Impact of SARS-CoV-2 spike antibody positivity on infection and hospitalisation rates in immunosuppressed populations during the omicron period: the MELODY study

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Summary

Background In the UK, booster COVID-19 vaccinations have been recommended biannually to people considered immune vulnerable. We investigated, at a population level, whether the absence of detectable anti-SARS-CoV-2 spike protein IgG antibody (anti-S Ab) following three or more vaccinations in immunosuppressed individuals was associated with greater risks of infection and severity of infection.

Methods In this prospective cohort study using UK national disease registers, we recruited participants with solid organ transplants (SOTs), rare autoimmune rheumatic diseases (RAIRDs), and lymphoid malignancies. All participants were tested for anti-S Ab using a lateral flow immunoassay, completed a questionnaire on sociodemographic and clinical characteristics, and were followed up for 6 months using linked data from the National Health Service in England. SARS-CoV-2 infection was primarily defined using UK Health Security Agency data and supplemented with hospitalisation and therapeutics data, and hospitalisation due to SARS-CoV-2 was defined as an admission within 14 days of a positive test.

Findings Between Dec 7, 2021, and June 26, 2022, we recruited 21 575 participants. Anti-S Ab was detected in 6519 (77·0%) of 8466 participants with SOTs, 5594 (85·9%) of 6516 with RAIRDs, and 5227 (79·3%) of 6593 with lymphoid malignancies. COVID-19 infection was recorded in 3907 (18·5%) participants, with 556 requiring a COVID-19-related hospital admission and 17 dying within 28 days of infection. Rates of infection varied by sociodemographic and clinical characteristics but, in adjusted analysis, having detectable anti-S Ab was independently associated with a reduced incidence of infection, with incident rate ratios (IRRs) of 0·69 (95% CI 0·65–0·73) in the SOT cohort, 0·57 (0·49–0·67) in the RAIRD cohort, and 0·62 (0·54–0·71) in the lymphoid malignancy cohort. In adjusted analysis, having detectable anti-S Ab was also associated with a reduced incidence of hospitalisation, with IRRs of 0·40 (0·35–0·46) in the SOT cohort, 0·32 (0·22–0·46) in the RAIRD cohort, and 0·41 (0·29–0·58) in the lymphoid malignancy cohort.

Interpretation All people with immunosuppression require ongoing access to COVID-19 protection strategies. Assessment of anti-S Ab responses, which can be performed at scale, can identify people with immunosuppression who remain most at risk, providing a mechanism to further individualise protection approaches.

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Introduction

With the declaration of the end of the COVID-19 pandemic in 2023, WHO launched a new initiative called Preparedness and Resilience for Emerging Threats, which aims to harness the lessons learnt from past pandemics.[1] The protection of immunocompromised populations from COVID-19 was, and remains, a major challenge to health policy makers globally.[2–5] In the UK, the COVID-19 Autumn 2024 vaccine booster campaign marks the tenth SARS-CoV-2 vaccination being offered to some immunocompromised individuals, with little evidence to guide scheduling.[3,6] Similarly, although therapeutic agents are available for individuals at high risk of serious COVID-19 infection, the proportion of immunocompromised people who can access these agents and the current effectiveness of the agents are not known.[7,8] Therefore, consideration of ongoing COVID-19 protection measures for this population has parallels with preparation for the next pandemic, particularly in identifying who remains at risk and establishing the efficacy of various protective interventions.[9]

Although the absolute risk of serious COVID-19 infection in immunocompromised individuals significantly fell with vaccination, the relative risk compared with the general population has remained elevated.[2,3,5] However, a limitation of population-level data in informing outcomes in

Research in context

Evidence before this study

We searched PubMed for articles published in English between March 1, 2020, and April 1, 2024, using the keywords ("COVID-19" OR "SARS-COV-2") AND ("VACCINE" OR "VACCINATION") AND ("IMMUNOCOMPROMISED" OR "IMMUNOSUPPRESSED") AND ("ANTIBODY" OR "SEROLOGY"), with no restrictions on study type. There is substantial evidence that COVID-19 vaccine immunogenicity and vaccine effectiveness are attenuated in immunocompromised individuals compared with healthy controls and the general population. A small number of studies report on the association between immunogenicity and effectiveness, but studies are frequently limited by sample size, restricted populations, and exposure to only primary vaccine courses. Population-level data on vaccine effectiveness do not have granular information on disease phenotype and treatment. Where the effect of shielding is investigated at a population level, assessment is made on eligibility rather than actual individual behaviours or consideration of other relevant sociodemographic data.

Added value of this study

To our knowledge, this is the first population-level study across three different immunosuppressed cohorts (individuals with solid organ transplants, rare autoimmune rheumatic diseases, and lymphoid malignancies) that assesses how detectable anti-SARS-CoV-2 spike protein antibody (anti-S Ab) following COVID-19 vaccination influences subsequent infection and hospitalisation rates in the SARS-CoV-2 omicron era. Through questionnaire return that captured the non-pharmaceutical modifications and sociodemographic data of participants, we further report how infection rates are influenced by individual living circumstances. We additionally describe the participant characteristics that were associated with uptake of COVID-19 therapeutics. Our study thus provides a comprehensive assessment of the serological, clinical, and behavioural factors influencing SARS-CoV-2 infection and outcomes in immunocompromised individuals.

Implications of all the available evidence

Individuals with immunosuppression comprise diverse subpopulations with differing demographics, underlying diseases, and treatments; consequently, their responses to COVID-19 vaccines and risks of infection are not uniform or easy to risk stratify. Our study shows that mass anti-S Ab testing of immunocompromised individuals is possible and that the result provides important prognostic information about subsequent SARS-CoV-2 infection and hospitalisation. For future pandemic planning, such mass testing could be used to stratify the individual risk and to personalise their further management, either through targeted booster vaccinations and therapeutics or through management of household contacts.

immunocompromised people is insufficient granularity in this heterogeneous population, across individual characteristics, disease phenotype, and treatments.[10] This challenge has primarily arisen due to the sparse data on immunosuppression held within primary care in the UK.[11] Insights into which immunocompromised populations might remain at risk from COVID-19 can be extrapolated from vaccine immunogenicity studies, with individuals receiving potent immunosuppression most likely to have undetectable immune responses.[10,12,13] However, despite the association between immunosuppressed populations and severe infection being mechanistically consistent with the groups having attenuated vaccine immunogenicity, serological assessment of vaccine responses to guide risk stratification and inform management for individuals within groups has not been applied clinically.[2,3,5]

The Mass Evaluation of Lateral Flow Immunoassays for the Detection of SARS-CoV-2 Antibody in Immunosuppressed People (MELODY) study aimed to assess, at a population level, whether the absence of detectable anti-SARS-CoV-2 spike protein antibody (anti-S Ab) after at least three COVID-19 vaccinations correlated with infection risk and severity in three of the immunosuppressed populations at highest risk: solid organ transplant (SOT) recipients, people with rare autoimmune rheumatic diseases (RAIRDs), and people with lymphoid malignancies.

Methods

Study design and participants

Study design and recruitment have previously been described.[10] In brief, in this prospective cohort study using UK national disease registers, we identified and recruited three cohorts of people with immunosuppression from national registries between Dec 7, 2021, and June 26, 2022. Participants completed an online questionnaire and received a lateral flow immunoassay test for anti-S Ab, and were asked to report the result on the study web portal. Each participant was followed up for 6 months from the date of their antibody test, and the follow-up period occurred between Dec 15, 2021, and Jan 31, 2023. Ethical approval for MELODY was granted by the London Central Research Ethics Committee (21/HRA/4858) on Nov 21, 2021. This study is registered with ClinicalTrials.gov, NCT05148806. Details on COVID-19 timelines and UK policies in relation to MELODY are reported in the appendix (p 1).

See Online for appendix

Data sources and linkage

COVID-19 infection data were sourced from the Second Generation Surveillance System, managed by the UK Health Security Agency (UKHSA). This system tracks laboratory-confirmed infectious diseases in England and includes both PCR and lateral flow test results from hospital, community, and home testing. The dataset

contains positive and negative results reported by both UK National Health Service (NHS) and private laboratories. COVID-19 therapeutic data were obtained from Blueteq, a national NHS system for managing high-cost drugs. NHS doctors were required to complete a Blueteq form to prescribe COVID-19 treatments, including antivirals (eg, nirmatrelvir, ritonavir, molnupiravir, and remdesivir) and the monoclonal antibody sotrovimab. These therapies were given to individuals at high risk during the study period. Hospitalisation data were sourced from the Hospital Episode Statistics Admitted Patient Care dataset, which records detailed information on all NHS hospital admissions in England, including diagnoses, treatments, demographics, hospital details, and length of stay. Data on deaths came from the Personal Demographics Service, which is the national master database of all NHS patients in England.

Data linkage was performed using deterministic matching based on the NHS number, a unique identifier for NHS patients, verified by the Personal Demographics Service. Additional personal details (eg, name, birth date, and gender identity [male or female]) ensured accuracy. For the RAIRD and lymphoid malignancy cohorts, data were linked and analysed within NHS England's secure environment. For the SOT cohort, COVID-19 infection data were linked within the UKHSA, with other datasets linked by NHS England and released via the Data Access Request Service to NHS Blood and Transplant for analysis.

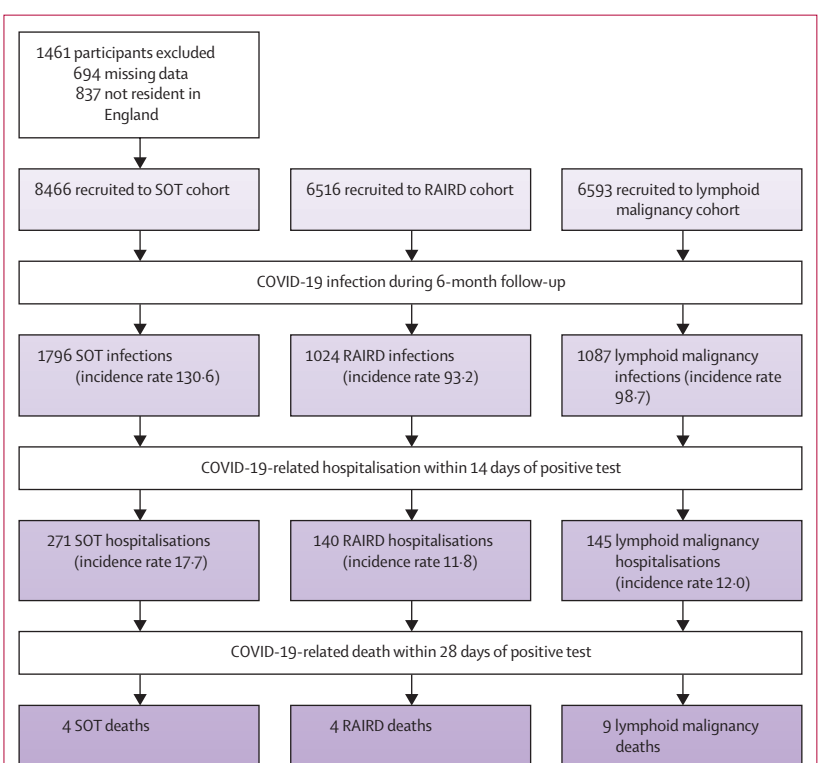

Figure: **Trial profile**
RAIRD=rare autoimmune rheumatic disease. SOT=solid organ transplant.

Definitions of infection, hospitalisation, and death due to SARS-CoV-2 infection

SARS-CoV-2 infection was primarily defined using UKHSA data and supplemented with hospitalisation and therapeutics data (appendix p 1). If a participant was hospitalised with a COVID-19 diagnosis (ICD-10 codes U071–U072) but had no positive UKHSA test, the infection date was recorded as the day before hospital admission. Similarly, if COVID-19 therapeutics were administered without a UKHSA infection record, the infection date was set as the day before treatment. Hospitalisation due to SARS-CoV-2 was defined as an admission within 14 days of a positive test. In line with publications related to the COVID-19 pandemic, death within 28 days of SARS-CoV-2 detection was assigned as COVID-19 related.[14]

Statistical analysis

Demographic characteristics that were common across all populations were summarised and stratified by shielding status. Differences in characteristics by antibody status were tested univariately using the χ^2 test for categorical variables.

For each of the three cohorts, we calculated incidence rates of SARS-CoV-2 detection within 6 months of anti-S Ab test completion for individuals who were antibody positive and antibody negative. To minimise temporal bias and to account for variations in community prevalence of SARS-CoV-2 infections during the study period, we defined incidence rate as the number of events divided by the person-time at risk, stratified by ethnicity, age, shielding status, presence of comorbidities, and children in household as well as calendar month. We used a Poisson regression model to derive incidence rate ratios (IRRs) with 95% CIs adjusted for the variables above. IRR is the incidence rate in participants who are antibody positive divided by the incidence rate for those who are antibody negative. An IRR result of less than 1 indicates reduced risk, whereas a result greater than 1 indicates increased risk of testing positive for SARS-CoV-2 in participants who are antibody positive. We evaluated the significance of antibody status using the likelihood ratio test.

We also applied this methodology to incidence rates of COVID-19-related hospitalisations in the same 6-month follow-up window following antibody testing. Incidence rates of deaths during the follow-up period were considered, but due to a small number of deaths in each cohort, analysis was not possible.

We performed a sensitivity analysis for each cohort for infection incidence and hospitalisation. This analysis considered terms found previously to influence anti-S Ab development in these cohorts[9] in the Poisson regression model, as well as the six terms adjusted for above, and then assessed the effect of antibody test result using the likelihood ratio test. These factors were not considered for adjusting in the main analysis due to colinearity between each factor and anti-S Ab status.

	Solid organ transplant cohort (N=8466)	Rare autoimmune rheumatic disease cohort (N=6516)	Lymphoid malignancy cohort (N=6593)
Age group, years			
18–64	5479 (64·7%)	3378 (52·1%)	2478 (37·7%)
65–74	2393 (28·3%)	2008 (31·0%)	2570 (39·1%)
≥75	594 (7·0%)	1111 (17·2%)	1527 (23·2%)
Not reported	0	19 (0·3%)	18 (0·3%)
Gender			
Male	4692 (55·4%)	1439 (22·1%)	3620 (54·9%)
Female	3774 (44·6%)	5070 (77·9%)	2971 (45·1%)
Not reported	0	7 (0·1%)	2 (<0·1%)
Ethnicity			
White	7916 (93·5%)	5992 (92·6%)	6401 (97·6%)
Asian	314 (3·7%)	231 (3·6%)	73 (1·1%)
Black	119 (1·4%)	130 (2·0%)	38 (0·6%)
Other	117 (1·4%)	142 (2·2%)	64 (1·0%)
Not reported	0	21 (0·3%)	17 (0·3%)
Previous COVID-19 infection			
Yes	3127 (39·3%)	2367 (39·3%)	2056 (33·7%)
No	4821 (60·7%)	3652 (60·7%)	4050 (66·3%)
Not reported	518 (6·1%)	497 (7·6%)	487 (7·4%)
Number of adults in household			
1 adult (live alone)	2276 (27·1%)	2019 (31·3%)	1927 (29·5%)
≥2 adults	6116 (72·9%)	4423 (68·7%)	4601 (70·5%)
Not reported	74 (0·9%)	74 (1·1%)	65 (1·0%)
Children in household			
Yes	1354 (16·2%)	945 (14·6%)	589 (9·0%)
No	7024 (83·8%)	5514 (85·4%)	5942 (91·0%)
Not reported	88 (1·0%)	57 (0·9%)	62 (0·9%)
Employment			
Employed or in education	3608 (43·4%)	1871 (29·2%)	1699 (26·2%)
Retired or otherwise not in employment or education	4702 (56·6%)	4540 (70·8%)	4790 (73·8%)
Not reported	156 (1·8%)	105 (1·6%)	104 (1·6%)
Workspace			
Work alone or from home	1205 (35·4%)	563 (30·8%)	621 (37·6%)
1–6 people	1410 (41·4%)	718 (39·3%)	649 (39·3%)
≥7 people	891 (26·2%)	548 (30·0%)	383 (23·2%)
Not reported	102 (1·2%)	42 (0·6%)	46 (0·7%)
Travel to work			
Work from home	765 (21·2%)	313 (17·4%)	320 (19·7%)
Private transport only	2308 (64·0%)	1277 (70·9%)	1165 (71·6%)
Shared transport	532 (14·8%)	211 (11·7%)	141 (8·7%)
Not reported	3 (<0·1%)	70 (1·1%)	73 (1·1%)
Shielding			
Yes	5629 (66·8%)	4033 (62·4%)	4137 (63·1%)
No	2793 (33·2%)	2435 (37·6%)	2418 (36·9%)
Not reported	44 (0·5%)	48 (0·7%)	38 (0·6%)
Wear face mask			
Yes	6759 (80·3%)	5150 (79·5%)	5250 (80·0%)
No	1662 (19·7%)	1331 (20·5%)	1314 (20·0%)
Not reported	45 (0·5%)	35 (0·5%)	29 (0·4%)
Antibody status			
Positive	6519 (77·0%)	5594 (85·9%)	5227 (79·3%)
Negative	1947 (23·0%)	922 (14·1%)	1366 (20·7%)

Data are n (%).

Table 1: **Sociodemographic characteristics of all participants**

For access to therapeutics, participants who had a positive SARS-CoV-2 infection in the 6-month follow-up window were considered. We summarised demographic characteristics, stratified by receipt of therapeutics, and compared them using the χ^2 test for categorical variables and the Kruskal–Wallis test for continuous variables. We calculated the NHS region of residence for each participant based on their postcode held on the respective registry. We obtained the number of participants receiving therapeutics per million population of those with a positive SARS-CoV-2 infection by NHS region for each cohort. We calculated the systematic component of variation to assess geographical variation across regions for access to therapeutics for those with infections using the per million population rate of therapeutics in the study populations who tested positive for SARS-CoV-2 infection.[15]

We conducted statistical analyses in SAS version 9.4 and R version 4.2.2 using the biostat3 and dplyr packages.[16,17]

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

The analysed cohort comprised 21575 of the 28411 participants recruited into the study who were resident in England and who returned a valid anti-S Ab test, completed all study questionnaires, and consented to data linkage (8466 SOT, 6516 RAIRD, and 6593 lymphoid malignancy; figure).[10]

Differences in baseline clinical demographics between the three cohorts reflected expected differences between people with SOTs, RAIRDs, and lymphoid malignancies (table 1),[10] with the RAIRD cohort containing the highest proportion of females and the SOT cohort being younger. The majority of participants in all cohorts were of White ethnicity. Participants also provided detailed social and

	Solid organ transplant cohort (N=8466)							Rare autoimmune rheumatic disease cohort (N=6516)							Lymphoid malignancy cohort (N=6593)						
	IRR	Number anti-S Ab negative	Anti-S Ab negative COVID-19 cases	Incidence rate	Number anti-S Ab positive	Anti-S Ab positive COVID-19 cases	Incidence rate	IRR	Number anti-S Ab negative	Anti-S Ab negative COVID-19 cases	Incidence rate	Number anti-S Ab positive	Anti-S Ab positive COVID-19 cases	Incidence rate	IRR	Number anti-S Ab negative	Anti-S Ab negative COVID-19 cases	Incidence rate	Number anti-S Ab positive	Anti-S Ab positive COVID-19 cases	Incidence rate
Total	0·59 (0·56–0·62)	1947	573	191	6519	1223	114	0·54 (0·46–0·62)	922	227	156	5594	797	83·7	0·58 (0·51–0·66)	1366	323	149	5227	764	86·4
Vaccines at test																					
3	0·58 (0·54–0·64)	699	246	237	1485	333	139	0·50 (0·39–0·64)	378	81	134	2237	257	66·4	0·53 (0·40–0·72)	277	65	149	991	133	79
4	0·63 (0·58–0·67)	1084	287	170	4199	726	104	0·55 (0·45–0·66)	507	136	172	3024	479	93·9	0·61 (0·53–0·71)	1006	234	147	3651	552	89·6
≥5	0·73 (0·61–0·87)	164	40	151	835	164	119	0·67 (0·34–1·31)	37	10	164	333	61	110	0·43 (0·27–0·68)	83	24	182	585	79	78·7
Vaccine type																					
AZ+mRNA	0·6 (0·56–0·64)	1117	315	181	3566	639	108	0·50 (0·41–0·61)	461	124	174	2855	422	87·2	0·53 (0·45–0·63)	700	179	163	2682	394	86·8
mRNA+	0·59 (0·54–0·63)	830	258	205	2953	584	121	0·58 (0·46–0·73)	397	92	144	2456	348	83·1	0·62 (0·51–0·76)	600	134	140	2303	339	87·1
Other	..	0	..	..	0	..	..	0·45 (0·22–0·92)	60	11	111	274	24	49·6	0·80 (0·39–1·64)	63	10	94·9	230	30	76
Not reported	..	0	..	..	0	..	..	..	4	0	0	9	3	224	..	3	0	0	12	1	45·5
Age group, years																					
18–64	0·60 (0·56–0·64)	1104	352	211	4375	905	127	0·54 (0·45–0·65)	482	137	185	2896	486	100	0·48 (0·39–0·58)	454	137	200	2024	325	95·6
65–74	0·53 (0·48–0·58)	655	178	174	1738	263	89·4	0·46 (0·35–0·61)	285	65	142	1723	196	65·8	0·73 (0·59–0·90)	548	114	128	2022	315	92·7
≥75	0·54 (0·44–0·66)	188	43	141	406	55	80	0·70 (0·45–1·09)	150	24	95·7	961	111	66·8	0·50 (0·38–0·68)	360	71	121	1167	124	61·2
Not reported	..	0	..	..	0	..	..	1·46 (0·16–13·0)	5	1	132	14	4	192	..	4	1	172	14	0	0
Gender																					
Male	0·54 (0·50–0·58)	1044	306	190	3648	632	104	0·46 (0·35–0·61)	261	72	175	1178	161	80·2	0·60 (0·51–0·72)	770	180	148	2850	427	88·8
Female	0·66 (0·61–0·71)	903	267	192	2871	591	126	0·57 (0·48–0·68)	660	155	148	4410	636	84·7	0·55 (0·45–0·67)	596	143	151	2375	337	83·6
Not reported	..	0	..	..	0	..	..	..	0	..	..	1	0	0	..	0	..	..	2	0	0

(Table 2 continues on next page)

	Solid organ transplant cohort (N=8466)							Rare autoimmune rheumatic disease cohort (N=6516)							Lymphoid malignancy cohort (N=6593)						
	IRR	Number anti-S Ab negative	Anti-S Ab negative COVID-19 cases	Incidence rate	Number anti-S Ab positive	Anti-S Ab positive COVID-19 cases	Incidence rate	IRR	Number anti-S Ab negative	Anti-S Ab negative COVID-19 cases	Incidence rate	Number anti-S Ab positive	Anti-S Ab positive COVID-19 cases	Incidence rate	IRR	Number anti-S Ab negative	Anti-S Ab negative COVID-19 cases	Incidence rate	Number anti-S Ab positive	Anti-S Ab positive COVID-19 cases	Incidence rate
(Continued from previous page)																					
Ethnicity																					
White	0·58 (0·55–0·62)	1831	547	195	6085	1144	114	0·54 (0·46–0·63)	844	208	156	5148	732	83·5	0·57 (0·50–0·65)	1334	318	151	5067	739	86·2
Asian	0·68 (0·49–0·93)	57	14	154	257	44	103	0·43 (0·22–0·86)	33	11	231	198	33	99·8	..	8	0	0	65	15	144
Black	0·79 (0·48–1·31)	32	6	114	87	14	96·2	0·81 (0·27–2·43)	24	4	102	106	15	82·4	0·41 (0·05–3·70)	4	1	162	34	4	66·7
Other	0·97 (0·62–1·52)	27	6	135	90	21	145	0·46 (0·15–1·40)	18	4	142	124	14	65·6	0·90 (0·18–4·48)	15	2	78·9	49	6	71·3
Not reported	..	0	..	..	0	..	..	..	3	0	0	18	3	101	..	5	2	304	12	0	0
Comorbidities																					
Yes	0·58 (0·52–0·64)	1473	425	186	4830	900	113	0·58 (0·49–0·70)	622	147	148	3860	566	86·3	0·59 (0·49–0·72)	713	148	128	2770	358	75·6
No	0·60 (0·56–0·63)	474	148	207	1689	323	116	0·46 (0·35–0·59)	300	80	171	1734	231	77·8	0·57 (0·48–0·68)	653	175	174	2457	406	98·8
Not reported	..	0	..	..	0	..	..	..	0	..	..	0	..	..	..	0	..	..	0	..	..
Previous COVID-19 infection																					
Yes	0·57 (0·49–0·66)	302	57	115	2825	331	68·2	0·55 (0·39–0·77)	222	38	104	2145	213	56·7	0·64 (0·46–0·91)	308	40	76	1748	150	48·9
No	0·74 (0·70–0·79)	1523	481	208	3298	802	152	0·60 (0·51–0·72)	641	170	169	3011	513	102	0·60 (0·52–0·70)	979	265	176	3071	538	105
Not reported	0·77 (0·62–0·95)	122	35	188	396	90	142	0·44 (0·27–0·73)	59	19	218	438	71	96·2	0·81 (0·48–1·35)	79	18	140	408	76	113
Number of adults in household																					
1 adult (live alone)	0·55 (0·50–0·61)	616	182	192	1660	298	109	0·48 (0·36–0·63)	310	69	141	1709	199	67·4	0·70 (0·54–0·91)	408	76	113	1519	204	78·7
≥2 adults	0·60 (0·57–0·64)	1313	389	193	4803	917	116	0·55 (0·47–0·66)	600	157	166	3823	593	91·8	0·54 (0·46–0·63)	935	243	167	3666	556	90
Not reported	0·83 (0·38–1·81)	18	2	63·1	56	8	86·1	0·95 (0·11–8·16)	12	1	48·2	62	5	46	0·52 (0·13–2·08)	23	4	106	42	4	55·2

(Table 2 continues on next page)

	Solid organ transplant cohort (N=8466)							Rare autoimmune rheumatic disease cohort (N=6516)							Lymphoid malignancy cohort (N=6593)						
	IRR	Number anti-S Ab negative	Anti-S Ab negative COVID-19 cases	Incidence rate	Number anti-S Ab positive	Anti-S Ab positive COVID-19 cases	Incidence rate	IRR	Number anti-S Ab negative	Anti-S Ab negative COVID-19 cases	Incidence rate	Number anti-S Ab positive	Anti-S Ab positive COVID-19 cases	Incidence rate	IRR	Number anti-S Ab negative	Anti-S Ab negative COVID-19 cases	Incidence rate	Number anti-S Ab positive	Anti-S Ab positive COVID-19 cases	Incidence rate
(Continued from previous page)																					
Children in household																					
Yes	0·52 (0·45–0·59)	206	91	332	1148	280	154	0·52 (0·36–0·74)	118	36	200	827	143	103	0·42 (0·28–0·63)	99	34	242	490	83	102
No	0·59 (0·55–0·62)	1719	478	178	5305	933	106	0·54 (0·46–0·63)	793	190	151	4721	651	80·8	0·59 (0·52–0·68)	1248	286	144	4694	676	84·9
Not reported	0·41 (0·23–0·73)	22	4	104	66	10	92·3	0·69 (0·07–6·64)	11	1	52·9	46	3	36·5	0·74 (0·18–3·08)	19	3	93·5	43	5	68·9
Employment																					
Employed or in education	0·54 (0·50–0·59)	602	219	251	3006	642	132	0·46 (0·36–0·59)	255	80	209	1616	260	95·5	0·53 (0·41–0·67)	300	88	196	1399	240	103
Retired or otherwise not in education or employment	0·59 (0·55–0·63)	1307	343	166	3395	566	99·5	0·60 (0·5–0·72)	652	139	131	3888	524	78·8	0·59 (0·50–0·68)	1030	227	137	3760	513	80·1
Not reported	0·42 (0·27–0·66)	38	11	193	118	15	74·8	0·18 (0·07–0·43)	15	8	470	90	13	83·9	0·71 (0·29–1·77)	36	8	140	68	11	99·5
Workspace																					
Work alone or from home	0·59 (0·52–0·67)	266	93	238	939	200	131	0·50 (0·32–0·78)	84	25	194	479	78	95·9	0·62 (0·42–0·92)	120	34	188	501	95	116
1–6 people	0·51 (0·44–0·59)	213	76	248	1197	241	124	0·48 (0·32–0·72)	102	30	195	616	97	93·6	0·48 (0·32–0·72)	123	34	181	526	78	87·2
≥7 people	0·50 (0·42–0·59)	109	46	302	782	185	148	0·40 (0·25–0·63)	64	23	252	484	81	100	0·46 (0·27–0·78)	50	17	238	333	60	109
Not reported	0·69 (0·38–1·26)	14	4	187	88	16	109	0·18 (0·07–0·43)	5	2	246	37	4	62·2	0·32 (0·08–1·24)	7	3	340	39	7	109

(Table 2 continues on next page)

	Solid organ transplant cohort (N=8466)							Rare autoimmune rheumatic disease cohort (N=6516)							Lymphoid malignancy cohort (N=6593)						
	IRR	Number anti-S Ab negative	Anti-S Ab negative COVID-19 cases	Incidence rate	Number anti-S Ab positive	Anti-S Ab positive COVID-19 cases	Incidence rate	IRR	Number anti-S Ab negative	Anti-S Ab negative COVID-19 cases	Incidence rate	Number anti-S Ab positive	Anti-S Ab positive COVID-19 cases	Incidence rate	IRR	Number anti-S Ab negative	Anti-S Ab negative COVID-19 cases	Incidence rate	Number anti-S Ab positive	Anti-S Ab positive COVID-19 cases	Incidence rate
(Continued from previous page)																					
Travel to work																					
Work from home	0·74 (0·63–0·88)	188	57	198	577	132	142	0·52 (0·29–0·94)	45	14	209	268	49	108	0·59 (0·37–0·96)	68	23	235	252	56	139
Private transport only	0·48 (0·43–0·53)	344	136	282	1964	416	131	0·48 (0·35–0·66)	170	51	195	1108	175	94	0·51 (0·38–0·69)	202	58	190	963	157	97·3
Shared transport	0·51 (0·41–0·65)	69	26	261	463	94	124	0·29 (0·15–0·57)	30	13	306	181	27	88·5	0·44 (0·16–1·21)	19	5	173	122	16	76·6
Not reported		1	0	..	2	0	..	0·44 (0·12–1·64)	10	3	199	60	9	88·2	0·92 (0·20–4·15)	11	2	116	62	11	106
Shielding																					
Yes	0·67 (0·63–0·71)	1549	444	184	4080	830	124	0·55 (0·47–0·66)	652	171	167	3381	527	92·1	0·59 (0·50–0·69)	981	239	153	3156	480	90·2
No	0·45 (0·40–0·50)	388	129	228	2405	389	97·1	0·57 (0·43–0·77)	258	52	126	2177	269	72	0·59 (0·46–0·76)	376	81	136	2042	281	80·9
Not reported	..	10	0	..	34	4	70·1	0·08 (0·01–0·65)	12	4	202	36	1	15·2	0·25 (0·05–1·24)	9	3	239	29	3	59·9
Wear face mask																					
Yes	0·63 (0·59–0·66)	1707	517	197	5052	1028	125	0·54 (0·46–0·63)	781	200	162	4369	650	87·6	0·56 (0·49–0·65)	1146	294	164	4104	635	92
No	0·55 (0·47–0·65)	230	55	152	1432	193	78·9	0·63 (0·41–0·97)	138	25	112	1193	145	70·7	0·91 (0·59–1·38)	210	26	73·4	1104	127	66·5
Not reported	0·36 (0·10–1·34)	10	1	57·4	35	2	33	0·06 (0·01–0·46)	3	2	565	32	2	34·6	0·29 (0·05–1·75)	10	3	208	19	2	60·8

Data are IRR (95% CI), n, or incidence rate. Anti-S Ab=SARS-CoV-2 spike protein antibody. IRR=incidence rate ratio of infection in participants who are anti-S Ab positive compared with anti-S Ab negative. AZ=AstraZeneca vaccine. mRNA=Moderna or Pfizer vaccine.

Table 2: **Demographic characteristics of participants who had three or more vaccinations, with incidence and IRR of COVID-19 infection**

	IRR	Anti-S Ab negative			Anti-S Ab positive		
		n	Cases	Incidence rate	n	Cases	Incidence rate
SOT							
Cohort total	0·34 (0·30–0·39)	1947	124	35·9	6519	147	12·4
Transplant type							
Kidney only	0·38 (0·33–0·45)	1343	81	33·9	4278	97	12·5
Liver only	0·31 (0·22–0·43)	278	16	32·5	1411	28	10·9
Pancreas, islet, or simultaneous pancreas or islet and kidney	0·52 (0·22–1·19)	75	3	22·3	221	3	7·4
Heart only	0·36 (0·22–0·58)	124	9	41·2	379	10	14·6
Lung (including heart–lung)	0·19 (0·11–0·32)	107	14	77·1	180	7	21·8
Other	0·35 (0·11–1·14)	20	1	27·2	50	2	22·7
Graft number							
First graft	0·32 (0·28–0·37)	1676	104	35·0	5752	121	11·6
Regraft	0·47 (0·35–0·64)	271	20	42·0	767	26	18·8
Cohort cancer diagnosis since transplant							
No	0·35 (0·30–0·40)	1688	103	34·3	5648	126	12·3
Yes	0·33 (0·24–0·44)	259	21	46·5	871	21	13·3
Cohort rejection							
No	0·35 (0·31–0·39)	1891	121	36·1	6410	146	12·6
Yes—before vaccine	..	14	1	40·4	58	0	..
Yes—after vaccine	..	35	2	31·8	37	0	..
Yes—before and after vaccine	..	7	0	..	14	1	42·1
Cohort steroid for immunosuppression							
No	0·40 (0·32–0·49)	820	34	23·0	3487	65	10·3
Yes	0·35 (0·30–0·41)	1127	90	45·6	3032	82	14·9
Cohort immunosuppression and steroid use							
Belatacept-based only	..	0	..	..	1	0	..
Antiproliferative and calcineurin only	0·45 (0·35–0·58)	622	26	23·2	2163	45	11·5
Antiproliferative only	1·13 (0·14–9·20)	24	1	23·6	145	3	11·4
Calcineurin inhibitor only	0·29 (0·19–0·45)	165	7	23·6	1090	17	8·6
Other only	..	9	0	..	75	0	..
Belatacept-based and steroid	..	4	0	..	3	0	..
Antiproliferative and calcineurin and steroid	0·33 (0·27–0·40)	738	62	47·9	1652	48	16·1
Antiproliferative and steroid only	0·33 (0·20–0·52)	83	10	71·1	299	10	18·5
Calcineurin inhibitor and steroid only	0·42 (0·31–0·59)	281	17	34·3	972	23	13·0
Other and steroid	0·64 (0·13–3·19)	21	1	28·0	106	1	5·1
None	..	0	..	..	13	0	..
Cohort time from transplant to most recent vaccine							
Before transplant	..	5	0	..	13	1	45·1
0–89 days after transplant	..	11	0	..	30	0	..
90–364 days after transplant	0·65 (0·35–1·21)	78	4	28·8	270	8	16·3
≥1 year after transplant	0·33 (0·29–0·38)	1853	120	36·6	6206	138	12·3
RAIRD							
Cohort total	0·29 (0·21–0·41)	922	50	30·3	5594	90	8·8
Cohort diagnosis							
Small vessel vasculitis	0·30 (0·17–0·54)	370	25	38·0	994	21	11·6
Large vessel vasculitis	..	43	0	0	531	10	10·3
Systemic lupus erythematosus	0·24 (0·13–0·44)	263	15	32·0	2149	30	7·6
Scleroderma	0·80 (0·18–3·50)	84	2	13·1	785	15	10·5
Myositis	0·23 (0·06–0·86)	70	4	31·9	370	5	7·3
Other diagnoses	0·14 (0·01–2·29)	15	1	37·3	102	1	5·3
None	0·30 (0·08–1·15)	77	3	21·7	663	8	6·6

(Table 3 continues on next page)

	IRR	Anti-S Ab negative			Anti-S Ab positive		
		n	Cases	Incidence rate	n	Cases	Incidence rate
(Continued from previous page)							
Cohort time from diagnosis to most recent vaccine							
<5 years	0·34 (0·16–0·70)	234	11	26·2	1180	19	8·8
5–10 years	0·39 (0·16–0·95)	190	7	20·4	1038	15	7·9
>10 years	0·23 (0·14–0·38)	341	24	39·7	2294	38	9·1
Not reported	0·32 (0·14–0·74)	157	8	28·4	1082	18	9·1
Cohort disease activity							
None	0·34 (0·14–0·83)	128	7	31·0	779	15	10·5
Mild	0·27 (0·14–0·50)	293	15	28·6	1921	27	7·7
Moderate	0·37 (0·19–0·70)	302	14	25·7	1620	28	9·4
Severe	0·22 (0·07–0·73)	46	5	61·8	241	6	13·7
Not reported	0·23 (0·10–0·52)	153	9	32·8	1033	14	7·4
Cohort time from flare-up to most recent vaccine							
Before flare-up	0·24 (0·08–0·67)	114	6	29·3	708	9	6·9
0–1 years	0·30 (0·14–0·65)	172	10	32·4	966	17	9·6
1–3 years	0·20 (0·08–0·53)	167	9	30·2	706	8	6·2
>3 years	0·47 (0·18–1·28)	134	5	20·8	942	17	9·9
Not reported	0·28 (0·16–0·48)	335	20	33·5	2272	39	9·4
Cohort immunosuppression							
Anti-CD20	0·30 (0·13–0·69)	404	23	31·9	406	7	9·4
Azathioprine	1·18 (0·15–9·04)	46	1	11·8	474	12	13·9
Cyclophosphamide	..	14	2	87·3	90	0	0
Methotrexate	0·20 (0·06–0·63)	54	4	42·1	656	10	8·3
Mycophenolate	0·14 (0·06–0·31)	119	12	57·7	808	12	8·1
Other	0·46 (0·17–1·23)	122	5	22·7	1040	20	10·5
None	1·46 (0·20–10·85)	107	1	5·1	1605	22	7·5
Not reported	0·38 (0·08–1·81)	56	2	19·8	515	7	7·4
Cohort steroid therapy							
Yes	0·28 (0·18–0·45)	453	33	41·0	2026	43	11·6
No	0·35 (0·20–0·64)	413	15	20·2	3053	40	7·1
Not reported	0·38 (0·08–1·81)	56	2	19·8	515	7	7·4
Lymphoid malignancy							
Cohort total	0·39 (0·28–0·54)	1366	58	23·6	5227	87	9·1
Cohort diagnosis							
Aggressive B-cell NHL	0·90 (0·24–3·41)	259	3	6·4	758	8	5·8
Indolent B-cell NHL	0·22 (0·14–0·37)	711	39	30·6	1995	25	6·8
Plasma cell malignancies	1·06 (0·33–3·43)	107	3	15·7	1220	37	16·7
Hodgkin lymphoma	0·14 (0·04–0·48)	86	6	38·9	413	4	5·3
Other NHL	0·24 (0·06–0·88)	132	5	21·0	437	4	5·0
Other diagnoses	..	13	1	42·5	70	0	0
None	1·58 (0·20–12·47)	58	1	9·3	334	9	14·7
Cohort time from diagnosis to most recent vaccine							
<1 year	0·95 (0·43–2·10)	382	9	12·9	847	19	12·3
1–3 years	0·31 (0·20–0·47)	783	38	27·0	3426	52	8·3
>3 years	0·14 (0·05–0·40)	129	9	39·7	576	6	5·7
Not reported	0·95 (0·21–4·34)	72	2	15·2	378	10	14·5

(Table 3 continues on next page)

behavioural information (table 1); the proportion in employment or education was highest in the SOT cohort, and the proportion living with children was lowest in the lymphoid malignancy cohort. 13799 (64·0%) participants, similar in proportion across the three cohorts, reported continued shielding behaviours (table 1, appendix p 2). At study entry, 17587 (81·5%) participants felt that COVID-19 posed a moderate to major risk to them, and 5914 (27·4%)

	IRR	Anti-S Ab negative			Anti-S Ab positive		
		n	Cases	Incidence rate	n	Cases	Incidence rate
(Continued from previous page)							
Cohort immunosuppression							
Radiotherapy 3 months	..	18	0	0	35	0	0
Chemotherapy 3 months, including methotrexate 4 weeks	1·00 (0·45–2·22)	180	9	28·2	357	18	28·1
Anti-CD20 12 months	0·88 (0·39–1·98)	270	21	43·7	117	8	38·4
Ibrutinib or acalabrutinib 3 months	0·11 (0·01–0·87)	84	7	48·3	106	1	5·1
Lenalidomide 3 months	..	26	0	0	366	7	10·5
Autologous stem cell transplant 12 months	0·13 (0·01–2·07)	12	1	47·5	88	1	6·2
Other treatment	0·62 (0·31–1·26)	376	13	19·1	877	19	11·9
None	0·55 (0·21–1·45)	341	5	8·0	2947	24	4·4
Not reported	0·79 (0·17–3·67)	59	2	18·6	334	9	14·7
Cohort steroid therapy							
Yes	0·24 (0·06–1·02)	62	5	46·0	147	3	11·2
No	0·37 (0·26–0·53)	1246	52	23·2	4748	75	8·6
Not reported	1·59 (0·20–12·55)	58	1	9·3	332	9	14·8

Data are IRR (95% CI), n, or incidence rate. Anti-S Ab=SARS-CoV-2 spike protein antibody. IRR=incidence rate ratio. SOT=solid organ transplant. RAIRD=rare autoimmune rheumatic disease. NHL=non-Hodgkin lymphoma.

Table 3: **Clinical characteristics of participants who had three or more vaccinations, with incidence and IRR of hospitalisation incidence within 14 days of a SARS-CoV-2 infection**

remained either very or extremely worried about COVID-19. Of those reporting, 19 558 (90·7%) felt that knowing their anti-S Ab status was either fairly or very important (appendix p 3).

During the 6 months following the date of anti-S Ab testing, 3907 (18·1%) participants had a SARS-CoV-2 infection, 556 (2·6%) participants had a COVID-19 related hospitalisation, and 17 (<0·1%) participants died within 28 days of infection (figure). The incidence of infection was 130·6 per 100 000 person days (95% CI 124·6–136·8) in the SOT cohort, 93·2 per 100000 person days (87·6–99·1) in the RAIRD cohort, and 98·7 per 100 000 person days (92·9–104·8) in the lymphoid malignancy cohort (appendix p 4). Incidence rates of infection varied by sociodemographic characteristics across the cohorts, with shared risk factors associated with infection including younger age, shielding, and living with children (table 2, appendix p 5). Incidence rates of infection by underlying clinical conditions and immunosuppression for each cohort are provided in the appendix (pp 6–8). The incidence of COVID-19-related hospitalisation was 17·7 per 100 000 person days (15·7–20·0) in the SOT cohort, 11·8 per 100000 person days (9·9–13·9) in the RAIRD cohort, and 12·0 per 100000 person days (10·2–14·2) in the lymphoid malignancy cohort (appendix p 4). Hospitalisation rates also varied by sociodemographic characteristics across the cohorts, with comorbidities a shared risk factor (appendix pp 5, 9–10). Incidences of COVID-19-related hospitalisation by clinical diagnosis and immunosuppression are provided in table 3.

In all cohorts, infection rates and COVID-19-related hospitalisation rates were significantly lower in participants with anti-S Ab compared with those without (table 4). The unadjusted IRRs in participants who were anti-S Ab positive compared with negative for infection were 0·59 (95% CI 0·56–0·62) in the SOT cohort, 0·54 (0·46–0·62) in the RAIRD cohort, and 0·58 (0·51–0·66) in the lymphoid malignancy cohort (tables 2 and 4); for COVID-19-related hospitalisation the unadjusted IRRs were 0·34 (0·30–0·39) in the SOT cohort, 0·29 (0·21–0·41) in the RAIRD cohort, and 0·39 (0·28–0·54) in the lymphoid malignancy cohort (table 4, appendix pp 9–10). After full adjustment for variables considered to be associated with infection (ethnicity, age, shielding status, presence of comorbidities, children in household, and calendar month; appendix p 5), rates of infection and hospitalisation remained lower in those with anti-S Ab: IRRs for infection were 0·69 (0·65–0·73) in the SOT cohort, 0·57 (0·49–0·67) in the RAIRD cohort, and 0·62 (0·54–0·71) in the lymphoid malignancy cohort; and IRRs for hospitalisation were 0·40 (0·35–0·46) in the SOT cohort, 0·32 (0·22–0·46) in the RAIRD cohort, and 0·41 (0·29–0·58) in the lymphoid malignancy cohort (table 4). In sensitivity analyses, in all cohorts, anti-S Ab status was still significant in models for infection and hospitalisation when including all confounding variables previously found to be associated with antibody status (appendix pp 11–16).[10]

Only 1697 (43·4%) of 3907 infected participants were recorded as having received COVID-19 therapeutics—893 (49·7%) of 1796 in the SOT cohort, 396 (38·7%) of 1024 in the RAIRD cohort, and 408 (37·5%) of 1087 in the lymphoid malignancy cohort—with some differences seen by area of deprivation and geographical region where participants

	Solid organ transplant cohort			Rare autoimmune rheumatic disease cohort			Lymphoid malignancy cohort		
	Unadjusted IRR	Risk-adjusted IRR	p value	Unadjusted IRR	Risk-adjusted IRR	p value	Unadjusted IRR	Risk-adjusted IRR	p value
Infection incidence									
Anti-S Ab negative	1	1	..	1	1	..	1	1	..
Anti-S Ab positive	0·59 (0·56–0·62)	0·69 (0·65–0·73)	<0·0001	0·43 (0·46–0·62)	0·57 (0·49–0·67)	<0·0001	0·58 (0·51–0·66)	0·62 (0·54–0·71)	<0·0001
Incidence of hospitalisation within 14 days of a SARS-CoV-2 infection									
Anti-S Ab negative	1	1	..	1	1	..	1	1	..
Anti-S Ab positive	0·34 (0·30–0·39)	0·40 (0·35–0·46)	<0·0001	0·29 (0·21–0·41)	0·32 (0·22–0·46)	<0·0001	0·39 (0·28–0·54)	0·41 (0·29–0·58)	<0·0001

Data are IRR (95% CI) or p. All adjusted for ethnicity, age, shielding status, presence of comorbidities, children in household, and month. Calculated using likelihood ratio test for comparing model without anti-S Ab status to model with anti-S Ab status. IRR=incidence rate ratio. Anti-S Ab=SARS-CoV-2 spike protein antibody.

Table 4: **Unadjusted and risk-adjusted IRRs for participants who had three or more vaccinations**

reside (appendix pp 17–18). A higher proportion of participants who were anti-S Ab negative in the RAIRD and lymphoid malignancy groups received therapeutics, although no proportional difference was seen in the SOT cohort (appendix pp 11–16). Participants who were shielding and who felt that COVID-19 posed a major risk to them were more likely to have received therapeutics across all cohorts (appendix p 17). The majority of participants in each cohort who received therapeutics did so in the community: 751 (84%) of 893 in the SOT cohort, 369 (93%) of 396 in the RAIRD cohort, and 374 (92%) of 408 in the lymphoid malignancy cohort (appendix pp 19–20).

Discussion

In a heterogeneous population of immunosuppressed individuals at increased risk of severe COVID-19 infection, in whom homogeneous protection strategies have been applied, we have shown that assessment of anti-S Ab following at least three COVID-19 vaccinations is possible at mass scale and that seropositivity is associated with a reduced risk of infection and hospitalisation. We have identified substantial differences in sociodemographic and clinical characteristics within this population that influence not only infection risk but also outcomes. Furthermore, we have shown that assessment of anti-S Ab status provides an additional method to identify immunosuppressed individuals who remain at highest risk. This could provide a unified practical assessment of risk, given our previous finding of the interplay of multiple confounding factors related to demographics, disease characteristics, and medication in predicting antibody responses.[10] Because granular data on disease-specific characteristics and immunosuppressive treatments are not centrally accessible in the UK, these findings could have important implications for policy makers.

Identifying immunocompromised individuals with no serological evidence of immunity following vaccination could inform protection strategies, such as bespoke vaccination scheduling, immunosuppression modulation before vaccination, prophylaxis, or pre-emptive treatments.[18–22] The concept of risk stratification for protective interventions is not new; the QCOVID4 risk algorithm—which was modelled using data from overlapping periods of the MELODY study—was refined to help inform which people would benefit from COVID-19 therapeutics.[23] Similarly, data from OpenSAFELY suggest that during the omicron period, those likely to have impaired immune responses remained at increased risk of COVID-19. However, neither QCOVID nor OpenSAFELY were able to further refine risk assessment in these populations due to insufficient data.[5] In addition to comprehensively reporting clinical characteristics and immunosuppressive therapy details not routinely held centrally in this population, and thus not available for incorporation into risk algorithms, we now show that assessment of immune status via anti-S Ab testing enables more effective personalised stratification.

We found that the incidence of infection was higher in participants who reported ongoing shielding behaviours. It is conceivable that participants who were shielding at the time of recruitment were subsequently more likely to be exposed to SARS-CoV-2 for the first time as shielding practice waned. Paradoxical relationships between shielding and infection have been reported previously, and it is now considered that shielding simply delays rather than prevents exposure to virus in infection-naive individuals.[24,25] In support of this, our data show that the shielding participants across all cohorts were less likely to report previous infection at study entry. An additional strength of our study is that our participant questionnaire captured self-reported shielding behaviour, as opposed to inferring individual behaviour from their shielding eligibility.[24,25] Importantly for future pandemic planning, we show that infection rates were higher in participants who had children in the household, reflecting the challenges in shielding and preventing respiratory virus transmission in this environment. Moving forward, recommendation of vaccine boosters for household contacts of immunosuppressed individuals could be beneficial, and the use of prophylactic therapies, effective against circulating variants, might be of benefit in vaccine non-responders.[18–20] As shown in the sensitivity analysis, incidence of infection varied over time, which is likely to be related to a combination of factors including community rates and changing behaviours.[26] We

hypothesise that these factors contributed to the variation of infection incidence by vaccination number and cohorts; irrespective of these non-clinical features, antibody status helped identify those who remained at risk.

Our study was not powered to adjust for effects of community therapeutic interventions, which were introduced in the UK in December, 2021, after study initiation. However, our findings relating to therapeutics use are important. The insufficient treatment received in this high-risk population was unexpected, although consistent with a previous report on low and inconsistent coverage in broader at-risk groups.[8] People eligible for treatments were informed by letter, and it is interesting to note the difference in therapeutics uptake in the SOT cohort compared with the RAIRD and lymphoid malignancy cohorts, which might reflect eligibility but perhaps reflects that the former are more readily identifiable in primary care records. Identification of RAIRD participants in MELODY was only possible through development of data validation methods, and these participants were unidentifiable centrally at the start of the COVID-19 pandemic.[11] It is also notable that participants who believed COVID-19 posed a major risk to them were more likely to receive treatment, and we hypothesise that their concern influenced their drive to access treatments. Whether knowledge of anti-S Ab status in the RAIRD and lymphoid malignancy groups influenced receipt of treatment, and affected infection outcomes, cannot be elucidated from our data, and these participants might have been more likely to qualify based on symptoms. If, however, an individual's knowledge of their anti-S Ab status does empower their receipt of antiviral treatments, this would be a further argument for wider clinical testing. The regional differences we and others have seen in access to therapeutics certainly warrants further consideration and remedial actions, with simple and efficient access pathways required.[8]

Limitations of our study include the absence of protocolised testing for infection. Although we used the best available infection data provided by the UKHSA, infections were likely to have been under-reported, because 15% of the cohort received COVID therapeutics before a positive COVID-19 test record. Inherent to the use of large linked electronic health data, our analysis is reliant on clinical coding, and we cannot exclude misclassification of cause of admission. Likewise, although we used established timeframes after infection to ascertain relationship to admission or death, we cannot exclude that COVID-19 did not contribute to subsequent clinical outcomes either directly or indirectly, particularly if infection interfered with immunotherapy treatment. As with other studies reliant on data linkage, we experienced substantial barriers to accessing data, which caused delays in reporting our findings, prohibiting their timely use in informing policy; this is an issue that requires urgent resolution.[10,27] We previously acknowledged that our serological assay has low sensitivity, and we did not assess other immune correlates of protection such as neutralisation or cellular responses.[10,12,28–31] Nevertheless, our primary aim was to assess a pragmatic assay deployable at scale. If anti-S Ab testing were to be implemented in clinical practice, it is likely that the assays used would be superseded, and it could be more feasible to test at times of routine clinic attendance, when blood tests are commonly taken. This practice might also overcome any potential misinterpretation of the lateral flow immunoassay by end users, which is another limitation of our study.[32,33] However, for future pandemic planning, our findings suggest that rapid point-of-care testing provides actionable clinical information. This could be especially useful in lower-income countries. Moving forward, as the proportion of non-responders decreases with serial vaccination, it could be more useful to investigate quantitative antibody testing, ideally still at point of care, to help define risk in immunosuppressed individuals compared with healthy populations, with repeated immunogenicity assessments required as vaccines change.[12]

In conclusion, we have shown that in immunocompromised populations, detectable anti-S Ab following multiple doses of COVID-19 vaccines is associated with reduced risk of infection and hospitalisation, independent of other clinical and treatment characteristics. With heterogeneity in response to vaccination, antibody testing could enable identification of people who remain the most vulnerable to COVID-19 disease within a clinically high-risk immunosuppressed population. Although we report a lower incidence of severe infection compared with early in the COVID-19 pandemic, hospitalisations remained high, and the data support the need for ongoing vaccination and access to therapeutics in this population, irrespective of antibody status.[2] Repeated vaccination will circumvent antibody waning in individuals who are antibody positive, and is likely to elicit seroconversion in some who are antibody negative.[10] Identification of people who are antibody negative, by testing those with risk factors based on clinical features and immunosuppressive therapies, might inform their risk perception and behaviours but also allows options for additional interventions such as pre-emptive prophylaxis, optimisation of timing of vaccine administration, or even immunosuppression modulation where it is safe to do so.[18,22] The ability to readily identify those at highest risk could also be important should new, and potentially more virulent, variants evolve. Importantly, our study shows the need for change so that immunosuppressed people can be readily identified, as many of our cohort were unrecognised at the start of the COVID-19 pandemic. De novo immunosuppression use occurs daily in people across the UK, and there is an urgent

need to routinely capture utilisation data in secondary care, which would have far-reaching benefits. Finally, with robust methods to identify immunosuppressed individuals in place, our methodology could be applied to allow prospective evaluation of immunity and risk in future pandemics, which could enable provision of tailored advice, rather than generic recommendations, which would help individuals, health-care providers, and policy makers alike.

Contributors

LL, SM, FAP, and MW conceptualised the study. GSC, LL, PL, SHL, SM, FAP, GJP, HT, HW, and MW were responsible for funding acquisition. GP was responsible for project administration. MB, GSC, LL, PL, SHL, SM, SPM, FAP, GJP, HT, HW, and MW designed the methodology. MB, RH, LM, FAP, SPM, and AT accessed, verified, cleaned, and analysed the data. RH, LM, FAP, AT, and MW wrote the original draft. MB, GSC, JC, RH, LL, PL, SHL, SM, SPM, FAP, GJP, AT, HT, HW, and MW reviewed and edited the manuscript. All authors approved the final text and were responsible for the decision to submit for publication.

Declaration of interests

FAP and PL report an investigator-led grant from Vifor Pharma. PL and SM report speaker honoraria from CSL Vifor. LL, PL, SHL, SM, and MW report consulting fees from Alexion, AstraZeneca, Biogen, GSK, Hansa Biopharma, Novartis, Pfizer, Otsuka, PanAngium Therapeutics, and Roche. SHL, LL, LM, GJP, and MW report speaker honoraria from Alexion, AstraZeneca, GSK, Otsuka, and Roche. All other authors declare no competing interests.

Data sharing

The data that support the findings of this study are available from the authors upon reasonable request and with permission from NHS Blood and Transplant or the National Disease Registration Service. Data are not publicly available due to restrictions such as their containing information that could compromise the privacy of research participants.

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