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SARS-CoV-2 antibody responses post-vaccination in healthcare workers with pre-existing medical conditions

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SARS-CoV-2 antibody responses post-vaccination in healthcare workers with pre-existing medical conditions

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Abstract

Objectives: To examine antibody responses after the second vaccination in healthcare workers (HCWs) with underlying health conditions.

Methods: We examined the peak anti-spike IgG responses after the second vaccination in 1,635 UK HCWs and associations with underlying health conditions and the estimated risk of severe COVID using an occupational health risk assessment tool. We used univariable and multivariable linear regression models to investigate associations between antibody levels and demographics (age, sex, ethnicity), health care role, body mass index, underlying health conditions, vaccination status, prior infection, and the Association of Local Authority Medical Advisors COVID-age risk score.

Results: 1,635 HCWs had anti-spike IgG measurements 14-84 days post second vaccination and data on any underlying health conditions. Only 5 HCWs (0.3%), all on immunosuppressive treatment, (including 4 organ transplant recipients), did not seroconvert after second vaccination. Antibody levels were independently lower with older age, diabetes, immunosuppression, respiratory disorders other than asthma, and markedly so in organ transplant recipients. Levels were independently lower in ChAdOx1 vs. BNT162b2 recipients and higher following previous infection. HCWs with 'very high' COVID-age risk scores had lower median antibody levels than those with 'low', 'medium' or 'high' risk scores; 4,379 AU/ml, compared with 12,337 AU/ml, 9,430 AU/ml, and 10,524 AU/ml respectively.

Conclusions: Two vaccine doses are effective in generating antibody responses among HCWs, including those with a high occupational risk. However, HCWs with underlying health conditions, especially diabetes, immunosuppression, and organ transplant, had lower antibody levels, and vaccine response monitoring may be needed.

Strengths and limitations of this study

- The study focuses on antibody levels post vaccination in healthcare workers (HCWs) with underlying health conditions.
- The study examines the association between the Association of Local Authority Medical Advisors COVID-age tool and vaccine response.
- The study only examines the peak anti-spike IgG levels after the second vaccination and does not assess antibody waning longitudinally.

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- The study is not widely generalizable given the cohort is predominantly working-age HCWs.

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Introduction

Healthcare workers (HCWs) have played a central role in the response to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) global pandemic. In many settings HCWs have been shown to be at an increased risk of SARS-CoV-2 infection, with risks relating both to proximity to infected patients and also to increased contact with colleagues compared with those working from home[1–3].

Several interventions have been made to protect HCWs, including risk assessments, improved access to personal protective equipment (PPE) and training, better understanding of effective PPE selection, and modifications to working environments including social distancing and improved ventilation. One widely used UK tool that has been developed to assist in SARS-CoV-2 occupational health risk assessments is the Association of Local Authority Medical Advisors (ALAMA) COVID-age score[4], which uses demographic and medical history factors to estimate the risk of death if a HCW were to become infected. For those at the highest risk, restriction of patient contact or alternative working patterns may be recommended.

Additionally, multiple vaccines have been developed that show good protection against COVID-19 infection, hospitalisation, and death[5–8], including in studies specifically looking at HCWs. Vaccination therefore plays an important role in facilitating those HCWs at higher risk of adverse outcomes from infection to remain in their usual work. Some HCWs, however, may not generate protective immunity following vaccination because of underlying medical conditions, especially those at the highest risk of adverse outcomes.

One potential way to assess which HCWs have responded to vaccination is to look at their antibody levels post vaccination. Various studies have examined antibody responses in HCWs, including looking at the duration, magnitude, and response trajectories[9–12], to understand the level of protection induced from vaccination, and its association with age, sex, and ethnicity[13]. However, few studies have examined the antibody responses in HCWs with underlying comorbidities. In particular, the association between estimated vulnerability of HCWs and antibody response to vaccination has not been studied.

Here we report findings from a retrospective observational study looking at anti-spike IgG antibody responses post second COVID-19 vaccination in HCWs with underlying health conditions, specifically

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focusing on the association between peak antibody levels with the pre-existing underlying health conditions.

Methods

Participants and settings

Oxford University Hospitals (OUH) consists of 4 teaching hospitals in Oxfordshire UK, providing acute and specialist services and employing 13,500 staff. OUH offered vaccination to all HCWs. The programme began on 8-December-2020, initially prioritising those at highest risk of severe COVID, starting with the Pfizer-BioNTech BNT162b2 vaccine, with Oxford-AstraZeneca ChAdOx1 nCoV-19 added from 4 January 2021 and predominately provided to all staff at one acute hospital. Some HCWs received the Oxford-AstraZeneca vaccine in clinical trials beginning 23 April 2020 and were included following unblinding if receiving active vaccine.

OUH has offered SARS-CoV-2 testing to all symptomatic and asymptomatic staff. SARS-CoV-2 PCR testing of combined nasal and oropharyngeal swabs for symptomatic staff (those with a new persistent cough, temperature ≥37.8°C, anosmia, or ageusia) was offered from 27 March 2020 onwards. Asymptomatic HCWs were invited to participate in voluntary nasal and oropharyngeal swab PCR testing and serologic testing from 23 April 2020 to 30 June 2021, as previously described[9,14]. All swabbing was performed by trained staff rather than self-administered. Additional serological testing of HCWs was undertaken by the Occupational Health department based on clinical assessment.

For occupational health purposes, all HCWs were asked to complete an individual COVID-19 risk assessment and those with underlying health conditions had more detailed risk assessments undertaken by the Occupational Health department. Staff members completed an online questionnaire about their age, sex, ethnicity, body mass index (BMI), underlying health conditions, smoking and pregnancy status, vaccination details, job role and location. COVID-age risk scores[4] were calculated based on this information to enable an appropriate risk assessment to be made by the Occupational Health team.

Laboratory tests

Anti-trimeric spike IgG antibody levels were measured using the Abbott SARS-CoV-2 IgG II Quant antibody test (Abbott, Maidenhead, UK) targeting the spike receptor binding domain (RBD), with the cut-off of ≥ 50 AU/mL reported as positive and a linear quantification of detected results from 50 to

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40,000 AU/mL[15]. Anti-spike IgG levels above 40,000 AU/ml were truncated at 40,000 AU/ml. The conversion between AU/ml and BAU/mL provided by the manufacturer is: 7 AU/ml= 1 BAU/mL. Pre-vaccination anti-nucleocapsid IgG levels were measured using the Abbott Architect i2000 chemiluminescent microparticle immunoassay (CMIA; Abbott, Maidenhead, UK), with antibody levels ≥1.40 manufacturer's arbitrary units reported as positive. Pre-vaccination anti-trimeric-spike IgG levels were measured using an enzyme-linked immunosorbent assay (ELISA) developed by the University of Oxford[16], with ≥ 8 million units reported as positive.

PCR was performed using the Public Health England SARS-CoV-2 assay (targeting the RdRp gene) or one of five commercial assays: Abbott RealTime (targeting RdRp and N genes; Abbott, Maidenhead, UK), Altona RealStar (targeting E and S genes; Altona Diagnostics, Liverpool, UK), Cepheid Xpert® Xpress SARS-CoV-2 (targeting N2 and E; Cepheid, California, USA), BioFire® Respiratory 2.1 (RP2.1) panel with SARS-CoV-2 (targeting ORF1ab and ORF8; Biofire diagnostics, Utah, USA), Thermo Fisher TaqPath assay (targeting S and N genes, and ORF1ab; Thermo Fisher, Abingdon, UK) or using the ABI 7500 platform (Thermo Fisher, Abingdon, UK) with the US Centers for Disease Control and Prevention Diagnostic Panel of two probes targeting the N gene.

Statistical analysis

We included HCWs aged 17-77 years who completed an occupational health risk assessment, received a two-vaccination course, and had antibody measurements after their second vaccination. The vaccination type was divided into a homologous ChAdOx1 course, homologous BNT162b2 course, and other vaccine types or mixed vaccination.

HCW's sex (grouped into male, female and non-disclosed), ethnicity (White, Asian, Black, Mixed, Other, and not stated), BMI (<16, 16-24.9, 25-29.9, 30-34.9, 35-39.9 and 40+) were included. Job role was grouped into nurse or healthcare assistant, doctor, administrative staff, physical, occupational, or speech therapist, laboratory staff, porter or domestic worker, medical or nursing student, or 'other', which included security, estates, catering staff, pharmacists, midwives, and other allied healthcare professionals.

Medical conditions and other potential risk factors included in the analysis were smoking and pregnancy status, and whether each HCW had asthma, hypertension, a thyroid disorder excluding malignancy, diabetes, immunosuppression, psoriasis, heart disease, a non-haematological malignancy, a rheumatological disorder, a respiratory disease other than asthma, a haematological disease excluding malignancy, liver disease, a neurological disorder, chronic kidney disease stage 3, 4 or 5, lupus, a splenic disorder excluding traumatic splenectomy, a haematological malignancy, and

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an organ transplant. Prior infection was defined as having had a positive PCR result or a positive anti-spike antibody result or a positive anti-nucleocapsid antibody result before the first vaccination dose.

The ALAMA COVID-age risk score was calculated based on age, sex, ethnicity, and presence of comorbidities. It estimates the probability of death should infection occur in the absence of vaccination or previous infection. A score ≥85 indicates very high vulnerability, 70-84 high vulnerability, 50-69 moderate vulnerability, and <50 low vulnerability. Details of the calculation formula and methods can be found online[4].

We used the peak antibody level 14-84 days post second vaccination as the outcome. Antibody response was divided into three groups: high response (peak anti-spike IgG level >700 AU/ml, converted from 100 BAU/mL which is associated with 67% protection against Delta infection [17]), low response (50-700 AU/ml), and no response (<50 AU/ml).

Antibody measurements after breakthrough infections post first vaccination were excluded from the analysis: 26 HCWs had evidence of infection at least 14 days after their first vaccination but prior to their second vaccination, and 37 HCWs had evidence of infection at least 14 days after their second vaccination. We first used the Kruskal-Wallis rank test to compare the outcome by different covariate groups. We then built univariable and multivariable linear regression models to examine the association between the outcome on the $\log_{10}$ scale and demographics (age, sex, ethnicity), health care role, BMI, underlying health conditions, vaccination status, prior infection, and COVID-age risk score. Age was truncated at the 2.5th and 97.5th percentile to avoid undue outlier influence and modelled with and without natural cubic splines to test for the non-linear effects. For the multivariable model, backward elimination was used and the model with the lowest Akaike information criteria (AIC) was selected. COVID-age score was not included in the multivariable model as it is based on other factors already included in the model.

All analyses were performed in R (version 4.1), using the following packages: tidyverse (version 1.3.1), splines (version 4.0.5), and stats (version 4.0.5).

Patient and public involvement

No patients and public were involved in the study design, interpretation or write up of the results.

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Results

A total of 5,968 HCWs had serological data available between 9 April 2020 and 26 August 2021, among which 1,635 HCWs had anti-spike IgG measurements 14-84 days post second vaccination and provided data on any underlying health conditions; these HCWs were included in the study. The median (IQR) [range] age was 46 (33-56) [17-77]. 1,344 (82.2%) were female, 1,169 (71.5%) were of white ethnicity, and 779 (47.6%) worked in a nursing or health-care assistant role. 872 (53.3%) did not have any underlying medical condition. The proportion reporting each condition ranged from 0.2% to 19.3%, with asthma being the most common comorbidity. 286 (17.5%) HCWs had evidence of infection prior to their first vaccination. The median (IQR) [range] COVID-age score was 50 (35-59) [16-124], with 120 (7.5%) and 22 (1.4%) HCWs falling in the 'High' and 'Very high' risk groups, respectively. 1,234 (75.5%) and 387 (23.7%) HCWs received two BNT162b2 and ChAdOx1 vaccinations, respectively, and 13 HCWs (0.8%) received other combinations, including mRNA-1273 (**Table 1, 2**). The characteristics were generally similar to the larger group of 5,968 HCWs with serological data, so the cohort included in the analysis should be representative (**Table S1**).

Among 1,635 HCWs, the median (IQR) peak anti-spike binding antibody level 14-84 days post second vaccination was 10,763 (3,925-22,017) AU/ml. The distribution of peak antibody levels is shown in **Figure S1**. Observed antibody levels were different across age groups, health care roles, vaccination types, with or without evidence of prior infection, and COVID-age scores ($p<0.001$). HCWs with 'Very high' vulnerability according to COVID-age scores had the lowest median level of 4,379 AU/ml, compared with 12,337 AU/ml, 9,430 AU/ml, and 10,524 AU/ml in the 'Low', 'Moderate', and 'High' vulnerability groups (**Table 1, Figure 1a**). HCWs with medical conditions and other risk factors had lower median antibody levels than those without (9,637 AU/ml vs. 11,681 AU/ml, $p=0.009$); specifically, antibody levels were lower in smokers (7,588 AU/ml, $p=0.003$), those with hypertension (8,770 AU/ml, $p=0.01$), diabetes (8,748 AU/ml, $p=0.04$), immunosuppression (7,451 AU/ml, $p=0.002$), a respiratory disease other than asthma (6,993 AU/ml, $p=0.01$), and those who had an organ transplant (11 AU/ml, $p<0.001$) (**Table 2, Figure 1b**). There was no evidence of an association between pregnancy and antibody levels (14,684 AU/ml, $p=0.6$).

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	Total (n=1,635)	Peak antibody levels >700 AU/ml (n=1,555)	Peak antibody levels 50-700 AU/ml (n=75)	Peak antibody levels <50 AU/ml (n=5)	Peak antibody levels 14-84 days post second vaccination (AU/ml)		
Age (years)					**Median**	**IQR**	**p value**
Median	46	46	49	34	(Overall) 10,763	3,925-22,017	
Q1, Q3	33, 56	33, 56	36, 56	33, 43			
Age group							
17-34	457 (100.0%)	439 (96.1%)	15 (3.3%)	3 (0.7%)	14,668	5,359-25,801	**<0.001**
35-54	723 (100.0%)	682 (94.3%)	39 (5.4%)	2 (0.3%)	10,153	3,773-20,578	
55-77	455 (100.0%)	434 (95.4%)	21 (4.6%)	0 (0.0%)	9,328	3,461-19,046	
Sex							
Female	1,344 (100.0%)	1,271 (94.6%)	68 (5.1%)	5 (0.4%)	10,779	3,856 – 22,541	0.7
Male	290 (100.0%)	283 (97.6%)	7 (2.4%)	0 (0.0%)	10,710	4,524 – 19,026	
Non-disclosed	1 (100.0%)	1 (100.0%)	0 (0.0%)	0 (0.0%)	5,438		
Ethnicity							
White	1,169 (100.0%)	1,110 (95.0%)	56 (4.8%)	3 (0.3%)	10,971	3,907 – 22,009	0.3
Asian	304 (100.0%)	290 (95.4%)	14 (4.6%)	0 (0.0%)	10,433	4,180 – 21,829	
Black	50 (100.0%)	45 (90.0%)	4 (8.0%)	1 (2.0%)	7,081	2,104 – 14,388	
Mixed	36 (100.0%)	36 (100.0%)	0 (0.0%)	0 (0.0%)	10,725	4,573 – 29,932	
Other	55 (100.0%)	53 (96.4%)	1 (1.8%)	1 (1.8%)	8,581	4,703 – 20,589	
Not stated	21 (100.0%)	21 (100.0%)	0 (0.0%)	0 (0.0%)	15,786	5,686 – 25,064	
Role							**<0.001**
Administrative Staff	245 (100.0%)	236 (96.3%)	8 (3.3%)	1 (0.4%)	11,653	5,660 – 15,013	
Doctor	106 (100.0%)	102 (96.2%)	4 (3.8%)	0 (0.0%)	12,003	6,677 – 22,113	
Laboratory Staff	61 (100.0%)	58 (95.1%)	2 (3.3%)	1 (1.6%)	20,279	8,790 – 31,137	
Medical or nursing Student	12 (100.0%)	12 (100.0%)	0 (0.0%)	0 (0.0%)	7,933	6,061 – 20,103	
Nurse/HCA	779 (100.0%)	737 (94.6%)	39 (5.0%)	3 (0.4%)	10,844	3,897 – 21,515	

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Other	331 (100.0%)	314 (94.9%)	17 (5.1%)	0 (0.0%)	9,208	2,533 – 20,284	
Porter or domestic worker	31 (100.0%)	27 (87.1%)	4 (12.9%)	0 (0.0%)	8,476	1,533 – 15,644	
OT/PT/SLT	70 (100.0%)	69 (98.6%)	1 (1.4%)	0 (0.0%)	11,849	6,021 – 24,371	
BMI							0.3
<16	3 (100.0%)	2 (66.7%)	1 (33.3%)	0 (0.0%)	17,716	9,195 – 18,471	
16-24.9	698 (100.0%)	667 (95.6%)	28 (4.0%)	3 (0.4%)	11,587	4,186 – 22,134	
25-29.9	517 (100.0%)	491 (95.0%)	24 (4.6%)	2 (0.4%)	10,169	3,404 – 19,046	
30-34.9	261 (100.0%)	247 (94.6%)	14 (5.4%)	0 (0.0%)	10,149	4,318 – 24,585	
35-39.9	85 (100.0%)	81 (95.3%)	4 (4.7%)	0 (0.0%)	10,743	4,534 – 27,281	
>40	71 (100.0%)	67 (94.4%)	4 (5.6%)	0 (0.0%)	11,199	5,877 – 28,260	
Vaccine combination							**<0.001**
ChAdOx1/ChAdOx1	387 (100.0%)	315 (81.4%)	70 (18.1%)	2 (0.5%)	1,603	879 – 3,521	
BNT162b2/BNT162b2	1,234 (100.0%)	1,227 (99.4%)	4 (0.3%)	3 (0.2%)	14,824	8,432 – 25,853	
Other	13 (100.0%)	13 (100.0%)	1 (0.0%)	0 (0.0%)	6,993	4,693 – 13,212	
Evidence of Covid-19 infection at baseline							**<0.001**
No	1,349 (100.0%)	1,269 (94.1%)	75 (5.6%)	5 (0.4%)	9,960	3,302-20,056	
Yes	286 (100.0%)	286 (100.0%)	0 (0.0%)	0 (0.0%)	17,227	7,111 – 28,277	
COVID-age score groups							**<0.001**
Low	769 (100.0%)	737 (95.8%)	32 (4.2%)	0 (0.0%)	12,337	4,634-23,170	
Medium	696 (100.0%)	659 (94.7%)	35 (5.0%)	2 (0.3%)	9,430	3,693-19,302	
High	120 (100.0%)	114 (95.0%)	5 (4.2%)	1 (0.8%)	10,524	3,106-23,939	
Very high	22 (100.0%)	17 (77.3%)	3 (13.6%)	2 (9.1%)	4,379	889-11,214	
COVID-age score							
Median	50	50	53	76			
Q1, Q3	35, 59	35, 60	36, 57	54, 85			

Table 1. Characteristics of the study cohort according to the peak anti-spike IgG levels post-second vaccination. Other for vaccine included mRNA-1273 and other vaccine combinations. OT/PT/SLT: occupational therapist, physiotherapist, and speech and language therapist. HCA: healthcare assistant.

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	Total (n=1,635)	Peak antibody levels >700 AU/ml (n=1,555)	Peak antibody levels 50-700 AU/ml (n=75)	Peak antibody levels <50 AU/ml (n=5)	Peak antibody levels 14-84 days post second vaccination (AU/ml)		
					Median	IQR	p value
Comorbidity							**0.009**
No	872 (100.0%)	830 (95.2%)	42 (4.8%)	0 (0.0%)	11,681	4,362 – 23,299	
Yes	763 (100.0%)	725 (95.0%)	33 (4.3%)	5 (0.7%)	9,637	3,493-19,750	
Smoking	106 (100.0%)	99 (93.4%)	7 (6.6%)	0 (0.0%)	7,588	1,828 – 19,639	**0.003**
Pregnant	23 (100.0%)	23 (100.0%)	0 (0.0%)	0 (0.0%)	14,684	8,199 – 19,453	0.6
Asthma	316 (100.0%)	300 (94.9%)	16 (5.1%)	0 (0.0%)	10,161	4,296 – 19,559	0.2
Hypertension	176 (100.0%)	168 (95.5%)	8 (4.5%)	0 (0.0%)	8,770	3,272 - 18,746	**0.01**
Thyroid disorder (excluding malignancy)	137 (100.0%)	128 (93.4%)	9 (6.6%)	0 (0.0%)	10,395	3,280 – 25,672	0.9
Diabetes	95 (100.0%)	89 (93.7%)	5 (5.3%)	1 (1.1%)	8,748	2,950 – 19,346	**0.04**
Immunosuppression	80 (100.0%)	68 (85.0%)	7 (8.8%)	5 (6.2%)	7,451	1,503 – 17,695	**0.002**
Psoriasis	48 (100.0%)	43 (89.6%)	5 (10.4%)	0 (0.0%)	7,435	2,573 – 13,850	0.06
Heart disease	34 (100.0%)	32 (94.1%)	2 (5.9%)	0 (0.0%)	13,925	4,999 – 22,430	0.7
Non-haematological malignancy	41 (100.0%)	40 (97.6%)	1 (2.4%)	0 (0.0%)	13,159	9,261 – 23,955	0.3
Rheumatological disorder	27 (100.0%)	24 (88.9%)	2 (7.4%)	1 (3.7%)	5,691	1,770 – 15,567	0.05
Respiratory disease (excluding asthma)	37 (100.0%)	33 (89.2%)	4 (10.8%)	0 (0.0%)	6,993	2,302 – 12,927	**0.01**
Haematological disease (excluding malignancy)	36 (100.0%)	35 (97.2%)	1 (2.8%)	0 (0.0%)	12,236	6,738 – 20,060	1
Liver disease	11 (100.0%)	11 (100.0%)	0 (0.0%)	0 (0.0%)	11,419	5,818 – 13,705	0.4
Neurological disorder	12 (100.0%)	12 (100.0%)	0 (0.0%)	0 (0.0%)	6,035	5,258 – 12,886	0.3
CKD stage 3, 4 or 5	6 (100.0%)	5 (83.3%)	0 (0.0%)	1 (16.7%)	10,129	5,672 – 17,965	0.7

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Lupus	7 (100.0%)	5 (71.4%)	1 (14.3%)	1 (14.3%)	1,478	695 – 13,582	0.1
Splenic disorder (excluding traumatic splenectomy)	4 (100.0%)	4 (100.0%)	0 (0.0%)	0 (0.0%)	1,796	1,040 – 9,695	0.2
Haematological malignancy	3 (100.0%)	3 (100.0%)	0 (0.0%)	0 (0.0%)	7,731	7,230 – 16,186	0.9
Organ transplant	5 (100.0%)	1 (20.0%)	0 (0.0%)	4 (80.0%)	11	6 - 21	**<0.001**

Table 2. Comorbidity status of the study cohort according to the peak anti-spike IgG levels post-second vaccination

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1,555 (95.1%) HCWs had a peak anti-spike IgG level >700 AU/ml, i.e. a level associated with >67% protection from infection (see Methods). 75 (4.6%) HCWs had a suboptimal antibody level between 50 and 700 AU/ml, and 5 (0.3%) HCWs did not generate a positive antibody response (<50 AU/ml) after the second vaccination. Of the 75 and 5 HCWs with low or no antibody response, the median COVID-age risk score was 53 (IQR 36-57) and 76 (IQR 54-85) respectively - higher than in the high response group (50, IQR 35-60) (p=0.03), but not sufficiently different for the low response group for COVID-age score alone to identify those likely to be in this group. Among the 80 HCWs with low or no antibody response, 72 received two ChAdOx1 vaccinations, accounting for 18.6% of all the ChAdOx1 recipients, whilst the proportion having a low response was only 0.5% of all the BNT162b2 recipients (**Table 1).** HCWs with specific medical conditions were more likely to be in the low or no response groups including 15% of those reporting taking immunosuppression and several other conditions that may also be treated with immunosupression, including low/no antibody responses in 10% with psoriasis, 11% with rheumatological disorders, 11% with other (non-asthma) respiratory disorders, 29% with lupus, and 80% with an organ transplant. Of the 5 HCWs with no detectable serological response, all were female and immunosuppressed, 4 HCWs had had organ transplants and the other HCW having an autoimmune disease for which they recieved rituximab (**Table 2**).

Associations between $\log_{10}$ antibody levels and covariates in univariable linear regression models are shown in **Table 3**. Older age, black ethnicity, working as a porter or domestic worker, and receiving two ChAdOx1 vaccines were associated with lower peak anti-spike antibody levels 14-84 days post second vaccination. Smoking, diabetes, a respiratory disease other than asthma, chronic kidney disease stage 3, 4, or 5, a rheumatological disorder, lupus, being immunosuppressed, or having had an organ transplant were all associated with lower antibody levels. A higher COVID-age score, which indicated higher risk of mortality from infection, was also associated with lower antibody levels (p<0.001). Having evidence of COVID-19 infection prior to vaccination, as well as being a laboratory staff worker, were both associated with having higher antibody levels. No evidence of an association was found between antibody levels and sex or BMI.

1,593 HCWs with complete information on all variables were included in the multivariable model. The baseline intercept in log10 scale was 4.25. Older age (-0.03 per 10 years older, 95% Confidence interval: -0.05, -0.01), diabetes (-0.14, 95%CI: -0.22, -0.05), a respiratory condition other than asthma (-0.17, 95%CI: -0.3, -0.04), an organ transplant (-2.66, 95%CI: -3.01, -2.31), being immunosuppressed (-0.22, 95%CI: -0.31, -0.13), and receiving two ChAdOx1 vaccinations (-0.91, 95%CI: -0.96, -0.87) were all independently associated with lower peak spike antibody levels 14-84 days post second vaccination. Having evidence of prior infection was associated with having higher antibody levels (0.29, 95%CI: 0.24, 0.34) (**Table 3**).

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		Univariable				Multivariable			
		Co-efficient	**p-value**	**95% CI**		**Co-efficient**	**p-value**	**95% CI**	
Age	per 10 year older	-0.034	**0.002**	-0.06	-0.01	-0.0	**<0.001**	-0.05	-0.01
Sex	Female	1(ref)							
	Male	0.02	0.6	-0.06	0.09	-0.0	0.1	-0.09	0.01
Ethnicity	White	1(ref)							
	Asian	0.01	0.7	-0.06	0.09				
	Black	-0.22	**0.009**	-0.38	-0.05				
	Mixed	0.07	0.5	-0.13	0.26				
	Other	-0.07	0.4	-0.23	0.09				
Role	Nurse / HCA	1(ref)							
	Doctor	0.1	0.1	-0.02	0.22				
	Administrative staff	0.07	0.1	-0.01	0.15				
	OT/PT/SLT	0.11	0.1	-0.03	0.26				
	Laboratory staff	0.24	**0.002**	0.09	0.39				
	Porter or domestic worker	-0.23	**0.03**	-0.44	-0.03				
	Medical or nursing student	0.07	0.7	-0.26	0.4				
	Other	-0.06	0.1	-0.14	0.01				
BMI	<16	-0.13	0.7	-0.8	0.53				
	16-24.9	1(ref)							
	25-29.9	-0.06	0.1	-0.12	0.01				
	30-34.9	0.01	0.9	-0.08	0.09				
	35-39.9	0.01	0.9	-0.12	0.14				
	40+	0.05	0.5	-0.09	0.19				
Comorbidity	Yes vs. No								
	Smoking	-0.17	**0.003**	-0.29	-0.06	-0.0	0.1	-0.14	0.02
	Pregnant	0.13	0.3	-0.11	0.37				
	Asthma	0.005	0.9	-0.15	0.04				
	Hypertension	-0.06	0.2	-0.15	0.03	-0.0	0.1	-0.12	0.01

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	Thyroid disorder (excluding malignancy)	0.01	0.9	-0.09	0.11	0.06	0.1	-0.02	0.12
	Diabetes	-0.14	**0.03**	-0.26	-0.01	-0.19	**<0.001**	-0.22	-0.05
	Immunosuppression	-0.38	**<0.001**	-0.51	-0.25	-0.21	**<0.001**	-0.31	-0.13
	Psoriasis	-0.13	0.1	-0.3	0.04				
	Heart disease	0.05	0.6	-0.14	0.25				
	Non-haematological malignancy	0.14	0.1	-0.04	0.32	0.13	**0.04**	0.01	0.25
	Rheumatological disorder	-0.28	**0.01**	-0.5	-0.06				
	Respiratory disease (excluding asthma)	-0.22	**0.02**	-0.41	-0.03	-0.15	**0.01**	-0.3	-0.04
	Haematological disease (excluding malignancy)	0.06	0.6	-0.14	0.25				
	Liver disease	-0.03	0.9	-0.38	0.32				
	Neurological disorder	-0.001	0.9	-0.33	0.33				
	CKD stage 3, 4 or 5	-0.84	**<0.001**	-1.3	-0.37				
	Lupus	-0.68	**0.002**	-1.1	-0.24				
	Splenic disorder (excluding traumatic splenectomy)	-0.42	0.2	-1	0.15				
	Haematological malignancy	0.13	0.7	-0.53	0.79				
	Organ transplant	-3.06	**<0.001**	-3.55	-2.57	-2.66	**<0.001**	-3.01	-2.31
Vaccination	BNT162b2/BNT162b2								
	ChAdOx1/ChAdOx1	-0.9	**<0.001**	-0.95	-0.85	-0.94	**<0.001**	-0.96	-0.87
Evidence of Covid-19 infection at baseline (Yes vs No)		0.25	**<0.001**	0.18	0.33	0.28	**<0.001**	0.24	0.34
COVID-age Score	per 10 score higher	-0.05	**<0.001**	-0.06	-0.03				

Table 3. Association between the peak anti-spike IgG antibody levels 14-84 days post-second vaccination dose with each characteristic from the univariable model and multivariable model. Bold indicates a significant p value <0.05. The outcome was modelled in $\log_{10}$ scale. Variables in the multivariable model were selected using backward selection by Akaike Information Criteria (AIC). OT/PT/SLT: occupational therapist, physiotherapist, and speech and language therapist. HCA: healthcare assistant.

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Discussion

While SARS-CoV-2 vaccination offers substantial protection from infection for most HCWs, we found several risk factors associated with lower antibody levels in HCWs after vaccination, including older age, diabetes, respiratory diseases other than asthma, being immunosuppressed, and having had an organ transplant. Infection before the first vaccination led to higher antibody levels post vaccination.

Only 5 (0.3%) HCWs did not seroconvert post second vaccination, which is a smaller proportion than the approximately 1% of the general population who do not seroconvert after two vaccinations[17], and reflects the effectiveness of two vaccine doses in generating antibody responses in this population of predominantly healthy adults of working age.

Receiving two ChAdOx1 vaccine doses yielded lower antibody levels than receiving two BNT162b2 vaccine doses. Although this has been previously reported[17] and may not reflect overall vaccine effectiveness, it was potentially an important factor in many of the 75 (4.6%) HCWs with low antibody responses. These HCWs had peak antibody levels lower than the level associated with 67% protection against the Delta variant infection in a previous study (100 BAU/mL, 700 AU/ml)[17]. Further, with new variants circulating, such as Omicron, with higher antibody levels required for the same level of protection[18,19], two doses of vaccination may not provide good levels of protection for this group.

Among the 80 HCWs who had no or low antibody response, most had underlying medical conditions, including immunosuppression or organ transplant, and 72 had received ChAdOx1 vaccination. These were also identified as the main risk factors for having lower antibody levels in the multivariable regression model, similar to previous studies reporting low antibody levels or seroconversion rate in organ transplant or immunosuppressed patients[20,21]. Therefore, it may be helpful to routinely assess post-vaccination antibody levels in HCWs with comorbidities, especially immunosuppression or organ transplantation. Booster mRNA vaccine doses should be prioritised for this population, in particular those with two prior ChAdOx1 doses, as evidence has shown that a third or fourth dose could significantly improve the suboptimal immune response in organ transplant recipients[22–24].

Other comorbidities independently associated with lower antibody levels post vaccination were diabetes and respiratory diseases other than asthma. Antibody response and seropositivity rates in diabetes patients were also found to be lower than in the healthy population after vaccination in a recent systematic review[25]. We did not find an association between peak antibody levels with BMI, but a study in Scotland suggested that obesity could lead to a short-lived antibody response after vaccination, which may explain some of the increased risk of severe disease in people with obesity[26].

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We also examined the relationship between a COVID-age risk stratification score and vaccine response. The ALAMA COVID-age score is based on OpenSafely data[4] and assesses demographic and health-related risk factors to calculate personal vulnerability to COVID-19, which can be quantified as the probability of death should infection occur in the absence of vaccination or previous infection. In our cohort, 6-7% of HCWs had a high risk, and 1-2% of HCWs had a very high risk based on the scoring system. Overall higher risk groups had lower antibody levels post second vaccination. The COVID-age score can thus potentially be used to identify HCWs at risk of lower antibody levels. However, in most instances these were still at levels associated with high levels of protection against infection, with a median peak level of around 10,000 for the low to high-risk groups. The peak level was lower in the 'very high' risk group, but more than 75% of HCWs in this group still generated peak levels >700 AU/ml (associated with 67% protection against the Delta variant infection[17]). Therefore, vaccination (or previous infection) could provide good immunity and potentially reduce the personal vulnerability to COVID-19 for most HCWs. However, a small minority of HCWs may not be well protected by vaccination and these individuals are also potentially at higher risk of adverse outcomes if infected. Therefore, HCWs assessed as at 'very high' risk of more severe outcome from COVID infection who do not have a history of previous COVID infection should have further vaccine outcome assessment as part of their occupational risk assessment. In those with limited antibody responses, if these remain after booster vaccinations, it may be appropriate to put in place enhanced additional risk mitigations for those HCWs wishing to remain in their current role.

Limitations of this study include that we only examined the peak anti-spike IgG levels after the second vaccination and did not assess antibody waning longitudinally. We therefore did not assess antibody responses after a third booster dose, and this requires further study. We only measured anti-spike IgG levels using a single assay and did not measure neutralizing antibodies or T-cell responses. Vaccine induces a broad range of both B and T cell responses and measure of quantitative IgG antibody is only a surrogate for a broad range of immune response[27]. However, the assay is commercially available and well-calibrated as previously described[15], and neutralizing antibodies are strongly correlated with anti-spike antibodies[17]. The wider generalizability of the analyses is limited given the cohort included in this analysis was predominantly working-age HCWs with 82% being female and 72% of white ethnicity. However, this cohort had diverse health care roles and comorbidities and provides useful data for decision making related to HCWs. Future work with HCWs could focus on creating risk models that adjust for vaccination status, and ideally markers of vaccination response such as antibody levels.

In conclusion, most HCWs seroconverted after their second vaccination including those who had a high risk of adverse outcomes from COVID-19, indicating that two vaccinations are generally

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effective in generating antibody responses among HCWs, such that large-scale antibody testing is not necessary. However, given the high exposure to SARS-CoV-2, routine antibody assessments among high-risk HCWs, such as immunosuppressed patients or organ transplant recipients, could be important, and further booster vaccinations should be prioritised for these groups to improve their immune response alongside careful use of other protective measures.

Ethics Approval

Following approval from the OUH's Caldicott guardian, deidentified data were obtained from the Infections in Oxfordshire Research Database (IORD), which has approvals from the National Research Ethics Service South Central – Oxford C Research Ethics Committee (19/SC/0403), the Health Research Authority and the national Confidentiality Advisory Group (19/CAG/0144).

Contribution statement

The study was designed and planned by WG, EB, SD, KJ, DWE, and AO. This specific analysis was designed by VW, JW, and DWE. VW and JW contributed to the statistical analysis of the data. VW, JW, DWE, and AO drafted the manuscript and all authors contributed to interpretation of the data and results and revised the manuscript. All authors approved the final version of the manuscript.

Competing Interests statement

DWE declares lecture fees from Gilead, outside the submitted work. No other author has a conflict of interest to declare.

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Data sharing statement

The data analysed during the current study are not publicly available as they contain personal data but are available from the Infections in Oxfordshire Research Database (https://oxfordbrc.nihr.ac.uk/research-themes-overview/antimicrobial-resistance-and-modernising-microbiology/infections-in-oxfordshire-research-database-iord/), subject to an application and research proposal meeting the ethical and governance requirements of the Database.

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Figure legend

Figure 1. Box and whisker plot of peak anti-spike IgG levels 14-84 days post-second vaccination according to COVID-age score (a) and comorbidities (b). The number on top of each panel indicates the total number of HCWs in each group. Thyroid disorder excludes malignancy, respiratory disease excludes asthma, haematological disease excludes malignancy, splenic disorder excludes traumatic splenectomy.

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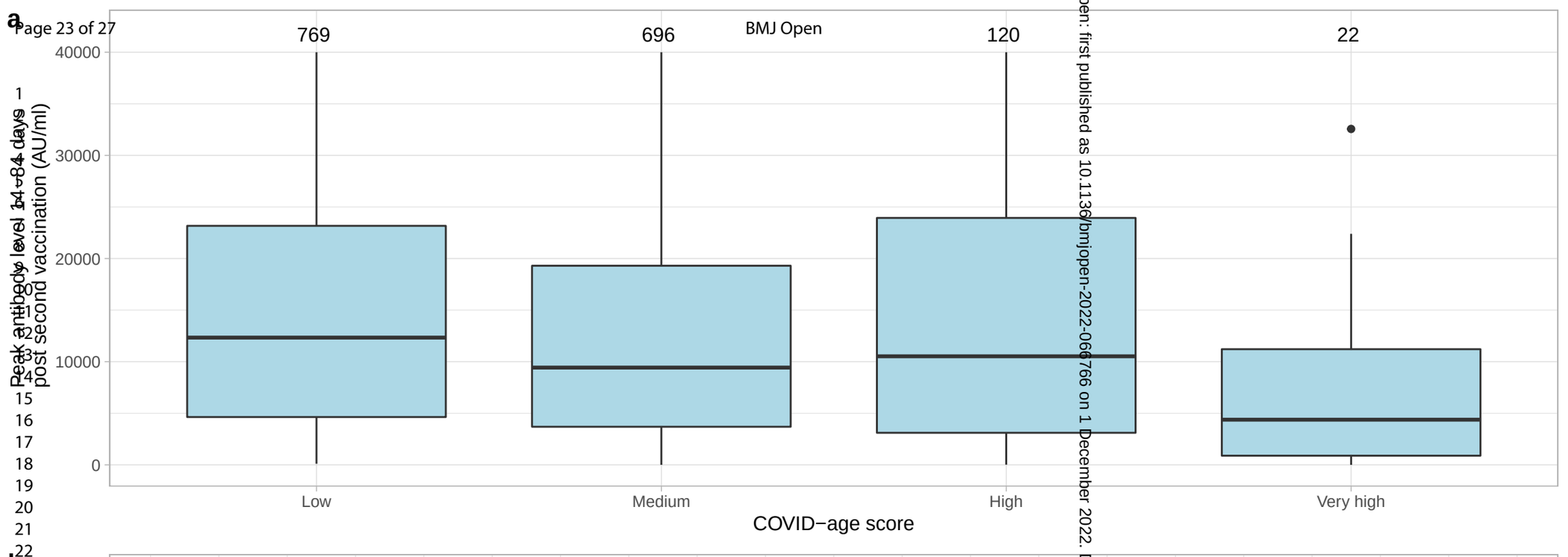

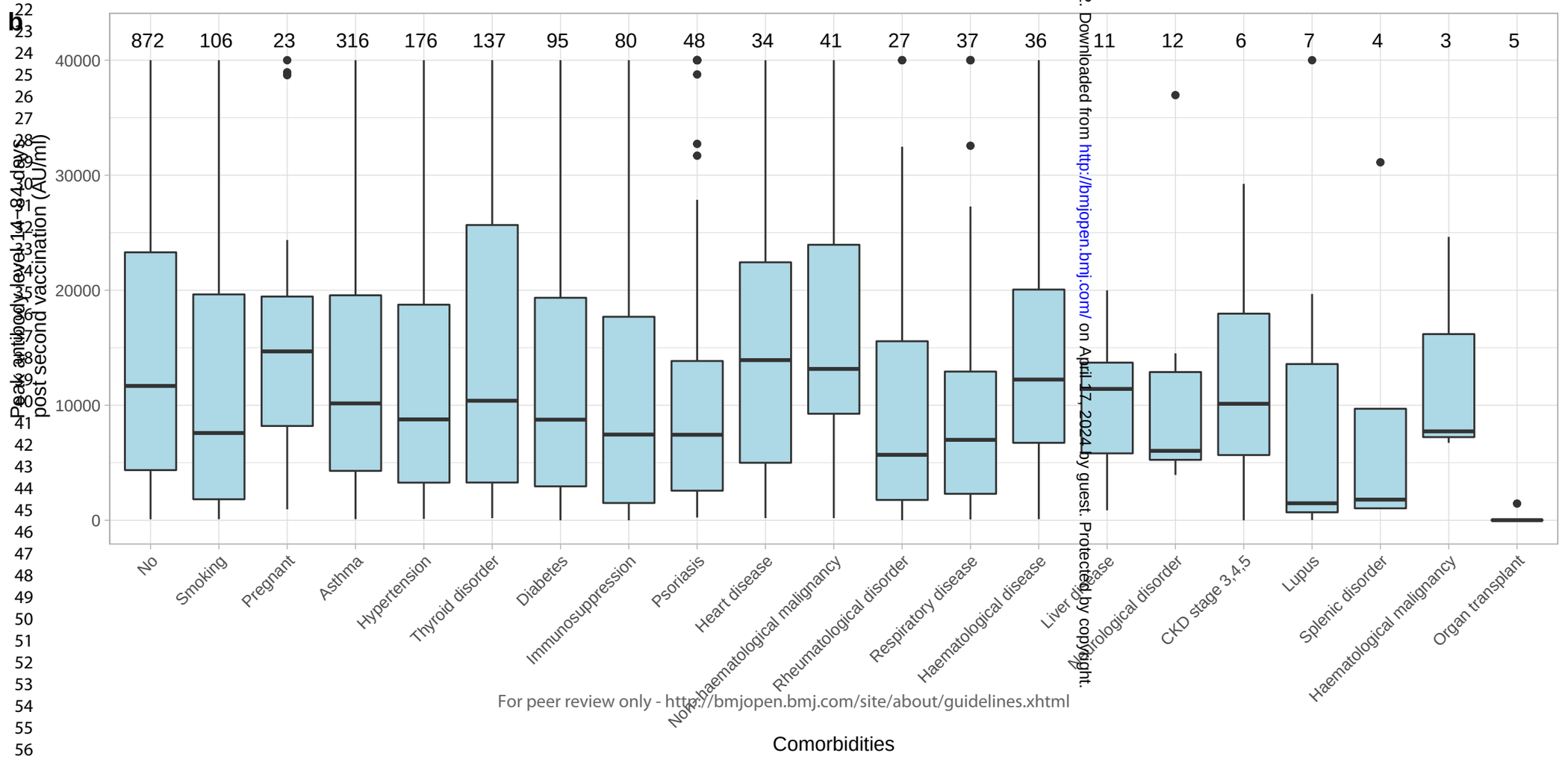

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	Overall (n=5,968)	Included in the analysis (n=1,635)
Age group		
17-34	2,162 (36.6%)	457 (28.0%)
35-54	2,509 (42.5%)	723 (44.2%)
55-77	1,232 (20.9%)	455 (27.8%)
Sex		
Female	4,594 (77.8%)	1,344 (82.2%)
Male	1,298 (22.0%)	290 (17.7%)
Other	11 (0.2%)	1 (0.1%)
Ethnicity		
White	3,623 (60.7%)	1,169 (71.5%)
Asian	1,479 (24.8%)	304 (18.6%)
Black	339 (5.7%)	50 (3.1%)
Mixed	137 (2.3%)	36 (2.2%)
Other	176 (2.9%)	55 (3.4%)
Not stated	214 (3.6%)	21 (1.3%)
Role		
Administrative Staff	912 (15.4%)	245 (15.0%)
Doctor	920 (15.6%)	106 (6.5%)
Laboratory Staff	138 (2.3%)	61 (3.7%)
Medical or nursing Student	65 (1.1%)	12 (0.7%)
Nurse/HCA	2,602 (44.1%)	779 (47.6%)
Other	959 (16.2%)	331 (20.2%)
Porter/Domestic	138 (2.3%)	31 (1.9%)
PT/OT/SLT	169 (2.9%)	70 (4.3%)
BMI		
<16	11 (0.2%)	3 (0.2%)
16-24.9	2,696 (45.2%)	698 (42.7%)
25-29.9	1,939 (32.5%)	517 (31.6%)
30-34.9	829 (13.9%)	261 (16.0%)
35-39.9	295 (4.9%)	85 (5.2%)
40+	198 (3.3%)	71 (4.3%)
Comorbidity		
No	3,336 (55.9%)	872 (53.3%)
Yes	2,632 (44.1%)	763 (46.7%)
Smoking	412 (6.9%)	106 (6.5%)
Pregnant	396 (6.6%)	23 (1.4%)
Asthma	939 (15.7%)	316 (19.3%)
Hypertension	478 (8.0%)	176 (10.8%)
Thyroid disorder (excluding malignancy)	390 (6.5%)	137 (8.4%)
Diabetes	314 (5.3%)	95 (5.8%)
Immunosuppression	216 (3.6%)	80 (4.9%)
Psoriasis	146 (2.4%)	48 (2.9%)
Heart disease	117 (2.0%)	34 (2.1%)

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Non-haematological malignancy	112 (1.9%)	41 (2.5%)
Rheumatological disorder	111 (1.9%)	27 (1.7%)
Respiratory disease (excluding asthma)	98 (1.6%)	37 (2.3%)
Haematological disease (excluding malignancy)	90 (1.5%)	36 (2.2%)
Liver disease	40 (0.7%)	11 (0.7%)
Neurological disorder	40 (0.7%)	12 (0.7%)
CKD stage 3, 4 or 5	26 (0.4%)	6 (0.4%)
Lupus	20 (0.3%)	7 (0.4%)
Splenic disorder (excluding traumatic splenectomy)	14 (0.2%)	4 (0.2%)
Haematological malignancy	12 (0.2%)	3 (0.2%)
Organ transplant	10 (0.2%)	5 (0.3%)
Vaccine combination		
ChAdOx1/ChAdOx1	678 (23.5%)	387 (23.7%)
BNT162b2/BNT162b2	2,164 (75.2%)	1,234 (75.5%)
Other	37 (1.3%)	13 (0.8%)
COVID-age score		
Low	3,433 (59.9%)	769 (47.9%)
Medium	1,867 (32.6%)	696 (43.3%)
High	366 (6.4%)	120 (7.5%)
Very high	65 (1.1%)	22 (1.4%)

Table S1. Comparison of characteristics between the overall population (HCWs with serological data) and the cohort included in the analysis (HCWs with anti-spike IgG measurement 14-84 days post-second vaccination dose). OT/PT/SLT: occupational therapist, physiotherapist, and speech and language therapist. HCA: healthcare assistant.

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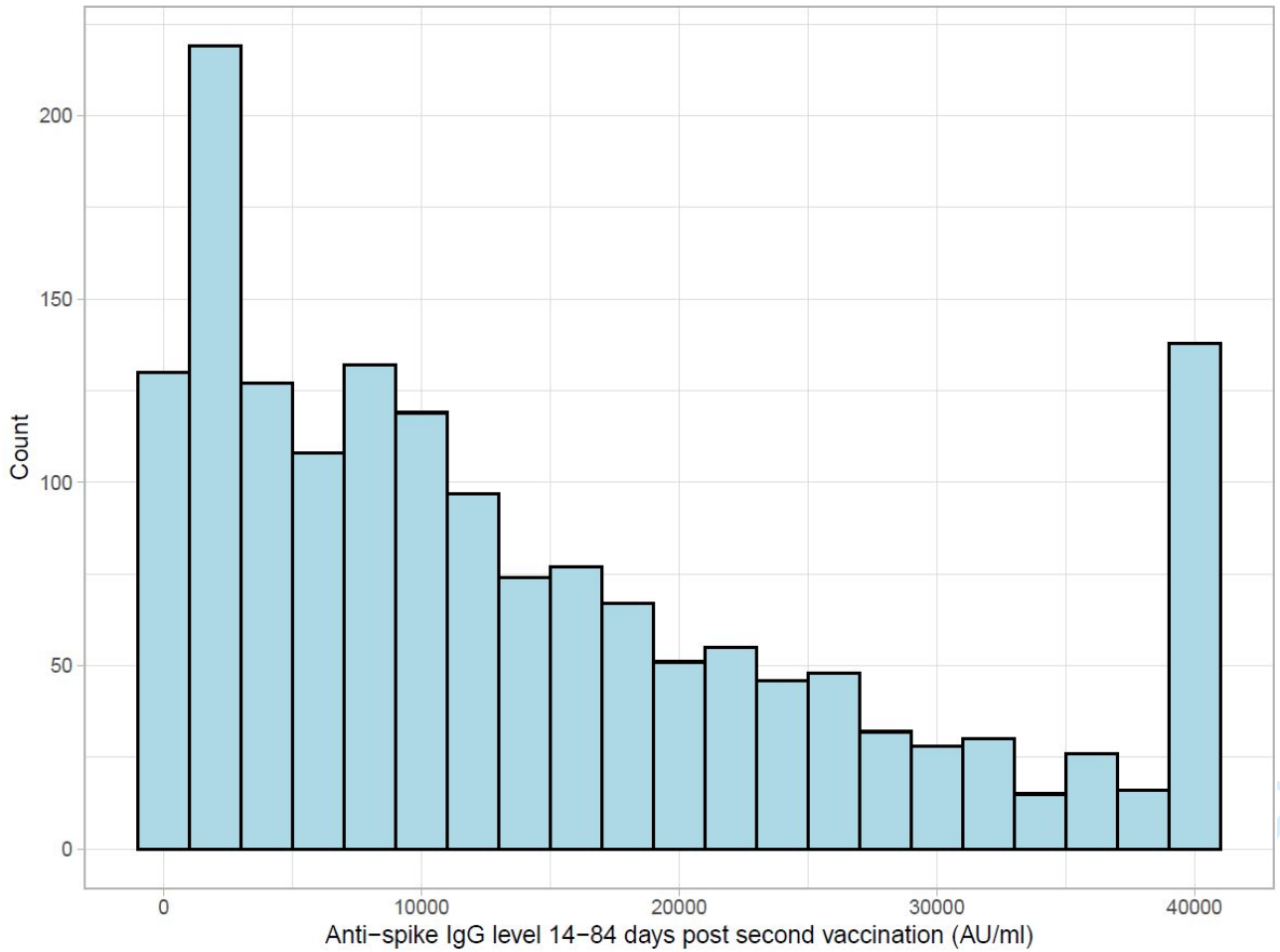

Figure S1. Distribution of peak anti-spike IgG levels 14-84 days post-second vaccination in 1635 HCWs.

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6-7*
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	6-7
		(*c*) Explain how missing data were addressed	6-7
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA

Continued on next page

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Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	8
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*NA*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	*NA*
		Cross-sectional study—Report numbers of outcome events or summary measures	*8-9*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-9
		(*b*) Report category boundaries when continuous variables were categorized	8-9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	9-10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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SARS-CoV-2 antibody responses post-vaccination in UK healthcare workers with pre-existing medical conditions: a cohort study

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SARS-CoV-2 antibody responses post-vaccination in UK healthcare workers with pre-existing medical conditions: a cohort study

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Abstract

Objectives: To examine antibody responses after the second vaccination in healthcare workers (HCWs) with underlying health conditions.

Methods: We examined the peak anti-spike IgG responses after the second vaccination in 1,635 UK HCWs and associations with underlying health conditions and the estimated risk of severe COVID using an occupational health risk assessment tool. We used univariable and multivariable linear regression models to investigate associations between antibody levels and demographics (age, sex, ethnicity), health care role, body mass index, underlying health conditions, vaccination status, prior infection, and the Association of Local Authority Medical Advisors COVID-age risk score.

Results: 1,635 HCWs had anti-spike IgG measurements 14-84 days post second vaccination and data on any underlying health conditions. Only 5 HCWs (0.3%), all on immunosuppressive treatment, (including 4 organ transplant recipients), did not seroconvert after second vaccination. Antibody levels were independently lower with older age, diabetes, immunosuppression, respiratory disorders other than asthma, and markedly so in organ transplant recipients. Levels were independently lower in ChAdOx1 vs. BNT162b2 recipients and higher following previous infection. HCWs with 'very high' COVID-age risk scores had lower median antibody levels than those with 'low', 'medium' or 'high' risk scores; 4,379 AU/ml, compared with 12,337 AU/ml, 9,430 AU/ml, and 10,524 AU/ml respectively.

Conclusions: Two vaccine doses are effective in generating antibody responses among HCWs, including those with a high occupational risk. However, HCWs with underlying health conditions, especially diabetes, immunosuppression, and organ transplant, had lower antibody levels, and vaccine response monitoring may be needed.

Strengths and limitations of this study

- The study focuses on antibody levels post vaccination in healthcare workers (HCWs) with underlying health conditions.
- The study examines the association between the Association of Local Authority Medical Advisors COVID-age tool and vaccine response.
- The study only examines the peak anti-spike IgG levels after the second vaccination and does not assess antibody waning longitudinally.

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- The study may not be widely generalizable given the study population is predominantly working-age HCWs.

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Word count: 3490

Introduction

Healthcare workers (HCWs) have played a central role in the response to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) global pandemic. In many settings HCWs have been shown to be at an increased risk of SARS-CoV-2 infection, with risks relating both to proximity to infected patients and also to increased contact with colleagues compared with those working from home[1–3].

Several interventions have been made to protect HCWs, including risk assessments, improved access to personal protective equipment (PPE) and training, better understanding of effective PPE selection, and modifications to working environments including social distancing and improved ventilation. One widely used UK tool that has been developed to assist in SARS-CoV-2 occupational health risk assessments is the Association of Local Authority Medical Advisors (ALAMA) COVID-age score[4], which uses demographic and medical history factors to estimate the risk of death if a HCW were to become infected. For those at the highest risk, restriction of patient contact or alternative working patterns may be recommended.

Additionally, multiple vaccines have been developed that show good protection against COVID-19 infection, hospitalisation, and death[5–8], including in studies specifically looking at HCWs. Vaccination therefore plays an important role in facilitating those HCWs at higher risk of adverse outcomes from infection to remain in their usual work. Some HCWs, however, may not generate protective immunity following vaccination because of underlying medical conditions, especially those at the highest risk of adverse outcomes.

One potential way to assess which HCWs have responded to vaccination is to look at their antibody levels post vaccination. Various studies have examined antibody responses in HCWs, including looking at the duration, magnitude, and response trajectories[9–12], to understand the level of protection induced from vaccination, and its association with age, sex, and ethnicity[13]. However, few studies have examined the antibody responses in HCWs with underlying comorbidities. In particular, the association between estimated vulnerability of HCWs and antibody response to vaccination has not been studied.

Here we report findings from a retrospective observational study looking at anti-spike IgG antibody responses post second COVID-19 vaccination in HCWs with underlying health conditions, specifically

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focusing on the association between peak antibody levels with the pre-existing underlying health conditions.

Methods

Participants and settings

Oxford University Hospitals (OUH) consists of 4 teaching hospitals in Oxfordshire UK, providing acute and specialist services and employing 13,500 staff. OUH offered vaccination to all HCWs. The programme began on 8-December-2020, initially prioritising those at highest risk of severe COVID, starting with the Pfizer-BioNTech BNT162b2 vaccine, with Oxford-AstraZeneca ChAdOx1 nCoV-19 added from 4 January 2021 and predominately provided to all staff at one acute hospital. Some HCWs received the Oxford-AstraZeneca vaccine in clinical trials beginning 23 April 2020 and were included following unblinding if receiving active vaccine.

OUH has offered SARS-CoV-2 testing to all symptomatic and asymptomatic staff. SARS-CoV-2 PCR testing of combined nasal and oropharyngeal swabs for symptomatic staff (those with a new persistent cough, temperature ≥37.8°C, anosmia, or ageusia) was offered from 27 March 2020 onwards. Asymptomatic HCWs were invited to participate in voluntary nasal and oropharyngeal swab PCR testing and serologic testing from 23 April 2020 to 30 June 2021, as previously described[9,14]. All swabbing was performed by trained staff rather than self-administered. Additional serological testing of HCWs was undertaken by the Occupational Health department based on clinical assessment (results are included from 9 April 2020 onwards).

For occupational health purposes, all HCWs were asked to complete an individual COVID-19 risk assessment and those with underlying health conditions had more detailed risk assessments undertaken by the Occupational Health department. Staff members completed an online questionnaire about their age, sex, ethnicity, body mass index (BMI), underlying health conditions, smoking and pregnancy status, vaccination details, job role and location. COVID-age risk scores[4] were calculated based on this information to enable an appropriate risk assessment to be made by the Occupational Health team.

A total of 5,968 HCWs had serological data available between 9 April 2020 and 26 August 2021, among which 2,878 received two vaccinations. 1,635 HCWs had anti-spike IgG measurements post second vaccination and provided data on any underlying health conditions; these HCWs were included in the study (Figure S1).

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Laboratory tests

Post-vaccination anti-trimeric spike IgG antibody levels were measured using the Abbott SARS-CoV-2 IgG II Quant antibody test (Abbott, Maidenhead, UK) targeting the spike receptor binding domain (RBD), with the cut-off of ≥ 50 AU/mL reported as positive and a linear quantification of detected results from 50 to 40,000 AU/mL[15]. Anti-spike IgG levels above 40,000 AU/ml were truncated at 40,000 AU/ml. The conversion between AU/ml and BAU/mL provided by the manufacturer is: 7 AU/ml= 1 BAU/mL. Pre-vaccination anti-nucleocapsid IgG levels were measured using the Abbott Architect i2000 chemiluminescent microparticle immunoassay (CMIA; Abbott, Maidenhead, UK), with antibody levels ≥1.40 manufacturer's arbitrary units reported as positive. Pre-vaccination anti-trimeric-spike IgG levels were measured using an enzyme-linked immunosorbent assay (ELISA) developed by the University of Oxford[16], with ≥ 8 million units reported as positive.

PCR was performed using the Public Health England SARS-CoV-2 assay (targeting the RdRp gene) or one of five commercial assays: Abbott RealTime (targeting RdRp and N genes; Abbott, Maidenhead, UK), Altona RealStar (targeting E and S genes; Altona Diagnostics, Liverpool, UK), Cepheid Xpert® Xpress SARS-CoV-2 (targeting N2 and E; Cepheid, California, USA), BioFire® Respiratory 2.1 (RP2.1) panel with SARS-CoV-2 (targeting ORF1ab and ORF8; Biofire diagnostics, Utah, USA), Thermo Fisher TaqPath assay (targeting S and N genes, and ORF1ab; Thermo Fisher, Abingdon, UK) or using the ABI 7500 platform (Thermo Fisher, Abingdon, UK) with the US Centers for Disease Control and Prevention Diagnostic Panel of two probes targeting the N gene.

Outcome

We included HCWs aged 17-77 years who completed an occupational health risk assessment, received a two-vaccination course, and had antibody measurements after their second vaccination. The vaccination type was divided into a homologous ChAdOx1 course, homologous BNT162b2 course, and other vaccine types or mixed vaccination.

We used the peak antibody level 14-84 days post second vaccination as the outcome. Antibody response was divided into three groups: high response (peak anti-spike IgG level >700 AU/ml, converted from 100 BAU/mL which is associated with 67% protection against Delta infection [17]), low response (50-700 AU/ml), and no response (<50 AU/ml).

Antibody measurements after breakthrough infections post first vaccination were excluded from the analysis: 26 HCWs had evidence of infection at least 14 days after their first vaccination but prior to their second vaccination, and 37 HCWs had evidence of infection at least 14 days after their second vaccination.

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Covariates

HCW's sex (grouped into male, female and non-disclosed), ethnicity (White, Asian, Black, Mixed, Other, and not stated), BMI (<16, 16-24.9, 25-29.9, 30-34.9, 35-39.9 and 40+) were included. Job role was grouped into nurse or healthcare assistant, doctor, administrative staff, physical, occupational, or speech therapist, laboratory staff, porter or domestic worker, medical or nursing student, or 'other', which included security, estates, catering staff, pharmacists, midwives, and other allied healthcare professionals.

Medical conditions and other potential risk factors included in the analysis were smoking and pregnancy status, and whether each HCW had asthma, hypertension, a thyroid disorder excluding malignancy, diabetes, immunosuppression, psoriasis, heart disease, a non-haematological malignancy, a rheumatological disorder, a respiratory disease other than asthma, a haematological disease excluding malignancy, liver disease, a neurological disorder, chronic kidney disease stage 3, 4 or 5, lupus, a splenic disorder excluding traumatic splenectomy, a haematological malignancy, and an organ transplant. Prior infection was defined as having had a positive PCR result or a positive anti-spike antibody result or a positive anti-nucleocapsid antibody result before the first vaccination dose.

The ALAMA COVID-age risk score was calculated based on age, sex, ethnicity, and presence of comorbidities. It estimates the probability of death should infection occur in the absence of vaccination or previous infection. We used the COVID-age risk score as a proxy for HCW's vulnerability to a poor outcome following SARS-CoV-2 infection and examined its association with antibody levels. A score ≥85 indicates very high vulnerability, 70-84 high vulnerability, 50-69 moderate vulnerability, and <50 low vulnerability. Details of the calculation formula and methods can be found online[4].

Statistical analysis

We first used the Kruskal-Wallis rank test to compare the outcome by different covariate groups. We then built univariable and multivariable linear regression models to examine the association between the outcome on the $\log_{10}$ scale and demographics (age, sex, ethnicity), health care role, BMI, underlying health conditions, vaccination status, prior infection, and COVID-age risk score. Age was truncated at the 2.5th and 97.5th percentile to avoid undue outlier influence and modelled with and without natural cubic splines to test for the non-linear effects. For the multivariable model, backward elimination was used and the model with the lowest Akaike information criteria (AIC) was

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selected. COVID-age score was not included in the multivariable model as it is based on other factors already included in the model.

All analyses were performed in R (version 4.1), using the following packages: tidyverse (version 1.3.1), splines (version 4.0.5), and stats (version 4.0.5).

Patient and public involvement

The oversight committee of the research database used by the study has patient and public representation who participated in reviewing and approving a study summary and analysis plan.

Results

Among 1,635 HCWs, the median (IQR) [range] age was 46 (33-56) [17-77]. 1,344 (82.2%) were female, 1,169 (71.5%) were of white ethnicity, and 779 (47.6%) worked in a nursing or health-care assistant role. 872 (53.3%) did not have any underlying medical condition. The proportion reporting each condition ranged from 0.2% to 19.3%, with asthma being the most common comorbidity. 286 (17.5%) HCWs had evidence of infection prior to their first vaccination. The median (IQR) [range] COVID-age score was 50 (35-59) [16-124], with 120 (7.5%) and 22 (1.4%) HCWs falling in the 'High' and 'Very high' risk groups, respectively. 1,234 (75.5%) and 387 (23.7%) HCWs received two BNT162b2 and ChAdOx1 vaccinations, respectively, and 13 HCWs (0.8%) received other combinations, including mRNA-1273 (**Table 1, 2**). The characteristics were generally similar to the larger group of 5,968 HCWs with serological data, so the cohort included in the analysis should be representative (**Table S1**).

Among 1,635 HCWs, the median (IQR) peak anti-spike binding antibody level 14-84 days post second vaccination was 10,763 (3,925-22,017) AU/ml. The distribution of peak antibody levels is shown in **Figure S2**. Observed antibody levels were different across age groups, health care roles, vaccination types, with or without evidence of prior infection, and COVID-age scores ($p<0.001$). HCWs with 'Very high' vulnerability according to COVID-age scores had the lowest median level of 4,379 AU/ml, compared with 12,337 AU/ml, 9,430 AU/ml, and 10,524 AU/ml in the 'Low', 'Moderate', and 'High' vulnerability groups (**Table 1, Figure 1a**). HCWs with medical conditions and other risk factors had lower median antibody levels than those without (9,637 AU/ml vs. 11,681 AU/ml, $p=0.009$); specifically, antibody levels were lower in smokers (7,588 AU/ml, $p=0.003$), those with hypertension (8,770 AU/ml, $p=0.01$), diabetes (8,748 AU/ml, $p=0.04$), immunosuppression (7,451 AU/ml, $p=0.002$), a respiratory disease other than asthma (6,993 AU/ml, $p=0.01$), and those who had an organ

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transplant (11 AU/ml, p<0.001) (**Table 2, Figure 1b**). There was no evidence of an association between pregnancy and antibody levels (14,684 AU/ml, p=0.6).

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	Total (n=1,635)	Peak antibody levels >700 AU/ml (n=1,555)	Peak antibody levels 50-700 AU/ml (n=75)	Peak antibody levels <50 AU/ml (n=5)	Peak antibody levels 14-84 days post second vaccination (AU/ml)		
Age (years)					**Median**	**IQR**	**p value**
Median	46	46	49	34	(Overall) 10,763	3,925-22,017	
Q1, Q3	33, 56	33, 56	36, 56	33, 43			
Age group							
17-34	457 (100.0%)	439 (96.1%)	15 (3.3%)	3 (0.7%)	14,668	5,359-25,801	**<0.001**
35-54	723 (100.0%)	682 (94.3%)	39 (5.4%)	2 (0.3%)	10,153	3,773-20,578	
55-77	455 (100.0%)	434 (95.4%)	21 (4.6%)	0 (0.0%)	9,328	3,461-19,046	
Sex							
Female	1,344 (100.0%)	1,271 (94.6%)	68 (5.1%)	5 (0.4%)	10,779	3,856 – 22,541	0.7
Male	290 (100.0%)	283 (97.6%)	7 (2.4%)	0 (0.0%)	10,710	4,524 – 19,026	
Non-disclosed	1 (100.0%)	1 (100.0%)	0 (0.0%)	0 (0.0%)	5,438		
Ethnicity							
White	1,169 (100.0%)	1,110 (95.0%)	56 (4.8%)	3 (0.3%)	10,971	3,907 – 22,009	0.3
Asian	304 (100.0%)	290 (95.4%)	14 (4.6%)	0 (0.0%)	10,433	4,180 – 21,829	
Black	50 (100.0%)	45 (90.0%)	4 (8.0%)	1 (2.0%)	7,081	2,104 – 14,388	
Mixed	36 (100.0%)	36 (100.0%)	0 (0.0%)	0 (0.0%)	10,725	4,573 – 29,932	
Other	55 (100.0%)	53 (96.4%)	1 (1.8%)	1 (1.8%)	8,581	4,703 – 20,589	
Not stated	21 (100.0%)	21 (100.0%)	0 (0.0%)	0 (0.0%)	15,786	5,686 – 25,064	
Role							**<0.001**
Administrative Staff	245 (100.0%)	236 (96.3%)	8 (3.3%)	1 (0.4%)	11,653	5,660 – 15,013	
Doctor	106 (100.0%)	102 (96.2%)	4 (3.8%)	0 (0.0%)	12,003	6,677 – 22,113	
Laboratory Staff	61 (100.0%)	58 (95.1%)	2 (3.3%)	1 (1.6%)	20,279	8,790 – 31,137	
Medical or nursing Student	12 (100.0%)	12 (100.0%)	0 (0.0%)	0 (0.0%)	7,933	6,061 – 20,103	
Nurse/HCA	779 (100.0%)	737 (94.6%)	39 (5.0%)	3 (0.4%)	10,844	3,897 – 21,515	

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Other	331 (100.0%)	314 (94.9%)	17 (5.1%)	0 (0.0%)	9,208	2,533 – 20,284	
Porter or domestic worker	31 (100.0%)	27 (87.1%)	4 (12.9%)	0 (0.0%)	8,476	1,533 – 15,644	
OT/PT/SLT	70 (100.0%)	69 (98.6%)	1 (1.4%)	0 (0.0%)	11,849	6,021 – 24,371	
BMI							0.3
<16	3 (100.0%)	2 (66.7%)	1 (33.3%)	0 (0.0%)	17,716	9,195 – 18,471	
16-24.9	698 (100.0%)	667 (95.6%)	28 (4.0%)	3 (0.4%)	11,587	4,186 – 22,134	
25-29.9	517 (100.0%)	491 (95.0%)	24 (4.6%)	2 (0.4%)	10,169	3,404 – 19,046	
30-34.9	261 (100.0%)	247 (94.6%)	14 (5.4%)	0 (0.0%)	10,149	4,318 – 24,585	
35-39.9	85 (100.0%)	81 (95.3%)	4 (4.7%)	0 (0.0%)	10,743	4,534 – 27,281	
>40	71 (100.0%)	67 (94.4%)	4 (5.6%)	0 (0.0%)	11,199	5,877 – 28,260	
Vaccine combination							**<0.001**
ChAdOx1/ChAdOx1	387 (100.0%)	315 (81.4%)	70 (18.1%)	2 (0.5%)	1,603	879 – 3,521	
BNT162b2/BNT162b2	1,234 (100.0%)	1,227 (99.4%)	4 (0.3%)	3 (0.2%)	14,824	8,432 – 25,853	
Other	13 (100.0%)	13 (100.0%)	1 (0.0%)	0 (0.0%)	6,993	4,693 – 13,212	
Evidence of Covid-19 infection at baseline							**<0.001**
No	1,349 (100.0%)	1,269 (94.1%)	75 (5.6%)	5 (0.4%)	9,960	3,302-20,056	
Yes	286 (100.0%)	286 (100.0%)	0 (0.0%)	0 (0.0%)	17,227	7,111 – 28,277	
COVID-age score groups							**<0.001**
Low	769 (100.0%)	737 (95.8%)	32 (4.2%)	0 (0.0%)	12,337	4,634-23,170	
Medium	696 (100.0%)	659 (94.7%)	35 (5.0%)	2 (0.3%)	9,430	3,693-19,302	
High	120 (100.0%)	114 (95.0%)	5 (4.2%)	1 (0.8%)	10,524	3,106-23,939	
Very high	22 (100.0%)	17 (77.3%)	3 (13.6%)	2 (9.1%)	4,379	889-11,214	
COVID-age score							
Median	50	50	53	76			
Q1, Q3	35, 59	35, 60	36, 57	54, 85			

Table 1. Characteristics of the study population according to the peak anti-spike IgG levels post second vaccination. Other for vaccine included mRNA-1273 and other vaccine combinations. OT/PT/SLT: occupational therapist, physiotherapist, and speech and language therapist. HCA: healthcare assistant.

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	Total (n=1,635)	Peak antibody levels >700 AU/ml (n=1,555)	Peak antibody levels 50-700 AU/ml (n=75)	Peak antibody levels <50 AU/ml (n=5)	Peak antibody levels 14-84 days post second vaccination (AU/ml)		
					Median	IQR	p value
Comorbidity							**0.009**
No	872 (100.0%)	830 (95.2%)	42 (4.8%)	0 (0.0%)	11,681	4,362 – 23,299	
Yes	763 (100.0%)	725 (95.0%)	33 (4.3%)	5 (0.7%)	9,637	3,493-19,750	
Smoking	106 (100.0%)	99 (93.4%)	7 (6.6%)	0 (0.0%)	7,588	1,828 – 19,639	**0.003**
Pregnant	23 (100.0%)	23 (100.0%)	0 (0.0%)	0 (0.0%)	14,684	8,199 – 19,453	0.6
Asthma	316 (100.0%)	300 (94.9%)	16 (5.1%)	0 (0.0%)	10,161	4,296 – 19,559	0.2
Hypertension	176 (100.0%)	168 (95.5%)	8 (4.5%)	0 (0.0%)	8,770	3,272 - 18,746	**0.01**
Thyroid disorder (excluding malignancy)	137 (100.0%)	128 (93.4%)	9 (6.6%)	0 (0.0%)	10,395	3,280 – 25,672	0.9
Diabetes	95 (100.0%)	89 (93.7%)	5 (5.3%)	1 (1.1%)	8,748	2,950 – 19,346	**0.04**
Immunosuppression	80 (100.0%)	68 (85.0%)	7 (8.8%)	5 (6.2%)	7,451	1,503 – 17,695	**0.002**
Psoriasis	48 (100.0%)	43 (89.6%)	5 (10.4%)	0 (0.0%)	7,435	2,573 – 13,850	0.06
Heart disease	34 (100.0%)	32 (94.1%)	2 (5.9%)	0 (0.0%)	13,925	4,999 – 22,430	0.7
Non-haematological malignancy	41 (100.0%)	40 (97.6%)	1 (2.4%)	0 (0.0%)	13,159	9,261 – 23,955	0.3
Rheumatological disorder	27 (100.0%)	24 (88.9%)	2 (7.4%)	1 (3.7%)	5,691	1,770 – 15,567	0.05
Respiratory disease (excluding asthma)	37 (100.0%)	33 (89.2%)	4 (10.8%)	0 (0.0%)	6,993	2,302 – 12,927	**0.01**
Haematological disease (excluding malignancy)	36 (100.0%)	35 (97.2%)	1 (2.8%)	0 (0.0%)	12,236	6,738 – 20,060	1
Liver disease	11 (100.0%)	11 (100.0%)	0 (0.0%)	0 (0.0%)	11,419	5,818 – 13,705	0.4
Neurological disorder	12 (100.0%)	12 (100.0%)	0 (0.0%)	0 (0.0%)	6,035	5,258 – 12,886	0.3
CKD stage 3, 4 or 5	6 (100.0%)	5 (83.3%)	0 (0.0%)	1 (16.7%)	10,129	5,672 – 17,965	0.7

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Lupus	7 (100.0%)	5 (71.4%)	1 (14.3%)	1 (14.3%)	1,478	695 – 13,582	0.1
Splenic disorder (excluding traumatic splenectomy)	4 (100.0%)	4 (100.0%)	0 (0.0%)	0 (0.0%)	1,796	1,040 – 9,695	0.2
Haematological malignancy	3 (100.0%)	3 (100.0%)	0 (0.0%)	0 (0.0%)	7,731	7,230 – 16,186	0.9
Organ transplant	5 (100.0%)	1 (20.0%)	0 (0.0%)	4 (80.0%)	11	6 - 21	**<0.001**

Table 2. Comorbidity status of the study population according to the peak anti-spike IgG levels post second vaccination. CKD: chronic kidney disease.

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1,555 (95.1%) HCWs had a peak anti-spike IgG level >700 AU/ml, i.e. a level associated with >67% protection from infection (see Methods). 75 (4.6%) HCWs had a suboptimal antibody level between 50 and 700 AU/ml, and 5 (0.3%) HCWs did not generate a positive antibody response (<50 AU/ml) after the second vaccination. Of the 75 and 5 HCWs with low or no antibody response, the median COVID-age risk score was 53 (IQR 36-57) and 76 (IQR 54-85) respectively - higher than in the high response group (50, IQR 35-60) (p=0.03), but not sufficiently different for the low response group for COVID-age score alone to identify those likely to be in this group. Among the 80 HCWs with low or no antibody response, 72 received two ChAdOx1 vaccinations, accounting for 18.6% of all the ChAdOx1 recipients, whilst the proportion having a low response was only 0.5% of all the BNT162b2 recipients (**Table 1).** HCWs with specific medical conditions were more likely to be in the low or no response groups including 15% of those reporting taking immunosuppression and several other conditions that may also be treated with immunosupression, including low/no antibody responses in 10% with psoriasis, 11% with rheumatological disorders, 11% with other (non-asthma) respiratory disorders, 29% with lupus, and 80% with an organ transplant. Of the 5 HCWs with no detectable serological response, all were female and immunosuppressed, 4 HCWs had had organ transplants and the other HCW having an autoimmune disease for which they recieved rituximab (**Table 2**).

Associations between $\log_{10}$ antibody levels and covariates in univariable linear regression models are shown in **Table 3**. Older age, black ethnicity, working as a porter or domestic worker, and receiving two ChAdOx1 vaccines were associated with lower peak anti-spike antibody levels 14-84 days post second vaccination. Smoking, diabetes, a respiratory disease other than asthma, chronic kidney disease stage 3, 4, or 5, a rheumatological disorder, lupus, being immunosuppressed, or having had an organ transplant were all associated with lower antibody levels. A higher COVID-age score, which indicated higher risk of mortality from infection, was also associated with lower antibody levels (p<0.001). Having evidence of COVID-19 infection prior to vaccination, as well as being a laboratory staff worker, were both associated with having higher antibody levels. No evidence of an association was found between antibody levels and sex or BMI.

1,593 HCWs with complete information on all variables were included in the multivariable model. The baseline intercept in log10 scale was 4.25. Older age (-0.03 per 10 years older, 95% Confidence interval: -0.05, -0.01), diabetes (-0.14, 95%CI: -0.22, -0.05), a respiratory condition other than asthma (-0.17, 95%CI: -0.3, -0.04), an organ transplant (-2.66, 95%CI: -3.01, -2.31), being immunosuppressed (-0.22, 95%CI: -0.31, -0.13), and receiving two ChAdOx1 vaccinations (-0.91, 95%CI: -0.96, -0.87) were all independently associated with lower peak spike antibody levels 14-84 days post second vaccination. Having evidence of prior infection was associated with having higher antibody levels (0.29, 95%CI: 0.24, 0.34) (**Table 3**).

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		Univariable				Multivariable			
		Co-efficient	**p-value**	**95% CI**		**Co-efficient**	**p-value**	**95% CI**	
Age	per 10 year older	-0.034	**0.002**	-0.06	-0.01	-0.07	**<0.001**	-0.05	-0.01
Sex	Female	1(ref)							
	Male	0.02	0.6	-0.06	0.09	-0.06	0.14	-0.09	0.01
Ethnicity	White	1(ref)							
	Asian	0.01	0.7	-0.06	0.09				
	Black	-0.22	**0.009**	-0.38	-0.05				
	Mixed	0.07	0.5	-0.13	0.26				
	Other	-0.07	0.4	-0.23	0.09				
Role	Nurse / HCA	1(ref)							
	Doctor	0.1	0.1	-0.02	0.22				
	Administrative staff	0.07	0.1	-0.01	0.15				
	OT/PT/SLT	0.11	0.1	-0.03	0.26				
	Laboratory staff	0.24	**0.002**	0.09	0.39				
	Porter or domestic worker	-0.23	**0.03**	-0.44	-0.03				
	Medical or nursing student	0.07	0.7	-0.26	0.4				
	Other	-0.06	0.1	-0.14	0.01				
BMI	<16	-0.13	0.7	-0.8	0.53				
	16-24.9	1(ref)							
	25-29.9	-0.06	0.1	-0.12	0.01				
	30-34.9	0.01	0.9	-0.08	0.09				
	35-39.9	0.01	0.9	-0.12	0.14				
	40+	0.05	0.5	-0.09	0.19				
Comorbidity	Yes vs. No								
	Smoking	-0.17	**0.003**	-0.29	-0.06	-0.08	0.12	-0.14	0.02
	Pregnant	0.13	0.3	-0.11	0.37				
	Asthma	0.005	0.9	-0.15	0.04				
	Hypertension	-0.06	0.2	-0.15	0.03	-0.08	0.09	-0.12	0.01

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	Thyroid disorder (excluding malignancy)	0.01	0.9	-0.09	0.11	0.06	0.13	-0.02	0.12
	Diabetes	-0.14	**0.03**	-0.26	-0.01	-0.19	**<0.001**	-0.22	-0.05
	Immunosuppression	-0.38	**<0.001**	-0.51	-0.25	-0.21	**<0.001**	-0.31	-0.13
	Psoriasis	-0.13	0.1	-0.3	0.04				
	Heart disease	0.05	0.6	-0.14	0.25				
	Non-haematological malignancy	0.14	0.1	-0.04	0.32	0.13	**0.04**	0.01	0.25
	Rheumatological disorder	-0.28	**0.01**	-0.5	-0.06				
	Respiratory disease (excluding asthma)	-0.22	**0.02**	-0.41	-0.03	-0.15	**0.01**	-0.3	-0.04
	Haematological disease (excluding malignancy)	0.06	0.6	-0.14	0.25				
	Liver disease	-0.03	0.9	-0.38	0.32				
	Neurological disorder	-0.001	0.9	-0.33	0.33				
	CKD stage 3, 4 or 5	-0.84	**<0.001**	-1.3	-0.37				
	Lupus	-0.68	**0.002**	-1.1	-0.24				
	Splenic disorder (excluding traumatic splenectomy)	-0.42	0.2	-1	0.15				
	Haematological malignancy	0.13	0.7	-0.53	0.79				
	Organ transplant	-3.06	**<0.001**	-3.55	-2.57	-2.66	**<0.001**	-3.01	-2.31
Vaccination	BNT162b2/BNT162b2								
	ChAdOx1/ChAdOx1	-0.9	**<0.001**	-0.95	-0.85	-0.94	**<0.001**	-0.96	-0.87
Evidence of Covid-19 infection at baseline (Yes vs No)		0.25	**<0.001**	0.18	0.33	0.28	**<0.001**	0.24	0.34
COVID-age Score	per 10 score higher	-0.05	**<0.001**	-0.06	-0.03				

Table 3. Association between the peak anti-spike IgG antibody levels 14-84 days post second vaccination with each characteristic from the univariable model and multivariable model. Bold indicates a significant p value <0.05. The outcome was modelled in $\log_{10}$ scale. Variables in the multivariable model were selected using backward selection by Akaike Information Criteria (AIC). OT/PT/SLT: occupational therapist, physiotherapist, and speech and language therapist. HCA: healthcare assistant. CKD: chronic kidney disease.

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Discussion

While SARS-CoV-2 vaccination generates antibody responses for most HCWs, we found several risk factors associated with lower antibody levels after vaccination, including older age, diabetes, respiratory diseases other than asthma, being immunosuppressed, and having had an organ transplant. Given antibody levels are associated with vaccine efficacy and protection against SARS-CoV-2 infection[18,19], HCWs with these risk factors could have a higher risk of infection. Infection before the first vaccination led to higher antibody levels post vaccination.

Only 5 (0.3%) HCWs did not seroconvert post second vaccination, which is a smaller proportion than the approximately 1% of the general population who do not seroconvert after two vaccinations[17], and reflects the effectiveness of two vaccine doses in generating antibody responses in this population of predominantly healthy adults of working age.

Receiving two ChAdOx1 vaccine doses yielded lower antibody levels than receiving two BNT162b2 vaccine doses. Although this has been previously reported[17] and may not reflect overall vaccine effectiveness, it was potentially an important factor in many of the 75 (4.6%) HCWs with low antibody responses. These HCWs had peak antibody levels lower than the level associated with 67% protection against the Delta variant infection in a previous study (100 BAU/mL, 700 AU/ml)[17]. Further, with new variants circulating, such as Omicron, with higher antibody levels required for the same level of protection[20,21], two doses of vaccination may not provide good levels of protection for this group.

Among the 80 HCWs who had no or low antibody response, most had underlying medical conditions, including immunosuppression or organ transplant, and 72 had received ChAdOx1 vaccination. These were also identified as the main risk factors for having lower antibody levels in the multivariable regression model, similar to previous studies reporting lower anti-spike IgG levels in HCWs with any comorbidity compared to healthy HCWs[22], and low antibody levels or seroconversion rates in organ transplant or immunosuppressed patients[23,24], leading to a higher risk of mortality following SARS-CoV-2 infection[25,26]. Therefore, it may be helpful to routinely assess post-vaccination antibody levels in HCWs with comorbidities, especially immunosuppression or organ transplantation. Booster mRNA vaccine doses should be prioritised for this population, in particular those with two prior ChAdOx1 doses, as evidence has shown that a third or fourth dose could significantly improve the suboptimal immune response in organ transplant recipients[27–29].

Other comorbidities independently associated with lower antibody levels post vaccination were diabetes and respiratory diseases other than asthma. Antibody response and seropositivity rates in

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diabetes patients were also found to be lower than in the healthy population after vaccination in a recent systematic review[30]. However, adequate glycaemic control after vaccination improved immunological responses and may even restore the protection against SARS-CoV-2 infection[31]. We did not find an association between peak antibody levels with BMI, but a study in Scotland suggested that obesity could lead to faster waning of immunity after vaccination, which may explain increased disease severity from breakthrough infections in people with obesity[32]. Previous studies also found that hypertension[33] and smoking[34,35] were associated with lower antibody responses post-vaccination; there was marginal evidence for a similar effect in our population (p=0.09; 0.12).

We also examined the relationship between a COVID-age risk stratification score and vaccine response. The ALAMA COVID-age score is based on OpenSAFELY data[4,36] and assesses demographic and health-related risk factors to calculate personal vulnerability to COVID-19, which can be quantified as the probability of death should infection occur in the absence of vaccination or previous infection. In our cohort, 6-7% of HCWs had a high risk, and 1-2% of HCWs had a very high risk based on the scoring system. Overall higher risk groups had lower antibody levels post second vaccination. The COVID-age score can thus potentially be used to identify HCWs at risk of lower antibody levels. However, in most instances these were still at levels associated with high levels of protection against infection, with a median peak level of around 10,000 for the low to high-risk groups. The peak level was lower in the 'very high' risk group, but more than 75% of HCWs in this group still generated peak levels >700 AU/ml (associated with 67% protection against the Delta variant infection[17]). Therefore, vaccination (or previous infection) could provide good immunity and potentially reduce the personal vulnerability to COVID-19 for most HCWs. However, a small minority of HCWs may not be well protected by vaccination and these individuals are also potentially at higher risk of adverse outcomes if infected. Therefore, HCWs assessed as at 'very high' risk of more severe outcome from COVID infection who do not have a history of previous COVID infection should have further vaccine outcome assessment as part of their occupational risk assessment. In those with limited antibody responses, if these remain after booster vaccinations, it may be appropriate to put in place enhanced additional risk mitigations for those HCWs wishing to remain in their current role.

Limitations of this study include that we only examined the peak anti-spike IgG levels after the second vaccination and did not assess antibody waning longitudinally. We therefore did not assess antibody responses after a third booster dose, and this requires further study. We only measured anti-spike IgG levels using a single assay and did not measure neutralizing antibodies or T-cell responses. Vaccine induces a broad range of both B and T cell responses and measure of quantitative IgG antibody is only a surrogate for a broad range of immune response[37]. However, the

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assay is commercially available and well-calibrated as previously described[15], and neutralizing antibodies are strongly correlated with anti-spike antibodies[17]. The wider generalizability of the analyses is limited given the cohort included in this analysis was predominantly working-age HCWs with 82% being female and 72% of white ethnicity. However, this cohort had diverse health care roles and comorbidities and provides useful data for decision making related to HCWs. Future work with HCWs could focus on creating risk models that adjust for vaccination status, and ideally markers of vaccination response such as antibody levels.

The study has several implications for occupational health assessment. Most HCWs seroconverted after their second vaccination including those who had a high risk of adverse outcomes from COVID-19, indicating that two vaccinations are generally effective in generating antibody responses among HCWs, such that large-scale antibody testing is not necessary. However, HCWs with 'very high' COVID-age risk score had lower antibody levels, suggesting the COVID-age tool may help to identify HCWs at risk of lower antibody levels and prioritise which HCWs require further assessment of vaccine responses. Multiple factors are associated with whether a HCW mounts a sufficient response to COVID vaccination. Assessment of these may be pertinent to decisions regarding workplace controls to support HCWs at high risk working safely. Given the high exposure to SARS-CoV-2, routine antibody assessments among high-risk HCWs, such as immunosuppressed patients or organ transplant recipients, could be important, and further booster vaccinations should be prioritised for these groups to improve their immune response alongside careful use of other protective measures.

Ethics Approval

Following approval from the OUH's Caldicott guardian, deidentified data were obtained from the Infections in Oxfordshire Research Database (IORD), which has approvals from the National Research Ethics Service South Central – Oxford C Research Ethics Committee (19/SC/0403), the Health Research Authority and the national Confidentiality Advisory Group (19/CAG/0144).

Contribution statement

The study was designed and planned by WG, EB, SD, KJ, DWE, and AO. This specific analysis was designed by VW, JW, and DWE. VW and JW contributed to the statistical analysis of the data. VW,

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JW, DWE, and AO drafted the manuscript and all authors contributed to interpretation of the data and results and revised the manuscript. All authors approved the final version of the manuscript.

Competing Interests statement

DWE declares lecture fees from Gilead, outside the submitted work. No other author has a conflict of interest to declare.

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Data sharing statement

The data analysed during the current study are not publicly available as they contain personal data but are available from the Infections in Oxfordshire Research Database (https://oxfordbrc.nihr.ac.uk/research-themes-overview/antimicrobial-resistance-and-modernising-microbiology/infections-in-oxfordshire-research-database-iord/), subject to an application and research proposal meeting the ethical and governance requirements of the Database.

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Figure legend

Figure 1. Box and whisker plot of peak anti-spike IgG levels 14-84 days post-second vaccination according to COVID-age score (a) and comorbidities (b). The number on top of each panel indicates the total number of HCWs in each group. Thyroid disorder excludes malignancy, respiratory disease excludes asthma, haematological disease excludes malignancy, splenic disorder excludes traumatic splenectomy.

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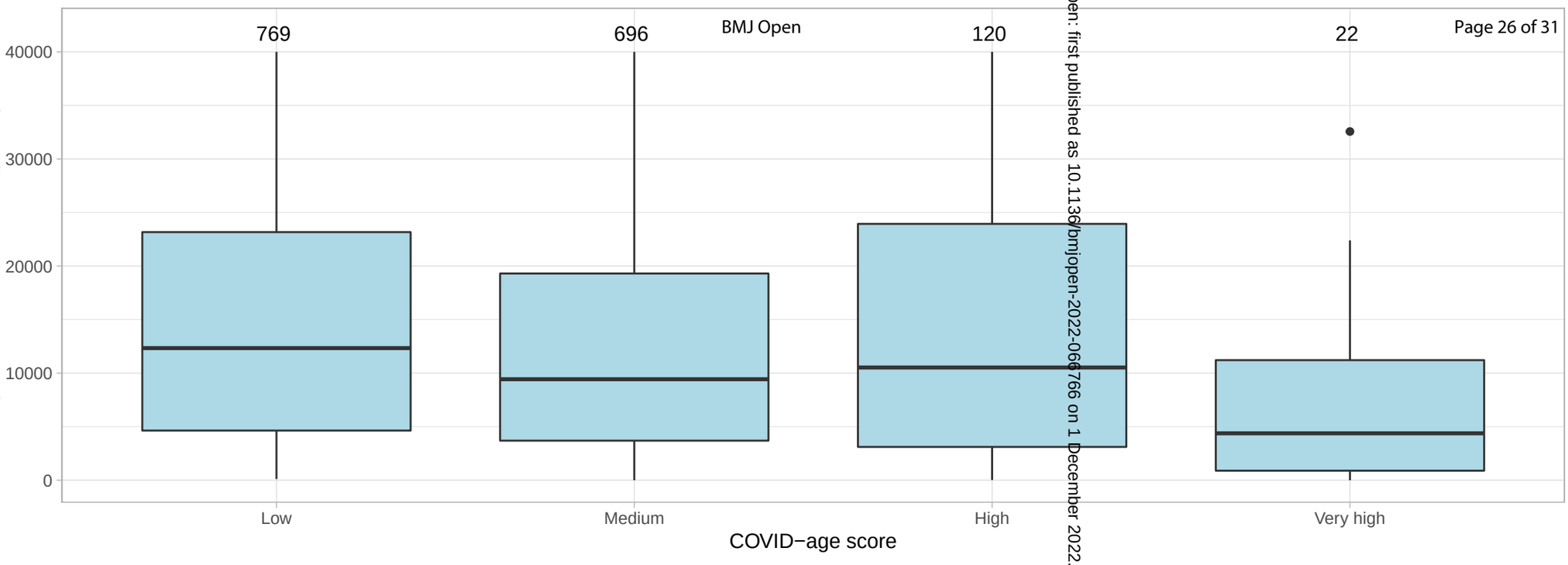
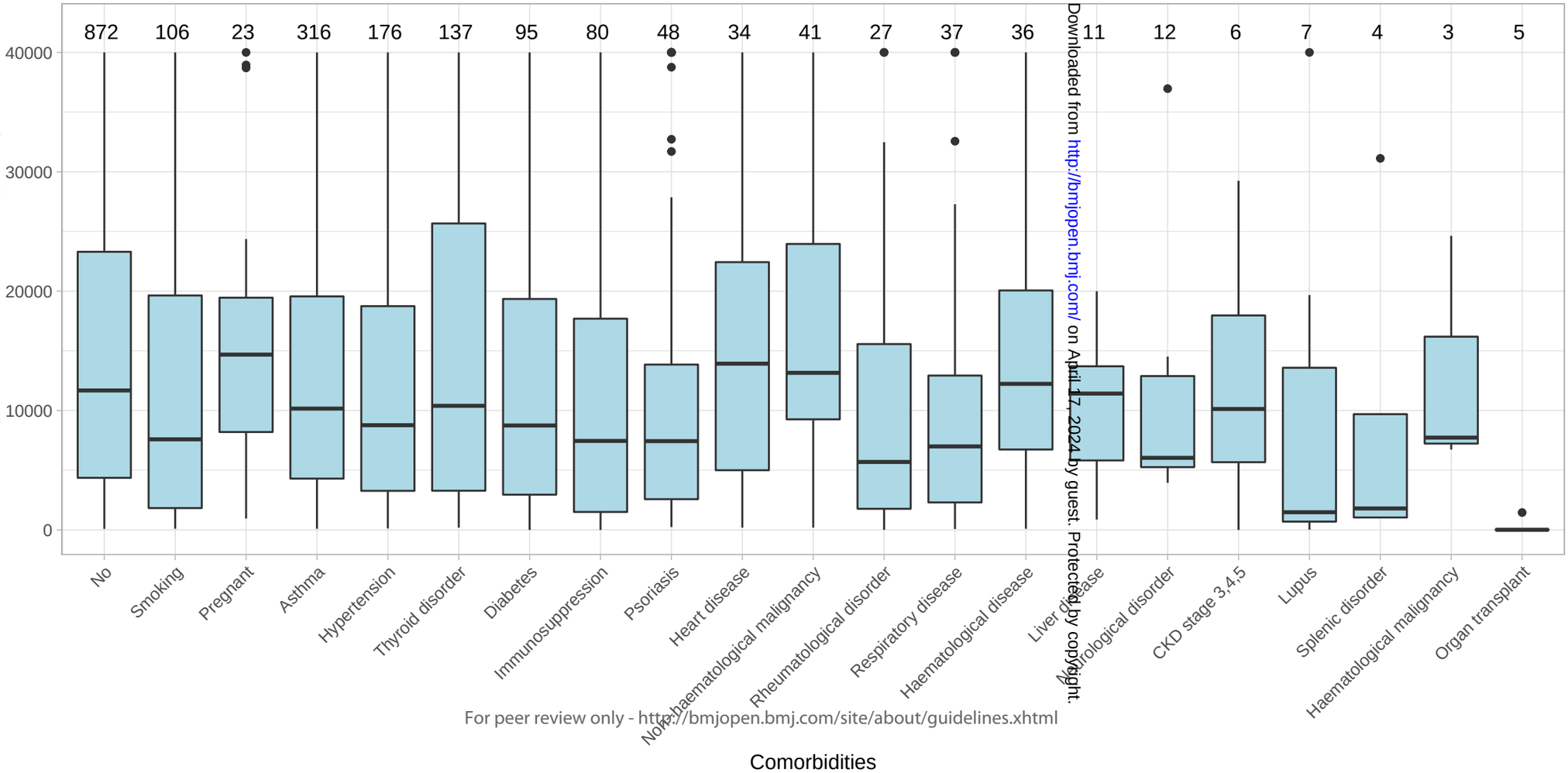
a



b



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	Overall (n=5,968)	Included in the analysis (n=1,635)
Age group		
17-34	2,162 (36.6%)	457 (28.0%)
35-54	2,509 (42.5%)	723 (44.2%)
55-77	1,232 (20.9%)	455 (27.8%)
Sex		
Female	4,594 (77.8%)	1,344 (82.2%)
Male	1,298 (22.0%)	290 (17.7%)
Other	11 (0.2%)	1 (0.1%)
Ethnicity		
White	3,623 (60.7%)	1,169 (71.5%)
Asian	1,479 (24.8%)	304 (18.6%)
Black	339 (5.7%)	50 (3.1%)
Mixed	137 (2.3%)	36 (2.2%)
Other	176 (2.9%)	55 (3.4%)
Not stated	214 (3.6%)	21 (1.3%)
Role		
Administrative Staff	912 (15.4%)	245 (15.0%)
Doctor	920 (15.6%)	106 (6.5%)
Laboratory Staff	138 (2.3%)	61 (3.7%)
Medical or nursing Student	65 (1.1%)	12 (0.7%)
Nurse/HCA	2,602 (44.1%)	779 (47.6%)
Other	959 (16.2%)	331 (20.2%)
Porter/Domestic	138 (2.3%)	31 (1.9%)
PT/OT/SLT	169 (2.9%)	70 (4.3%)
BMI		
<16	11 (0.2%)	3 (0.2%)
16-24.9	2,696 (45.2%)	698 (42.7%)
25-29.9	1,939 (32.5%)	517 (31.6%)
30-34.9	829 (13.9%)	261 (16.0%)
35-39.9	295 (4.9%)	85 (5.2%)
40+	198 (3.3%)	71 (4.3%)
Comorbidity		
No	3,336 (55.9%)	872 (53.3%)
Yes	2,632 (44.1%)	763 (46.7%)
Smoking	412 (6.9%)	106 (6.5%)
Pregnant	396 (6.6%)	23 (1.4%)
Asthma	939 (15.7%)	316 (19.3%)
Hypertension	478 (8.0%)	176 (10.8%)
Thyroid disorder (excluding malignancy)	390 (6.5%)	137 (8.4%)
Diabetes	314 (5.3%)	95 (5.8%)
Immunosuppression	216 (3.6%)	80 (4.9%)
Psoriasis	146 (2.4%)	48 (2.9%)
Heart disease	117 (2.0%)	34 (2.1%)

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Non-haematological malignancy	112 (1.9%)	41 (2.5%)
Rheumatological disorder	111 (1.9%)	27 (1.7%)
Respiratory disease (excluding asthma)	98 (1.6%)	37 (2.3%)
Haematological disease (excluding malignancy)	90 (1.5%)	36 (2.2%)
Liver disease	40 (0.7%)	11 (0.7%)
Neurological disorder	40 (0.7%)	12 (0.7%)
CKD stage 3, 4 or 5	26 (0.4%)	6 (0.4%)
Lupus	20 (0.3%)	7 (0.4%)
Splenic disorder (excluding traumatic splenectomy)	14 (0.2%)	4 (0.2%)
Haematological malignancy	12 (0.2%)	3 (0.2%)
Organ transplant	10 (0.2%)	5 (0.3%)
Vaccine combination		
ChAdOx1/ChAdOx1	678 (23.5%)	387 (23.7%)
BNT162b2/BNT162b2	2,164 (75.2%)	1,234 (75.5%)
Other	37 (1.3%)	13 (0.8%)
COVID-age score		
Low	3,433 (59.9%)	769 (47.9%)
Medium	1,867 (32.6%)	696 (43.3%)
High	366 (6.4%)	120 (7.5%)
Very high	65 (1.1%)	22 (1.4%)

Table S1. Comparison of characteristics between the overall population (HCWs with serological data) and the cohort included in the analysis (HCWs with anti-spike IgG measurement 14-84 days post-second vaccination dose). OT/PT/SLT: occupational therapist, physiotherapist, and speech and language therapist. HCA: healthcare assistant.

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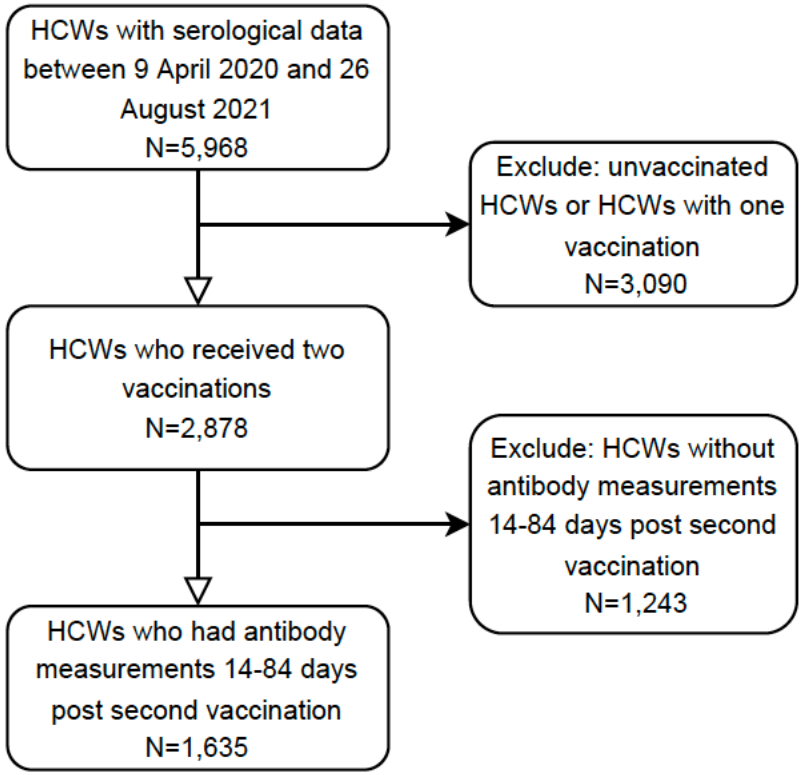

Figure S1. Participants inclusion flowchart.

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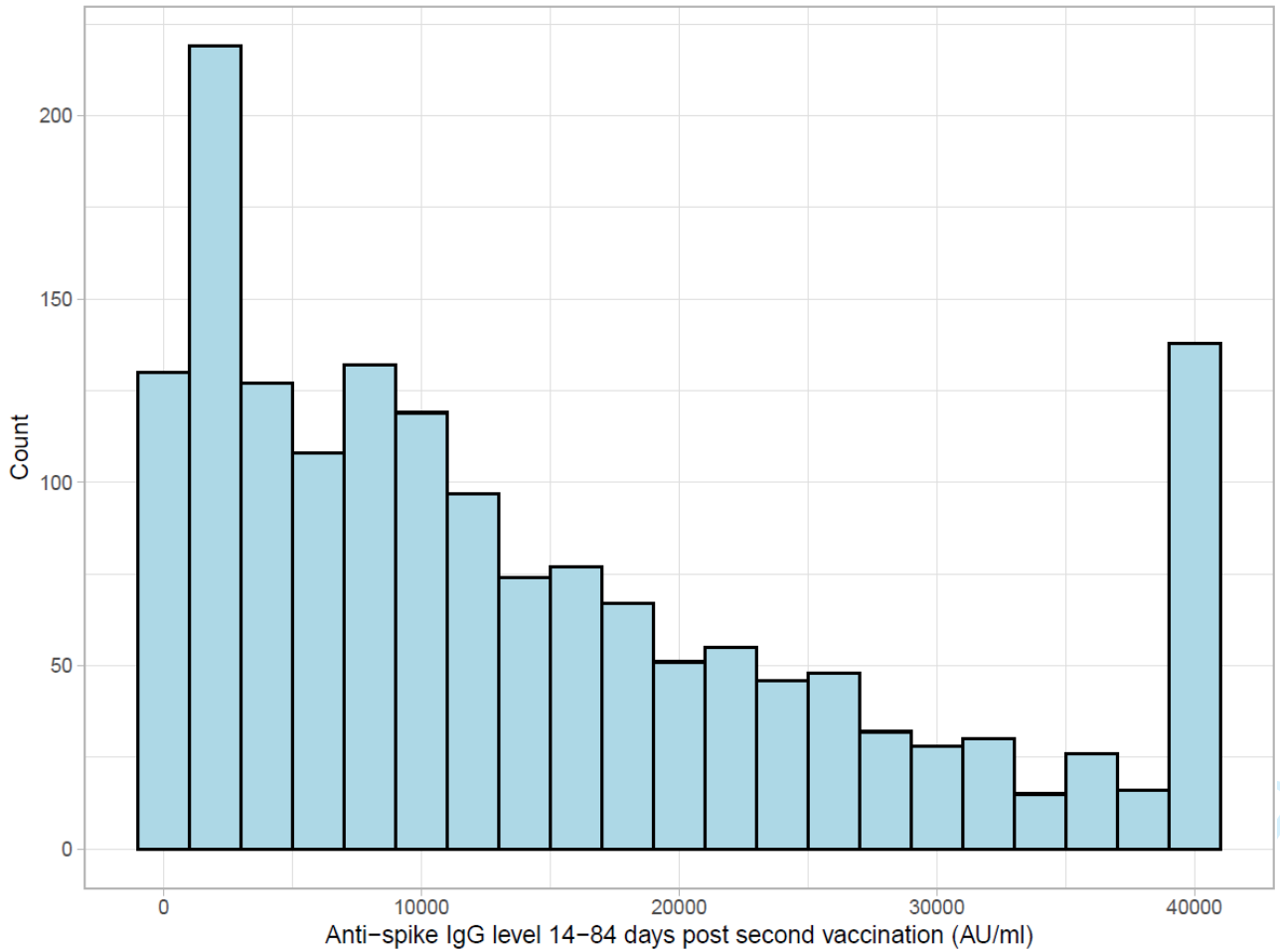

Figure S2. Distribution of peak anti-spike IgG levels 14-84 days post-second vaccination in 1635 HCWs.

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6-7*
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA

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Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	5
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	8
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*NA*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	*NA*
		Cross-sectional study—Report numbers of outcome events or summary measures	*8*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-15
		(*b*) Report category boundaries when continuous variables were categorized	8-15
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	16-17
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	17-18
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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