Ethnic differences in cellular and humoral immune responses to SARS-CoV-2 vaccination in UK healthcare workers: a cross-sectional analysis

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Summary

Background Few studies have compared SARS-CoV-2 vaccine immunogenicity by ethnic group. We sought to establish whether cellular and humoral immune responses to SARS-CoV-2 vaccination differ according to ethnicity in UK Healthcare workers (HCWs).

Methods In this cross-sectional analysis, we used baseline data from two immunological cohort studies conducted in HCWs in Leicester, UK. Blood samples were collected between March 3, and September 16, 2021. We excluded HCW who had not received two doses of SARS-CoV-2 vaccine at the time of sampling and those who had serological evidence of previous SARS-CoV-2 infection. Outcome measures were SARS-CoV-2 spike-specific total antibody titre, neutralising antibody titre and ELISpot count. We compared our outcome measures by ethnic group using univariable (*t* tests and rank-sum tests depending on distribution) and multivariable (linear regression for antibody titres and negative binomial regression for ELISpot counts) tests. Multivariable analyses were adjusted for age, sex, vaccine type, length of interval between vaccine doses and time between vaccine administration and sample collection and expressed as adjusted geometric mean ratios (aGMRs) or adjusted incidence rate ratios (aIRRs). To assess differences in the early immune response to vaccination we also conducted analyses in a subcohort who provided samples between 14 and 50 days after their second dose of vaccine.

Findings The total number of HCWs in each analysis were 401 for anti-spike antibody titres, 345 for neutralising antibody titres and 191 for ELISpot. Overall, 25.4% (19.7% South Asian and 5.7% Black/Mixed/Other) were from ethnic minority groups. In analyses including the whole cohort, neutralising antibody titres were higher in South Asian HCWs than White HCWs (aGMR 1.47, 95% CI [1.06–2.06], P = 0.02) as were T cell responses to SARS-CoV-2 S1 peptides (aIRR 1.75, 95% CI [1.05–2.89], P = 0.03). In a subcohort sampled between 14 and 50 days after second vaccine dose, SARS-CoV-2 spike-specific antibody and neutralising antibody geometric mean

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titre (GMT) was higher in South Asian HCWs compared to White HCWs (9616 binding antibody units (BAU)/ml, 95% CI [7178–12,852] vs 5888 BAU/ml [5023–6902], P = 0.008 and 2851 95% CI [1811–4487] vs 1199 [984–1462], P < 0.001 respectively), increments which persisted after adjustment (aGMR 1.26, 95% CI [1.01–1.58], P = 0.04 and aGMR 2.01, 95% CI [1.34–3.01], P = 0.001). SARS-CoV-2 ELISpot responses to S1 and whole spike peptides (S1 + S2 response) were higher in HCWs from South Asian ethnic groups than those from White groups (S1: aIRR 2.33, 95% CI [1.09–4.94], P = 0.03; spike: aIRR, 2.04, 95% CI [1.02–4.08]).

Interpretation This study provides evidence that, in an infection naïve cohort, humoral and cellular immune responses to SARS-CoV-2 vaccination are stronger in South Asian HCWs than White HCWs. These differences are most clearly seen in the early period following vaccination. Further research is required to understand the underlying mechanisms, whether differences persist with further exposure to vaccine or virus, and the potential impact on vaccine effectiveness.

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Keywords: SARS-CoV-2; COVID-19; Vaccine; Ethnicity; Heathcare worker

Research in context

Evidence before this study

We searched PubMed on 4th January 2023 using the following search terms ((((ethnicity) OR (race)) AND ((immune response) OR (antibody))) AND (Vaccine)) AND ((COVID-19) OR (SARS-CoV-2)). The search returned 87 articles. 76 were excluded after abstract screening either because they did not use quantitative immune responses as the outcome, did not assess immune responses to vaccination or they did not stratify results by ethnicity. Of the remaining 11 articles, 6 studies were conducted in populations defined by a particular comorbidity or treatment. 4 of these 6 studies found higher anti-spike antibody titres after vaccination in ethnic minority participants compared to White with 2 studies finding no differences by ethnicity. 4 of the 5 remaining studies were conducted in healthcare worker (HCW) population: 2 Israeli studies demonstrated no difference in antibody titres after vaccination by ethnicity; a small US study found higher antibody responses in 'non-Caucasian' than Caucasian HCW; a UK study found that Black HCWs had lower antibody responses to vaccination than White and found no difference between White and Asian groups. Finally, an observational study in the UK general population found that post-vaccination antibody titres were 16.2% higher in South Asian than White groups. No studies presented data on antibody titres, serum neutralising activity and cellular immune responses.

Added value of this study

The evidence base on SARS-CoV-2 vaccine responses by ethnicity is both limited and conflicting. Our study adds considerably to the literature by providing evidence that humoral and cellular immune responses to SARS-CoV-2 vaccine are higher in HCWs from South Asian groups, as compared to those from White groups, particularly in the early phase after vaccine administration. This is the first study to provide data on anti-SARS-CoV-2 antibodies, SARS-CoV-2 neutralising antibodies and cellular responses to SARS-CoV-2 peptides stratified by ethnic group.

Implications of all the available evidence

There appear to be differences in the immune response to SARS-CoV-2 vaccination according to ethnicity. The majority of studies that compare Asian or South Asian groups to White have found that vaccine responses are higher in the Asian group. The current work demonstrates that these differences extend to neutralising antibody and T cell responses and that such differences are more apparent in the early stages after vaccination.

Introduction

The COVID-19 pandemic has led to significant morbidity and mortality globally.[1] Several demographic and occupational risk factors for infection with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) have been identified as the pandemic has progressed.[2–4]

Studies from the US and the UK have shown that those from minoritised ethnic groups are at higher risk of infection than those of White ethnicity.[5,6] However,

the underlying reasons for this increased risk of infection have not been clearly delineated. Given that ethnicity itself is a complex construct that relates to many facets of one's life (including "language, diet, religion, ancestry and physical features traditionally associated with race"[7]), mechanisms underlying this association are likely to be multi-faceted.[8] Sociodemographic drivers of this increased infection risk have been hypothesised to include: a greater likelihood of working in 'frontline' or 'key-worker' positions that increase exposure to SARS-CoV-2 (particularly whilst 'lockdown' measures were being employed early in the pandemic),[9,10] increased likelihood of living in deprived areas with higher population density making social distancing more difficult; living in smaller more poorly ventilated houses than those living in more affluent areas,[11,12] and a greater propensity for multi-generational living and therefore a greater number of household contacts.[6,11] As well as increased infection risk, there is some evidence to suggest that those from ethnic minority groups face a higher risk of severe COVID-19 (including hospitalisation, intensive care unit admission and death) than White groups.[6,13]

The development of safe and effective vaccines against SARS-CoV-2 has been a significant milestone in the response to the COVID-19 pandemic. Mass vaccination programmes provided a mechanism to reduce the risk of infection and severe disease on a population level.[14,15]

However, despite the observed differences in infection risk and COVID-19 outcome between ethnic groups, evidence concerning differences to vaccine immunogenicity by ethnic group is limited and conflicting. Studies conducted in populations defined by particular diseases or treatment (such as autoimmune conditions treated with immunosuppressive agents, myeloma, lung cancer and dialysis) have provided mixed results relating to the impact of ethnicity on immunogenicity of SARS-CoV-2 vaccine.[16–21] A recent study reporting findings from a large cohort of UK healthcare workers (HCWs) found higher SARS-CoV-2 anti-spike titres in ethnic minority vaccinees than in their White counterparts,[22] which contrasts with another UK HCW study which found lower peak anti-spike antibody titres in Black HCWs compared to White HCWs and did not find differences between the White and Asian groups.[23] A large UK observational study in the general population found South Asians vaccinees to have higher combined IgG, A and M titres against SARS-CoV-2 than those from White groups.[24] Crucially, there are no studies that present data relating to both cellular immune responses and SARS-CoV-2 neutralising activity after vaccination stratified by ethnicity.

Ethnicity has been shown to be a determinant of the immunogenicity of other vaccines, with previous studies showing higher titres of antibody against pertussis toxin in Black children than White children after vaccination,[25] higher post-vaccine measles antibody levels in Innu and Inuit children compared to White children,[26] and higher titres of rubella-specific neutralising antibodies in vaccinees from African ethnic groups compared to those from European ethnic groups.[27]

The aim of this study was to determine whether the humoral and cellular immune profiles of UK HCWs vaccinated against SARS-CoV-2 differ according to ethnicity using baseline data from two cohort studies.

Methods

Overview

This cross-sectional study utilises data and samples collected as part of two HCW cohort studies conducted in Leicester, UK. These are:

1) DIRECT (Determining the Immune Response in Ethnic minority healthcare workers to COVID-19 infecTion), which was established with the overarching aim of determining if immune responses to COVID-19 infection and vaccination differ according to ethnicity
2) BELIEVE (Broadening our understanding of Early versus Late InfluEnza Vaccine Effectiveness), which aims to understand whether there is significant waning of influenza vaccination effectiveness during an influenza season (banked serum samples from this study were sent for SARS-CoV-2 serology and neutralising assays. See below).

Study population and recruitment

Both studies recruited HCWs (including ancillary workers) aged 16 or over who were employed either by University Hospitals of Leicester NHS Trust (UHL), one of the largest acute hospital trusts in the UK, or by Leicestershire partnership NHS Trust (LPT). HCWs could participate regardless of previous SARS-CoV-2 infection or vaccination status.

The studies were advertised in hospital-wide email communications and on the staff intranet. This was supplemented by direct recruitment from clinical and non-clinical areas of the hospital. Sample size calculations were not performed for this exploratory study.

Study visits

After providing written, informed consent, participants provided information on occupational and demographic characteristics.

DIRECT participants provided blood samples (for SARS-CoV-2 serology, neutralisation activity, and enzyme-linked immunosorbent spot [ELISpot] assays) at a time of their convenience, the only restriction being that the blood sample should not be collected within two weeks of receipt of a SARS-CoV-2 vaccine. Baseline blood samples were collected between 3rd March and 16th September 2021.

BELIEVE participants provided blood samples (for SARS-CoV-2 serology and neutralisation activity) on four occasions which related to timing of influenza vaccination and the peak and end of the influenza season. The samples analysed for this study come from the fourth study visit, between 4th May and 1st June 2021 (this visit was selected in order to align with the period of sample collection for DIRECT).

Demographic and clinical data

We collected information on self-reported ethnicity (participants could select an ethnic group corresponding to the 18 Office for National Statistics [ONS] ethnic groups[28]), age, sex, type of SARS-CoV-2 vaccine received (BNT162b2 [Pfizer-BioNTech] or ChAdOx1-S [Oxford-AstraZeneca], hereafter referred to as BNT162b2 and ChAdOx1 respectively), number of SARS-CoV-2 vaccine doses received and the dates of receipt. We also collected data on the presence or absence of long-term conditions or medications associated with immunosuppression and body mass index (BMI) for use in sensitivity analyses (see below and Supplementary text 1 for details).

Laboratory methods

SARS-CoV-2 serology assays

Anti-spike and anti-nucleocapsid SARS-CoV-2 serology were performed at UKHSA Porton Down on serum samples using the Roche Elecsys anti-SARS-CoV-2 S (Product code: 09203079190) and Roche Elecsys anti-SARS-CoV-2 (Product code: 09289275190) assays, respectively. Samples were considered positive for anti-spike antibodies if $\geq$ 0.8 BAU/ml, and positive for anti-nucleocapsid antibodies if $\geq$ 1 COI.

SARS-CoV-2 neutralising antibody assay

Plasmid constructs and 293-ACE2 cells were as described previously.[29,30] Sera were screened for neutralising activity against HIV(SARS-CoV-2) pseudotypes bearing the spike glycoprotein of Wuhan D614G.[29,30] Neutralising activity in each sample was measured by a serial dilution approach. Each sample was serially diluted in triplicate from 1:50 to 1:36,450 in complete Dulbecco's Modified Eagle Medium (DMEM) prior to incubation with approximately 1×10^6 CPS per well of HIV (SARS-CoV-2) pseudotypes, incubated for 1 h, and plated onto 239-ACE2 target cells. After 48–72 h, luciferase activity was quantified by the addition of Steadylite Plus chemiluminescence substrate and analysis on a PerkinElmer EnSight multimode plate reader (PerkinElmer, Beaconsfield, UK). Antibody titre was then estimated by interpolating the point at which infectivity had been reduced to 50% of the value for the no serum control samples.

SARS-CoV-2 ELISpot assay

To quantify T cell responses, we used T-SPOT® Discovery SARS-CoV-2 platform (Oxford Immunotec), which use ELISpot technology to detect IFN-γ release from immune cells after exposure to SARS-CoV-2 peptides. This test is similar in methodology to the T-SPOT®.TB test which identifies patients infected with *M. tuberculosis*, and has been widely used clinically.

A peripheral venous blood sample of 6 mL was collected from participants and placed in a test tube of heparin anticoagulant. Peripheral blood mononuclear cells were isolated within 32 h of test performance. The T-SPOT *Discovery* SARS-CoV-2 test was performed according to the instructions of the kit. In brief, the peripheral blood mononuclear cells were counted, normalised and 250,000 PBMCs were plated into each well of a T-SPOT® Discovery SARS-CoV-2 plate. Four different but overlapping peptides pools to cover protein sequences of SARS-CoV-2—Spike 1 (S1), Spike 2 (S2), Nucleocapsid and membrane plus negative and positive controls were used (for further details see Supplementary Table S1). Cells were incubated overnight (16–20 h) at 37 °C with 5% CO^2, washed with phosphate-buffered saline, and developed using an anti-IFN-γ antibody conjugate and substrate to detect the presence of secreted IFN-γ. Spot-forming cells (SFCs) were counted with an automated spot reader (Cellular Technology Ltd). As our analysis focussed on immune responses to vaccination, we present responses to the spike peptides S1, S2 and spike (S1 + S2).

Statistical analysis

This analysis focuses on the immune response to vaccination. In order to ensure homogeneity with regard to previous exposure to SARS-CoV-2 we excluded those with a history of SARS-CoV-2 infection (determined by a positive SARS-CoV-2 anti-nucleocapsid antibody assay) and those who had not received the first two doses of SARS-CoV-2 vaccine at the point of sampling. To ensure that sufficient time had elapsed for an immune response to vaccination to develop and that we were not examining data from samples collected during the induction phase of the antibody response, we also excluded those whose blood samples were collected within 14 days of the second dose of vaccine.

For each immune parameter measured, we examined a subcohort who were sampled within 50 days of second vaccine dose. This time period was chosen to include only those close to their peak SARS-CoV-2 anti-spike antibody titre.[31]

We summarised categorical variables as frequency and percentage and non-normally distributed continuous variables and median and interquartile range (IQR). Continuous variables were assessed for normality of distribution by visual inspection.

Comparisons of immune responses between White and South Asian groups were possible as a large proportion of the UHL workforce are from South Asian ethnic groups. In order to maintain statistical power to detect differences by ethnicity whilst preventing

exclusion of particular individuals of minority ethnicity from the analysis, we created a three-level variable collapsing three of the five broad ONS ethnic groups into one (Black/Mixed/Other). Note that this group also includes the low number of those from Chinese ethnic groups.

Antibody titres and neutralising titres were $\log_{10}$ transformed prior to analysis. Raw ELISpot counts were transformed first by subtracting the count from an unstimulated control sample and then multiplied by four to give a value in spot forming units (SFUs) per million peripheral blood mononuclear cells (PBMCs).

For unadjusted comparisons of immune parameters between ethnic groups, we used *t* tests to compare $\log_{10}$ antibody levels and SARS-CoV-2 neutralising titres and Wilcoxon rank-sum test to compare ELISpot results using the White group as the reference. We also presented unadjusted analysis with the cohort stratified by the vaccine they had received (BNT162b2 or ChAdOx1). Geometric mean titres (GMTs) for total anti-spike antibodies and 50% neutralisation are also presented.

We used linear regression to determine the effects of ethnicity on SARS-CoV-2 antibody levels after adjustment for age, sex, vaccine type, time between receipt of second vaccine and collection of sample and time between the first and second doses of vaccine. Regression coefficients were exponentiated for expression as adjusted geometric mean ratios (aGMRs).

After examination of the mean and variance of the ELISpot results, we used negative binomial regression to investigate the impact of ethnicity on an outcome of ELISpot count after adjustment for the same variables used in the linear models. Results were expressed as adjusted incidence rate ratios (aIRRs).

Only those who had serum SARS-CoV-2 neutralising activity greater or equal to 90% at 1:50 dilution underwent further assays to determine the 50% neutralisation titre. Those who did not meet this threshold were excluded from the main analysis of serum neutralising activity. To investigate the impact this had on results we conducted two sensitivity analyses: 1) a comparison of demographic and vaccine related parameters in those excluded and included; 2) an analysis including those not meeting the threshold recoded as a titre of 50.

We conducted further sensitivity analyses to investigate the effect of the 50 day sampling threshold on results. We changed the threshold by −10 and +10 days and repeated the adjusted analyses.

To determine if differences in health factors known to affect vaccine response (long-term conditions and body mass index [BMI]) by ethnicity might have influenced our results, we repeated our multivariable analyses after adjustment for BMI and after exclusion of a small group of those with long-term conditions associated with immunosuppression or those taking immunosuppressive medication. As BMI was not collected in the BELIEVE study we used multiple imputation by chained equations to impute missing BMI data (for further details see Supplementary text 1).

Finally, we repeated our multivariable analyses of SARS-CoV-2 serology and neutralising activity after adjustment for a binary variable indicating which study (DIRECT or BELIEVE) a participant was enrolled in (for those that were enrolled in both studies we used the data collected as part of DIRECT and thus these participants were coded as such in this analysis).

All analyses were conducted using Stata 17 (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC.). Figures were created in GraphPad Prism version 9.4.1 for macOS (GraphPad Software, San Diego, California USA, www.graphpad.com). We considered P values < 0.05 to be statistically significant.

Ethical approval

DIRECT was approved by the Health Research Authority (Brighton and Sussex Research Ethics Committee; ethics reference: 20/HRA/4718). BELIEVE was approved by the Wales National Research Ethics Service, UK (REC number 20/WA/0247). All participants gave informed consent.

Role of the funding source

The funders had no role in study design, data collection, data analysis, interpretation, or writing of the report. All authors have had the opportunity to access the underlying data used in this study. All authors reviewed the manuscript and approved the final version prior to submission.

Results

Formation of the analysed sample

Fig. 1 shows the formation of the analysed cohort and the numbers of individuals included in each analysis.

Description of the cohort

Table 1 summarises the demographic and vaccine related information gathered for the uninfected and double vaccinated participants included in the analyses. Overall, 401 participants were included in the serology analyses with 102 (25.4%) being from ethnic minority groups (19.7% South Asian and 5.7% Black/Mixed/Other). Median (IQR) age was 45 (33–54) and 78.8% were female. The majority (n = 314, 78.8%) received BNT162b2 vaccine.

In comparison, a greater proportion of the 191 participants included in the ELISpot analyses (n = 73, 38.2%) were from ethnic minority groups (29.3% South Asian and 8.9% Black/Mixed/Other). A similar proportion received BNT162b2 (n = 152, 79.6%).

Supplementary Table S2 contains a detailed cohort description of demographic, health and vaccine related parameters by ethnicity. There was a higher proportion of males in the South Asian (34.2%) and Black/Mixed/

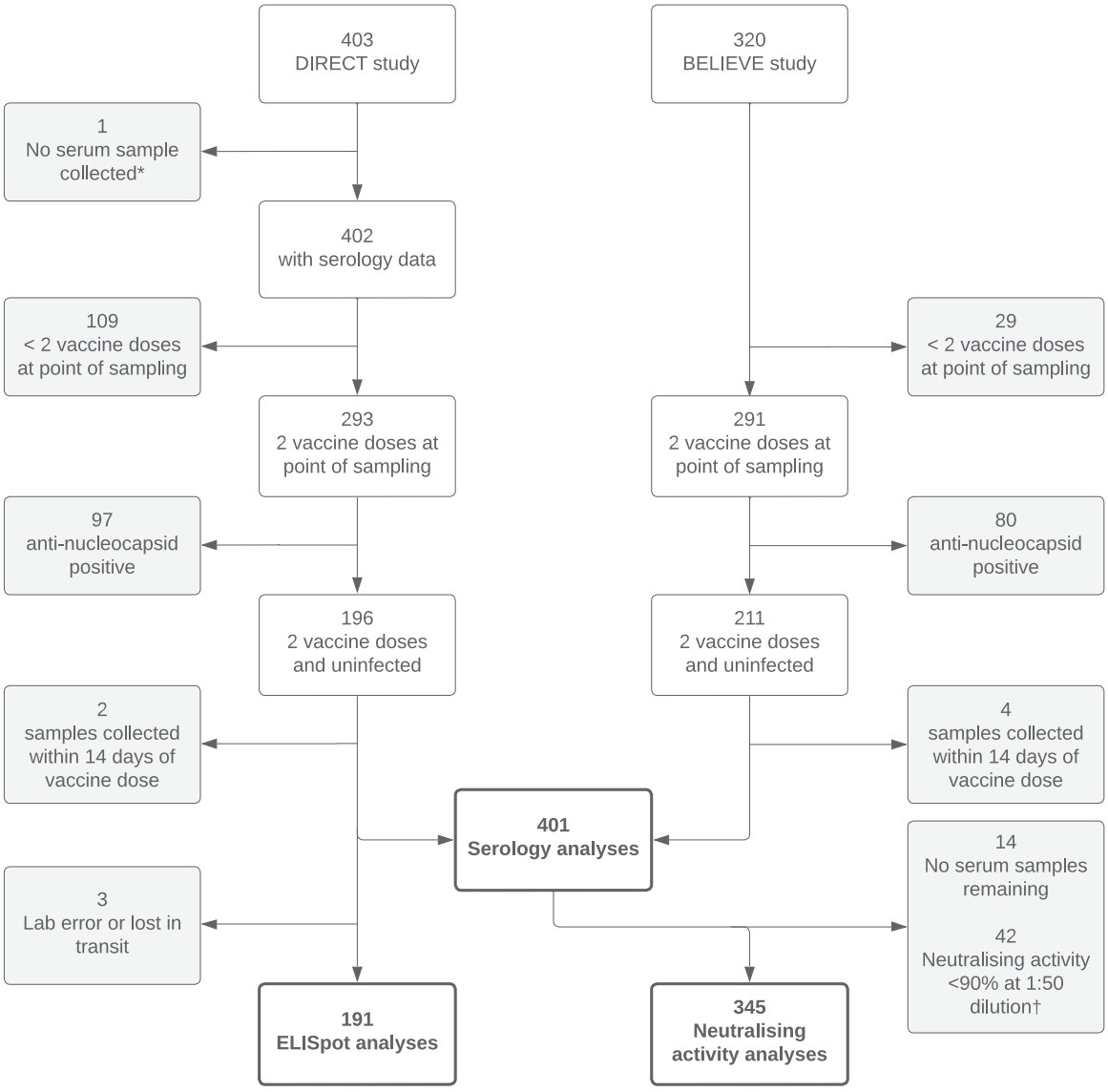


***Fig. 1:* Formation of the analysed cohort**. Fig. 1 shows how the final number of observations in each analysis were derived. The number of observations included in the analyses conducted in the subcohort whose sample was collected within 50 days of a second vaccine dose are detailed in the relevant figures/tables. There are 40 participants who were enrolled into both studies. For clarity, these participants are included in the figures for DIRECT. *Excluded from all analyses as no data on anti-nucleocapsid antibody status. † included in sensitivity analysis of neutralising activity data.

Other cohort (30.4%) compared to the White cohort (17.1%). A greater proportion of those in the South Asian and Black/Mixed/Other cohorts had an interval of <6 weeks between vaccine doses (84.8% and 78.3% vs 94.3% respectively). Prevalence of long term conditions that might impact upon vaccine immunogenicity and distribution across BMI categories did not differ by ethnicity.

SARS-CoV-2 serology

Scatter plots showing anti-spike antibody titres over time between second vaccine dose and sample collection stratified by ethnic group are shown in Supplementary Figure S1 and dot plots showing anti-spike antibody titres by ethnic group and by vaccine type in the whole cohort and in those sampled within 50 days of second vaccine dose are shown in Fig. 2.

Anti-spike titres decreased with increasing time since second vaccine in all ethnic groups. There were no significant differences in anti-spike titre by ethnicity when considering the whole cohort. However, in the subcohort sampled between 14 and 50 days of second vaccine administration, GMT was higher in South Asian HCWs

	Serology analyses (n = 401)	ELISpot analyses (n = 191)
Ethnicity		
White	299 (74.6)	118 (61.8)
South Asian	79 (19.7)	56 (29.3)
Black/Mixed/Other	23 (5.7)	17 (8.9)
Age		
(years), med (IQR)	45 (33–54)	46 (33–55)
Sex		
Male	85 (21.2)	52 (27.2)
Female	316 (78.8)	139 (72.8)
Healthcare role		
Non-patient facing	92 (22.9)	50 (26.2)
Patient facing	297 (74.1)	130 (68.1)
Missing	12 (3)	11 (5.8)
Vaccine		
BNT162b2	314 (78.3)	152 (79.6)
ChAdOx1	87 (21.7)	39 (20.4)
Time between first and second vaccine doses		
≤6 weeks	34 (8.5)	27 (14.1)
>6 weeks	364 (91.5)	164 (85.9)
Median (IQR)	77 (70–77)	74 (68–77)
Time between second vaccine dose and sampling		
≥14 days and ≤50 days	248 (61.9)	81 (42.4)
>50 days	153 (38.2)	110 (57.6)
Median (IQR)	43 (31–76)	65 (31–118)

Table 1 shows the participants included in the serology (from the DIRECT and BELIEVE studies) and ELISpot (from the DIRECT study only) analyses. Analyses of neutralising activity contain those in the serology cohort less 14 (excluded as there was no serum remaining after the serology assay and a further 42 who were excluded on the basis of neutralising activity <90% at 1:50 dilution (see Fig. 1 and Supplementary Table S3 for details)). All data are n (%) unless otherwise stated. Percentages are computed column-wise. Med–median; IQR–interquartile range. For a detailed description of the cohort by ethnicity, see Supplementary Table S2.

Table 1: **Description of the cohort.**

compared to White HCWs (9616 BAU/ml, 95% CI [7178–12,852] vs 5888 BAU/ml [5023–6902], P = 0.008) and when analysis was further restricted to those receiving BNT162b2 vaccine, GMT was higher in South Asian and Black/Mixed/Other groups compared to White (South Asian: 12,134BAU/ml [9397–15,631], Black/Mixed/Other: 15,524 BAU/ml [9333–25,942] vs White: 9484 BAU/ml [8590–10,471], P = 0.038 and P = 0.027 respectively) (Fig. 2).

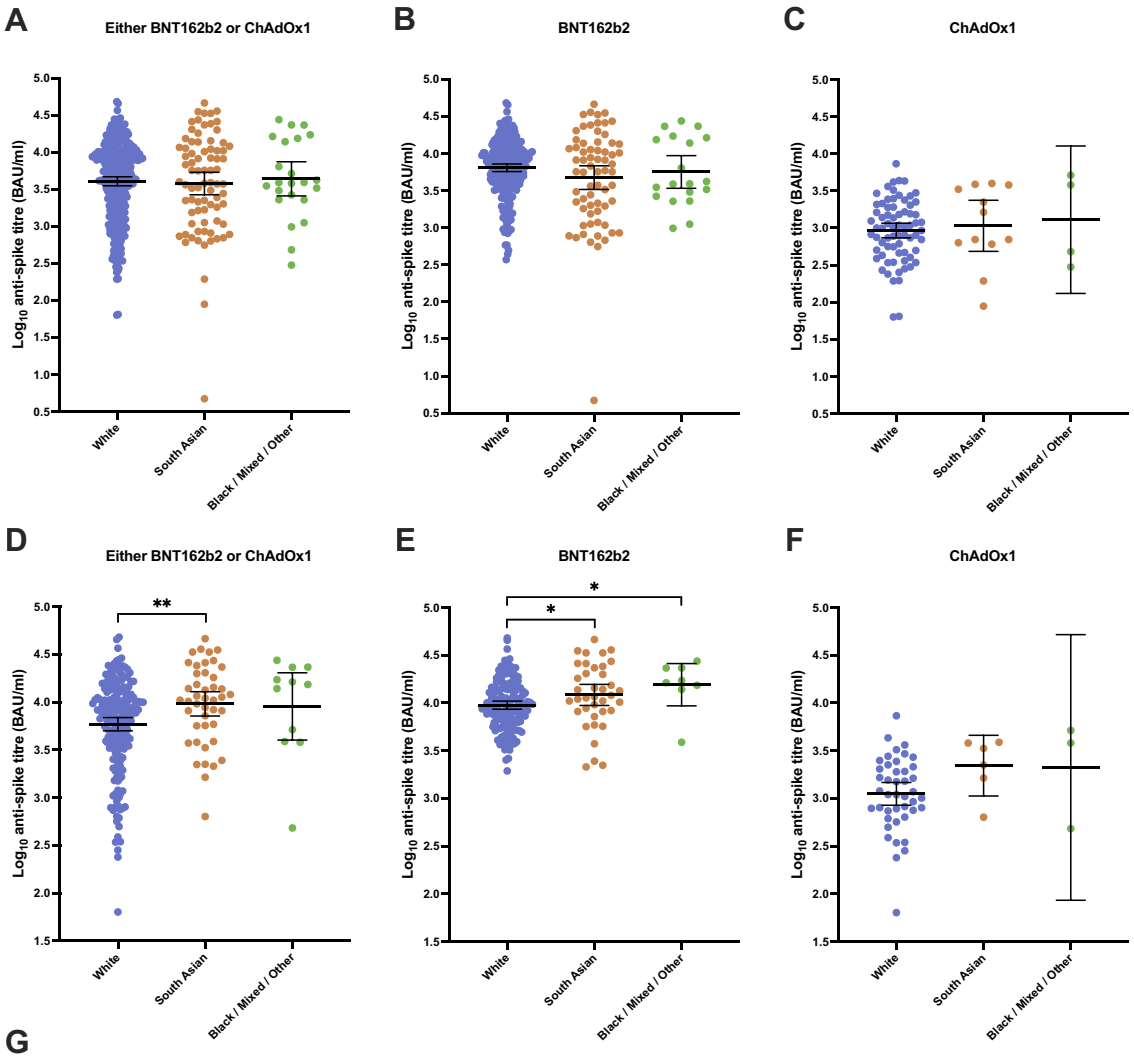
Table 2 shows results from the multivariable linear regression analysis showing the association between ethnicity and anti-spike titre both in the whole cohort and in those sampled within 50 days of second vaccine dose. When the whole cohort are included, there were no significant differences by ethnic group. However, in the subcohort sampled within 50 days of second vaccine administration, anti-spike titres in the South Asian cohort were higher than in the White cohort (aGMR 1.26, 95% CI [1.01–1.58], P = 0.04).

Age was found to be negatively associated with anti-spike titre (aGMR 0.86, 95% CI [0.81–0.93], P < 0.001, per decade increase) as was increasing time between second vaccination and sample collection (aGMR 0.91, 95% CI [0.90–0.92], P < 0.001, per week increase). Anti-spike titre was far lower in those receiving ChAdOx1 compared to those receiving BNT162b2 (aGMR 0.15, 95% CI [0.12–0.18], P < 0.001).

SARS-CoV-2 neutralising activity

As with the serology assays, neutralising activity decreased with time between second vaccine administration and sample collection in each ethnic group (Supplementary Figure S2). In the unadjusted analysis, no significant differences were seen between mean neutralising titres by ethnicity when the whole cohort were included. In the subcohort sampled between 14 and 50 days of vaccine administration, GMT (for 50% neutralisation) was higher in the South Asian group compared to the White group (2851 [1811–4487] vs 1199 [984–1462], P < 0.001). These differences persisted when the analysis was further restricted to those who had received the BNT162b2 vaccine (South Asian: 3515 [2269–5458] vs White: 1674 [1396–2013], P < 0.001) (Fig. 3).

On multivariable linear regression (Table 2), those from South Asian ethnic groups had higher serum SARS-CoV-2 neutralising activity than those from White ethnic groups (aGMR 1.47, 95% CI [1.06–2.06], P = 0.02). This association was more marked when the



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Panel	White GMT (95% CI)	South Asian GMT (95% CI)	Black / Mixed / Other GMT (95% CI)
A	4,055 (3,524 – 4,667), n=299	3,784 (2,666 – 5,357), n=79	4,365 (2,570 – 7,430), n=23
B	6,427 (5,701 – 7,228), n=228	4,742 (3,281 – 6,839), n=67	5,649 (3,396 – 9,375), n=19
C	924 (737 – 1,161), n=71	1,074 (486 – 2,366), n=12	1,297 (132 – 12,589), n=4
D	5,888 (5,023 – 6,902), n=193	9,616 (7,178 – 12,852), n=44	9,016 (3,999 – 20,323), n=11
E	9,484 (8,590 – 10,471), n=150	12,134 (9,397 – 15,631), n=38	15,524 (9,333 – 25,942), n=8
F	1,114 (847 – 1,465), n=43	2,203 (1,059 – 4,581), n=6	2113 (85.7 – 52,119), n=3

***Fig. 2:* Comparison of total SARS-CoV-2 spike-specific antibody titres by ethnic group and vaccine type**. Fig. 2 shows a comparison of log10 total SARS-CoV-2 anti-spike antibody titres (BAU/ml), stratified by by ethnic group and vaccine type. Panels A, B and C include all participants. Panels D, E and F include only those sampled within 50 days of second vaccine dose. Panel G shows geometric mean titres (GMTs) and their 95% confidence intervals with the number of participants in each ethnic group for panels A–F. Groups were compared (with the White group as reference) using unpaired t tests. *P < 0.05, **P < 0.01.

analysis was restricted to those sampled within 50 days of second vaccine dose (aGMR 2.01, 95% CI [1.34–3.01], P = 0.001).

As with the serology analysis, those who received ChAdOx1 had lower serum SARS-CoV-2 neutralising activity than those who received BNT162b2 (aGMR 0.18 95% CI [0.13–0.25], P < 0.001). Increasing time between second vaccination and sample collection was associated with lower neutralising activity (aGMR 0.92, 95% CI [0.90–0.94], P < 0.001, per week increase) and increasing

	Outcome—Log_{10} SARS-CoV-2 anti-spike antibody titre (BAU/ml)			
	In whole cohort (n = 401)		In those sampled within 50 days of second vaccine dose (n = 248)	
	aGMR (95% CI)	P value	aGMR (95% CI)	P value
Ethnicity				
White	Ref	–	Ref	–
South Asian	0.94 (0.77–1.15)	0.55	1.26 (1.01–1.58)	0.04
Black/Mixed/Other	1.21 (0.86–1.69)	0.27	1.51 (1.00–2.29)	0.05
Age				
per decade increase	0.86 (0.81–0.93)	<0.001	0.88 (0.82–0.95)	0.001
Sex				
Male	Ref	–	Ref	–
Female	1.01 (0.83–1.24)	0.88	0.99 (0.78–1.25)	0.92
Vaccine				
BNT162b2	Ref	–	Ref	–
ChAdOx1	0.15 (0.12–0.18)	<0.001	0.13 (0.10–0.16)	<0.001
Time between second vaccine dose and sampling				
per week increase	0.91 (0.90–0.92)	<0.001	0.89 (0.83–0.95)	0.001
Time between first and second vaccine doses				
≤6 weeks	Ref	–	–	–
>6 weeks	2.16 (1.60–2.94)	<0.001	–	–
	Outcome—Log_{10} mean titre for 50% neutralisation			
	In whole cohort (n = 345)		**In those sampled within 50 days of second vaccine dose (n = 221)**	
	aGMR (95% CI)	P value	aGMR (95% CI)	P value
Ethnicity				
White	Ref	–	Ref	–
South Asian	1.47 (1.06–2.06)	0.02	2.01 (1.34–3.01)	0.001
Black/Mixed/Other	1.25 (0.71–2.21)	0.44	1.66 (0.76–3.62)	0.20
Age				
per decade increase	0.92 (0.82–1.02)	0.11	0.85 (0.75–0.97)	0.02
Sex				
Male	Ref	–	Ref	–
Female	1.25 (0.89–1.75)	0.20	1.19 (0.78–1.81)	0.42
Vaccine				
BNT162b2	Ref	–	Ref	–
ChAdOx1	0.18 (0.13–0.25)	<0.001	0.18 (0.12–0.27)	<0.001
Time between second vaccine dose and sampling				
per week increase	0.92 (0.90–0.94)	<0.001	0.92 (0.81–1.04)	0.24
Time between first and second vaccine doses				
≤6 weeks	Ref	–	–	–
>6 weeks	2.41 (1.41–4.13)	0.001	–	–

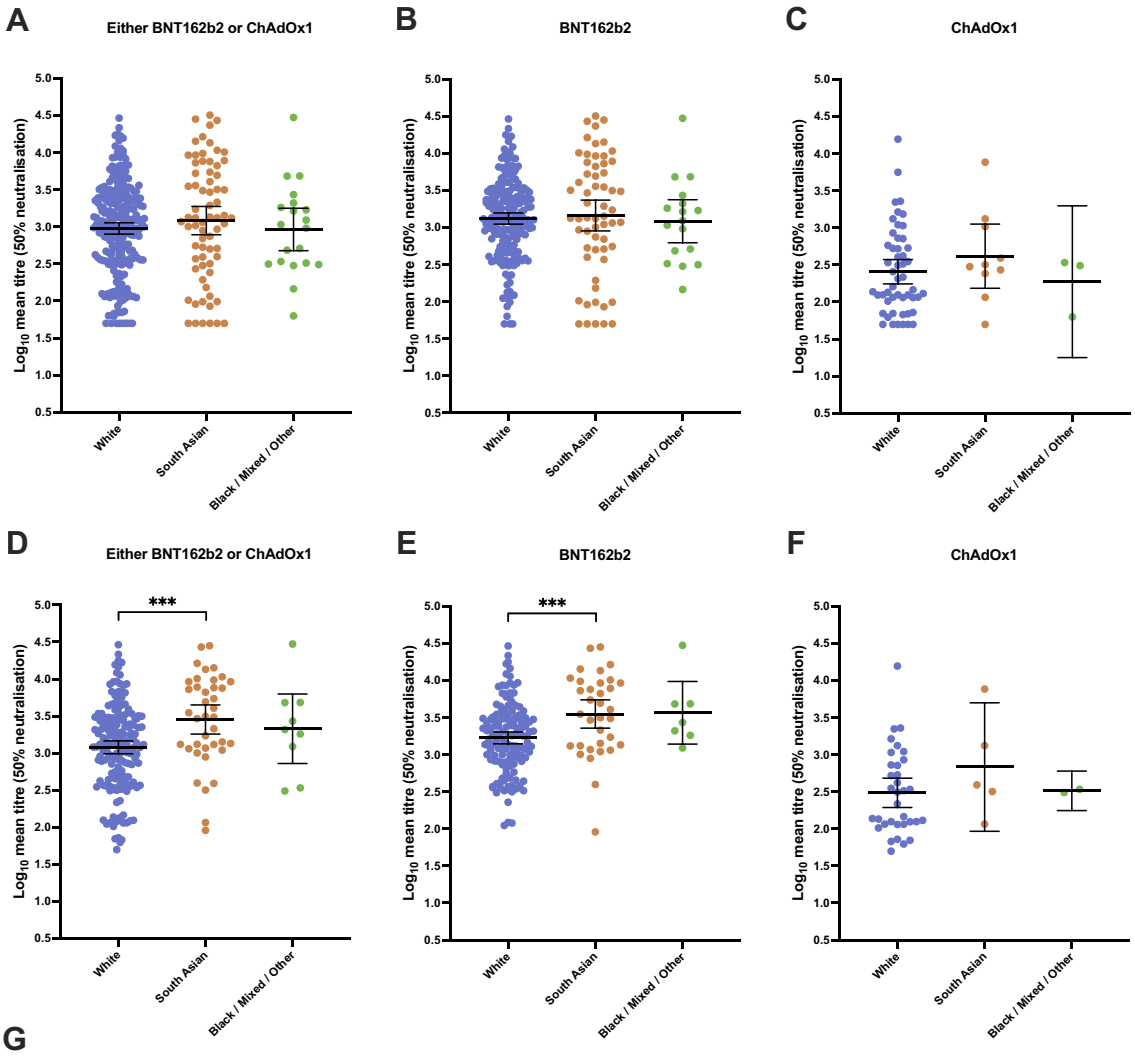
Table 2 shows multivariable linear regression models for the following outcomes: 1. log_{10} total SARS-CoV-2 anti-spike antibody titre (BAU/ml) both in the whole serology cohort and in those sampled between 14 and 50 days of their second vaccine dose (top panel). 2. log_{10} mean titre for 50% neutralisation in a pseudotype-based neutralisation assay against SARS-CoV-2 (Wuhan-Hu-1) both in all those who had samples sent for neutralisation assays and in a subcohort sampled between 14 and 50 days of their second vaccine dose (bottom panel). Coefficients were exponentiated to give adjusted Geometric Mean Ratios (aGMRs). Coefficients were adjusted for all variables in the table. Only 1 participant who was sampled within 50 days of their second dose of vaccine had their initial vaccine doses ≤6 weeks apart, therefore this variable was omitted from the relevant model. Ref–reference group for categorical variable; 95%CI–95% confidence interval.

Table 2: **Linear regression models showing the association between ethnicity and other sociodemographic and vaccine related parameters with log_{10} SARS-CoV-2 total anti-spike titre (top) and log_{10} mean titre for 50% neutralisation (bottom).**

time between vaccine doses with higher neutralising activity (>6 weeks between vaccines: aGMR 2.41, 95% CI [1.41–4.13], P = 0.001 [compared to ≤6 weeks between vaccines]).

SARS-CoV-2 ELISpot

Fig. 4 shows T cell responses to peptides from SARS-CoV-2 S1 domain, S2 domain and total spike (S1 + S2) by ELISpot. Spot count after stimulation with S1

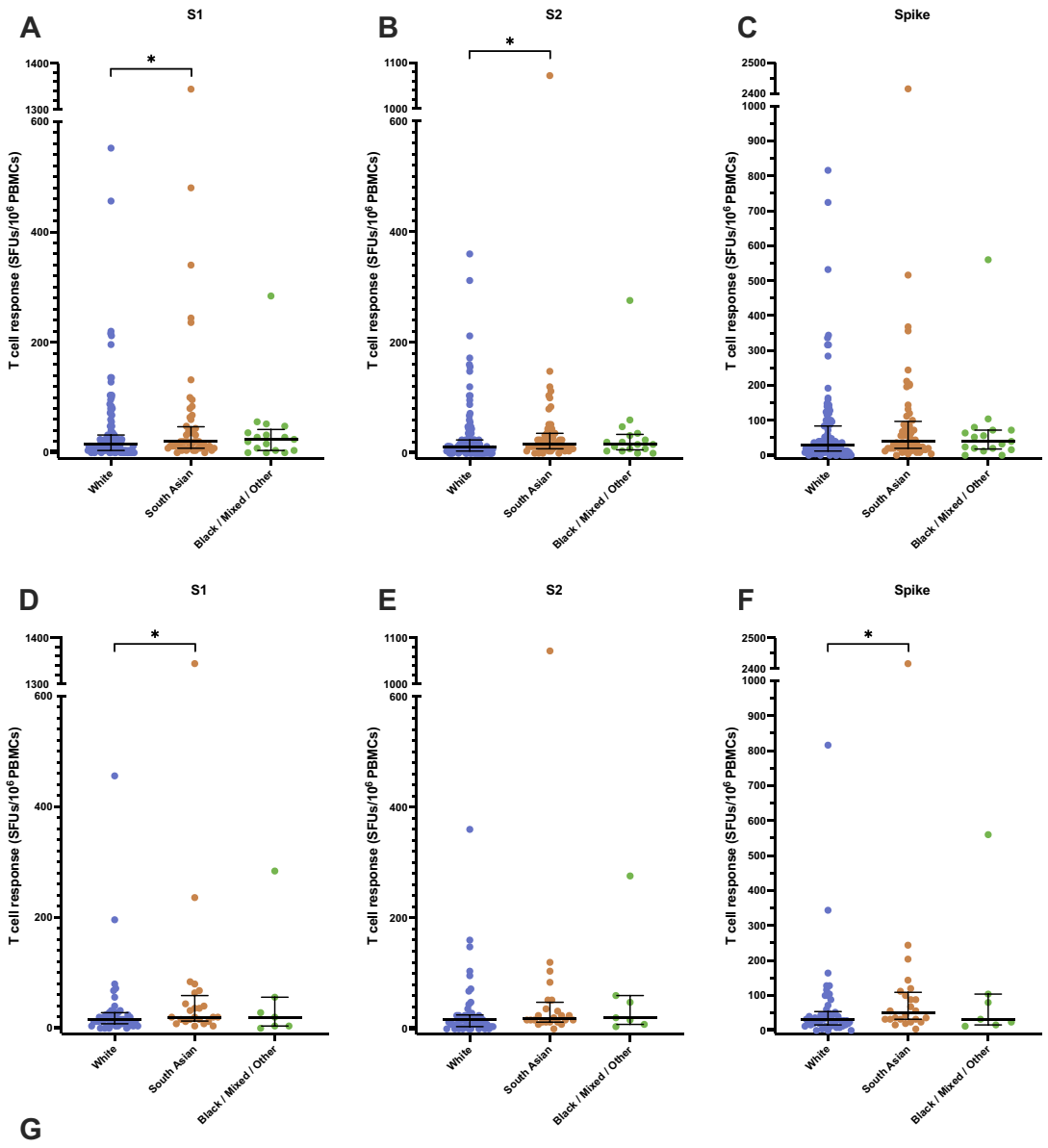


G

Panel	White GMT (95% CI)	South Asian GMT (95% CI)	Black / Mixed / Other GMT (95% CI)
A	948 (796 – 1,122), n=255	1,270 (782 – 1,875), n=70	558 (111 – 2,818), n=20
B	1,318 (1,109 – 1,563), n=204	1,448 (897 – 2,333), n=60	1,213 (622 – 2,371), n=17
C	256 (175 – 372), n=51	413 (153 – 1,119), n=10	188 (18 – 1,982), n=3
D	1,199 (984 – 1,462), n=173	2,851 (1,811 – 4,487), n=39	2,133 (726 – 6,280), n=9
E	1,674 (1,396 – 2,013), n=139	3,515 (2,269 – 5,458), n=34	3,656 (1,384 – 9,661), n=7
F	305 (194 – 482), n=34	680 (93 – 4,989), n=5	324 (175 – 598), n=2

***Fig. 3:* Comparison of serum SARS-CoV-2 neutralising antibody titre by ethnic group and vaccine type**. Fig. 3 shows a comparison of log10 mean titre for 50% neutralisation from the pseudotype-based neutralisation assay stratified by ethnic group and vaccine type. Panels A, B and C include all participants. Panels D, E and F include only those sampled within 50 days of second vaccine dose. Panel G shows geometric mean titres (GMTs) and their 95% confidence intervals with the number of participants in each ethnic group for panels A–F. Groups were compared (with the White group as reference) with unpaired t tests. ***P < 0.001.

and S2 peptides was higher in the South Asian group than the White group (med 20, IQR [8–46] vs 16 [4–32], P = 0.0498 and 16 [8–36] vs 12 [4–24], P = 0.0413 respectively). When the analysis was restricted to those sampled within 50 days of second vaccine dose, responses to S1 peptides were higher in the South Asian group compared to the White group (20 [14–54] vs 16 [8–28], P = 0.029) as were the responses to spike (32 [16–104] vs 30 [16–52], P = 0.03).



G

Panel	White Med (IQR) A – C, n=118 D – F, n=50	South Asian Med (IQR) A – C, n=56 D – F, n=24	Black / Mixed / Other Med (IQR) A – C, n= 17 D – F, n=7
A	16 (4 – 32)	20 (8 – 46)	24 (4 – 36)
B	12 (4 – 24)	16 (8 – 36)	16 (8 – 32)
C	28 (12 – 84)	40 (20 – 94)	40 (20 – 72)
D	16 (8 – 28)	20 (14 – 54)	20 (4 – 56)
E	16 (4 – 24)	18 (12 – 44)	20 (8 – 60)
F	30 (16 – 52)	50 (32 – 106)	32 (16 – 104)

***Fig. 4:* Comparison of T cell responses to SARS-CoV-2 S1, S2 and spike (S1 + S2) epitopes by ethnic group**. Fig. 4 shows results from the ELISpot assay. Results are expressed as spot forming units (SFU/10^6 PBMCs) in response to peptides derived from SARS-CoV-2 spike protein (regions S1, S2 and spike [S1 + S2]) stratified by ethnic group. Panels A, B and C include all participants. Panels D, E and F include only those sampled within 50 days of second vaccine dose. Panel G shows median (IQR) SFU/10^6 PBMCs for each ethnic group in panels A–F. Groups were compared (with the White group as reference) with Wilcoxon rank sum tests. *P < 0.05.

	In whole cohort (n = 191)					
	S1		S2		Spike	
	aIRR (95% CI)	P value	aIRR (95% CI)	P value	aIRR (95% CI)	P value
Ethnicity						
White	Ref	–	Ref	–	Ref	–
South Asian	1.75 (1.05–2.89)	0.03	1.23 (0.77–1.96)	0.38	1.50 (0.96–2.35)	0.08
Black/Mixed/Other	0.84 (0.38–1.86)	0.66	0.81 (0.39–1.67)	0.56	0.82 (0.40–1.65)	0.57
Age						
per decade increase	0.97 (0.82–1.17)	0.66	0.93 (0.79–1.11)	0.44	0.95 (0.81–1.12)	0.56
Sex						
Male	Ref	–	Ref	–	Ref	–
Female	1.10 (0.66–1.84)	0.71	1.19 (0.75–1.88)	0.45	1.07 (0.68–1.67)	0.78
Vaccine						
BNT162b2	Ref	–	Ref	–	Ref	–
ChAdOx1	0.63 (0.35–1.12)	0.12	0.29 (0.18–0.48)	<0.001	0.48 (0.29–0.79)	0.004
Time between second vaccine dose and sampling						
per week increase	0.99 (0.96–1.02)	0.50	0.94 (0.92–0.97)	<0.001	0.97 (0.95–1.00)	0.048
Time between first and second vaccine doses						
≤6 weeks	Ref	–	Ref	–	Ref	–
>6 weeks	0.59 (0.32–1.08)	0.09	0.43 (0.24–0.77)	0.005	0.56 (0.32–0.96)	0.03
	In those sampled within 50 days of second vaccine dose (n = 81)					
	S1		S2		Spike	
	aIRR (95% CI)	P value	aIRR (95% CI)	P value	aIRR (95% CI)	P value
Ethnicity						
White	Ref	–	Ref	–	Ref	–
South Asian	2.33 (1.09–4.94)	0.03	1.74 (0.78–3.91)	0.18	2.04 (1.02–4.08)	0.04
Black/Mixed/Other	1.21 (0.37–3.98)	0.76	1.47 (0.45–4.75)	0.52	1.34 (0.47–3.81)	0.58
Age						
per decade increase	0.93 (0.70–1.26)	0.66	0.90 (0.67–1.21)	0.48	0.93 (0.72–1.20)	0.58
Sex						
Male	Ref	–	Ref	–	Ref	–
Female	2.75 (1.29–5.85)	0.009	1.79 (0.79–4.06)	0.16	2.21 (1.10–4.42)	0.03
Vaccine						
BNT162b2	Ref	–	Ref	–	Ref	–
ChAdOx1	0.32 (0.13–0.76)	0.01	0.25 (0.10–0.64)	0.004	0.28 (0.13–0.63)	0.002
Time between second vaccine dose and sampling						
per week increase	0.98 (0.74–1.31)	0.92	0.97 (0.71–1.32)	0.85	0.98 (0.76–1.28)	0.91

Table 3 shows the results of negative binomial regression analyses for an outcome of ELISpot count in response to peptides derived from SARS-CoV-2 S1, S2 and spike (S1 + S2) for all DIRECT participants meeting inclusion criteria and in a subcohort sampled within 50 days of second vaccine dose. Coefficients were exponentiated to give adjusted incidence rate ratios (aIRRs). Coefficients were adjusted for all variables in the table. There were no participants in the subcohort sampled within 50 days of their second dose of vaccine who had their initial vaccine doses ≤6 weeks apart, therefore this variable was omitted from the relevant model. Ref–reference group for categorical variable; 95%CI–95% confidence interval.

***Table 3*: Negative binomial regression model showing the association between ethnicity and S1, S2 and Spike specific T cell responses after adjustment for demographic and vaccine related factors.**

On multivariable negative binomial regression analyses (Table 3), those from South Asian ethnic groups had higher numbers of circulating T cells responsive to SARS-CoV-2 S1 peptides than those from White groups (aIRR 1.75, 95% CI 1.05–2.89, P = 0.03). In the subcohort sampled within 50 days of second vaccine dose, the number of circulating T cells responsive to both S1 (aIRR 2.33, 95% CI [1.09–4.94], P = 0.03) and spike (aIRR 2.04, 95% CI [1.02–4.08], P = 0.04) peptides were higher amongst South Asian HCWs than White HCWs.

Vaccination with ChAdOx1 was associated with lower S2 and spike T cell responses compared to BNT162b2 (aIRR 0.29, 95% CI [0.18–0.48], P = 0.004 and aIRR 0.48, 95% CI [0.29–0.79], P = 0.002 respectively). An increased time between vaccine doses was associated with reduced T cell responses to S2 and spike peptides (aIRR 0.43, 95% CI [0.24–0.77], P = 0.005 and

aIRR 0.56, 95% CI [0.32–0.96], P = 0.03 respectively). Female HCWs had higher S1 and spike T cell responses than males in the period 14–50 days after second vaccine dose (aIRR 2.75, 95% CI [1.29–5.85] and aIRR 2.21, 95% CI [1.10–4.42] respectively).

Sensitivity analyses

A comparison of those who were excluded from the neutralising activity analysis due to having a percentage neutralisation <90% at 1:50 dilution by ethnicity is shown in Supplementary Table S3. Exclusion was associated with receiving ChAdOx1 and having samples collected more than 50 days after second vaccine dose. There were no differences in exclusion by ethnicity. Significant findings were unchanged when those with neutralising activity <90% at a dilution of 1:50 were coded as a titre of 50 (Supplementary Table S4).

Changing the upper boundary of the time window for inclusion in the analyses of early immune responses by –10 and +10 days did not have a significant impact on results (see Supplementary Tables S5 and S6).

Findings relating to ethnicity did not change after exclusion of those with immunosuppressive conditions or taking immunosuppressive medications and after adjustment for BMI (Supplementary Tables S7 and S8).

Adjustment for study (DIRECT vs BELIEVE) did not materially change the findings from the analyses of serology or neutralising activity (Supplementary Table S9).

Discussion

In this cross-sectional analysis of a large multi-ethnic cohort of HCWs who had received two doses of vaccine against SARS-CoV-2 but who had no serological evidence of previous infection, we found that immune responses to SARS-CoV-2 vaccination differed according to ethnicity. In the early period of 14–50 days after vaccination, SARS-CoV-2 spike-specific antibody titre, neutralising antibody titre, and T cell responses to SARS-CoV-2 S1 and spike peptides were all higher in South Asian HCWs compared to White HCWs, associations that persisted after adjustment for other demographic and vaccine related factors. Serum SARS-CoV-2 neutralising activity and T cell responses to S1 peptides were higher throughout the study period in those from South Asian ethnic groups compared to White ethnic groups.

There are few studies that have explored SARS-CoV-2 vaccine induced immune responses by ethnicity. Our serology results are concordant with those from a large cohort study of UK HCWs which found that adjusted anti-spike GMT was higher in infection naïve ethnic minority HCWs than White HCWs after two SARS-CoV-2 vaccine doses and with a large observational study of adults in the UK, which found that combined IgG/IgA/IgM responses to the SARS-CoV-2 spike protein were 16.2% higher in South Asian vaccinees when compared to those from White ethnic groups.[22,32] However, neither study presented data on neutralising activity or cellular responses. In contrast, another UK HCW study found Black HCW to have lower serologic responses to vaccination than their White counterparts and found no differences between the White and Asian groups.[23]

The explanation for the differences in immunogenicity of SARS-CoV-2 vaccination by ethnicity are likely to be complex and multifaceted. Cultural differences between ethnic groups may have an impact on this association, for example diet, which varies by ethnic group,[33] has previously been shown to affect immune response to infection and vaccination.[34] Close contact with COVID-19 has been shown to affect T cell responses even in the absence of seropositivity for anti-nucleocapsid antibody[35] and risk of such contact would be expected to increase with household occupancy, a factor known to differ by ethnicity.[3] Biological/genetic differences between ethnic groups may also play a role.[36] For example, immunoglobulin germline gene polymorphisms have previously been demonstrated to affect neutralising activity of serum after influenza H5N1 vaccination and to differ according to ethnicity[37] and increased transcription of B cell-specific genes compatible with higher antibody responses to influenza vaccine has been shown in younger African Americans compared to their White counterparts.[38]

It is unclear whether the differences in immune response to SARS-CoV-2 vaccination by ethnicity shown in our study and elsewhere translate to differences in the effectiveness of vaccines for reducing the risk of SARS-CoV-2 infection and severe COVID-19. The limited information in the literature may relate to underrepresentation of ethnic minority groups in vaccine trials.[39,40] In a study evaluating efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine, vaccine efficacy at preventing COVID-19 was reported to be 97.5% (87.1–96.4%) in 'communities of colour' (all non-White ethnic groups were combined for statistical power) compared to 93.2% (87.1–96.4%) in the White group.[41] In a study reporting results of the phase 3 trial of the BNT162b2 vaccine, efficacy for preventing COVID-19 was reported as 95.2% (89.8–98.1%) for the White group which was similar to the Hispanic or Latinx (94.4% [82.7–98.9%]) and Non-Hispanic, non-Latinx (95.4% [88.9%–98.5%]) groups. Estimates of efficacy were higher for the Black or African American group (100.0% [31.2%–100.0%]) and lower for the 'All others' group (89.3% [22.6–99.8%]) but confidence intervals were wide due to low numbers of participants in these groups.[42]

Outside of the findings relating to ethnicity our study adds further weight to the accumulating evidence that immunogenicity of SARS-CoV-2 vaccine may be increased by increasing the interval between the first two doses[43,44] and that vaccination with ChAdOx1

compared to BNT162b2 elicits lower antibody and cellular immune responses to SARS-CoV-2 spike protein.[45,46]

This study has several strengths. Our cohort is large, ethnically diverse and has been extensively phenotyped. Therefore, we are able to add significantly to the limited information in the literature concerning ethnic differences in immunogenicity of SARS-CoV-2 vaccines by presenting the first data on differences in serum SARS-CoV-2 neutralising activity and T cell responses by ethnicity. Our study design also allows us to postulate that ethnic differences in immunogenicity of SARS-CoV-2 vaccines may be more marked in the early phase after vaccination. A significant proportion of our cohort are from South Asian ethnic groups which allows for meaningful comparisons between the White and South Asian cohort, rather than restricting analyses to 'White vs non-White'. Our sample is broadly similar to the NHS workforce in terms of age and sex distribution but has a higher proportion of HCWs from minority ethnic groups[47]

Our study also has limitations. The low numbers of participants from ethnic groups other than White and South Asian necessitated collapsing other ethnic groups into a single third group. Whilst this was done to avoid exclusion of participants and to maintain as much granularity as possible, we accept that there is considerable heterogeneity in the Black/Mixed/Other group and suggest that further research is needed to determine whether there are differences in immunogenicity of SARS-CoV-2 vaccines in these ethnic groups. The majority of participants received the BNT162b vaccine and therefore our conclusions are mainly drawn based on responses to this vaccine. Data are from a single centre; however, our results align with the few available studies examining SARS-CoV-2 vaccine immunogenicity by ethnicity suggesting that they are representative. There were differences between ethnic groups in terms of vaccine schedule and sex distribution but these were adjusted for in the multivariable models and thus are unlikely to have affected our conclusions. As with any observational study, we cannot be sure that reported associations are not the result of residual confounding. We used anti-nucleocapsid antibody status to determine which participants had previously been infected with SARS-CoV-2 and as these would be expected to wane with time and we cannot rule out the possibility that, for a participant infected early in the pandemic, anti-nucleocapsid titres have waned to a point below the limit of detection. However the anti-nucleocapsid assay used in this work has been shown to have a sensitivity of 92% 18 months after SARS-CoV-2 infection,[48] a time period that would span from March 2020 (when cases of COVID-19 began to significantly rise in the UK) through to September 2021 when the study closed for recruitment. We also cannot rule out the possibility that a participant was sampled in an early phase of infection prior to seroconversion. However, in a population of HCW who had ready access to SARS-CoV-2 PCR testing and were encouraged to undergo testing as soon as symptoms consistent with COVID-19 developed, we think it unlikely that this had any meaningful impact on our results. Crucially, there is no reason to suspect that either of these antibody related effects would impact differently according to the ethnicity of the participant and introduce bias. We made many comparisons over the course of this analysis, as this is exploratory work we felt it would be unnecessarily restrictive to adjust the alpha level to account for this and we accept that this will increase the risk of type 1 error. We therefore strongly recommend that future studies explore the associations reported here. Follow up work from the current study will also seek to confirm these association in analyses using data from further sampling events.

This cross sectional analysis of an extensively immunophenotyped population provides evidence that serologic response to SARS-CoV-2 vaccination in the early phase after vaccination may be higher in South Asian ethnic groups than White ethnic groups. Our study is the first to demonstrate higher T cell responses to SARS-CoV-2 spike protein epitopes and serum SARS-CoV-2 neutralising activity after vaccination in South Asian ethnic groups compared to White groups. Further research is required to establish: the mechanisms underlying these differences; whether these differences persist over time and with repeated exposure to vaccine; whether these differences impact upon vaccine effectiveness in different ethnic groups; and how natural infection with SARS-CoV-2 might impact upon these differences.

Contributors

MP conceived the ideas for DIRECT and BELIEVE and led the applications for funding with input from CAM, JN, PH and AC. Online consent and questionnaire tools were designed and implemented by CAM and LB. Recruitment for the studies was done by CAM, JN, DP, A Ahmed, SB, JM, MM, AM and MP. Sample and additional data collection was done by CAM, JN, AJ, MD, NA, TA, A Asif, NG, MG, RK, MM, VR and DV. SARS-CoV-2 anti-spike antibody assays were performed by BH, ADO and CR. Pseudotype-based neutralisation assays were performed by NL, SS and BJW. ELISpot assays were performed by AT. Data were linked and cleaned by CAM with input from JN, AJ, DP, VR, DV, and MP. Data analysis was by CAM with input from JN, DP, MD, LJG, LT, PM, PH, AC and MP. CAM wrote the first draft of the manuscript with input from JN, DP, KK, AT, BH, ADO, CR, BJW, PH, AC and MP.

All authors have had the opportunity to access the underlying data used in this study. The analysis has been verified by CAM and MP. All authors reviewed the manuscript and approved the final version prior to submission.

Data sharing statement

To access data or samples produced by the DIRECT or BELIEVE studies, the working group representative must first submit a request to the Core Management Group by contacting the UK-REACH Project Manager in the first instance. For ancillary studies outside of the core deliverables, the Steering Committee will make final decisions once they have been approved by the Core Management Group. Decisions on granting the access to data/materials will be made within eight weeks. Third party requests from outside the Project will require explicit approval of the Steering Committee once approved by the Core Management Group.

Declaration of interests

KK is Chair of the Ethnicity Subgroup of the UK Government Scientific Advisory Group for Emergencies (SAGE) and a member of SAGE. PM has received honoraria from Moderna, AstraZeneca and GSK, support for attending meetings from AstraZeneca and has participated on an advisory board for AstraZeneca. PH received an honorarium for hosting a COVID-19 webinar, on behalf of Oxford Immunotec who are manufacturers of the ELISpot technology used in the manuscript. MP reports grants from UKRI-MRC for the current work and UKRI-MRC, NIHR, Sanofi and Gilead outside the current work and has received consulting fees from QIAGEN.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.101926.

References

1 World Health Organisation. *WHO Coronavirus (COVID-19) dashboard*; 2022. https://covid19.who.int. Accessed April 25, 2022.
2 de Lusignan S, Dorward J, Correa A, et al. Risk factors for SARS-CoV-2 among patients in the Oxford royal college of general practitioners research and surveillance centre primary care network: a cross-sectional study. *Lancet Infect Dis*. 2020;20(9):1034–1042.
3 Martin CA, Jenkins DR, Minhas JS, et al. Socio-demographic heterogeneity in the prevalence of COVID-19 during lockdown is associated with ethnicity and household size: results from an observational cohort study. *eClinicalMedicine*. 2020;25:100466.
4 Ward H, Atchison C, Whitaker M, et al. SARS-CoV-2 antibody prevalence in England following the first peak of the pandemic. *Nat Commun*. 2021;12(1):905.
5 Sze S, Pan D, Nevill CR, et al. Ethnicity and clinical outcomes in COVID-19: a systematic review and meta-analysis. *eClinicalMedicine*. 2020;29:100630.
6 Mathur R, Rentsch CT, Morton CE, et al. Ethnic differences in SARS-CoV-2 infection and COVID-19-related hospitalisation, intensive care unit admission, and death in 17 million adults in England: an observational cohort study using the OpenSAFELY platform. *Lancet*. 2021;397(10286):1711–1724.
7 Bhopal R. Glossary of terms relating to ethnicity and race: for reflection and debate. *J Epidemiol Community Health*. 2004;58(6):441.
8 Katikireddi SV, Lal S, Carrol ED, et al. Unequal impact of the COVID-19 crisis on minority ethnic groups: a framework for understanding and addressing inequalities. *J Epidemiol Community Health*. 2021;75(10):970.
9 Office for National Statistics. *Which occupations have the highest potential exposure to the coronavirus (COVID-19)?*; 2020. https://www.ons.gov.uk/employmentandlabourmarket/peopleinwork/employmentandemployeetypes/articles/whichoccupationshavethehighestpotentialexposuretothecoronaviruscovid19/2020-05-11. Accessed May 16, 2020.
10 Hawkins D. Differential occupational risk for COVID-19 and other infection exposure according to race and ethnicity. *Am J Ind Med*. 2020;63(9):817–820.
11 SAGfES-e. *Housing, household transmission and ethnicity, 26 November 2020*; 2020. https://www.gov.uk/government/publications/housing-household-transmission-and-ethnicity-26-november-2020. Accessed April 25, 2022.
12 Lo C-H, Nguyen LH, Drew DA, et al. Race, ethnicity, community-level socioeconomic factors, and risk of COVID-19 in the United States and the United Kingdom. *eClinicalMedicine*. 2021;38:101029.
13 Nafilyan V, Islam N, Ayoubkhani D, et al. Ethnicity, household composition and COVID-19 mortality: a national linked data study. *J R Soc Med*. 2021;114(4):182–211.
14 Pritchard E, Matthews PC, Stoesser N, et al. Impact of vaccination on new SARS-CoV-2 infections in the United Kingdom. *Nat Med*. 2021;27(8):1370–1378.
15 Agrawal U, Katikireddi SV, McCowan C, et al. COVID-19 hospital admissions and deaths after BNT162b2 and ChAdOx1 nCoV-19 vaccinations in 2.57 million people in Scotland (EAVE II): a prospective cohort study. *Lancet Respir Med*. 2021;9(12):1439–1449.
16 Kennedy NA, Lin S, Goodhand JR, et al. Infliximab is associated with attenuated immunogenicity to BNT162b2 and ChAdOx1 nCoV-19 SARS-CoV-2 vaccines in patients with IBD. *Gut*. 2021;70(10):1884.
17 Valanparambil RM, Carlisle J, Linderman SL, et al. Antibody response to COVID-19 mRNA vaccine in patients with lung cancer after primary immunization and booster: reactivity to the SARS-CoV-2 WT virus and Omicron variant. *J Clin Oncol*. 2022;40(33):3808–3816.
18 Li T, Gandra S, Reske KA, et al. Predictors of humoral response to SARS-CoV-2 mRNA vaccine BNT162b2 in patients receiving maintenance dialysis. *Antimicrob Steward Healthc Epidemiol*. 2022;2(1):e48.
19 Kister I, Curtin R, Pei J, et al. Hybrid and vaccine-induced immunity against SAR-CoV-2 in MS patients on different disease-modifying therapies. *Ann Clin Transl Neurol*. 2022;9(10):1643–1659.
20 Nooka AK, Shanmugasundaram U, Cheedarla N, et al. Determinants of neutralizing antibody response after SARS CoV-2 vaccination in patients with myeloma. *J Clin Oncol*. 2022;40(26):3057–3064.
21 G S Saad C, S R Silva M, D Sampaio-Barros P, et al. Interaction of TNFi and conventional synthetic DMARD in SARS-CoV-2 vaccine response in axial spondyloarthritis and psoriatic arthritis. *Joint Bone Spine*. 2022;90(1):105464.
22 Otter AD, D'Arcangelo S, Whitaker H, et al. Determinants of SARS-CoV-2 anti-spike antibody levels following BNT162b2 vaccination: cross-sectional analysis of 6,000 SIREN study participants. *medRxiv*. 2022. https://doi.org/10.1101/2022.04.21.22274025.
23 Ward V, Wei J, Gordon W, et al. SARS-CoV-2 antibody responses post-vaccination in UK healthcare workers with pre-existing medical conditions: a cohort study. *BMJ Open*. 2022;12(12):e066766.
24 Jolliffe DA, Faustini SE, Holt H, et al. Determinants of antibody responses to SARS-CoV-2 vaccines: population-based longitudinal study (COVIDENCE UK). *Vaccines*. 2022.
25 Christy C, Pichichero ME, Reed GF, et al. Effect of gender, race, and parental education on immunogenicity and reported reactogenicity of acellular and whole-cell pertussis vaccines. *Pediatrics*. 1995;96(3 Pt 2):584–587.
26 Poland GA, Jacobson RM, Colbourne SA, et al. Measles antibody seroprevalence rates among immunized Inuit, Innu and Caucasian subjects. *Vaccine*. 1999;17(11–12):1525–1531.
27 Haralambieva IH, Salk HM, Lambert ND, et al. Associations between race, sex and immune response variations to rubella vaccination in two independent cohorts. *Vaccine*. 2014;32(17):1946–1953.
28 Office for National Statistics. Ethnic group, national identity and religion. https://www.ons.gov.uk/methodology/classificationsandstandards/measuringequality/ethnicgroupnationalidentityandreligion. Accessed July 7, 2021.
29 Willett BJ, Grove J, MacLean OA, et al. SARS-CoV-2 Omicron is an immune escape variant with an altered cell entry pathway. *Nat Microbiol*. 2022;7(8):1161–1179.
30 Dowell AC, Butler MS, Jinks E, et al. Children develop robust and sustained cross-reactive spike-specific immune responses to SARS-CoV-2 infection. *Nat Immunol*. 2022;23(1):40–49.
31 Aldridge RW, Yavlinsky A, Nguyen V, et al. SARS-CoV-2 antibodies and breakthrough infections in the Virus Watch cohort. *Nat Commun*. 2022;13(1):4869.
32 Talaei M, Faustini S, Holt H, et al. Determinants of pre-vaccination antibody responses to SARS-CoV-2: a population-based longitudinal study (COVIDENCE UK). *BMC Med*. 2022;20(1):87.
33 Storey M, Anderson P. Income and race/ethnicity influence dietary fiber intake and vegetable consumption. *Nutr Res*. 2014;34(10):844–850.

34 Falahi S, Kenarkoohi A. Host factors and vaccine efficacy: implications for COVID-19 vaccines. *J Med Virol*. 2022;94(4):1330–1335.
35 Wang Z, Yang X, Zhong J, et al. Exposure to SARS-CoV-2 generates T-cell memory in the absence of a detectable viral infection. *Nat Commun*. 2021;12(1):1724.
36 Jethwa H, Wong R, Abraham S. Covid-19 vaccine trials: ethnic diversity and immunogenicity. *Vaccine*. 2021;39(27):3541–3543.
37 Avnir Y, Watson CT, Glanville J, et al. IGHV1-69 polymorphism modulates anti-influenza antibody repertoires, correlates with IGHV utilization shifts and varies by ethnicity. *Sci Rep*. 2016;6:20842.
38 Kurupati R, Kossenkov A, Haut L, et al. Race-related differences in antibody responses to the inactivated influenza vaccine are linked to distinct pre-vaccination gene expression profiles in blood. *Oncotarget*. 2016;7(39):62898–62911.
39 Woolf K, McManus IC, Martin CA, et al. Ethnic differences in SARS-CoV-2 vaccine hesitancy in United Kingdom healthcare workers: results from the UK-REACH prospective nationwide cohort study. *Lancet Reg Health Eur*. 2021;9:100180.
40 Etti M, Fofie H, Razai M, Crawshaw AF, Hargreaves S, Goldsmith LP. Ethnic minority and migrant underrepresentation in Covid-19 research: causes and solutions. *eClinicalmedicine*. 2021;36:100903.
41 Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med*. 2020;384(5):403–416.
42 Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med*. 2020;383(27):2603–2615.
43 Payne RP, Longet S, Austin JA, et al. Immunogenicity of standard and extended dosing intervals of BNT162b2 mRNA vaccine. *Cell*. 2021;184(23):5699–5714.e11.
44 Angyal A, Longet S, Moore SC, et al. T-cell and antibody responses to first BNT162b2 vaccine dose in previously infected and SARS-CoV-2-naive UK health-care workers: a multicentre prospective cohort study. *Lancet Microbe*. 2022;3(1):e21–e31.
45 Munro APS, Janani L, Cornelius V, et al. Safety and immunogenicity of seven COVID-19 vaccines as a third dose (booster) following two doses of ChAdOx1 nCov-19 or BNT162b2 in the UK (COV-BOOST): a blinded, multicentre, randomised, controlled, phase 2 trial. *Lancet*. 2021;398(10318):2258–2276.
46 Kang YM, Minn D, Lim J, et al. Comparison of antibody response elicited by ChAdOx1 and BNT162b2 COVID-19 vaccine. *J Korean Med Sci*. 2021;36(46):e311.
47 Naqvi H, Kline R. *Equality analysis on the NHS workforce race equality standard*; 2016. https://www.england.nhs.uk/wp-content/uploads/2014/10/equality-analysis-wres-april-16.pdf. Accessed February 21, 2023.
48 Nakagama Y, Komase Y, Kaku N, et al. Detecting waning serological response with commercial immunoassays: 18-month longitudinal follow-up of anti-SARS-CoV-2 nucleocapsid antibodies. *Microbiol Spectr*. 2022;10(4):e0098622.