Antibody prevalence after three or more COVID-19 vaccine doses in individuals who are immunosuppressed in the UK: a cross-sectional study from MELODY

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Summary

Background In the UK, additional COVID-19 vaccine booster doses and treatments are offered to people who are immunosuppressed to protect against severe COVID-19, but how best to choose the individuals that receive these vaccine booster doses and treatments is unclear. We investigated the association between seropositivity to SARS-CoV-2 spike protein with demographic, disease, and treatment-related characteristics after at least three COVID-19 vaccines in three cohorts of people who are immunosuppressed.

Methods In a cross-sectional study using UK national disease registries, we identified, contacted, and recruited recipients of solid organ transplants, participants with rare autoimmune rheumatic diseases, and participants with lymphoid malignancies who were 18 years or older, resident in the UK, and who had received at least three doses of a COVID-19 vaccine. The study was open to recruitment from Dec 7, 2021, to June 26, 2022. Participants received a lateral flow immunoassay test for SARS-CoV-2 spike antibodies to complete at home, and an online questionnaire. Multivariable logistic regression was used to estimate the mutually adjusted odds of seropositivity against each characteristic.

Findings Between Feb 14 and June 26, 2022, we screened 101 972 people (98 725 invited, 3247 self-enrolled) and recruited 28 411 (27·9%) to the study. 23 036 (81·1%) recruited individuals provided serological data. Of these, 9927 (43·1%) were recipients of solid organ transplants, 6516 (28·3%) had rare autoimmune rheumatic diseases, and 6593 (28·6%) had lymphoid malignancies. 10 485 (45·5%) participants were men and 12 535 (54·4%) were women (gender was not reported for 16 [<0·1%] participants), and 21661 (94·0%) participants were of White ethnicity. The median age of participants with solid organ transplants was 60 years (SD 50–67), with rare autoimmune rheumatic diseases was 65 years (54–73), and with lymphoid malignancy was 69 years (61–75). Of the 23 036 participants with serological data, 6583 (28·6%) had received three vaccine doses, 14 234 (61·8%) had received four vaccine doses, and 2219 (9·6%) had received five or more vaccine doses. IgG anti-spike antibodies were undetectable in 2310 (23·3%) of 9927 patients with solid organ transplants, 922 (14·1%) of 6516 patients with rare autoimmune rheumatic diseases, and 1366 (20·7%) of 6593 patients with lymphoid malignancies. In all groups, seropositivity was associated with younger age, higher number of vaccine doses (ie, five *vs* three), and previous COVID-19. Immunosuppressive medication reduced the likelihood of seropositivity: the lowest odds of seropositivity were found in recipients of solid organ transplants receiving a combination of an anti-proliferative agent, a calcineurin inhibitor, and steroids, and those with rare autoimmune rheumatic diseases or lymphoid malignancies treated with anti-CD20 therapies.

Interpretation Approximately one in five recipients of solid organ transplants, individuals with rare autoimmune rheumatic diseases, and individuals with lymphoid malignancies have no detectable IgG anti-spike antibodies despite three or more vaccine doses, but this proportion decreases with sequential booster doses. Choice of immunosuppressant and disease type is strongly associated with serological response. Antibody testing using lateral flow immunoassay tests could enable rapid identification of individuals who are most likely to benefit from additional COVID-19 interventions.

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Introduction

Despite vaccination, people who are immunocompromised have poorer outcomes from SARS-CoV-2 infection than do those in the general population.[1–6] Population-level analyses have highlighted that individuals with solid organ transplants, lymphoid malignancies such as lymphoma, and individuals on immunosuppressive medications have the highest risk of admission to hospital or death from COVID-19.[2,4] These groups were included in the WHO definition of

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Research in context

Evidence before this study

On Oct 21, 2022, we searched PubMed for articles published in English between March 1, 2020 and Oct 21, 2022, using the keywords ("COVID-19" OR "SARS-COV-2") AND ("VACCINE" OR "VACCINATION") AND ("IMMUNOCOMPROMISED" OR "IMMUNOSUPPRESSED"), with no restrictions on study type. Epidemiological studies of vaccine effectiveness uniformly report a heightened risk of breakthrough infection in people who are immunocompromised, irrespective of the particular primary or booster vaccine course administered, or the dominant virus variant circulating during the reporting period. Bespoke approaches are therefore required to protect these at-risk groups, but development of these approaches is hampered by a lack of granularity in data characterising the risk to the individual. Within populations who are immunocompromised, there are likely to be marked differences in the degree of functional immunosuppression. Thus, although immunogenicity studies have reported attenuated serological responses to vaccination against SARS-CoV-2 across different populations who are immunocompromised, these studies often have limited power to adjust for confounding factors associated with immune responsiveness, and often assess single populations of individuals who are immunocompromised. These limitations have prevented the findings from informing national policy on future strategies for protecting populations who are immunocompromised.

Added value of this study

National disease registries were used to identify and contact a sizeable proportion of people living in the UK who are immunocompromised and considered to be most at risk of severe COVID-19: recipients of solid organ transplants, people with rare autoimmune rheumatic diseases, and people with lymphoid malignancies. Participants received a lateral flow immunoassay test for SARS-CoV-2 anti-spike antibodies to complete at home, enabling analysis of immunogenicity data at a population level. A central study web platform facilitated patient self-reporting of variables that were likely to affect immune responsiveness and that had not previously been evaluated at the population level. This approach has also provided unique insights of the effect of the COVID-19 pandemic on people who are immunocompromised, including an assessment of psychological distress from self-completed depression (8-item PHQ-8) and anxiety (GAD-7) questionnaires.

Implications of all the available evidence

Approximately one in five people who are immunocompromised have no serological responses to COVID-19 vaccines despite receiving three or more vaccine doses. Importantly, the prevalence of anti-spike antibodies increases with number of doses received, providing support for the benefit of booster vaccines in this population. Knowledge of the type of immunosuppressant and underlying disease will help to identify those at particular risk of not responding to vaccination, and antibody testing will enable rapid confirmation of individuals who are seronegative and likely to benefit most from additional COVID-19 interventions.

people who are moderately to severely immunocompromised, in whom an extended primary vaccine series was recommended.[7] Aligned with WHO recommendations, these populations have since been prioritised for additional booster vaccinations, and in the UK, for COVID-19 therapeutics in the community.[8] However, the groups defined are broad, and there is probably considerable variation in the risk of COVID-19 at an individual level; vaccine immunogenicity studies to date were not powered to examine this heterogeneity or how it relates to protection against disease.[9–11]

Because it is recognised that a substantial proportion of people who are immunocompromised do not generate serological responses to vaccination against SARS-CoV-2, despite multiple inoculations, assessment of serological responses in this population might enable risk stratification and facilitate personalised targeting of additional antiviral interventions.[9–13] However, mass antibody testing has not been implemented at the population level in the UK or internationally. This situation is in part due to the development of multiple antibody assays with different sensitivities, but also to the absence of a defined correlate of protection and hence clinical application.[14,15]

The availability of a rapid, point-of-care test that provides a result that correlates with the risk of severe infection or death within broadly-defined high-risk groups would redefine our approach to managing these individuals. In response to this need, we sought to evaluate whether mass antibody testing using a lateral flow immunoassay test, when coupled with self-reporting of participant factors likely to affect immune responsiveness, could establish particular risk factors for absence of antibody responses following three or more COVID-19 vaccine doses across three different groups of individuals who are immunocompromised.

Methods

Study design and data sources

Mass Evaluation of Lateral Flow Immunoassays for the Detection of SARS-CoV-2 Antibody Responses in Immunosuppressed People (MELODY) was a prospective, observational cohort study of three populations who are immunosuppressed: recipients of solid organ transplants, people with rare autoimmune rheumatic diseases, and people with lymphoid malignancies. Here we report the baseline cross-sectional data from MELODY. The study design was adapted from

the REACT2 study and was applied to a population who were immunocompromised.[16] Participants were identified and invited by accessing the comprehensive UK national disease registers: National Health Service Blood and Transplant (NHSBT) Transplant Registry for individuals in the UK who had received a solid organ transplant; and the National Disease Registration Service (NDRS) at NHS England for identifying individuals within England with rare autoimmune rheumatic diseases or lymphoid malignancies.

Participants with lymphoid malignancies and rare autoimmune rheumatic diseases were identified within the NDRS, under the National Disease Registries Directions 2021, made in accordance with sections 254(1) and 254(6) of the 2012 Health and Social Care Act. Recipients of solid organ transplants were identified by NHSBT under the Data Protection Act 2018. The Data Protection Act 2018 states that, as a government body, NHSBT can process personal data as necessary for the effective performance of a task carried out in the public interest. Ethical approval for MELODY was granted by London Central Research Ethics Committee (21/HRA/4858) on Nov 21, 2021. Confidentiality Advisory Group (ie, section 251 support) approval to process confidential patient information without consent for the purpose of sending personal invitation letters (22/CAG/0004) was granted on Dec 10, 2021. National data opt-outs, and NDRS data opt-outs were applied. This study is registered with clinicaltrials.gov, NCT05148806.

Participant recruitment and consent

The study was open to recruitment between Dec 7, 2021, and June 26, 2022. All participants had to be 18 years or older and have had at least three COVID-19 vaccine doses at the time of recruitment. Initial recruitment of recipients of solid organ transplants differed from the cohorts with rare autoimmune rheumatic diseases or lymphoid malignancies, which was a pragmatic decision made on the basis of differences in patient-identifiable data recorded by NHSBT and NDRS registries. Self-registration of UK recipients of solid organ transplants directly via the study web-portal without invitation commenced from Dec 7, 2021, with eligibility confirmed by verification of the provided NHS number (or Community Health Index number in Scotland) against the NHSBT Transplant Registry.

Between Feb 14, 2022, and June 26, 2022, invitations were sent by post to all residents in England who were registered in cancer registration datasets between 2019 and 2021 with a diagnosis of lymphoma or multiple myeloma or who had received hospital care for a probable diagnosis of a rare autoimmune rheumatic disease (small vessel vasculitis, systemic lupus erythematosus, myositis, systemic sclerosis, or giant cell arteritis) between April 1, 2019, and Aug 31, 2021. Individuals with rare autoimmune rheumatic diseases were identified by the NDRS data using algorithms applied to Hospital Episode Statistics (appendix p 1).[17] Individuals with lymphoid malignancies were registered in the National Cancer Registration Dataset in 2019 or in the Rapid Cancer Registration Dataset in 2020 or 2021 (appendix p 2).[17,18] Between March 31 and June 26, 2022, invitations were sent by post to all eligible recipients of solid organ transplants in England on the UK Transplant Registry who had not previously registered.

Following invitation, participants registered via a web portal developed by Ipsos (London, UK). Consent was given through an online form for participation in the study, subsequent data linkage, and willingness to be contacted about any future interventional research. At the time of registration, participants were asked to complete a questionnaire including information on sociodemographic variables, vaccination against SARS-CoV-2 and history of COVID-19, clinical diagnoses, and immunosuppressive treatment. Via the questionnaire, participants self-reported their gender as male, female, or another, or they could choose not to say. Following registration into the study, participants were sent a lateral flow immunoassay test with instructions and asked to read and report the result on the study web portal, uploading a photograph of the test result if possible. Participants then completed a second short online questionnaire on shielding history, psychological distress, and experience of taking the test and reading the test result to get feedback on the practicality of the test. Data on participant experience of the test and shielding history are not included in this Article. Self-reported depression and anxiety was evaluated using the 8-item Patient Health Questionnaire depression scale (PHQ-8) and 7-item Generalized Anxiety Disorder scale (GAD-7) scores, which were combined to form a composite measure of psychological distress, the Patient Health Questionnaire Anxiety and Depression Scale (PHQ-ADS).[19] A PHQ-ADS score of 20 or higher was used to indicate moderate-to-severe symptoms of depression and anxiety (ie, psychological distress).

Rapid antibody testing

The Fortress Diagnostics COVID-19 Total Antibody lateral flow immunoassay test device (Fortress Diagnostics, Belfast, UK) was used for the detection of IgM and IgG antibodies directed against the SARS-CoV-2 spike protein; the assay has a reported sensitivity of 92% and specificity of 95% in recipients of solid organ transplants.[16] Participants who tested positive for IgG only or IgG and IgM were classified as antibody positive, whereas those who tested positive for IgM only or tested negative were classified as antibody negative.

Statistical analysis

The study planned to recruit 36 000 participants (12 000 in each patient population) and of these participants, it was expected that 85% (n=30 600) would return a valid lateral flow test result. Following a third vaccine dose, we estimated that approximately one-third of patients in

See Online for appendix

each group (n=4000) would have no anti-SARS-CoV-2 antibodies, so the sample size would give a 95% CI for the proportion of patients with no antibodies of plus or minus 0·91% for each patient group.[13]

Demographic characteristics that were common across all populations (ie, number of vaccines at the time of lateral flow test, vaccine type, gender, ethnicity, anxiety, depression, previous COVID-19, age, height, weight, BMI, and comorbidities) and population-specific demographic characteristics were summarised, stratified by antibody status. Population-specific demographic characteristics for recipients of solid organ transplants were: transplant type, graft number, time from transplant, cancer, rejection (12 months before first vaccine or from first vaccine to time of study registration), and immunosuppression. For individuals with rare autoimmune rheumatic diseases, these characteristics were: diagnosis, time from diagnosis to most recent vaccine, disease activity at the time of enrolment, time from last disease flare to most recent vaccine, immunosuppression, and time (days) from most recent vaccine to the lateral flow test. For individuals with lymphoid malignancies, these characteristics were: diagnosis, time from diagnosis to most recent vaccine, immunosuppression, and time (days) from most recent vaccine to lateral flow test. Differences in characteristics by antibody status were tested univariately using the χ^2 test for categorical variables and Kruskal-Wallis test for continuous variables.

Multivariable analysis was done using a binary logistic regression model to identify which factors were independently associated with developing anti-SARS-CoV-2 spike antibodies. A manual stepwise variable selection process alongside clinical input was used to identify factors deemed to significantly reduce model deviance. Regression models were performed for each cohort separately. We conducted a complete case analysis, excluding individuals with missing variables, except for individuals with an unknown previous SARS-CoV-2 infection, because we could not assume this was missing at random. A stepwise variable selection process was used to identify factors, using a 10% significance level for inclusion and to subsequently remain in the model, and individual variables in the model should be interpreted in the presence of all other factors in the model. To further assess model validity, a logistic regression model was fitted that included all covariates for each of the cohorts separately (appendix pp 9–17). A subanalysis was done by adding psychological distress to the multivariable model to assess if this variable was also linked to antibody development. This subanalysis was not part of the main analysis due to a large proportion of missing data, which was also expected to be missing not at random. To assess the ability of the model to distinguish patients who had a positive antibody status, concordance statistics (C statistic; equal to the area under the receiver operating curve) and 95% CIs were calculated (appendix p 19). Assessment of the standardised Pearson residuals were used for model checking. Statistical analysis was conducted in R version 3.6.1.

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

A total of 98725 individuals (38802 from the NHSBT registry and 59923 from the NDRS registry) were invited

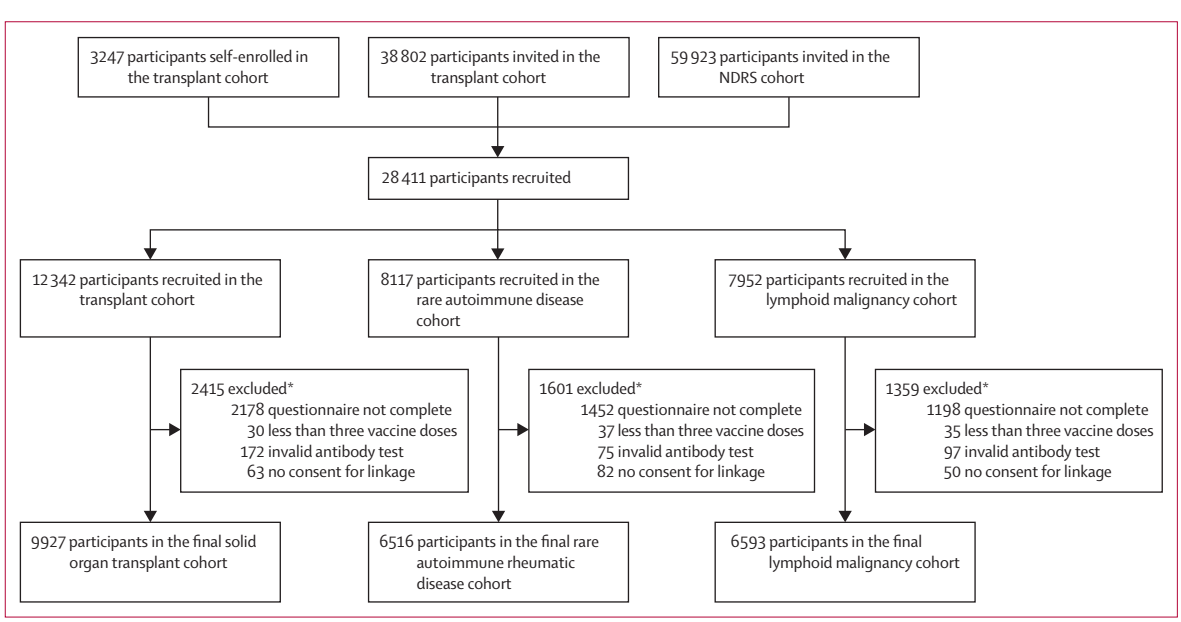

Figure 1: **Flow diagram of cohort inclusion**
NDRS=National Disease Registration Service. *Exclusions are not mutually exclusive.

	Solid organ transplant cohort				Rare autoimmune rheumatic disease cohort				Lymphoid malignancy cohort			
	Total	Antibody negative*	Antibody positive†	p value‡	Total	Antibody negative*	Antibody positive†	p value‡	Total	Antibody negative*	Antibody positive†	p value‡
Vaccine doses at time of LFIA test				<0·0001				0·062				<0·0001
Three	2700	875 (32·4%)	1825 (67·6%)		2615	378 (14·5%)	2237 (85·5%)		1268	277 (21·8%)	991 (78·2)	
Four	6046	1242 (20·5%)	4804 (79·5%)		3531	507 (14·4%)	3024 (85·6%)		4657	1006 (21·6%)	3651 (78·4)	
Five or more	1181	193 (16·3%)	988 (83·7%)		370	37 (10·0%)	333 (90·0%)		668	83 (12·4%)	585 (87·6)	
Vaccine type§				<0·0001				0·19				0·14
AZ and mRNA	5368	1293 (24·1%)	4075 (75·9%)		3316	461 (13·9%)	2855 (86·1%)		3382	700 (20·7%)	2682 (79·3%)	
mRNA and mRNA	4266	934 (21·9%)	3332 (78·1%)		2853	397 (13·9%)	2456 (86·1%)		2903	600 (20·7%)	2303 (79·3%)	
AZ and AZ	168	58 (34·5%)	110 (65·5%)		155	30 (19·4%)	125 (80·6%)		91	27 (29·7%)	64 (70·3%)	
Other	74	11 (14·9%)	63 (85·1%)		179	30 (16·8%)	149 (83·2%)		202	36 (17·8%)	166 (82·2%)	
Not reported	51	14 (27·5%)	37 (72·5%)		13	4 (30·8%)	9 (69·2%)		15	3 (20·0%)	12 (80·0%)	
Gender				0·032				<0·0001				0·24
Male	5426	1218 (22·4%)	4208 (77·6%)		1439	261 (18·1%)	1178 (81·9%)		3620	770 (21·3%)	2850 (78·7%)	
Female	4494	1091 (24·3%)	3403 (75·7%)		5070	660 (13·0%)	4410 (87·0%)		2971	596 (20·1%)	2375 (79·9%)	
Another¶	NS	NS	NS		NS	NS	NS		NS	NS	NS	
Not reported	7	1 (14·3%)	6 (85·7%)		7	1 (14·3%)	6 (85·7%)		2	0	2 (100·0%)	
Ethnicity				0·30				0·52				0·07
White	9268	2166 (23·4%)	7102 (76·6%)		5992	844 (14·1%)	5148 (85·9%)		6401	1334 (20·8%)	5067 (79·2%)	
Asian	351	68 (19·4%)	283 (80·6%)		231	33 (14·3%)	198 (85·7%)		73	8 (11·0%)	65 (89·0%)	
Black	134	35 (26·1%)	99 (73·9%)		130	24 (18·5%)	106 (81·5%)		38	4 (10·5%)	34 (89·5%)	
Other	133	31 (23·3%)	102 (76·7%)		142	18 (12·7%)	124 (87·3%)		64	15 (23·4%)	49 (76·6%)	
Not reported	41	10 (24·4%)	31 (75·6%)		21	3 (14·3%)	18 (85·7%)		17	5 (29·4%)	12 (70·6%)	
Anxiety (GAD-7)				<0·0001				0·92				0·29
None	5965	1295 (21·7%)	4670 (78·3%)		3541	482 (13·6%)	3059 (86·4%)		4521	917 (20·3%)	3604 (79·7%)	
Mild	1540	384 (24·9%)	1156 (75·1%)		1141	162 (14·2%)	979 (85·8%)		839	176 (21·0%)	663 (79·0%)	
Moderate	649	180 (27·7%)	469 (72·3%)		519	75 (14·5%)	444 (85·5%)		271	68 (25·1%)	203 (74·9%)	
Severe	551	163 (29·6%)	388 (70·4%)		429	61 (14·2%)	368 (85·8%)		197	42 (21·3%)	155 (78·7%)	
Not reported	1222	288 (23·6%)	934 (76·4%)		886	142 (16·0%)	744 (84·0%)		765	163 (21·3%)	602 (78·7%)	
Depression (PHQ-8)				<0·0001				0·045				0·80
None	5663	1221 (21·6%)	4442 (78·4%)		3010	399 (13·3%)	2611 (86·7%)		4249	868 (20·4%)	3381 (79·6%)	
Mild	1689	416 (24·6%)	1273 (75·4%)		1361	218 (16·0%)	1143 (84·0%)		1049	214 (20·4%)	835 (79·6%)	
Moderate	792	194 (24·5%)	598 (75·5%)		656	94 (14·3%)	562 (85·7%)		362	81 (22·4%)	281 (77·6%)	
Severe	603	192 (31·8%)	411 (68·2%)		562	67 (11·9%)	495 (88·1%)		223	43 (19·3%)	180 (80·7%)	
Not reported	1180	287 (24·3%)	893 (75·7%)		927	144 (15·5%)	783 (84·5%)		710	160 (22·5%)	550 (77·5%)	

(Table 1 continues on next page)

	Solid organ transplant cohort				Rare autoimmune rheumatic disease cohort				Lymphoid malignancy cohort			
	Total	Antibody negative*	Antibody positive†	p value‡	Total	Antibody negative*	Antibody positive†	p value‡	Total	Antibody negative*	Antibody positive†	p value‡
(Continued from previous page)												
Previous SARS-CoV-2 infection‖				<0·0001				<0·0001				<0·0001
Yes, confirmed by test	3113	269 (8·6%)	2844 (91·4%)		1920	179 (9·3%)	1741 (90·7%)		1692	255 (15·1%)	1437 (84·9%)	
Yes, suspected by doctor	79	17 (21·5%)	62 (78·5%)		84	6 (7·1%)	78 (92·9%)		51	5 (9·8%)	46 (90·2%)	
Yes, own suspicions	446	79 (17·7%)	367 (82·3%)		363	37 (10·2%)	326 (89·8%)		313	48 (15·3%)	265 (84·7%)	
No	5664	1795 (31·7%)	3869 (68·3%)		3652	641 (17·6%)	3011 (82·4%)		4050	979 (24·2%)	3071 (75·8%)	
Not reported	625	150 (24·0%)	475 (76·0%)		497	59 (11·9%)	438 (88·1%)		487	79 (16·2%)	408 (83·8%)	
Age				<0·0001				0·53				<0·0001
Age, years	60 (50–67)	62 (54–69)	59 (49–67)		65 (54–73)	64 (54–73)	65 (54–73)		69 (61–75)	70 (62–76)	69 (61–75)	
Not reported	15	2 (13·3%)	13 (86·7%)		19	5 (26·3%)	14 (73·7%)		18	4 (22·2%)	14 (77·8%)	
Height				0·0007				0·0052				0·24
Height, cm	170 (163–178)	170 (163–178)	170 (163–178)		165 (160–170)	165 (160–173)	165 (160–173)		170 (163–178)	173 (163–178)	170 (163–178)	
Not reported	56	10 (17·9%)	46 (82·1%)		29	4 (13·8%)	25 (86·2%)		24	6 (25·0%)	18 (75·0%)	
Weight				<0·0001				0·035				0·0066
Weight, kg	77 (66–89)	75 (65–88)	78 (66–89)		72 (62–86)	74 (63–86)	72 (61–85)		77 (67–88)	76 (66–87)	77 (67–89)	
Not reported	207	44 (21·3%)	163 (78·7%)		200	26 (13·0%)	174 (87·0%)		121	25 (20·7%)	96 (79·3%)	
BMI				0·0020				0·47				0·0002
BMI, kg/m²	26 (23–30)	26 (23 -30)	26 (23 -30)		26 (23–31)	26 (23–30)	26 (23–31)		26 (23–29)	26 (23–29)	26 (24–29)	
Not reported	245	52 (21·2%)	193 (78·8%)		213	29 (13·6%)	184 (86·4%)		139	30 (21·6%)	109 (78·4%)	
Comorbidities				0·0024				0·68				0·37
Number of comorbidities	1 (0–2)	1 (0–2)	1 (0–2)		1 (0–2)	1 (0–2)	1 (0–2)		1 (0–1)	1 (0–1)	1 (0–1)	
Not reported	0	0	0		0	0	0		0	0	0	
Total	9927	2310 (23·3%)	7617 (76·7%)		6516	922 (14·1%)	5594 (85·9%)		6593	1366 (20·7%)	5227 (79·3%)	

Data are n (%) or median (IQR). AZ=ChAdOx1 nCoV-19 vaccine. GAD-7=7-item Generalized Anxiety Disorder scale. mRNA=BNT162b2 or mRNA-1723 vaccines. NS=not stated. PHQ-8=8-item Patient Health Questionnaire depression scale. *Negative or IgM only. †IgG only or IgG and IgM. ‡p values relate to the difference between antibody-negative and antibody-positive participants for the categories as a whole. §Represented by first two doses and third primary dose type. ¶Because <10 participants in each cohort selected this option, they have been grouped together with participants who did not report gender. ‖Up until time of enrolment.

Table 1: **Demographic characteristics by antibody status**

to participate, and 3247 recipients of solid organ transplants self-enrolled into the study. In total, 28 411 participants were recruited into the study. The response rate to invitations was 23·4% (9095 of 38 802) from the NHSBT registry (after 3247 had self-enrolled and were therefore not re-invited) and 26·8% (16 069 of 59 923) from the NDRS registry. Of the 28 411 recruited participants, 23 036 (81·1%) returned a valid lateral flow immunoassay test result and formed the analysed cohort (9927 participants with solid organ transplants, 6516 with rare autoimmune rheumatic diseases, and 6593 with lymphoid malignancies; figure 1). Of these 23 036 in the analysed cohorts, 10 485 (45·5%) were men, 12 535 (54·4%) were women, and 16 (<0·1%) were of another gender or did not report gender; these categories were grouped together. Details of how the analysed cohorts compare with the invited populations are in the appendix (pp 6–7).

The demographic and vaccine data for each group are shown in table 1. Of 23 036 participants with serological data, 6583 (28·6%), had received three vaccine doses at the time of testing, 14 234 (61·8%) had received four vaccine doses at the time of testing, and 2219 (9·6%) had received at least five vaccine doses at the time of testing. Confirmed previous SARS-CoV-2 infection was reported in 3113 (31·4%) of 9927 recipients of solid organ transplants, 1920 (29·5%) of 6516 participants with rare autoimmune rheumatic diseases, and 1692 (25·7%) of 6593 participants with lymphoid malignancies. Home-based lateral flow immunoassay testing identified a positive antibody response in 7617 (76·7%) recipients of solid organ transplants, 5594 (85·9%) participants with rare autoimmune rheumatic diseases, and 5227 (79·3%) participants with lymphoid malignancies (table 1; appendix p 8).

Most participants (8696 [87·6%] of 9927) in the solid organ transplant cohort had received one previous transplant. 6591 (66·4%) participants received a kidney only transplant, 1981 (20·0%) received a liver only transplant, and 596 (6·0%) received a heart only transplant. For 9419 (94·9%) of 9927 participants, at least 1 year had passed since the transplant at the time of the latest vaccine dose (table 2). Regarding immuno-suppression, 6121 (61·7%) of 9927 participants were prescribed both an antiproliferative agent and a calcineurin inhibitor, and 4876 (49·1%) were receiving steroids as part of their treatment regimen. Rejection episodes had occurred in 199 (2·0%) participants (table 2).

Of the 9927 participants in the solid organ transplant cohort, 9233 (93·0%) were included in the logistic regression analysis; 694 were excluded owing to missing data (figure 2A; appendix pp 9–11). Older age (odds ratio [OR] 0·70 [95% CI 0·66–0·73] for each 10-year increase) was associated with a negative antibody response, whereas number of vaccine doses received (five *vs* three, 2·76 [2·28–3·35]) and previous self-reported SARS-CoV-2 infection (4·16 [3·65–4·75]) were associated with a positive antibody response (appendix p 9). Recipients of liver transplants were most likely to develop antibodies (1·27 [1·09–1·49]), and recipients of lung transplants

	Total	Antibody negative*	Antibody positive†	p value‡
Transplant type				<0·0001
Kidney only	6591	1601 (24·3%)	4990 (75·7%)	..
Liver only	1981	327 (16·5%)	1654 (83·5%)	..
Simultaneous pancreas and kidney, pancreas, islet, or simultaneous islet and kidney	350	88 (25·1%)	262 (74·9%)	..
Heart only	596	153 (25·7%)	443 (74·3%)	..
Lung (including heart-lung)	333	118 (35·4%)	215 (64·6%)	..
Other	76	23 (30·3%)	53 (69·7%)	..
Graft number				0·021
First graft	8696	1991 (22·9%)	6705 (77·1%)	..
Regraft	1231	319 (25·9%)	912 (74·1%)	..
Cancer diagnosis since transplant				0·74
No	8599	2001 (23·3%)	6598 (76·7%)	..
Yes	1276	291 (22·8%)	985 (77·2%)	..
Not reported	52	18 (34·6%)	34 (65·4%)	..
Rejection				<0·0001
No	9648	2220 (23·0%)	7428 (77·0%)	..
Yes, before first vaccine dose	88	17 (19·3%)	71 (80·7%)	..
Yes, after vaccine	86	39 (45·3%)	47 (54·7%)	..
Yes, before and after vaccine	25	9 (36·0%)	16 (64·0%)	..
Not reported	80	25 (31·3%)	55 (68·8%)	..
Immunosuppression				<0·0001
Belatacept based only	1	0	1 (100·0%)	..
Antiproliferative and calcineurin inhibitor only	3274	740 (22·6%)	2534 (77·4%)	..
Antiproliferative only	199	32 (16·1%)	167 (83·9%)	..
Calcineurin inhibitor only	1467	191 (13·0%)	1276 (87·0%)	..
Other only	92	9 (9·8%)	83 (90·2%)	..
Belatacept-based and steroid	10	5 (50·0%)	5 (50·0%)	..
Antiproliferative, calcineurin inhibitor, and steroid	2847	891 (31·3%)	1956 (68·7%)	..
Antiproliferative and steroid only	434	98 (22·6%)	336 (77·4%)	..
Calcineurin inhibitor and steroid only	1434	318 (22·2%)	1116 (77·8%)	..
Other and steroid	151	25 (16·6%)	126 (83·4%)	..
None	18	1 (5·6%)	17 (94·4%)	..
Time from transplant to most recent vaccine				0·84
Vaccine before transplant	21	6 (28·6%)	15 (71·4%)	..
0–89 days after transplant	52	14 (26·9%)	38 (73·1%)	..
90–364 days after transplant	435	104 (23·9%)	331 (76·1%)	..
≥1 year after transplant	9419	2186 (23·2%)	7233 (76·8%)	..
Days from most recent vaccine to test	9927	88 (60–126)	89 (56–127)	0·83
Total	9927	2310 (23·3%)	7617 (76·7%)	

Data are n (%) or median (IQR). *Negative or IgM only. †IgG only or IgG and IgM. ‡p values relate to the difference between antibody-negative and antibody-positive participants for the categories as a whole.

Table 2: **Demographic characteristics of recipients of solid organ transplants who had three or more vaccines by antibody status**

were least likely to develop antibodies (0·59 [0·46–0·77]), when compared with recipients of a kidney transplant. The number of prescribed immunosuppressants (rather than the particular agents) correlated with antibody response. Compared with patients receiving dual antiproliferative and calcineurin inhibitor therapy, the odds of detectable antibodies were lower in patients on triple immunosuppression (0·61 [0·53–0·70]), but higher in patients receiving either antiproliferative (1·71 [1·11–2·64]) or calcineurin inhibitor monotherapy (2·02 [1·66–2·45]). A documented rejection episode (0·51 [0·36–0·71]) and receipt of a ChAdOx1 nCoV-19 vaccine (0·86 [0·78–0·96]) were also associated with absent antibody responses.

Of the 6516 participants in the rare autoimmune rheumatic disease cohort, 2412 (37·0%) had systemic lupus erythematosus, 1364 (20·9%) had small vessel vasculitis, 869 (13·3%) had systemic sclerosis, 574 (8·8%) had large vessel vasculitis, and 440 (6·8%) had myositis. 3863 (57·8%) of 5277 participants with available data had longstanding disease, diagnosed at least 5 years before recruitment (table 3). Most participants (4136 [77·6%] of 5330) reported mild or moderate disease activity, whereas 287 (5·4%) participants reported severe disease activity at recruitment. 1960 (50·1%) of 3909 participants with available data had experienced a disease flare up before, or up to 1 year after, their most recent vaccine dose. Most participants (4231 [71·2%] of 5945) were currently receiving immunosuppressive medication and 2479 (41·7%) of 5945 participants were receiving steroids (table 3).

Of the 6516 participants in the rare autoimmune rheumatic disease cohort, 4866 (74·7%) were included in

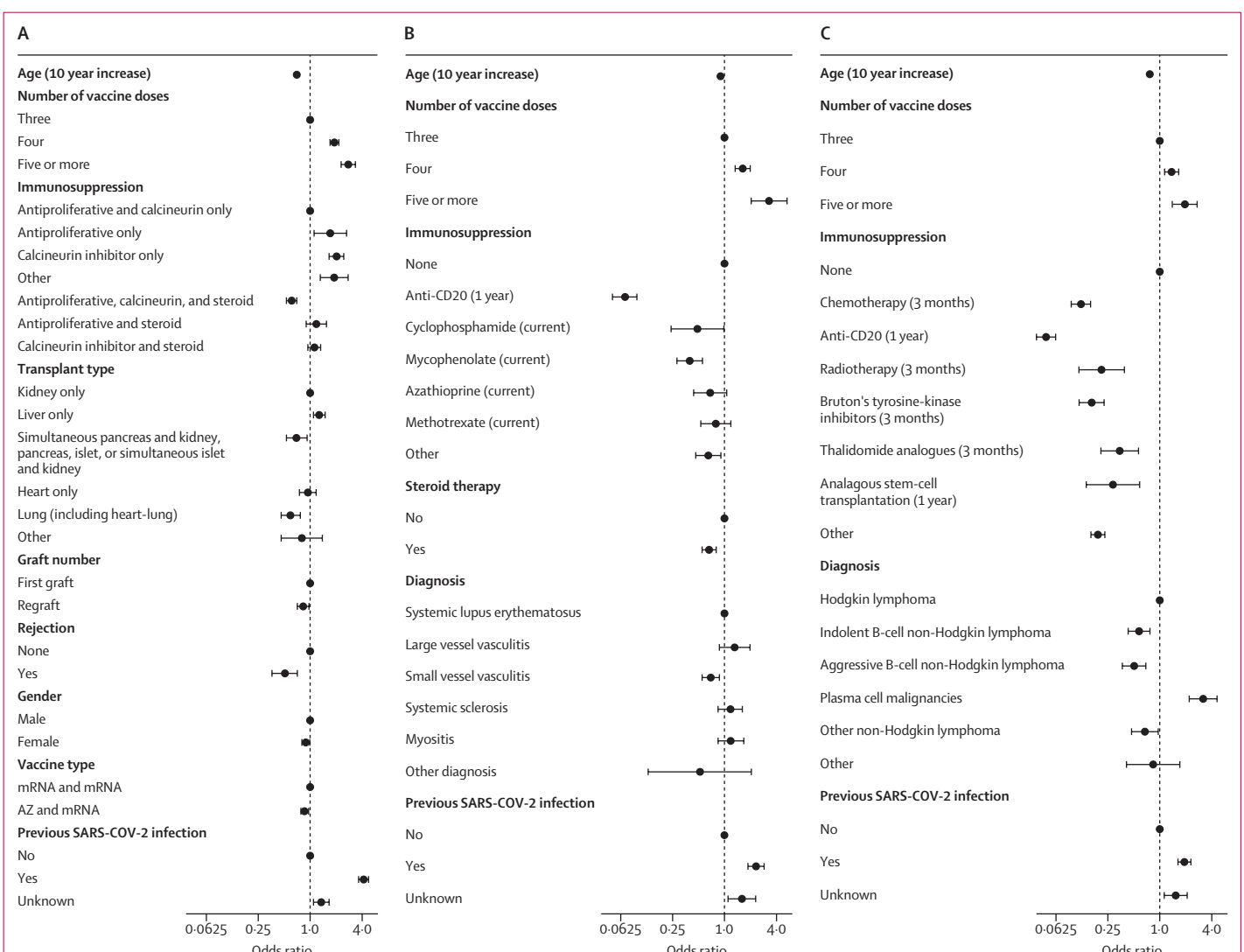

Figure 2: **Logistic regression analysis for antibody positivity across three cohorts of people who are immunocompromised**
(A) Solid organ transplant cohort (appendix p 9). (B) Rare autoimmune rheumatic disease cohort (appendix p 12). (C) Lymphoid malignancy cohort (appendix p 15). Error bars represent 95% CIs. AZ=ChAdOx1 nCoV-19 vaccine. mRNA=BNT162b2 or mRNA-1723 vaccine.

the logistic regression analysis (figure 2B; appendix pp 12–14). After adjustment, older age was associated with a negative antibody response (OR 0·90 [95% CI 0·83–0·97] for every 10-year increase), whereas increasing number of vaccine doses (five vs three, 3·28 [2·03–5·30]) and previous SARS-CoV-2 infection (2·32 [1·87–2·87]) were associated with a positive antibody response, in keeping with findings in the solid organ transplant cohort. Among disease subtypes, participants with small vessel disease were least likely to have a positive antibody response (OR 0·69 [0·55–0·87]), independent of all other factors. Current receipt of any immunosuppression (including hydroxycholoroquine only) except cyclophosphamide or anti-CD20 therapies, or receipt of cyclophosphamide or anti-CD20 therapies within the past 1 year, was associated with a reduced odds of positive antibody response compared with no immunosuppression, but to a variable extent. Receipt of anti-CD20 therapies within the previous year had greatest effect on reduced odds of a positive antibody response (OR 0·07 [0·05–0·10]); reduced odds of a positive antibody response were also associated with cyclophosphamide within the previous year (0·49 [0·24–0·98]) and current mycophenolate (0·39 [0·28–0·55])). Current azathioprine or methotrexate did not have a significant effect on odds of a positive antibody response; however, the category including all other biological and conventional immunosuppressants was associated with modestly reduced odds (appendix pp 12–14). Current steroid treatment was also associated with reduced odds of positive antibody response (0·66 [0·55–0·80]), irrespective of other immunosuppression.

6201 (94·1%) of the 6593 participants in the lymphoid malignancy cohort reported a diagnosis; 2706 (43·6%) of 6201 had indolent B-cell non-Hodgkin lymphoma, 1327 (21·4%) had plasma cell malignancies, 1017 (16·4%) had aggressive B-cell non-Hodgkin lymphoma, and 499 (8·0%) had Hodgkin lymphoma (table 4). Most participants (5438 [88·5%] of 6144) were diagnosed within 3 years of their latest vaccine dose. Active anticancer treatment was received (in the previous 3 or 12 months, depending on treatment) by 2912 (47·0%) of 6200 participants, and 3288 (53·0%) participants received no treatment.

Of the 6593 participants in the lymphoid malignancy cohort, 5737 (87·0%) were included in the logistic regression analysis (figure 2C; appendix pp 15–17). Similar to the solid organ transplant and rare autoimmune rheumatic disease cohorts, older age was associated with a negative antibody response (OR 0·76 [0·71–0·82] for every 10-year increase), whereas a positive antibody response was associated with previous SARS-CoV-2 infection (1·93 [1·63–2·29]) and vaccine dose (five *vs* three, 1·96 [1·42–2·71]). Participants with aggressive or indolent B-cell non-Hodgkin lymphoma were less likely to have a positive response compared with participants with Hodgkin lymphoma

	Total	Antibody negative*	Antibody positive†	p value‡
Diagnosis				<0·0001
Small vessel vasculitis	1364	370 (27·1%)	994 (72·9%)	
Large vessel vasculitis	574	43 (7·5%)	531 (92·5%)	
Systemic lupus erythematosus	2412	263 (10·9%)	2149 (89·1%)	
Systemic sclerosis	869	84 (9·7%)	785 (90·3%)	
Myositis	440	70 (15·9%)	370 (84·1%)	
Other	117	15 (12·8%)	102 (87·2%)	
None	740	77 (10·4%)	663 (89·6%)	
Time from diagnosis to most recent vaccine				0·0043
0–5 years	1414	234 (16·5%)	1180 (83·5%)	
5–10 years	1228	190 (15·5%)	1038 (84·5%)	
>10 years	2635	341 (12·9%)	2294 (87·1%)	
Not reported	1239	157 (12·7%)	1082 (87·3%)	
Disease activity				0·12
None	907	128 (14·1%)	779 (85·9%)	
Mild	2214	293 (13·2%)	1921 (86·8%)	
Moderate	1922	302 (15·7%)	1620 (84·3%)	
Severe	287	46 (16·0%)	241 (84·0%)	
Not reported	1186	153 (12·9%)	1033 (87·1%)	
Time from flare-up to most recent vaccine				0·0004
Vaccine before flare-up	822	114 (13·9%)	708 (86·1%)	
0–1 years	1138	172 (15·1%)	966 (84·9%)	
1–3 years	873	167 (19·1%)	706 (80·9%)	
>3 years	1076	134 (12·5%)	942 (87·5%)	
Not reported	2607	335 (12·9%)	2272 (87·1%)	
Immunosuppression				<0·0001
Anti-CD20 (1 year)	810	404 (49·9%)	406 (50·1%)	
Cyclophosphamide (1 year)	104	14 (13·5%)	90 (86·5%)	
Mycophenolate (current)	927	119 (12·8%)	808 (87·2%)	
Azathioprine (current)	520	46 (8·8%)	474 (91·2%)	
Methotrexate (current)	710	54 (7·6%)	656 (92·4%)	
Other	1160	122 (10·5%)	1038 (89·5%)	
None§	1714	107 (6·2%)	1607 (93·8%)	
Not reported	571	56 (9·8%)	515 (90·2%)	
Steroid therapy				<0·0001
Yes	2479	453 (18·3%)	2026 (81·7%)	
No	3466	413 (11·9%)	3053 (88·1%)	
Not reported	571	56 (9·8%)	515 (90·2%)	
Days from latest vaccine to test	6503	99·5 (50–154)	108 (57–159)	0·0044
Not reported	13	4 (30·8%)	9 (69·2%)	
Total	6516	922 (14·1%)	5594 (85·9%)	

Data are n (%) or median (IQR). *Negative or IgM only. †IgG only or IgG and IgM. ‡p values relate to the difference between antibody-negative and antibody-positive participants for the categories as a whole. §Includes hydroxychloroquine.

Table 3: **Demographic characteristics of participants with rare autoimmune rheumatic diseases who had three or more vaccines by antibody status**

	Total	Antibody negative*	Antibody positive†	p value‡
Diagnosis				<0·0001
Aggressive B-cell non-Hodgkin lymphoma	1017	259 (25·5%)	758 (74·5%)	
Indolent B-cell non-Hodgkin lymphoma	2706	711 (26·3%)	1995 (73·7%)	
Plasma cell malignancies	1327	107 (8·1%)	1220 (91·9%)	
Hodgkin lymphoma	499	86 (17·2%)	413 (82·8%)	
Other non-Hodgkin lymphoma	569	132 (23·2%)	437 (76·8%)	
Other	83	13 (15·7%)	70 (84·3%)	
Not reported	392	58 (14·8%)	334 (85·2%)	
Time from diagnosis to most recent vaccine				
<1 year including before diagnosis	1229	382 (31·1%)	847 (68·9%)	
1–3 years	4209	783 (18·6%)	3426 (81·4%)	
>3 years	706	129 (18·3%)	577 (81·7%)	
Not reported	449	72 (16·0%)	377 (84·0%)	
Immunosuppression				<0·0001
Radiotherapy (in the previous 3 months)	53	18 (34·0%)	35 (66·0%)	
Chemotherapy (in the previous 3 months)	537	180 (33·5%)	357 (66·5%)	
Anti-CD20 (in the previous 12 months)	387	270 (69·8%)	117 (30·2%)	
Bruton's tyrosine kinase inhibitors (in the previous 3 months)	190	84 (44·2%)	106 (55·8%)	
Thalidomide analogues§ (in the previous 3 months)	392	26 (6·6%)	366 (93·4%)	
Autologous stem-cell transplantation (in the previous 12 months)	100	12 (12·0%)	88 (88·0%)	
Other	1253	376 (30·0%)	877 (70·0%)	
None	3288	341 (10·4%)	2947 (89·6%)	
Not reported	393	59 (15·0%)	334 (85·0%)	
Steroid therapy				0·0026
Yes	209	62 (29·7%)	147 (70·3%)	
No	5994	1246 (20·8%)	4748 (79·2%)	
Not reported	390	58 (14·9%)	332 (85·1%)	
Days from latest vaccine to test	6578	75 (42–130)	83 (43–131)	0·20
Not reported	15	3 (20·0%)	12 (80·0%)	
Total	6593	1366 (20·7%)	5227 (79·3%)	

Data are n (%) or median (IQR). *Negative or IgM only. †IgG only or IgG and IgM. ‡p values relate to the difference between antibody-negative and antibody-positive participants for the categories as a whole. §Thalidomide, lenalidomide, or pomalidomide.

Table 4: **Demographic characteristics of participants with lymphoid malignancies who had three or more vaccines by antibody status**

(0·50 [0·37–0·69] and 0·58 [0·43–0·77], respectively). By contrast, participants with plasma cell malignancies had an increased likelihood of a positive antibody response compared with participants with Hodgkin lymphoma (OR 3·19 [2·20–4·62]). Among the anticancer treatments, participants treated with anti-CD20 therapies in the previous 3 months were least likely to have a positive antibody response (0·05 [0·04–0·06]), followed by participants treated with chemotherapy (0·12 [0·09–0·16]), with Bruton's tyrosine-kinase inhibitors (0·16 [0·12–0·23]), with radiotherapy (0·21 [0·12–0·39]), with autologous stem-cell transplantation (0·29 [0·14–0·58]), and with thalidomide analogues (0·34 [0·21–0·57]).

In a subanalysis, we also assessed the influence of psychological distress on antibody response in each cohort (appendix pp 18–19). Moderate-to-severe psychological distress was present in 951 (12·4%) of 7666 participants in the solid organ transplant cohort who completed the PHQ-ADS, 664 (16·9%) of 3934 participants in the rare autoimmune rheumatic disease cohort who completed the PHQ-ADS, and 356 (7·4%) of 4822 participants in the lymphoid malignancy cohort who completed the PHQ-ADS. In the solid organ transplant cohort, after adjustment for other significant variables, participants who reported moderate-to-severe psychological distress had significantly reduced odds of a positive antibody response compared with participants who reported no distress (0·64 [0·54–0·76]; appendix p 19). Non-response to the PHQ-ADS was also associated with reduced odds of a positive antibody response (0·86 [0·74–0·99]). In a separate unadjusted analysis (post-hoc), a self-reported history of depression was associated with negative antibody responses in the solid organ transplant cohort, but no associations with other mental health conditions were observed (appendix p 18).

Conversely, in the rare autoimmune rheumatic disease cohort, psychological distress was not associated with antibody status, yet similarly to the solid organ transplant cohort, participants in the rare autoimmune rheumatic disease cohort who did not respond to the PHQ-ADS were more likely to have negative antibody responses than the group who reported no distress after adjustment for other outcomes. In the lymphoid malignancy cohort, no association was found between psychological distress and antibody status (appendix p 19).

Discussion

MELODY has identified the demographic, clinical, and therapeutic characteristics associated with the absence of detectable SARS-CoV-2 antibodies following three or more doses of COVID-19 vaccine in more than 23 000 people across three distinct populations of individuals who are immunosuppressed. We showed that it is possible to find, identify, invite, and test cohorts of people who are immunosuppressed. Our key findings were that a higher number of vaccine doses, previous SARS-CoV-2 infection, and younger age were associated with increased odds of detectable anti-SARS-CoV-2 spike IgG antibodies in all cohorts. Our large study size has enabled estimation of the odds of detectable anti-SARS-CoV-2 spike IgG antibodies in more specific cohorts of people who are immunocompromised compared with those reported previously, thereby enabling stratification by disease and treatment type. Risk stratification has three main implications for public health strategies: groups that have a higher risk of absent anti-SARS-CoV-2 IgG antibodies could be offered antibody testing; groups

with undetectable serological responses could be offered specific interventions (eg, further vaccine doses or pre-exposure prophylaxis); and future immunotherapies recommended for each underlying disease could be modified in view of different levels of risk of impaired vaccine-induced immunity. The data also reinforce the prudence of ongoing personal protective measures and vaccination of those in close contact of people who are immunocompromised.

Our results are consistent with previous subgroup-specific immunogenicity studies that incorporated more sensitive serological assays than used in our study, thereby supporting the rationale of our approach.[9–12] However, we also reported shared characteristics associated with antibody status across all three cohorts. As the public develops increasing vaccine fatigue,[20] our data—which show that more vaccine doses are associated with higher rates of seropositivity in people who are immunocompromised—will be crucial for promoting future vaccine boosting. Our findings also present potential options for developing bespoke booster vaccination schedules for this population. In addition to shared characteristics, we were also able to report on differences between cohorts; for example, we found reduced responses following vaccination with combinations that included adenovector viral vaccines (ie, the ChAdOx1 nCoV-19 vaccine; compared with mRNA vaccines) in the solid organ transplant cohort only. We hypothesise that this finding could reflect the dominance of T-cell directed immunosuppression therapy in recipients of solid organ transplants, which could block crucial T-cell help for antibody production by impairing the robust cellular responses elicited by adenovector viral vaccines.[21,22]

Cohort-specific observations consistent with previous studies include the importance of immunosuppression burden in determining odds of seroconversion in recipients of solid organ transplants, with patients receiving triple immunosuppression at highest risk of remaining seronegative following vaccination.[10,13,23,24] For people with rare autoimmune rheumatic diseases, it is accepted that patients receiving anti-CD20 therapy are less likely to have detectable anti-SARS-CoV-2 IgG antibodies post-vaccination compared with patients receiving non-CD20-targeted medications.[9,12] Whereas for people with haematological malignancies, systemic anticancer therapy is recognised to be the biggest predictor of the humoral response to vaccination.[11] In particular, B-cell-targeted treatments such as anti-CD20 and Bruton's tyrosine-kinase inhibitors have been strongly associated with negative seroprevalence.[11] However, all these observations have been largely derived from relatively small, heterogeneous datasets. The MELODY study differs in its ability to estimate the adjusted odds of seroconversion associated with each disease, and each type of immunosuppression, which might influence immunotherapy decisions when potential treatment benefit is equal.

MELODY has also been able to assess the prevalence of psychological distress, defined as a composite score of anxiety and depression (ie, PHQ-ADS), in cohorts who are immunosuppressed. The reported prevalence of psychological distress in the general population has varied during the different phases of the pandemic, with direct comparisons hampered by methodological differences in assessment.[25] From the MELODY participants who completed the PHQ-ADS, moderate-to-severe psychological distress was found in 7·4–16·9% of participants across the cohorts. However, the proportion of non-respondents was high, which probably attenuated this estimate. Because antibody results were known to the participants when they completed their questionnaires, it is not known whether, or how, this knowledge might have affected the psychological scoring. There are recognised mechanisms whereby psychological status might affect adaptive immune responses, although this has not been studied in the setting of co-existing immunotherapy.[26,27] Furthermore, it is possible that some of this observed effect is attributable to unmeasured confounding, including the effect of multimorbidity and cumulative disease burden. However, irrespective of causation, assessment of distress is important because observational data has shown an association between neuropsychiatric diagnoses and poorer COVID-19 outcomes.[28] Our data suggest there remains a substantial prevalence of psychological distress in the immunocompromised population, which warrants recognition and consideration.

MELODY has recognisable limitations. First, participation required self-engagement among the community, and although the methodology offered broad and targeted reach to vulnerable populations with rare conditions, this does not necessarily overcome recognised barriers to research recruitment, such as the engagement and participation of people from minority ethnic backgrounds.[29] Although the number of participants included in our study was large enough to provide meaningful multi-ethnicity data, the relative predominance of White participants is noticeable across all cohorts. Second, we used a non-quantitative test that does not distinguish between absent and very low anti-SARS-CoV-2 IgG antibody concentrations, and our study does not assess antigen-specific T-cell responses.[30] However, our aim was not to undertake a detailed immune response analysis, but rather to address whether mass antibody testing can discriminate the risk of severe COVID-19 in individuals who are immunocompromised. Furthermore, although we used one immunoassay, any approved assay testing for the presence of anti-SARS-CoV-2 IgG could be used. We also acknowledge that we did not assess all groups of people who are immunocompromised as defined by the WHO (eg, people living with HIV), and other groups will need further consideration.[7] Third, the covariates we selected for the analysis were based on data captured

via the research questionnaire that were determined to be clinically appropriate. We did not plot a causal directed acrylic graph due to the numerous possible variables. We therefore cannot exclude the possibility that our results are affected by measurement bias, residual confounding, or unmeasured confounders. Finally, although substantial barriers have been overcome to deliver MELODY, data processing approvals have meant that a single intracohort comparison analysis was not possible, even though similar methodology and analysis has been applied to the different cohorts. MELODY shows a novel approach to recruiting and involving patients in rare disease research without using COVID-19-specific legislation, and its strengths include the large numbers of participants, and its ability to assess heterogeneity within broadly defined immunocompromised groups.

Although it is reassuring that the absolute risk of severe COVID-19 has reduced for patients who are immunocompromised over the course of the pandemic, a substantial relative risk compared with the general population remains.[2] There is a paucity of evidence for the optimal scheduling of booster doses for this population, and continued monitoring of the MELODY cohort might help inform this. Furthermore, the methodology used in MELODY could be applied to future emerging pathogens that might disproportionally affect individuals who are immunocompromised individuals, enabling assessment of immune responses and protection afforded by vaccination.

To conclude, the MELODY study has shown that individuals who are immunocompromised can be identified and reached via national disease registration services and the linkage of unique data sets. We plan to assess how the results of the home-based lateral flow antibody tests relate to disease prevention by analysing SARS-CoV-2–related infection, admission to hospital, and death rates in the cohorts with immunosuppression included in our study. In this report, we corroborated risk factors associated with seronegativity in immunogenicity studies in distinct sub-cohorts of individuals who are immunocompromised, and describe commonality across cohorts. Given the influence of confounding characteristics, we show serological testing of populations who are immunosuppressed could provide personalised risk stratification not achieved by clinical characteristics alone. We also provide insight into how this stratification might be achieved in the community, and how sero-testing this population could identify those individuals who might maximally benefit from pre-exposure prophylaxis.[31] Furthermore, our data also support the continued uptake of boosters in patients who are immunosuppressed, with seroconversion rates increasing with sequential vaccine doses. As a key challenge is to improve the vaccine-induced immunity of individuals who are immunosuppressed, our data might also provide insight into further bespoke booster schedules for this population, which could be guided by community antibody surveillance.

Contributors

All authors contributed to the design, execution, and delivery of this cross specialty, collaborative study. LL, SPM, FAP, and MW conceptualised the study. GSC, LL, PL, SHL, SPM, FAP, GJP, HT, HW, and MW acquired funding. GP contributed to project administration. MB, GSC, LL, PL, SHL, SPMc, FAP, GJP, HT, HW, and MW created the methodology. MB, JC, RH, SHL, LM, FAP, and AT contributed to data curation, cleaning, and analysis. FAP, AT, LM, and RH accessed and verified the underlying data. SHL, GJP, FAP, and MW wrote original draft. Review and editing (MB, GSC, JC, RH, LL, PL, SHL, SPMc, FAP, GJP, AT, HT, HW, and MW reviewed and edited the final manuscript. All authors have seen and approved the final text and gave final approval of the version to be published.

Declaration of interests

FAP and PL are recipients of an investigator-led grant from Vifor pharma. FAP is a member of the Strategy and Integration Group at Health Data Research UK. PL has received consultation fees from Pfizer, and is the Rare Diseases Clinical Lead in NHS England, and co-chair of the Rare Autoimmune Rheumatic Disease Alliance. LL has received consultancy fees or honoraria from Alexion, AstraZeneca, BMS, Biogen, GSK, Kezar, Novartis, and Pfizer. MW and GP have received honoraria from AstraZeneca. SPMc has received independent study support from TheriniBio, GSK, PanAngium Therapeutics, Vifor, Celltrion, and Hansa Pharmaceuticals. SHL is a Blood Cancer UK Vaccine Task Force member and has received honoraria from AstraZeneca. GSC is a non-executive director of the UK Medicines and Healthcare products Regulatory Agency. There was no influence related to these declarations on the design, conduct or interpretation of this study. All other authors declare no competing interests.

Data sharing

The data used in this study are sensitive and will not be made publicly available.

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