Immunogenicity of third dose COVID-19 vaccine strategies in patients who are immunocompromised with suboptimal immunity following two doses (OCTAVE-DUO): an open-label, multicentre, randomised, controlled, phase 3 trial

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Summary

Background The humoral and T-cell responses to booster COVID-19 vaccine types in multidisease immunocompromised individuals who do not generate adequate antibody responses to two COVID-19 vaccine doses, is not fully understood. The OCTAVE DUO trial aimed to determine the value of third vaccinations in a wide range of patients with primary and secondary immunodeficiencies.

Methods OCTAVE-DUO was a prospective, open-label, multicentre, randomised, controlled, phase 3 trial investigating humoral and T-cell responses in patients who are immunocompromised following a third vaccine dose with BNT162b2 or mRNA-1273, and of NVX-CoV2373 for those with lymphoid malignancies. We recruited patients who were immunocompromised from 11 UK hospitals, aged at least 18 years, with previous sub-optimal responses to two doses of SARS-CoV-2 vaccine. Participants were randomly assigned 1:1 (1:1:1 for those with lymphoid malignancies), stratified by disease, previous vaccination type, and anti-spike antibody response following two doses. Individuals with lived experience of immune susceptibility were involved in the study design and implementation. The primary outcome was vaccine-specific immunity defined by anti-SARS-CoV-2 spike antibodies (Roche Diagnostics UK and Ireland, Burgess Hill, UK) and T-cell responses (Oxford Immunotec, Abingdon, UK) before and 21 days after the third vaccine dose analysed by a modified intention-to-treat analysis. The trial is registered with the ISRCTN registry, ISRCTN 15354495, and the EU Clinical Trials Register, EudraCT 2021-003632-87, and is complete.

Findings Between Aug 4, 2021 and Mar 31, 2022, 804 participants across nine disease cohorts were randomly assigned to receive BNT162b2 (n=377), mRNA-1273 (n=374), or NVX-CoV2373 (n=53). 356 (45%) of 789 participants were women, 433 (55%) were men, and 659 (85%) of 775 were White. Anti-SARS-CoV-2 spike antibodies measured 21 days after the third vaccine dose were significantly higher than baseline pre-third dose titres in the modified intention-to-treat analysis (median 1384 arbitrary units [AU]/mL [IQR 4·3–7990·0] compared with median 11·5 AU/mL [0·4–63·1]; p<0·001).Of participants who were baseline low responders, 380 (90%) of 423 increased their antibody concentrations to more than 400 AU/mL. Conversely, 166 (54%) of 308 baseline non-responders had no response after the third dose. Detectable T-cell responses following the third vaccine dose were seen in 494 (80%) of 616 participants. There were 24 serious adverse events (BNT612b2 eight [33%] of 24, mRNA-1273 12 [50%], NVX-CoV2373 four [17%]), two (8%) of which were categorised as vaccine-related. There were seven deaths (1%) during the trial, none of which were vaccine-related.

Interpretation A third vaccine dose improved the serological and T-cell response in the majority of patients who are immunocompromised. Individuals with chronic renal disease, lymphoid malignancy, on B-cell targeted therapies, or with no serological response after two vaccine doses are at higher risk of poor response to a third vaccine dose.

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Introduction

Pivotal trials of COVID-19 vaccines excluded patients who were clinically susceptible with an immunocompromised state, yet more than 60% of people older than 65 years live with one or more such chronic disease.[1] Studies that specifically recruited from clinically vulnerable groups,[2,3,4–6] suggest that many individuals who are immunocompromised generate sub-optimal or

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Research in context

Evidence before this study

UK and international COVID-19 vaccination strategies were initially based on clinical trial evidence of safety and efficacy in healthy populations. The pivotal trials that led to the COVID-19 vaccine's conditional approval by the regulatory authorities did not include participants with impaired immunity owing either to their disease or their medication. Emerging evidence from our multidisease OCTAVE trial and several disease-specific cohort studies indicated that the antibody responses induced by two doses of COVID-19 vaccine in patients who are immunocompromised was less than those measured in healthy individuals. The consequent potential for inadequate protection from COVID-19 was a concern and there were also multiple SARS-CoV-2 variants of concern emerging, leading to the realisation that third-or-more booster dose strategies were necessary, especially within the susceptible populations including patients with impaired immunity.

The COV-BOOST trial investigated a healthy population and reported that seven different COVID-19 vaccines were effective in boosting neutralising antibody and cellular responses within 28 days of administration with no safety concerns. Conversely, few disease-specific cohort and observational studies were published on the relative benefit of multiple vaccinations in individuals with different disease or treatment-related immune susceptibilities. On Feb 19, 2024, we searched PubMed for clinical trials investigating three or more doses of COVID-19 vaccines in immunocompromised individuals using the terms- ("SARS-CoV-2" OR "COVID-19") AND ("immunocompromised" OR "immunodeficient") AND ("vaccination"). Filtered on 5 years and Clinical Trials, the search returned 23 publications, of which only five studies included data on immune responses to multiple SARS-CoV-2 vaccine doses in immunocompromised patient groups. Two studies reported serological responses after each vaccine dose in immunocompromised participants from national vaccination programmes. Although both studies provided real world data on positive serological responses at a range of timepoints following the third and where applicable fourth vaccine dose, there was no predetermined vaccine dosing schedule within the studies, which limited interpretation.

A phase 1 trial of two and three doses of the BNT162b2 mRNA vaccine in patients with solid cancers reported neutralising antibody responses, but no improvement in T-cell responses, measured 1 week after a third vaccine dose. A further two prospective single-arm studies evaluated immune responses following a third mRNA vaccine in patients with cancers or haematological malignancies and renal transplant. These studies showed seroconversion of 57% and 35% in patients after three doses. This PubMed search did not find any prospective randomised, controlled, multicentre, clinical trials evaluating the immune response against multiple vaccine doses in patients known to have low or no humoral response to two vaccine doses measuring both humoral responses and T-cell responses in multiple clinically vulnerable disease groups, including rheumatological conditions.

Added value of this study

To our knowledge, OCTAVE-DUO is the largest prospective, randomised controlled trial that has evaluated both the humoral and T-cell responses to a third vaccine dose in patients with conditions associated with impaired immunity and no or inadequate serological responses to previous vaccination, including neutralising antibodies for variants of concern in patients across a spectrum of conditions associated with impaired immunity. The trial has provided robust evidence of the benefit of further vaccination beyond two doses in a wide range of patients with primary and secondary immunodeficiencies. The study showed that the majority of patients who are immunocompromised who mounted a poor response to two vaccine doses, can generate anti-spike antibodies and T-cell responses, to titres equivalent to those seen in the healthy population following a third vaccine dose. Importantly, the study highlights the group of individuals who either do not seroconvert or continue to have a sub-optimal immune response and, therefore, remain susceptible to COVID-19. OCTAVE-DUO also provides insights into the factors that can predict no response to multiple COVID-19 vaccines, and thus help identify individuals where an alternative COVID-19 protection strategy would be indicated.

Implications of all the available evidence

The collective evidence supports national and international COVID-19 vaccination strategies for booster vaccines to enhance both serological and humoral immune protection in susceptible populations. Nevertheless, there remain patient groups for whom this strategy is ineffective but the factors contributing to vaccine failure are complex and multi-dimensional. There should be specific focus on enhancing protective measures for patients with chronic renal disease and lymphoid malignancies and those on B-cell targeted therapies. In addition, consideration should be given to strategies to identify patients who are non-responders after two vaccine doses, where a multiple vaccination strategy is unlikely to be effective and an alternative approach to COVID-19 protection should be considered.

no detectable antibodies after two homologous doses of COVID-19 vaccines. A crucial contemporary question concerns the effect of multiple vaccine exposures. The OCTAVE-DUO trial commenced when data on the effect of a third dose of COVID-19 vaccines were scarce and the COV-BOOST trial in healthy volunteers was ongoing.[7] Several case reports, cohort studies, and single disease clinical trials suggest a variable response to a third COVID-19 vaccine in patients with solid organ transplant,[8–10] cancer,[5,6,11–13] and other immune-mediated diseases,[14] but prospective evidence from randomised controlled trials remains scarce.

The OCTAVE-DUO trial included patients with immune-mediated inflammatory diseases, hepatic and intestinal disease, renal failure, breast and lymphoid malignancies, haematopoietic stem cell transplant (HSCT) and chimeric antigen receptor (CAR) T-cell therapy recipients, and patients with primary immune deficiency. It recruited patients with known a priori suboptimal SARS-CoV-2 antibody responses following two vaccine doses and evaluated whether immunological reactivity could be enhanced by re-boosting with either of the mRNA vaccines BNT162b2 or mRNA-1273, or the nanoparticle vaccine Novavax NVX-CoV2373.

Methods

Study design

OCTAVE-DUO was an open-label, multicentre, randomised, controlled, phase 3 trial, conducted in 11 UK hospitals, recruiting patients who were immunocompromised and had inadequate or no response to two COVID-19 vaccine doses (appendix p 3). Immune responses were compared with a third dose of BNT162b2 or mRNA-1273, and to BNT162b2, mRNA-1273, or NVX-CoV2373 in a sub-group of patients with lymphoid malignancy. The protocol (version 6.0) is available online.

OCTAVE-DUO was coordinated by the Cancer Research UK Clinical Trials Unit (CRCTU) and sponsored by the University of Birmingham and was done in accordance with the principles of the Good Clinical Practice guidelines and the Declaration of Helsinki. It was first approved by the UK Medicines and Healthcare Products Regulatory Agency on July 19, 2021 and amendments approved on July 23, 2021, Oct 13, 2021, Nov 26, 2021 and June 14, 2022. First approval by the London and Fulham Research Ethics Committee (REC 302634) was July 23, 2021 and subsequent amendments on Nov 1, 2021, Dec 3, 2021, and June 6, 2022. A separate CAR T-cell therapy disease cohort was introduced in the November 2022 amendment. All participants gave written informed consent. The trial was overseen by an independent data monitoring committee who reviewed data 3-monthly after the interim assessment to ensure patient safety. There were no formal stopping rules. The trial is registered with the ISRCTN registry, ISRCTN 15354495, and the EU Clinical Trials Register, EudraCT2021-003632-87.

Involvement of patient representatives with relevant lived experience has been core to the OCTAVE-DUO Consortium. Representatives from several immunocompromised groups were in the OCTAVE-DUO Trial Management Group, with direct engagement in the initial study concept and in the trial design development to ensure the feasibility and acceptability from the start and continued involvement throughout the trial, including discussions regarding recruitment strategies and dissemination of results both to study participants and the wider public. In addition, patient representation was included on the trial steering committee to ensure patient–public involvement in the oversight of the trial conduct.

Participants

Patients who were immunocompromised and met disease criteria of one (or more) of the permitted cohorts (appendix p 4) were recruited; solid cancers, lymphoid malignancies, immune-mediated rheumatic diseases, chronic renal disease, chronic liver disease, gastrointestinal disease on immune suppressive therapy, primary immunodeficiency, HSCT, or CAR T-cell therapy.

Eligible patients were aged 18 years or older and had an inadequate response to two doses of COVID-19 vaccine based on anti-SARS-CoV-2 spike antibodies measured at least 14 days after receipt of the second vaccine dose. An inadequate response was defined as either antibody no-response, anti-SARS-CoV-2 spike antibodies below the level of detection by the Roche Elecsys Anti-SARS-CoV-2 immunoassay (Roche Diagnostics UK and Ireland, Burgess Hill, UK]; or equivalent assay, see appendix p 5) <0·8 arbitrary units (AU)/mL; or antibody low response, anti-SARS-CoV-2 spike antibodies of at least 0·8 and less than 400 AU/mL by use of the Roche Elecsys platform, equating to the lowest value measured in healthy control participants in the PITCH study[2] (or equivalent assay, see appendix p 5). Exclusion criteria are detailed in the appendix (p 29).

Eligible participants were identified from their participation in other COVID-19 vaccine studies[2–6] or if anti-SARS-CoV-2 spike antibody concentrations were available from local clinics. To increase recruitment in the solid cancer, HSCT, and CAR T-cell therapy disease cohorts only, an anti-SARS-CoV-2 spike antibody response could be measured as a screening assessment by use of the protocol permitted assays (appendix p 5).

Concomitant treatments were categorised into nine drug classifications: corticosteroids, B-cell targeted therapy (including rituximab), anti-metabolites, conventional synthetic disease-modifying antirheumatic drugs, Janus kinase inhibitors, cytotoxic chemotherapy, hormonal therapies, biological therapies, and calcineurin inhibitors (appendix pp 6–8).

Randomisation and masking

Randomisation used automated minimisation to balance important factors. Eligible patients were randomly assigned 1:1 to receive BNT162b2 or mRNA-1273. The minimisation algorithm used stratification factors: disease cohort, previous COVID-19 vaccine type (BNT162b2 or ChAdOx1-nCov19), and baseline post-two dose antibody response (ie, no or low response) and balanced within participating sites.

Patients with lymphoid malignancy were randomly assigned 1:1:1 to receive BNT162b2, mRNA-1273, or NVX-CoV2373 and stratified by lymphoid malignancies

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See **Online** for appendix

For the **protocol** see https://www.birmingham.ac.uk/research/crctu/trials/octave/octave-duo

subcohort diseases, previous COVID-19 vaccine type, baseline post-two dose antibody response (ie, no or low response) and balanced within participating sites.

A random component was included when the treatment group was allocated at random, irrespective of stratifying variables, 20% of the time. Treatment allocation was via an electronic CRCTU-based randomisation system and not masked after randomisation.

Procedures

Sex was captured by local investigator on case report forms as male or female. Baseline research samples, including whole blood and serum plasma were collected from participants within 14 days before receiving the allocated trial vaccine, which was delivered via intramuscular injection after their second dose, according to local practice. Standard doses of vaccines were administered (BNT162b2, 30 µg in 0·3 mL; mRNA-1273 100 µg in 0·5 mL; NVX-CoV2373 5 µg recombinant spike protein with 5 µg Matrix-M1 adjuvant in 0·5 mL). After the third vaccine dose, further research samples were collected between day 21 and 35. Clinical data were collected at 3 months following the third dose. All samples were handled as detailed in standard operating procedures for blood sampling and processing.[15]

Adverse events were reported from the date of third vaccine to 21 days. Serious adverse events were captured from consent to 28 days. Adverse events and serious adverse events were graded by use of the Common Terminology Criteria for Adverse Events, version 5.0.

Outcomes

The primary outcome was vaccine-specific immunogenicity as defined by the concentrations of anti-SARS-CoV-2 spike antibodies and T-cell responses to SARS-CoV-2 spike peptides 21 days after the third vaccine dose compared with pre-third vaccine responses. To ensure standardisation of outcome measures, all anti-SARS-CoV-2 spike antibodies at baseline and following third dose vaccination were measured by use of the Roche Elecsys platform by the UK Health Security Agency Laboratories at Porton Down. Neutralising antibody titres 21 days after the third vaccine dose was a secondary outcome. High-throughput live virus microneutralisation assays to wild-type, delta, and BA.1 omicron SARS-CoV-2 were done as previously described.[16] T-cell responses to SARS-CoV-2 peptides at baseline and following third vaccine dose were measured by use of the Oxford Immunotec modified T-spot discovery SARS-CoV-2 assay (Abingdon, UK). This interferon-γ (IFNγ) enzyme-linked immunosorbent spot (ELISpot) assay measured T-cell reactivity to SARS-CoV-2 spike (S1, S2), nucleocapsid, and membrane peptides. T-cell responses were reported as either present or absent by use of the manufacturer's cutoff thresholds. T-cell responses against wild-type and BA.1 omicron were measured with an in-house IFNγ ELISpot assay by use of 18-mer S1 and S2 peptide pools containing only those peptides with omicron variant amino acids relative to wild-type to measure responses pre-third and post-third vaccination.[17]

In participants with lymphoid malignancies, vaccine specific immunogenicity in response to third vaccination (as defined for the primary outcome) with BNT162b2, mRNA-1273, or NVX-CoV2373 vaccines was included as a secondary outcome.

All participants who received a third vaccine dose were included in the safety analysis. A descriptive analysis of the reported participants' adverse events was included as an exploratory outcome.

Statistical analysis

The primary analysis was the immune response observed in the total combined participants recruited to both the BNT162b2 and mRNA-1273 groups in the main study. Analysis was based on the difference in immune response measured by anti-SARS-CoV-2 spike antibody concentrations at baseline (pre-third vaccination) and day 21 after the third vaccine. We analysed differences between the two timepoints using a paired *t*-test or used the non-parametric Wilcoxon signed rank test .

A power calculation based on a paired *t* test was done to estimate the detectable effect size based on a proposed recruitment of 1100 participants; enabling detection of a minimum difference in the means of 0·0978 with 90% power and significance (alpha) of 5%.

Assay data from participants with lymphoid malignancies, randomly assigned to receive BNT162b2, mRNA-1273, or NVX-CoV2373 were analysed by use of repeated measure ANOVA with a Tukey's post-hoc test to detect differences in groups. A power calculation based on an ANOVA statistical test was carried out to estimate the detectable effect size based on total sample size number of 300 participants, recruited into one of the three treatment groups (n=100 in each group). With power of 80%, significance (alpha) set at 5%, an effect size of 0·18 would be detected. Analyses were done by use of R4.0.3 and Stata 17.0.

An analysis was done on the first 160 participants recruited (combining all disease groups, including participants in the main and substudy randomisation) as a mandated confidential report to the UK Government's Vaccine Task Force. This was a descriptive analysis of the magnitude of the anti-SARS-CoV-2 spike antibody response and the T-cell responses as measured by the Oxford Immunotec modified T-SPOT Discovery SARS-CoV-2 assay and did not influence the subsequent conduct of the study.

Primary and secondary outcomes were analysed by use of a modified intention-to-treat approach, which included data from those participants where both baseline and day 21 assay data were available. Participants who did not receive their third vaccination were excluded from these

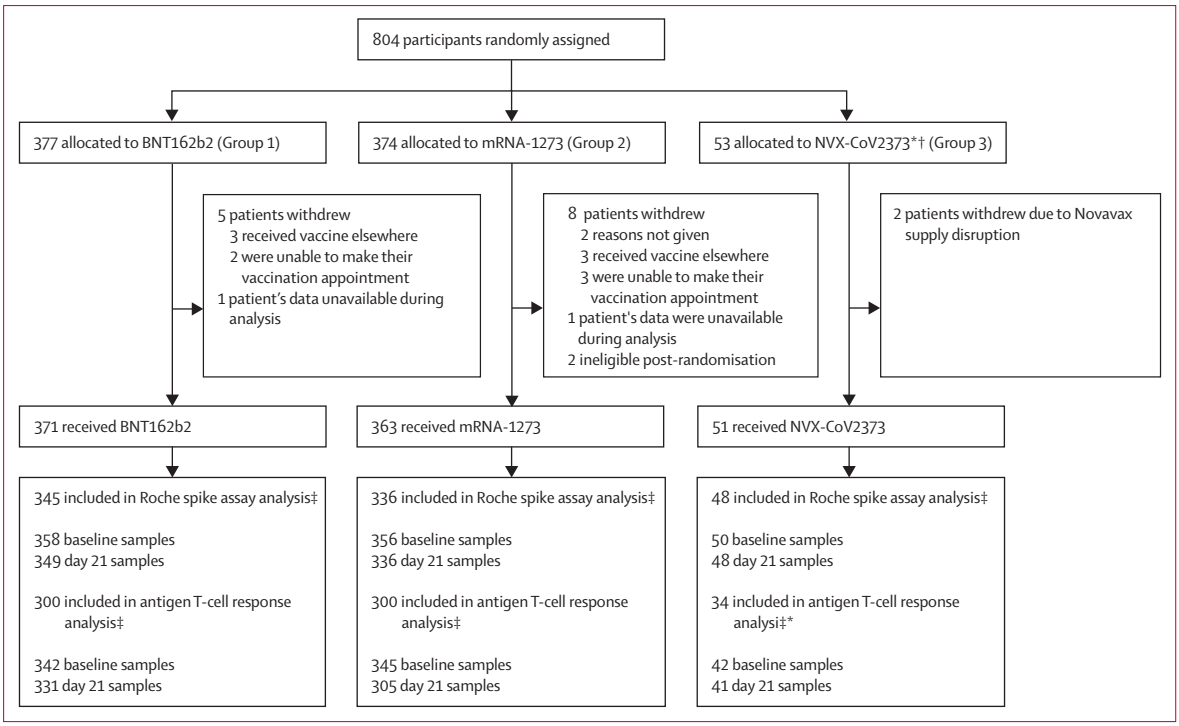

Figure 1: **OCTAVE-DUO trial profile**
*NVX-COV2373 was given to patients with lymphoid malignancies only. †Initially 58 participants were randomly assigned to NVX-CoV2373 but owing to a temporary halt in supply of this vaccine, five were randomly re-assigned. ‡Only patients who had results from both baseline and day 21 samples were included within the analyses. It was identified that 32 (4%) of 804 participants included in the analysis were ineligible post-randomisation owing to site administrative error which led to an incorrect SARS-COV-2 antibody result being used to confirm eligibility. Post-analysis, it was also found that five patients were ineligible post-randomisation, two owing to having received a flu vaccine 30 days before trial entry, and three owing to a sensitivity issue checking serology status pretrial entry. All were included in the analysis

analyses. No data were available for the participants receiving CAR T-cell therapy, therefore this cohort was excluded from these analyses.

Four logistic regression models were used to further analyse anti-SARS-CoV-2 spike antibody and T-cell responses. Two models analysed the anti-SARS-CoV-2 spike antibody responses, one for data from the BNT162b2 and mRNA-1273 groups, one for data from the BNT162b2, mRNA-1273, and NVX-CoV2372 groups specifically for the lymphoid malignancy cohort. Similarly, there were two models for T-cell responses, one analysing data from two groups (BNT162b2 and mRNA-1273), and one for the three groups (BNT162b2, mRNA-1273, and NVX-CoV2372) for the lymphoid malignancy cohort. We established four datasets for each of the models using the population for analysis that included all eligible patients who have both baseline and post-third vaccination results available. The following variables were considered for use in the models; third vaccine type, response at randomisation–baseline (for antibody and T-cell response, respectively), previous vaccine received (BNT162b2, mRNA-1273, ChAdOx1), disease cohort, ethnicity, BMI, age, sex, time interval from second vaccination, previous SARS-CoV-2 infection, and treatment usage. Treatment usage was classified into nine variables associated with the drug classifications defined previously (appendix p 6). Participants with any unknown data were removed from the model such that only complete cases were used.

Role of the funding source

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

Results

Between Aug 4, 2021 and March 31, 2022, 804 participants across nine disease cohorts were randomly assigned; 377 (47%) of 804 were assigned to receive BNT162b2, 374 (47%) to mRNA-1273, and 53 (7%) to NVX-CoV2373 (figure 1). 356 (45%) of 789 participants were women, 433 (55%) were men, and 659 (85%) of 775 were White. Post-randomisation, five (of 804 [1%]) participants were randomly reassigned owing to a pause in the availability of NVX-CoV2373 and the data presented for these participants are for the randomly reassigned vaccine allocation only. 15 (2%) of 804 participants withdrew; the main reasons for withdrawal were participant decision not to receive the third dose vaccine or to have the third dose outside the study (eg, in primary care). Participant characteristics by treatment group are described in table 1, with comorbidities, previous vaccines, self-reported

	BNT162b2 (n=377)	mRNA-1273 (n=374)	NVX-CoV2373 (n=53)
Age, years			
15–44	74 (20%)	87 (23%)	1 (2%)
45–64	170 (45%)	159 (43%)	16 (30%)
65–74	93 (25%)	84 (22%)	27 (51%)
≥75	40 (11%)	44 (12%)	9 (17%)
Sex			
Female	170/370 (46%)	173/368 (47%)	13/51 (25%)
Male	200/370 (54%)	195/368 (53%)	38/51 (75%)
Missing	7	6	2
Ethnicity			
Black	9/365 (2%)	8/359 (2%)	2/51 (4%)
East Asian	3/365 (1%)	3/359 (1%)	0
Mixed race	2/365 (1%)	4/359 (1%)	0
Other	13/365 (4%)	17/359 (5%)	3/51 (6%)
South Asian	26/365 (7%)	26/359 (7%)	0
White	312/365 (85%)	301/359 (84%)	46/51 (90%)
Missing	12	15	2
BMI			
Underweight, <18·5	8/326 (3%)	3/315 (1%)	1/49 (2%)
Normal weight, 18·5–24·9	103/326 (32%)	112/315 (36%)	13/49 (27%)
Overweight, 25–29·9	133/326 (41%)	123/315 (39%)	24/49 (49%)
Obese, 30–39·9	82/326 (25%)	77/315 (24%)	11/49 (22%)
Very obese, ≥40	0	0	0
Missing	51	59	4
Disease cohort			
Immune-mediated rheumatic diseases	95 (25%)	94 (25%)	0
Lymphoid malignancy	62 (16%)	63 (17%)	53 (100%)
Chronic renal disease	83 (22%)	81 (22%)	0
Gastrointestinal disease on immune suppressive therapy	48 (13%)	47 (13%)	0
Chronic liver disease	40 (11%)	42 (11%)	0
Haemopoietic stem cell transplant	22 (6%)	22 (6%)	0
Primary immunodeficiency	20 (5%)	20 (5%)	0
Solid cancer	5 (1%)	5 (1%)	0
CAR T-cell therapy	2 (1%)	0	0
Smoking status			
Current smoker	30/285 (11%)	20/287 (7%)	5/46 (11%)
Never smoked	149/285 (52%)	176/287 (61%)	19/46 (41%)
Not known	2/285 (1%)	2/287 (1%)	0
Previous smoker	104/285 (36%)	89/287 (31%)	22/46 (48%)
Missing	92	87	7
WHO performance status			
0	230/361 (64%)	219/358 (61%)	34/50 (68%)
1	98/361 (27%)	91/358 (25%)	15/50 (30%)
2	27/361 (7%)	38/358 (11%)	0
3	6/361 (2%)	9/358 (3%)	1/50 (2%)
4	0	1/358 (<1%)	0
Missing	16	16	3

Data are n (%) or n/N (%).

Table 1: **Patient baseline characteristics**

COVID-19 history, and baseline characteristics by disease cohort shown in the appendix (pp 9–11, 13).

Anti-SARS-CoV-2 spike antibodies were measured at baseline and at day 21 after the third vaccine for 729 (91%) of 804 participants, of whom 185 (25%) had an immune-mediated rheumatic disease, 169 (23%) had lymphoid malignancies, 142 (19%) had chronic renal disease, 83 (11%) had a gastrointestinal disease, 76 (10%) had chronic liver disease, 35 (5%) had primary immunodeficiency, 30 (4%) had undergone a haematopoietic stem cell transplant, and nine (1%) had a solid cancer. This permitted accurate allocation of participants at baseline accounting for the effect of previous (non-trial) assay error or intercurrent native infection since non-trial antibody testing was done. Of 423 participants categorised as previous low responders at trial entry, 51 (12%) had baseline anti-SARS-CoV-2 spike antibody concentrations greater than 400 AU/mL (range 409–6337) and were, therefore, re-designated as responders. Of the remaining 306 participants categorised at randomisation as previous antibody non-responders at trial entry, 68 (22%) had baseline anti-SARS-CoV-2 spike antibody concentrations greater than 0·8 AU/mL (range 0·857–1968) and were re-designated as either low responders or responders (appendix p 14). These response data are presented disaggregated by sex in the appendix (p 15). At baseline anti-nucleocapsid antibody results were available for 743 participants, of which 39 were positive, suggesting a previous SARS-CoV-2 infection.

Anti-SARS-CoV-2 spike antibodies measured 21 days after the third dose were significantly higher than baseline pre-third dose concentrations in the modified intention-to-treat analysis (median 1384 AU/mL [IQR 4·3–7990·0] compared with median 11·5 AU/mL [0·4–63·1]; p<0·001). Results are presented for each vaccine group (figure 2A) and split by baseline responder status (figure 2B). Most baseline low responders (380 [90%] of 423) had an increase in antibody concentration to more than 400 AU/mL following the third vaccine dose, however, 166 (54%) of 306 who were baseline non-responders after two doses, still had no antibody response following the third vaccine dose. Five patients developed de novo anti-nucleocapsid antibody titres between baseline and day 21 post-vaccine.

Results from both the baseline and day 21 antigen specific T-cell assay were available for 616 (77%) of 804 participants and included in the modified intention-to-treat analysis. Detectable anti-spike T-cell responses following the third vaccine were seen in 494 (80%) of 616 participants. Moreover, 106 (56%) of the 191 participants who had no measurable T-cell response before the third vaccine mounted a T-cell response following the third dose. A similar proportion of T-cell responses were seen for all three vaccine types (table 2). T-cell responses varied between disease cohorts with the

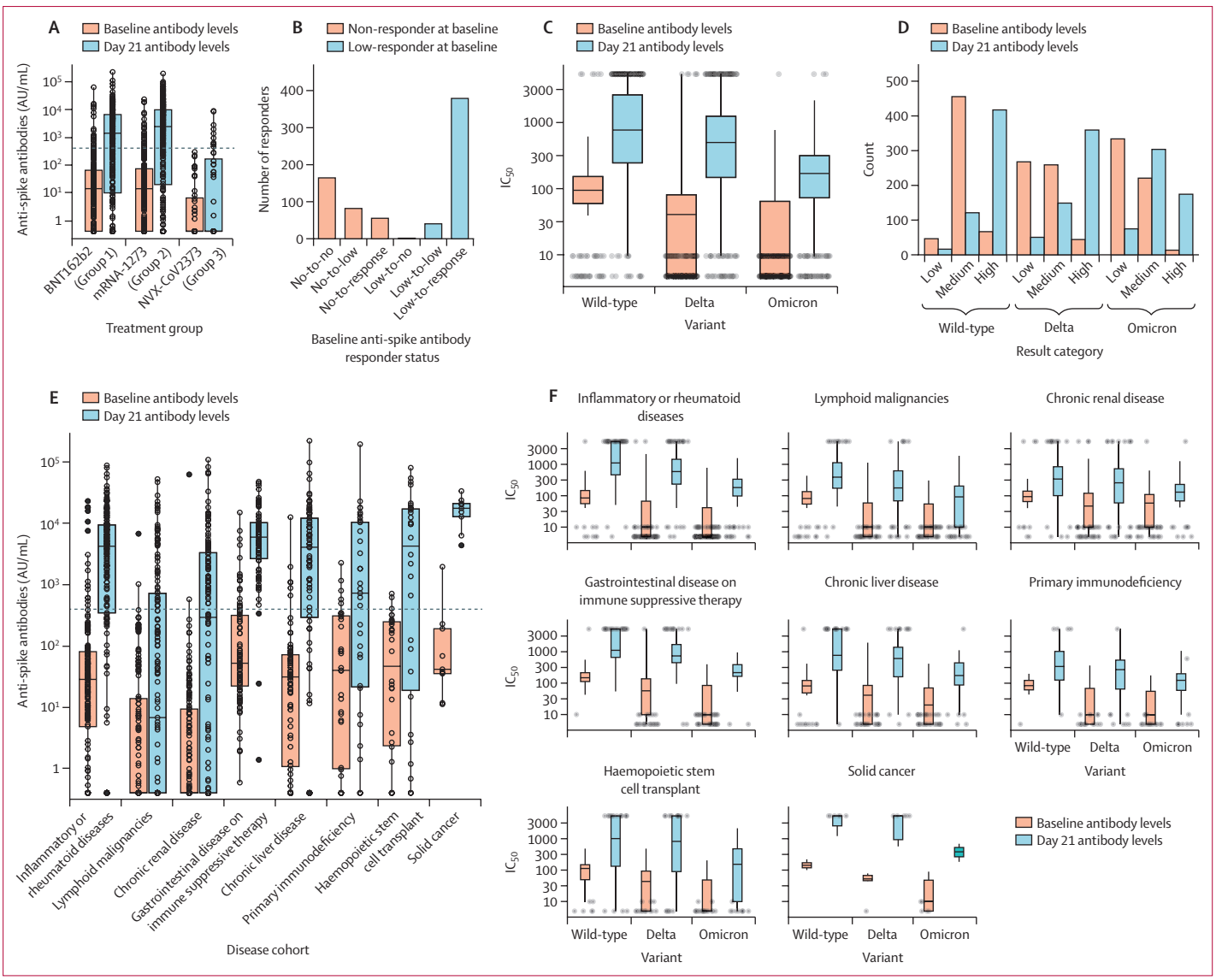

Figure 2: **Serum anti-SARS-CoV-2 spike antibody responses and neutralising antibody titres**

Anti-spike antibody concentrations pre-third dose and 21 days post-vaccination are shown for each vaccine group (A) and split by baseline anti-spike antibody responder status (B). The dashed horizontal line indicates the lowest concentration of anti-spike antibody response in healthy controls (as measured in participants of the PITCH study). Quantifiable neutralising antibody titres (median 50% inhibitory concentration [IC_{50}]) before the third dose and at day 21 against ancestral (wild-type), delta (B.1.617.2), and omicron (B.1.1.529, BA.1) variants are shown (C) and split by IC_{50} concentration (D; low <40, medium=40–256, high >256). Anti-spike antibody concentrations before the third dose and 21 days post-vaccination are shown for each vaccine group split by disease cohort (E) and neutralising antibody titres against ancestral (wild-type), delta (B.1.617.2), and omicron (B.1.1.529, BA.1) variants split by disease cohort (F) are shown. The dashed horizontal line indicates the lowest concentrations of anti-spike antibody response in healthy controls (as measured in participants of the PITCH study.[2] AU=arbitrary unit. IC_{50}=median 50% inhibitory concentration.

chronic renal disease cohort having the largest proportion of negative T-cell responses after the third dose (61 [46%] of 132; appendix p 18).

The T-cell immunogenicity against variants following the third vaccine dose was investigated in 72 participants where evaluable samples were available; 26 (36%) had an immune-mediated rheumatic diseases, 19 (26%) of 72 had chronic renal disease, 16 (22%) had chronic liver disease, and 11 (15%) had a gastrointestinal disease. T-cell responses post-third vaccine revealed only one (2%) of 66 participants did not have a detectable T-cell response to wild-type, and three (5%) of 66 did not have a detectable T-cell response to omicron. Compared with the T-cell response to wild-type, there was a significant decrease in responses to omicron at baseline and post-third dose. This fold difference in T-cell response to omicron decreased following a third dose (decrease by 1/1·4 × the wild-type response) compared with baseline (1·9-fold), suggesting that the cross-reactivity of T cells was amplified by a third dose (appendix p 19).

Neutralising antibody titres against ancestral (wild-type), delta (B.1.617.2), and omicron (B.1.1.529, BA.1) variants were evaluated in 562 participants who were seropositive

	Negative	Positive
BNT162b2		
Negative	38 (46%)	45 (54%)
Positive	23 (11%)	194 (89%)
Total	61 (20%)	239 (80%)
mRNA-1273		
Negative	39 (43%)	51 (57%)
Positive	13 (7%)	179 (93%)
Total	52 (18%)	230 (82%)
NVX-CoV2373		
Negative	8 (44%)	10 (56%)
Positive	1 (6%)	15 (94%)
Total	9 (26%)	25 (74%)

Data are n (%). Denominator is total of negative and positive for each row.

Table 2: **Comparison of T-cell response at baseline and post-third vaccine dose**

at day 21. Quantifiable neutralising antibody titres (median 50% inhibitory concentration [IC_{50}]) at day 21 were substantially higher than baseline with fold increases for wild-type of 7·2, for delta of 15·6, and omicron not reported (NR) as one group median was outside the quantitative range (NR 40–2560; wild-type median 752·5 [IQR 243·8–2512·4] compared with 95·3 [60·6–152·8], delta median 491·0 [148·2–1207·1] compared with 41·5 [5·0–81·7], omicron median 169·7 [73·6–312·9] compared with <40 [<40–65·2]; figure 2C). Categorising the neutralising antibody response to each variant at baseline and day 21 as low, medium, or high (IC_{50}; <40, 40–256, >256, respectively) revealed that the majority of participants had a high neutralising antibody response to wild-type and delta after the third vaccine dose (figure 2D). The neutralising antibody response to omicron increased across the studied population but most individuals only had a medium neutralising antibody response (figure 2D).

There were clear differences between disease cohorts in the extent of anti-SARS-CoV-2 spike antibody response to the third dose. Notably participants with lymphoid disease (77 [46%] of 169 non-responders, 41 [24%] of 169 low responders) and chronic renal disease (49 [35%] of 142 non-responders, 28 [20%] of 142 low responders) exhibited lower antibody responses compared with the other disease cohorts (figure 2E). Evaluation of the neutralising antibody titres also showed clear differences between the disease cohorts (figure 2F). Participants with lymphoid disease (wild type 4.1, delta NR, omicron NR) and chronic renal disease (wild-type 4·4, delta 13·8, omicron 2·5), exhibited lower fold increases in neutralising antibody titres compared with other disease cohorts such as those with immune-mediated rheumatic diseases (wild-type 10·0, delta NR, omicron NR) and solid cancer (all variants were NR).

Antibody responses to the three vaccines investigated were largely equivalent for most groups, with two exceptions reaching significance (appendix p 16). First, a difference between the BNT162b2 and mRNA-1273 groups for low responders in the chronic renal disease cohort was seen, however, the absolute difference was small and unlikely to be of clinical significance (mean difference for BNT162b2=10 829, mRNA-1273=9997; p=0·016). Second, in the lymphoid malignancy cohort of low responders, a substantial difference was seen between the NVX-CoV2373 and mRNA-1273 groups (mean difference for mRNA-1273=11 088, NVX-CoV2373=1436; p=0·013), which is potentially of clinical significance. Within each vaccine group, participants showed increases in neutralising antibody titres to each variant (appendix p 17).

The effect of relevant concomitant medications on the serological response after the third dose was evaluated (figure 3). There was a substantially lower serological response in participants receiving treatment with rituximab and other B-cell targeted therapies compared with those not receiving these agents. Similarly, lower responses were observed for participants receiving corticosteroids and calcineurin inhibitors. Comparative analysis was not possible for participants receiving hormonal therapies or Janus kinase inhibitors inhibitors as the number of participants were too small.

Logistic regression analyses established any potential variables that could contribute to the likelihood of immune responses to the third vaccine (appendix p 20). The two-group model logistic regression analysis on the anti-spike antibody response data included 518 participants. The odds of having a detectable anti-spike antibody response (≥0·8 AU/mL) following the third vaccine was 2·0 (95% CI 1·08–3·64; p=0·029) in those who previously received a two dose BNT162b2 course compared with those who previously received the ChAdOx1-nCov19 vaccine. Age also had a significant effect, with reduced odds of a response in those older than 75 years compared with those aged 15–44 years (odds ratio [OR] 0·24 [95% CI 0·09–0·57]). Several therapeutic agents had reduced odds of a response including B-cell targeted therapy (0·10 [0·05–0·18]), anti-metabolites (0·14 [0·06–0·31]), and calcineurin inhibitors (0·26 [0·07–0·82]). The logistic regression analysis for the three-group model included 163 participants and showed that the odds ratio of an anti-spike antibody response following a third vaccine dose was 155·00 (95% CI 27·00–3411·00) in those participants who were classified as antibody low responders at baseline compared with those classified as non-responders.

The two-group logistic regression analysis model was also used to explore baseline variables contributing to a T-cell response and included data from 500 participants. The odds ratio of a T-cell response following a third vaccination was 4·9 (95% CI 2·76–8·70) in those participants classified as positive T-cell responders at baseline compared with those classified as negative T-cell responders. Age was a contributory factor, with

participants aged at least 75 years (OR 0·20 [95% CI 0·06–0·58]), and those aged 65–74 years (0·29 [0·11–0·74]) having a reduced odds of response compared with those aged 15–44 years. The regression analyses also confirmed the effect of disease-directed treatments on T-cell response with calcineurin inhibitors (0·22 [95% CI 0·11–0·42]) or corticosteroids associated with reduced response (0·38 [0·20–0·73]). Conversely, participants who received B-cell targeted therapy were more likely to have a T-cell response after third vaccination (OR 4·1 [95% CI 1·52–13·5]). In the three-group model (n=104), baseline T-cell response was again a predictor of T-cell response to a third dose (OR 9·0 [2·81–36·0]) and supported the results of the two-group model that patients who received B-cell targeted therapy are more likely to have a T-cell response after a third vaccination compared with participants not receiving treatments from that drug category (5·95 [1·89–21·3]).

There were 44 participants whose post-third vaccine dose had neither a measurable T-cell or anti-SARS-CoV-2 spike antibody response. These participants are detailed in the appendix (pp 23–25) but were a highly heterogenous group and no conclusions can be drawn to predict which patients would consistently mount neither a serological nor a T-cell response.

The safety analysis population included all participants who received a third vaccine dose (table 3; appendix p 26). There were 24 serious adverse events (BNT612b2 eight [33%] of 24, mRNA-1273 12 [50%], NVX-CoV2373 four [17%]) of which one (4%) was categorised as grade 5, five (21%) were grade 4, 14 (58%) were grade 3, and four (17%) were grade 1–2. Two (8%) were categorised as vaccine related; one was reported as chest pain (cardiac) and a second as diarrhoea. The diarrhoea occurred in a participant in the NVX-CoV2373 group and was reported as a suspected unexpected serious adverse reaction because, in accordance with the protocol, all NVX-CoV2373 related serious adverse events needed to be reported as unexpected. Serious adverse events have been split by treatment group and disease group in the appendix (p 27). There were seven (1%) of 804 deaths during the trial, none of which were vaccine-related. Two (29%) of seven were related to COVID-19, three (43%) were related to the participants underlying disease, and two (29%) were due to other unrelated causes.

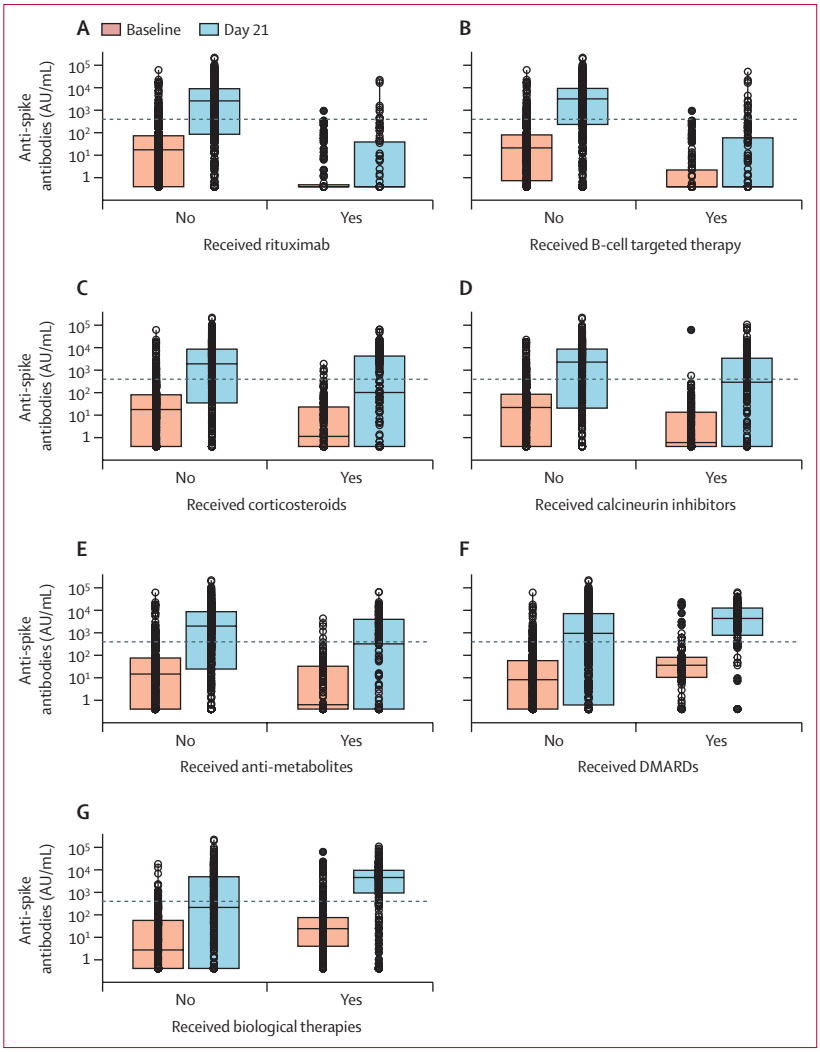

Figure 3: **Effect of disease-specific treatments on serum anti-SARS-CoV-2 spike antibody responses**
DMARDs=disease-modifying antirheumatic drugs. Anti-spike antibody concentrations measured before the third dose and 21 days after the third dose vaccination are shown to compare those patients receiving disease-specific treatments compared with those who were not. The grey horizontal line indicates the lowest concentration of anti-spike antibody response in healthy controls (as measured in participants of the PITCH study.[2]

Discussion

SARS-CoV-2 remains prevalent globally and as such it is vital that the effect of sequential vaccine exposure is characterised in patient groups most susceptible to poor outcomes after SARS-CoV-2 infection or diminished immune responses to vaccination. There remains a paucity of randomised clinical trials assessing the humoral and cellular response to different COVID-19 vaccine types in patients with multiple diseases who are immunocompromised. OCTAVE-DUO was launched when the value of booster (third and subsequent vaccinations) was not known. The trial was done with the support of the UK Government's Vaccine Task Force, who requested sight of the confidential interim data to contribute to decision making regarding the launch of the booster vaccine programme. After evaluating the data, booster vaccines for immune susceptible patients were implemented in September, 2021, and have been continued biannually since this time.

We show that 380 (90%) of 423 patients who were immunocompromised who mounted a low but detectable serological immune response to two doses of COVID-19 vaccines respond to a third vaccine dose, and that cross-reactive neutralising antibodies are induced against three variants of the virus including omicron, which

	BNT162b2 (n=377)	mRNA-1273 (n=374)	NVX-CoV2373 (n=53)
Arrhythmia			
No	349 (93%)	337 (90%)	49 (92%)
Yes	5 (1%)	10 (3%)	1 (2%)
Missing	23 (6%)	27 (7%)	3 (6%)
Arthralgia			
No	291 (77%)	277 (74%)	45 (85%)
Yes	63 (17%)	70 (19%)	5 (9%)
Missing	23 (6%)	27 (7%)	3 (6%)
Chest pain			
No	346 (92%)	335 (90%)	50 (94%)
Yes	8 (2%)	12 (3%)	0
Missing	23 (6%)	27 (7%)	3 (6%)
Chills			
No	308 (82%)	278 (74%)	46 (87%)
Yes	46 (12%)	69 (18%)	4 (8%)
Missing	23 (6%)	27 (7%)	3 (6%)
Dyspnoea			
No	338 (90%)	327 (87%)	47 (89%)
Yes	16 (4%)	20 (5%)	3 (6%)
Missing	23 (6%)	27 (7%)	3 (6%)
Fever–pyrexia			
No	324 (86%)	293 (78%)	47 (89%)
Yes	30 (8%)	54 (14%)	3 (6%)
Missing	23 (6%)	27 (7%)	3 (6%)
Headache			
No	230 (61%)	205 (55%)	39 (74%)
Yes	124 (33%)	142 (38%)	11 (21%)
Missing	23 (6%)	27 (7%)	3 (6%)
Myalgia			
No	238 (63%)	217 (58%)	40 (75%)
Yes	116 (31%)	130 (35%)	9 (17%)
Missing	23 (6%)	27 (7%)	4 (8%)
Myocarditis			
No	354 (94%)	346 (93%)	50 (94%)
Yes	0	1 (<1%)	0
Missing	23 (6%)	27 (7%)	3 (6%)
Nausea			
No	302 (80%)	275 (74%)	45 (85%)
Yes	52 (14%)	73 (20%)	5 (9%)
Missing	23 (6%)	26 (7%)	3 (6%)
Palpitations			
No	351 (93%)	341 (91%)	49 (92%)
Yes	3 (1%)	6 (2%)	0
Missing	23 (6%)	27 (7%)	4 (8%)
Vaccination			
No	153 (41%)	116 (31%)	37 (70%)
Yes	202 (54%)	231 (62%)	13 (25%)
Missing	22 (6%)	27 (7%)	3 (6%)

Data are n (%).

Table 3: **Adverse events: number and percentage of patients who experienced clinically relevant harms**

continues to circulate. In 494 (80%) of 616 of those with a low response to two doses, a third vaccine dose enhances serological responses to a level similar to those observed in healthy individuals after two vaccine doses. Although not a definitive surrogate, this suggests that patients who are immune susceptible might have a level of protection that equates to the healthy population with additional vaccines. Conversely, only a modest proportion of those who did not respond to two doses of COVID-19 vaccines generated any detectable serological response to a third dose (142 [46%] of 308), with only 58 (19%) reaching the concentrations of antibodies seen in healthy individuals, suggesting that a subset of patients remain at high risk of COVID-19.

The reasons for sub-optimal serological responses are complex and probably multi-factorial, and varying across diseases. We noted that patients with chronic renal disease and lymphoid malignancy mounted lower antibody responses and cross-reactive neutralising antibodies after the third vaccine than other disease groups. Previous studies assessing single disease types have shown that some disease types (in particular renal disease,[10] haematological malignancies,[5] and solid organ transplant recipients[18]) have a poor response to booster vaccines. However, our head-to-head comparisons allow for the identification of particularly susceptible groups. In principle, diminished antibody responses could reflect inherent properties of the underlying disease or, in parallel, the chemotherapy, or immune directed therapeutics. Multivariate logistic regression modelling identified factors most likely to increase the risk of a serological non-response to a booster vaccination including age (most notably older than 75 years), treatment with B-cell targeted therapies including rituximab, anti-metabolites, or calcineurin inhibitors as the greatest contributory factors.

The majority (500 [80%] of 623) of patients who were immunocompromised who mounted an inadequate immune response to two doses of COVID-19 vaccines did generate a T-cell response to a third dose, including 188 (38%) of 500 participants who had no measurable T-cell response after two vaccine doses. Again, there were disease specific variations, with participants in the chronic renal disease cohort least likely to mount a T-cell response. Our logistic regression analysis suggested that risk factors for no T-cell response after three doses included lack of T-cell response after two doses, age older than 75 years, and treatment with calcineurin inhibitors, or corticosteroids. However, B-cell directed therapy increased the odds of a T-cell response.

The trial outcomes were serological and T-cell responses, which might be indicative but are not proof of clinical protection. However, several studies have shown that higher SARS-CoV-2 antibody titres are protective against SARS-CoV-2 infections in the general population,[19–25] and in immune susceptible single disease cohorts.[26,27] More recent data have shown that the

generation of a robust SARS-CoV-2 specific T-cell response provides protection from severe COVID-19 in patients who were immunocompromised,[2,28] including patients on B-cell depleting therapies.[19] However, in spite of these data, a precise correlate of protection is not clearly defined.

Our data do not suggest that a third dose of either of the mRNA vaccines gave an advantage over the other in this cohort of immunocompromised people. They also confirm the previous observation that heterologous vaccine strategies can be effective.[7] However, in the lymphoid malignancies group, a re-boost vaccination with the protein-based vaccine NVX-CoV2373 did not appear to be as effective at inducing serological response as the mRNA-based vaccines, although T-cell responses generated were similar. Although there should be caution in extrapolation of the NVX-CoV2373 data in patients with lymphoid malignancies to other patient populations, different vaccines might have differential effects in patients who were immune susceptible and this might warrant further study. We were precluded from evaluating NVX-CoV2373 in the other disease groups recruited to OCTAVE-DUO because at the time of trial initiation, safety data for NVX-CoV2373 was not available in conditions with an inflammatory component, and we were therefore restricted to evaluating this vaccine only in the those with lymphoid malignancies.

An effective national multidisciplinary collaboration delivered OCTAVE-DUO, contributing substantially to our understanding of COVID-19 vaccine responses across different groups of patients who are immuno-compromised. Study limitations include varying cohort sizes reflecting recruitment during a period of very rapid public health-driven vaccine uptake, particularly in susceptible patient groups, and the heterogeneity in disease status and immunosuppressive treatments. There was under-representation of participants from ethnic minorities, consistent with disparities reported in many COVID-19 vaccine trials,[29] and the resultant bias in the outcome needs to be considered when implementing public health strategies based on these studies. For a small number of patients, their measured baseline serological status was found to differ from pretrial entry status. This might reflect true within-host variation, assay reproducibility, or interim exposure to SARS-CoV-2 infection leading to enhanced anti-SARS-CoV-2 spike antibody responses. Despite under-recruitment, a power recalculation based on a sample size of 800, by use of original effect size and alpha, resulted in a new power of 78·9%. Although this is a reduction from the original trial design power of 90%, this new power remains statistically favourable. It is acknowledged that low numbers causing sparce data and collinearity did affect the ANOVA tests and logistic regressions, and the non-adjustment for stratification variables could potentially cause biases. However, the models were exploratory and were not involved with the primary outcome analysis. Use of a modified intention-to-treat approach can be seen as introducing selection bias owing to post-randomisation exclusions, however this was minimised by analysing all appropriate and available data.

We identified that anti-SARS-CoV-2 spike antibodies induced by the third vaccine dose increased the capacity to recognise and potentially neutralise omicron and other variants of concern. The responses varied between disease groups, with comparatively less neutralising activity in patients with lymphoid malignancy and chronic renal disease. We show that there is only a moderate decrease in T-cell responses against omicron compared with wild-type antigens after a third vaccination, and that a third dose enhances T-cell responses to omicron. These data were generated in a small subset of trial participants in which the samples were available and are therefore subject to potential bias. Our data provide mechanistic evidence to support the notion that sufficiently high titre responses might protect against variants of concern, even in the context of wild-type vaccine administration. The longer-term clinical implication of this in terms of functional protection now needs to be evaluated in public health datasets.

Although several studies have shown that booster vaccines might enhance anti-SARS-CoV-2 spike antibody responses in patients who are immunocompromised in single disease groups,[10,12,13] OCTAVE-DUO remains the only large trial of BNT162b2 versus mRNA-1273 in patients who are susceptible due to multiple diseases assessing both safety and immune responses. A single previous masked randomised controlled trial in 60 patients receiving rituximab treatment who had not seroconverted compared the efficacy and safety of BNT162b2, mRNA-1273, or ChAdOx1 nCoV-19 after a third vaccine dose and showed no difference between vaccine groups for seroconversion rates (27%) 4 weeks after the third dose, although higher T-cell responses were seen within the ChAdOx1 nCoV-19 group (20 [100%] of 20) compared with the mRNA vaccinated participants (13 [81%] of 16).[14] Our finding that vaccine type has no effect on serological or T-cell responses has enabled the on-going administration of both mRNA vaccine types to patients who are susceptible. We also show lower antibody responses in patients with lymphoid malignancies receiving the protein-based NVX-CoV2373 vaccines (compared with mRNA vaccines). This remains relevant since access to NVX-CoV2373 continues via pharmacies in the UK. Furthermore, many healthy people will move into the immune susceptible categories as they age and develop disease. These people might not have received COVID-19 boosters for many years, and SARS-CoV-2 immune responses will have waned in these individuals. Understanding that reboosting might recover antibody and T-cell responses in some disease groups, but less so in others, will remain relevant for emerging populations of patients who are immune susceptible.

In conclusion, OCTAVE-DUO is a comprehensive trial evaluating both serological and T-cell responses to booster vaccinations, which compares the effects of different vaccine types in the immunocompromised population and also provides data on the immune response to variants of concern. The study provides robust unbiased evidence that supports the UK decision to proceed with multiple vaccinations, initially prioritising patients who are immunocompromised. The majority will have gained benefit from the additional vaccine, both in terms of serological and T-cell responses affording protection from COVID-19. The NVX-CoV2373 vaccine, evaluated in the lymphoid malignancies cohort only, did not appear as effective in inducing serological responses compared with mRNA-based vaccines.

Identifying specific cohorts that remain immune unresponsive even after three doses is complex but our study highlights that patients with chronic renal disease or lymphoid malignancies, non-responders after two vaccine doses, and those patients on B-cell targeted therapies are particularly susceptible and an alternative approach to COVID-19 protection should be considered.

Contributors

PK and IBM are co-chief investigators for the OCTAVE-DUO trial. IBM, PK, CSG, and EB conceptualised the trial. CSG, IBM, PK, EB, SMM, JAS, and TIdS wrote the grant for funding. IBM, AK, CSG, AP, PK, SJB, DR, EB, GC, MW, DT, SS, SHL, TIdS, JAS, AH, PM, and AR wrote the trial protocol and developed the Case Report Form for collection of clinical data. A-MH, LE, AH, and SJB managed the trial and curated the data. CSG and AG developed the laboratory procedures. AP, AK, LB, CSG, ZL, SHL, PK, and IBM developed the statistical plan. AP, AK, SP, and LB did the statistical analyses, including directly accessing and verifying the underlying data reported in the manuscript. AR, CP, DR, DT, EB, GC, GM, HP, JS, JAS, KLY, KO, LG, MBCK, MJA, MP, MW, NB, SD, SHL, SM, SMM, SOB, SS, TIdS, TT, VK, and ZL contributed to patient recruitment and data collection. SL, MC, SMM, GM, SJD, and EB analysed variants of concern. EJC and RB contributed to the neutralisation antibody assays and analysis. SJD is the joint chief investigator of the PITCH study and contributed expertise on the immune response in healthy populations. AP, AK, SP, and LB accessed and verified the underlying data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

DR reports research funding from Roche, Biotheranostics, RNA diagnostics, and Celgene; and honoraria or consultancy fees from Novartis, Pfizer, Lily, Roche, and AstraZeneca–Diiachi Sankyo. EB reports research funding from Vaccitech; consultancy fees from Roche, Vaccitech, and AstraZeneca; and holds patents in ChAdOx1 hepatitis B virus and hepatitis C virus vaccines. HP reports honoraria from AstraZeneca. IBM reports research funding or consultancy fees from AbbVie, Amgen, Bristol-Myers Squibb (BMS), Causeway Therapeutics Cabaletta, Eli Lilly, Evelo Biosciences, Gilead, GSK, Janssen, Novartis, Pfizer, Sanofi Regeneron, and UCB; consultancy fees from AbbVie, Amgen, BMS, Causeway Therapeutics Cabaletta, Eli Lilly, Gilead, Janssen, Novartis, Pfizer, Sanofi Regeneron, and UCB; and is on the board of directors of Evelo Biosciences. KO reports royalties to his institution from Telix Pharmaceuticals for Radiolabelled anti-CD66 antibody; consulting fees from Sanofi and Takeda; and stocks in GSK. KLY reports honoraria from Sanofi Genzyme, Takeda, and Amgen; support for meeting attendance from Takeda; and participation on a trial steering committee for Sanofi and an advisory board for Janssen. MJA reports research funding from Pfizer. MW reports research funding from Oxford Immunotech. MBCK reports honoraria from Gilead. MC reports consultancy fees from VacciTech. PK reports research funding from Bayer; and consultancy fees from AstraZeneca, Merck, and BMS. SM reports stock options in TCB BioPharm. SHL reports honoraria from AstraZeneca. SS reports research funding from Amgen, Boehringer-Ingelheim, BMS, GSK, Janssen, and UCB; and consultancy fees or honoraria from AbbVie, Eli Lilly, GSK, Janssen, and UCB. SOB reports research funding from CSL Behring; and consultancy fees, honoraria, or support for attending meetings from GSK, Baxalta US, and Biotest. JAS reports honoraria from Novartis and Gilead; advisory board fees from the Kiadis clinical trial, Medac, and NHS England National Specialised Commissioning Clinical Reference Group for Blood and Marrow Transplantation; and unpaid roles as President of British Society of Blood and Marrow Transplantation and Cellular Therapy, secretary of the European Society for Blood and Marrow Transplantation and as a board member of the British Society of Haematology. SJD is a Scientific Advisor to the Scottish Parliament on COVID-19 for which she receives a fee. All other authors declare no conflicts of interest.

Data sharing

Participant data and the associated supporting documentation will be available within 6 months after the publication of this manuscript. Details of our data request process are available on the Cancer Research UK Clinical Trials Unit (CRCTU) website. Only scientifically sound proposals from appropriately qualified research groups will be considered for data sharing. The decision to release data will be made by the CRCTU Director's Committee, who will consider the scientific validity of the request, the qualifications and resources of the research group, the views of the chief investigator and the trial steering committee, consent arrangements, the practicality of anonymising the requested data, and contractual obligations. A data sharing agreement will cover the terms and conditions of the release of trial data and will include publication requirements, authorship and acknowledgments, and obligations for the responsible use of data. An anonymised encrypted dataset will be transferred directly by use of a secure method and in accordance with the University of Birmingham's IT guidance on encryption of data sets.

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