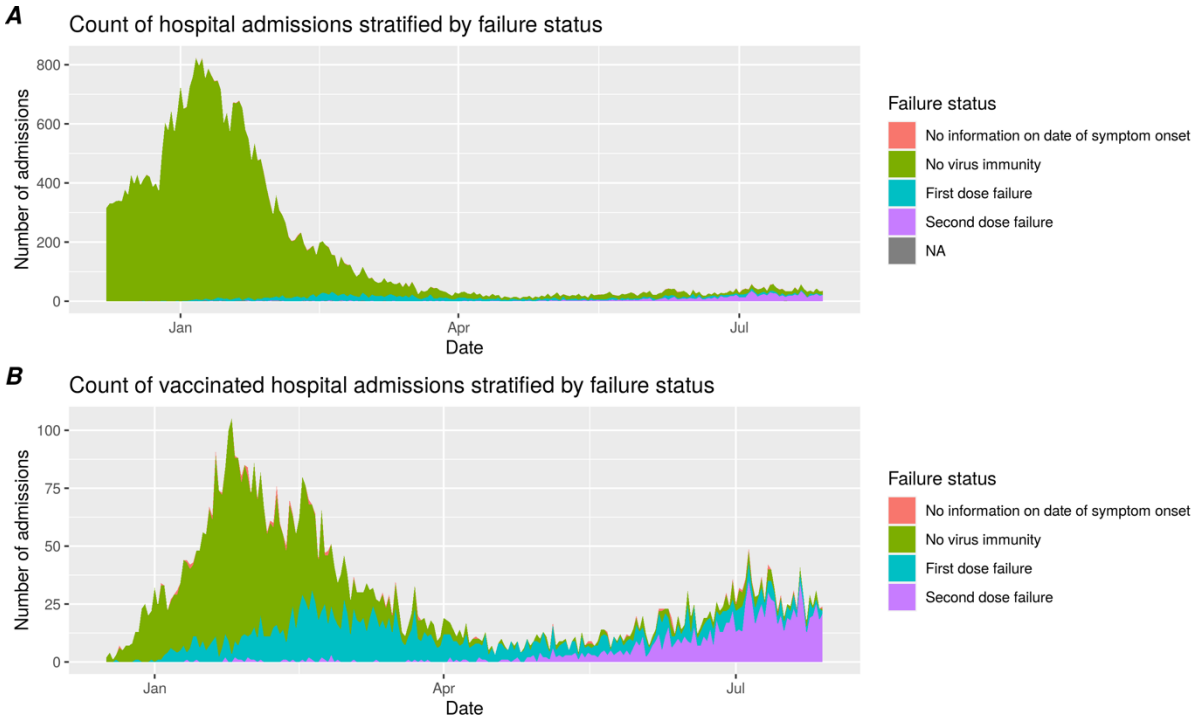


Figure 1: Admission trends for unvaccinated and vaccinated population.
A: stratified by "vaccine failure status": No information on date of symptom onset; "no presumption of virus immunity": unvaccinated patients and patients experiencing symptoms ≤ 20 days of first vaccination dose; "first dose failure": patients experiencing symptoms 21 days or more from first vaccination dose or patients experiencing symptoms ≤13 days of second vaccination dose; "second dose failure": patients experiencing symptoms 14 days or more after second vaccination dose. B: Vaccinated patients only, n = 6,472.

Vaccinated hospitalised cases stratified by failure status.

Plot of time to symptom onset from first vaccination:

- -7-20 days (Green): In this group, infection will have occurred either before vaccination, or before immunity has fully developed.
- >=28 days (Blue): Admissions in this population are classified as first dose failure. Diminishing numbers over time can reflect both development of immunity and the rolling sequential nature of the vaccine program.
- The vaccinated patients below only include patients that experienced symptoms 7 days prior to vaccination and onwards.

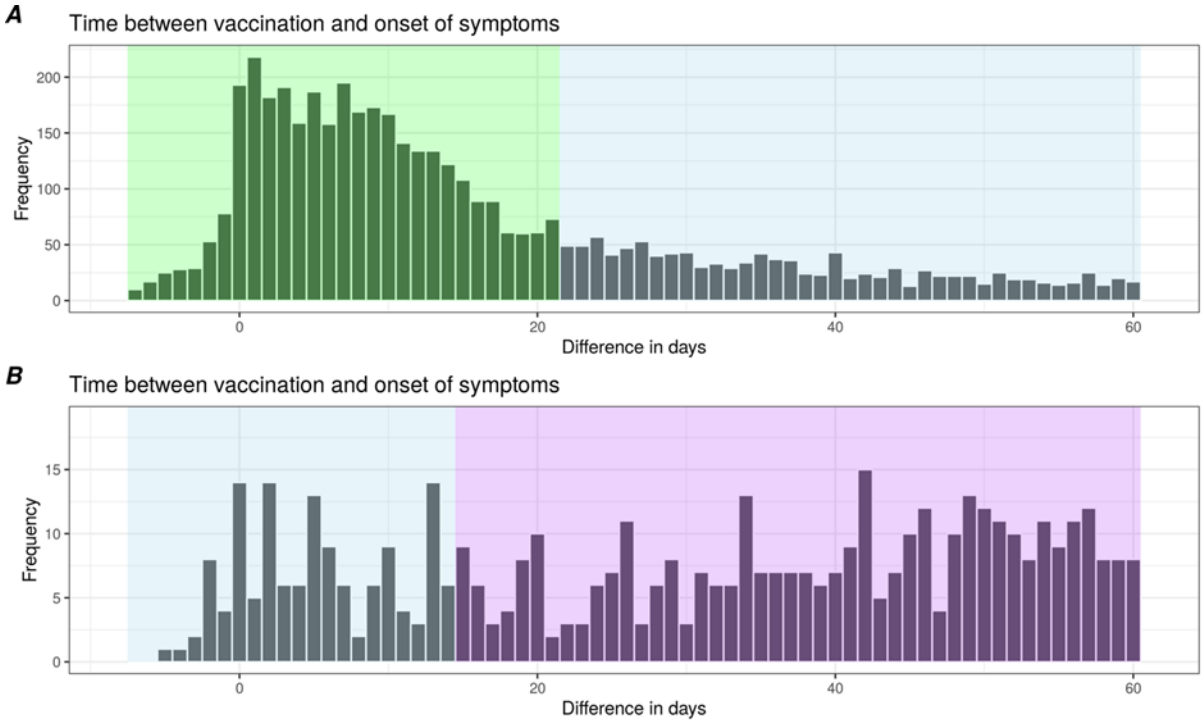


Figure 2:
A: Time from first vaccination to symptom onset. Green: -7-20 days, "no virus immunity. Blue: 21 days after first dose/ <14 days after second dose, "first dose failure".
B: Time from second vaccination to symptom onset. Blue: 21 days after first dose/ <14 days after second dose, "first dose failure". Purple: >=14 days after second dose, "second dose failure". Note that the y axis scale is different between A and B. All patients included have at least 60 days follow up

Illness severity at hospital admission

Illness severity at hospital admission was similar across the vaccine groups. This most likely reflects the threshold of illness required for hospital admission (Figure 3).

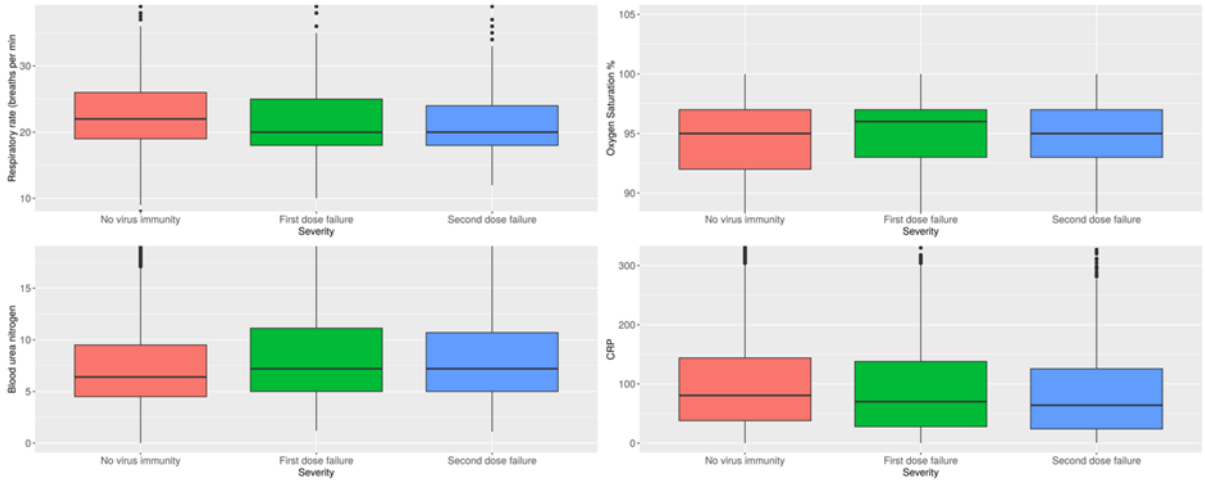


Figure 3: Boxplot of physiological variables of 4C score stratified by failure status.

Immunocompromise

There is biological plausibility that patients with immunocompromise are less likely to be able to mount a full immunological response to the vaccine, and therefore remain at higher risk of moderate to severe covid-19.

Immunocompromised is defined as: pre-existing immunological or metabolic disorder (for example, severe combined immunodeficiency, SCID, or common variable immunodeficiency, CVID); solid organ transplant; HIV/AIDs; actively being treated for cancer; being treated with immunosuppression therapies enough to significantly increase risk of infection.

Those patients aged <70yrs will naturally fall into Tier 4 (clinically extremely vulnerable individuals) or Tier 6 (adults aged 18-65 in an at-risk group). Immunocompromised patients have accounted for 13% of hospital admissions.

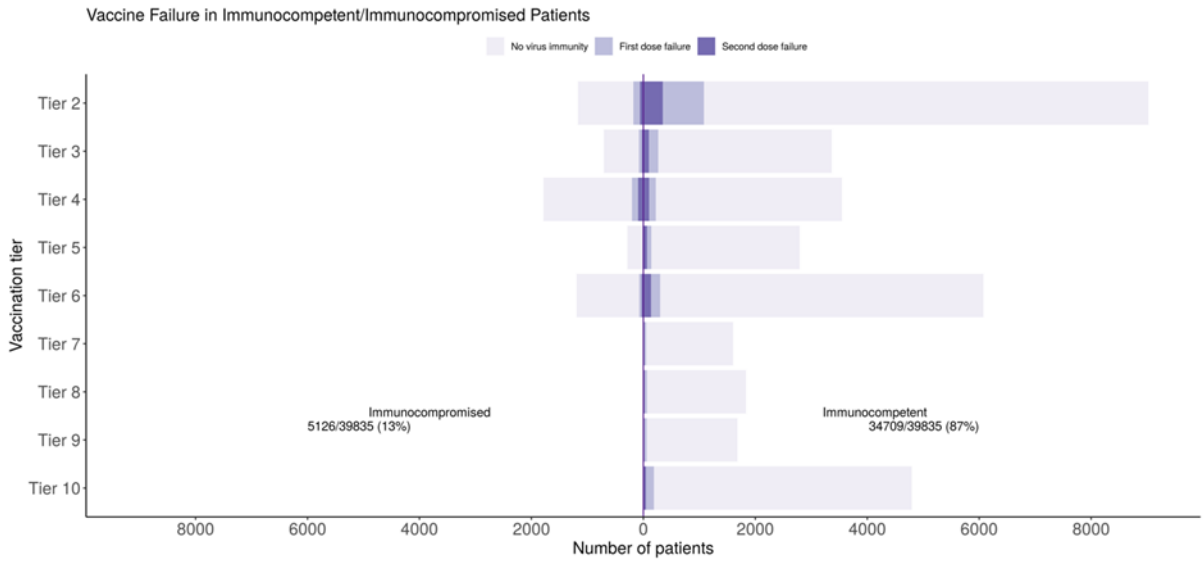


Figure 6: Type of vaccination failure (number of cases) stratified by vaccination priority tier for vaccinated patients. Left hand side immunocompromised patients, Right hand side immunocompetent patients. Pale purple – no vaccine immunity, mid-purple - first dose failure, dark purple - second dose failure.

Outcomes

All patients had at least 28 days of follow-up. ISARIC4C/CO-CIN is unable to separately identify care home residents (people in vaccination tier 1) and can only assign people to vaccination tier by their age and known co-morbidities. In this analysis, we expect that most care home residents will have been assigned to tier 2. Frontline healthcare workers were removed from tier 2. Vaccination tier 10 is comprised of patients aged 18-50 not in a higher vaccination tier.

Admissions remained proportionately highest for elderly “Tier 2” patients (Figure 4) across the different vaccine status categories, however absolute numbers were significantly lower in the first and second dose failures (Figure 4). The greater presence of “Tier 2” vs “Tier 10” vaccine failures may in part represent the vaccination programme in the UK, where vulnerable patients have had more opportunity to receive two vaccines by the time of this analysis.

Similar to the previous outcome analysis, admissions remain relatively high for Tier 2 patients across all vaccine statuses with an overall much lower absolute total of immunocompromised patients versus immunocompetent patients. Despite lower absolute values, the relative proportion of immunocompromised increased from no virus immunity (13%) to first dose failure (20%) to second dose failure (24%).

In addition to increasing proportions of immunocompromised patients between vaccine statuses, there is a notable increase of immunocompromised patients, including a distinct rise in death, for “Tier 4” patients with second dose vaccine failure. This may reflect the fact that this group contains the bulk of those who are extremely clinically vulnerable.

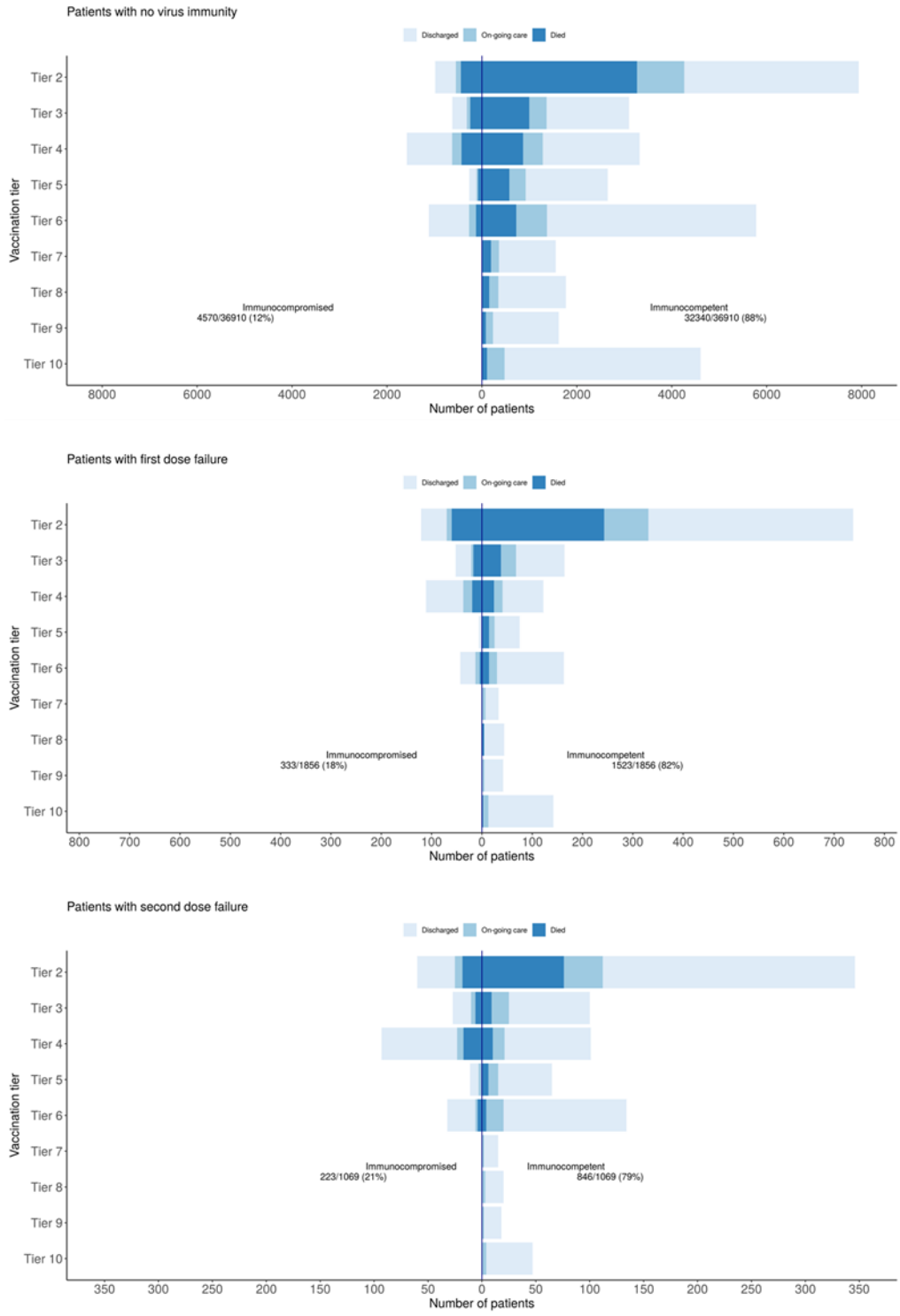


Figure 4: Outcomes (number of cases) stratified by vaccination priority tier for patients with A: no virus immunity, B: first dose failure, C: second dose failure. Left – immunocompromised, Right - immunocompetent

Multivariable logistic regression

We explored “no immunity”, “first dose failure” and “second dose failure” separately, and compared the impact of vaccination on the odds ratios for each variable.
After adjustment for patient demographics (sex, ethnicity, deprivation, comorbidity), increasing age remained significantly associated with mortality throughout (Figure 5). The point estimates of Odds Ratios for death for all demographics were reduced in the first dose and second dose failure groups,

though confidence intervals are wide, this may represent the smaller sample size. There was no attenuation from vaccination of the risk of in-hospital mortality in patients with immunocompromise. Vaccinated patients may systematically differ from unvaccinated patients in the same JCVI tier, and this analysis is unable to explore these factors further.

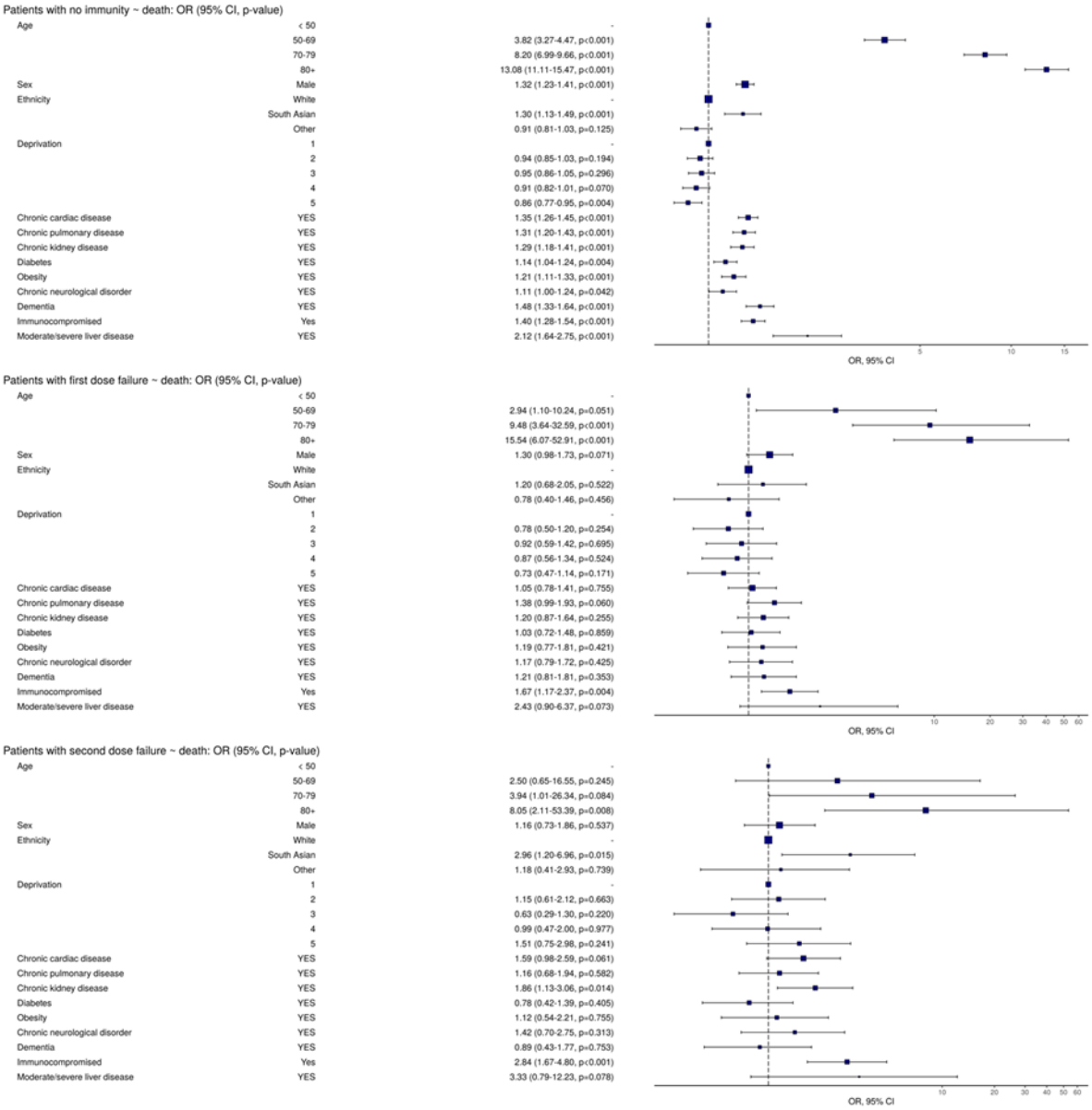


Figure 5: Odds ratio plots for in-hospital mortality stratified by vaccine failure status. Deprivation (IMD) quintile. Quintile 1 is the most deprived and quintile 5 is the least deprived.

Current situation (from 16th June 2021)

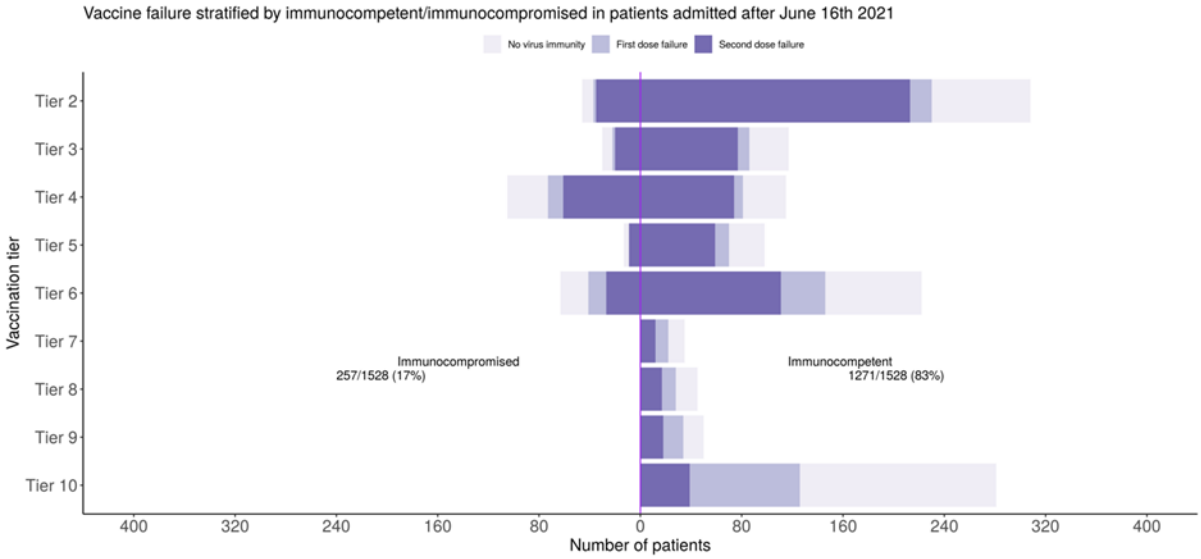


Figure 6: Vaccine failure stratified by immunocompromised vs immunocompetent in patients admitted June 16th – August 25th 2021. Left hand side immunocompromised patients, Right hand side immunocompetent patients. Pale purple – no vaccine immunity, mid-purple - first dose failure, dark purple - second dose failure.

Table 1: patient demographics stratified by vaccine failure status.

	No virus immunity (N=36956)	First dose failure (N=1859)	Second dose failure (N=1071)	Overall (N=39886)
Sex				
Female	16316 (92.3%)	882 (5%)	481 (2.7%)	17679
Male	20601 (92.9%)	975 (4.4%)	588 (2.7%)	22164
Missing	39 (90.7%)	2 (4.7%)	2 (4.6%)	43
Ethnicity				
White	25362 (91.8%)	1398 (5.1%)	862 (3.1%)	27622
South Asian	2267 (92.5%)	139 (5.7%)	45 (1.8%)	2451
Black	980 (97.3%)	16 (1.6%)	11 (1.1%)	1007
East Asian	176 (93.1%)	8 (4.2%)	5 (2.7%)	189
Other	2492 (94%)	112 (4.2%)	47 (1.8%)	2651
Missing	5679 (95.2%)	186 (3.1%)	101 (1.7%)	5966
Vaccination tier				
Tier 10	4609 (96.1%)	142 (3%)	47 (0.9%)	4798
Tier 9	1620 (96.4%)	42 (2.5%)	18 (1.1%)	1680
Tier 8	1769 (96.5%)	44 (2.4%)	20 (1.1%)	1833
Tier 7	1558 (97%)	33 (2.1%)	15 (0.9%)	1606
Tier 6	6900 (94.9%)	206 (2.8%)	166 (2.3%)	7272
Tier 5	2919 (94.9%)	81 (2.6%)	77 (2.5%)	3077
Tier 4	4907 (92%)	235 (4.4%)	194 (3.6%)	5336
Tier 3	3727 (91.6%)	216 (5.3%)	127 (3.1%)	4070
Tier 2	8947 (87.6%)	860 (8.4%)	407 (4%)	10214
IMD quintile				
1	9575 (92.1%)	492 (4.7%)	329 (3.2%)	10396
2	7683 (93.1%)	350 (4.2%)	222 (2.7%)	8255
3	6841 (93.4%)	320 (4.4%)	161 (2.2%)	7322
4	6312 (92.9%)	317 (4.7%)	169 (2.4%)	6798
5	5748 (92.1%)	334 (5.4%)	160 (2.5%)	6242
Missing	797 (91.3%)	46 (5.3%)	30 (3.4%)	873
Fever				
YES	19481 (93.9%)	781 (3.8%)	481 (2.3%)	20743
Cough				
YES	21698 (93.5%)	901 (3.9%)	618 (2.6%)	23217
Shortness of breath				
YES	25116 (93.4%)	1092 (4.1%)	670 (2.5%)	26878
Chronic kidney disease				
YES	4339 (87.4%)	399 (8%)	227 (4.6%)	4965
Solid organ transplant				
Yes	249 (82.7%)	27 (9%)	25 (8.3%)	301

	No virus immunity (N=36956)	First dose failure (N=1859)	Second dose failure (N=1071)	Overall (N=39886)
Chronic cardiac disease				
YES	8153 (89%)	664 (7.2%)	342 (3.8%)	9159
Chronic pulmonary disease				
YES	4825 (89.6%)	337 (6.3%)	226 (4.1%)	5388
Diabetes				
YES	4874 (91.1%)	296 (5.5%)	183 (3.4%)	5353
Obesity				
YES	5387 (93.5%)	220 (3.8%)	155 (2.7%)	5762
Chronic neurological disorder				
YES	3127 (90.3%)	222 (6.4%)	115 (3.3%)	3464
Dementia				
YES	2843 (90.5%)	197 (6.3%)	103 (3.2%)	3143
Immunocompromised				
Yes	4576 (89.2%)	333 (6.5%)	223 (4.3%)	5132
Moderate/severe liver disease				
YES	424 (89.3%)	32 (6.7%)	19 (4%)	475

Table 2: Population restricted to those who died, stratified by failure status. Tier 1 cannot be identified separately and is likely included in Tier 2

	No virus immunity (N=8887)	First dose failure (N=460)	Second dose failure (N=154)	Overall (N=9501)
Vaccination tier				
Tier 10	119 (98.3%)	2 (1.7%)	0 (0%)	121
Tier 9	94 (100%)	0 (0%)	0 (0%)	94
Tier 8	160 (97.6%)	4 (2.4%)	0 (0%)	164
Tier 7	206 (99.5%)	1 (0.5%)	0 (0%)	207
Tier 6	922 (97.3%)	18 (1.9%)	8 (0.8%)	948
Tier 5	706 (97.1%)	15 (2.1%)	6 (0.8%)	727
Tier 4	1391 (95%)	46 (3.1%)	27 (1.9%)	1464
Tier 3	1338 (94.7%)	58 (4.1%)	17 (1.2%)	1413
Tier 2	3951 (90.6%)	316 (7.2%)	96 (2.2%)	4363

Table 3: patient demographics stratified by immunocompetency.

	Immunocompetent (N=34814)	Immunocompromised (N=5133)	Overall (N=39947)
Sex			
Female	15313 (86.5%)	2388 (13.5%)	17701
Male	19468 (87.7%)	2735 (12.3%)	22203
Missing	33 (76.7%)	10 (23.3%)	43
Ethnicity			
White	23848 (86.2%)	3812 (13.8%)	27660
South Asian	2178 (88.6%)	279 (11.4%)	2457
Black	895 (88.9%)	112 (11.1%)	1007
East Asian	172 (91.5%)	16 (8.5%)	188
Other	2342 (88.2%)	313 (11.8%)	2655
Missing	5379 (89.9%)	601 (10.1%)	5980
Vaccination Tier			
Tier 10	4806 (100%)	0 (0%)	4806
Tier 9	1682 (100%)	0 (0%)	1682
Tier 8	1836 (100%)	0 (0%)	1836
Tier 7	1602 (100%)	0 (0%)	1602
Tier 6	6085 (83.6%)	1193 (16.4%)	7278
Tier 5	2796 (90.8%)	282 (9.2%)	3078
Tier 4	3560 (66.6%)	1784 (33.4%)	5344
Tier 3	3373 (82.8%)	703 (17.2%)	4076
Tier 2	9074 (88.6%)	1171 (11.4%)	10245
IMD quantile			
1	9229 (88.6%)	1189 (11.4%)	10418
2	7187 (86.9%)	1081 (13.1%)	8268
3	6403 (87.3%)	932 (12.7%)	7335
4	5880 (86.4%)	922 (13.6%)	6802
5	5362 (85.7%)	892 (14.3%)	6254
Missing	753 (86.6%)	117 (13.4%)	870
Fever			
YES	17971 (86.5%)	2793 (13.5%)	20764
Cough			
YES	20022 (86.1%)	3219 (13.9%)	23241
Shortness of breath			
YES	23089 (85.8%)	3824 (14.2%)	26913
Chronic kidney disease			
YES	4080 (82%)	898 (18%)	4978
Solid organ transplant			
Yes	0 (0%)	302 (100%)	302
Chronic cardiac disease			
YES	7740 (84.3%)	1446 (15.7%)	9186
Chronic pulmonary disease			
YES	4063 (75.3%)	1333 (24.7%)	5396
Diabetes			

	Immunocompetent (N=34814)	Immunocompromised (N=5133)	Overall (N=39947)
YES	4587 (85.6%)	770 (14.4%)	5357
Obesity			
YES	4974 (86.2%)	796 (13.8%)	5770
Chronic neurological disorder			
YES	3028 (87.2%)	443 (12.8%)	3471
Dementia			
YES	2839 (90%)	317 (10%)	3156
Vaccine Failure			
No information on date of symptom onset	75 (92.6%)	6 (7.4%)	81
No virus immunity	32340 (87.6%)	4570 (12.4%)	36910
First dose failure	1523 (82.1%)	333 (17.9%)	1856
Second dose failure	846 (79.1%)	223 (20.9%)	1069

Table 4: patient outcome stratified by immunocompetency.

	Immunocompetent (N=34814)	Immunocompromised (N=5133)	Overall (N=39947)
Status			
Died	7448 (83.5%)	1473 (16.5%)	8921
Discharged	23416 (88.5%)	3045 (11.5%)	26461
On-going care	3950 (86.5%)	615 (13.5%)	4565

Appendix A

Table A.1: Population stratified by symptomatic vs asymptomatic.

	Symptomatic (N=38206)	Asymptomatic (N=10099)	Overall (N=48305)
Sex			
Female	16982 (76.1%)	5347 (23.9%)	22329
Male	21183 (81.7%)	4740 (18.3%)	25923
Missing	41 (77.4%)	12 (22.6%)	53
Ethnicity			
White	26377 (77%)	7883 (23%)	34260
South Asian	2380 (90%)	263 (10%)	2643
Black	955 (84.8%)	170 (15.2%)	1125
East Asian	176 (88.4%)	23 (11.6%)	199
Other	2548 (84.9%)	454 (15.1%)	3002
Missing	5770 (81.5%)	1306 (18.5%)	7076
Vaccination tier			
Tier 10	4526 (81.5%)	1028 (18.5%)	5554
Tier 9	1622 (91.7%)	147 (8.3%)	1769
Tier 8	1782 (92.2%)	150 (7.8%)	1932
Tier 7	1547 (91.2%)	149 (8.8%)	1696
Tier 6	6926 (86.4%)	1086 (13.6%)	8012
Tier 5	2958 (85.7%)	492 (14.3%)	3450
Tier 4	5097 (81.8%)	1132 (18.2%)	6229
Tier 3	3912 (75.9%)	1243 (24.1%)	5155
Tier 2	9836 (67.8%)	4672 (32.2%)	14508
IMD quintile			
1	9898 (81.1%)	2304 (18.9%)	12202
2	7912 (81.2%)	1829 (18.8%)	9741
3	7057 (78.4%)	1940 (21.6%)	8997
4	6502 (77.1%)	1936 (22.9%)	8438
5	6006 (76%)	1892 (24%)	7898
Missing	831 (80.8%)	198 (19.2%)	1029
Vaccine status at admission			
Unvaccinated	32671 (80.1%)	8093 (19.9%)	40764
First	4905 (75%)	1637 (25%)	6542
Second	600 (63.6%)	343 (36.4%)	943
Missing	30 (53.6%)	26 (46.4%)	56

	Symptomatic (N=38206)	Asymptomatic (N=10099)	Overall (N=48305)
Type of vaccine failure			
No information on date of symptom onset	66 (3.2%)	2006 (96.8%)	2072
No virus immunity	36373 (81.8%)	8093 (18.2%)	44466
First dose failure	1305 (100%)	0 (0%)	1305
Second dose failure	433 (100%)	0 (0%)	433
Missing	29 (100%)	0 (0%)	29