SARS-CoV-2 Vaccine Responses in Individuals with Antibody Deficiency: Findings from the COV-AD Study

Adrian M. Shields1,2 · Sian E. Faustini1 · Harriet J. Hill3 · Saly Al-Taei1 · Chloe Tanner1 · Fiona Ashford1 · Sarita Workman4 · Fernando Moreira4 · Nisha Verma4 · Hollie Wagg5 · Gail Heritage5 · Naomi Campton5 · Zania Stamatakis3 · Paul Klenerman6 · James E. D. Thaventhiran7 · Sarah Goddard8 · Sarah Johnston9 · Aarnoud Huissoon2 · Claire Bethune10 · Suzanne Elcombe11 · David M. Lowe4,12 · Smita Y. Patel6,13 · Sinisa Savic14 · Siobhan O. Burns4,12 · Alex G. Richter1,2 · on behalf of the COV-AD consortium

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Abstract
Background Vaccination prevents severe morbidity and mortality from COVID-19 in the general population. The immunogenicity and efficacy of SARS-CoV-2 vaccines in patients with antibody deficiency is poorly understood.

Objectives COVID-19 in patients with antibody deficiency (COV-AD) is a multi-site UK study that aims to determine the immune response to SARS-CoV-2 infection and vaccination in patients with primary or secondary antibody deficiency, a population that suffers from severe and recurrent infection and does not respond well to vaccination.

Methods Individuals on immunoglobulin replacement therapy or with an IgG less than 4 g/L receiving antibiotic prophylaxis were recruited from April 2021. Serological and cellular responses were determined using ELISA, live-virus neutralisation and interferon gamma release assays. SARS-CoV-2 infection and clearance were determined by PCR from serial nasopharyngeal swabs.

Results A total of 5.6% (n = 320) of the cohort reported prior SARS-CoV-2 infection, but only 0.3% remained PCR positive on study entry. Seropositivity, following two doses of SARS-CoV-2 vaccination, was 54.8% (n = 168) compared with 100% of healthy controls (n = 205). The magnitude of the antibody response and its neutralising capacity were both significantly reduced compared to controls. Participants vaccinated with the Pfizer/BioNTech vaccine were more likely to be seropositive (65.7% vs. 48.0%, p = 0.03) and have higher antibody levels compared with the AstraZeneca vaccine (IgGAM ratio 3.73 vs. 2.39, p = 0.0003). T cell responses post vaccination was demonstrable in 46.2% of participants and were associated with better antibody responses but there was no difference between the two vaccines. Eleven vaccine-breakthrough infections have occurred to date, 10 of them in recipients of the AstraZeneca vaccine.

Conclusion SARS-CoV-2 vaccines demonstrate reduced immunogenicity in patients with antibody deficiency with evidence of vaccine breakthrough infection.

Keywords COVID-19 · CVID · Inborn errors of immunity · Primary immunodeficiency · Secondary immunodeficiency · Vaccination · SARS-CoV-2

Abbreviations

APDS-1 Activated PI3K delta syndrome 1
CID Combined immunodeficiency
COVID-19 Coronavirus disease 2019
CTLA-4 Cytotoxic T-lymphocyte-associated protein 4
CVID Common variable immunodeficiency disorder
DBS Dried blood spot
ELISA Enzyme-linked immunosorbent assay
NFKB2 Nuclear factor kappa B subunit 2
Introduction

The immunological correlates of protection against SARS-CoV-2 infection and severe COVID-19 are not yet known. The passive acquisition [1] or development of anti-SARS-CoV-2 spike glycoprotein antibodies following infection [2–4] confers significant protection against future disease and, in some cases, facilitates viral clearance in individuals that fail to mount effective immune responses following infection [5–9].

Vaccination against SARS-CoV-2 is the most effective public health intervention to prevent severe morbidity and mortality from COVID-19 in the general population [10–12]. A meta-analysis of vaccine efficacy studies has suggested that neutralising antibody levels are strongly associated with protection from symptomatic infection [13]. However, it is well recognised that patients with immunodeficiency may not respond optimally to vaccination. To date, SARS-CoV-2 vaccine immunogenicity and efficacy has not been comprehensively studied in individuals with primary and secondary immunodeficiency; preliminary studies suggest seropositivity rates following vaccination vary between 20.0 and 83.0% [14–18]. Given the significantly increased risk of morbidity and mortality from COVID-19 that these patients face [19, 20], understanding the immunogenicity and efficacy of vaccines in this population is of critical importance.

COVID-19 in patients with antibody deficiency (COV-AD) is a multi-site UK study that aims to: (i) determine the prevalence of asymptomatic and symptomatic SARS-CoV-2 infection in patients with primary and secondary antibody deficiency, (ii) determine how frequently SARS-CoV-2 viral persistence occurs in patients with primary and secondary antibody deficiency and (iii) characterise the immune response of these patients following SARS-CoV-2 infection and vaccination. This manuscript presents an interim analysis of 320 participants in the COV-AD study to describe responses to the primary course of vaccination and the risk of vaccine breakthrough and viral persistence.

Methods

Patient Eligibility and Recruitment

From March 2021, patients with primary or secondary antibody deficiency were recruited from the following immunology centres across the UK: University Hospitals Birmingham NHS Foundation Trust, Royal Free London NHS Foundation Trust, North Bristol NHS Trust, Oxford University Hospitals NHS Foundation Trust, Leeds Teaching Hospitals NHS Trust, University Hospitals North Midlands NHS Trust, University Hospitals Plymouth NHS Trust, Newcastle Upon Tune Hospitals NHS Foundation Trust.

Patients were eligible for the study entry if (i) they were over 18 years of age and (ii) they were receiving immunoglobulin replacement therapy or they had a serum IgG concentration less than 4 g/L and were receiving regular antibiotic prophylaxis to prevent infections. Participants’ underlying immunological diagnosis was made according the European Society of Immunodeficiency Clinical Working Party criteria. In this manuscript, “other primary antibody deficiency” has been used to encompassing individuals who do not fulfil the diagnostic criteria for CVID, XLA or any monogenic immunodeficiency but are still believed to have a primary humoral immunodeficiency.

At study entry, meta-data including demographics, immunological diagnosis and immunological parameters (e.g. baseline IgG concentration, trough IgG concentration, lymphocyte enumeration and whether an individual had previously tested positive for SARS-CoV-2 by PCR) were documented. All participants submitted a postal nasopharyngeal swab to determine SARS-CoV-2 status by PCR as previously described [21]. Individuals with a positive SARS-CoV-2 PCR were sent follow-up swabs at two-weekly intervals until a negative swab was returned. Results of routine clinical swabs were also documented as part of this study.

Study participants were then followed longitudinally through the UK routine SARS-CoV-2 vaccination schedule. Participants received two doses of either the AstraZeneca ChAdOx1 nCoV-19 (Vaxzevria) or the Pfizer BioNTech 162b2 (Tozinameran) vaccine according to the extended vaccine schedule mandated by the UK Chief Medical Officers (https://www.gov.uk/government/publications/prioritising-the-first-covid-19-vaccine-dose-jcvi-statement/optimising-the-covid-19-vaccination-programme-for-maximum-short-term-impact).

A cohort of 205 healthy control participants was recruited from the COVID-19 convalescent (COCO) study undertaken at University Hospitals Birmingham NHS Foundation Trust. These participants were otherwise healthy health care workers (median age 44 years, (range 22–66 years), 28% male), vaccinated with two doses of Pfizer BioNTech 162b2 on
the extended UK dosing schedule and sampled 1–2 month after vaccination.

Participants were sampled, whenever possible, prior to their second vaccine dose and between 1 and 2 months following their second vaccine dose. When this was not possible, a single sample was taken at no fixed time point following their second vaccine dose. To facilitate sampling, individuals were given the option of remote sampling by dried blood spot (DBS) or for an enhanced cohort venous blood sampling to enable cellular analysis. We have previously recorded excellent concordance between serum and DBS samples using this assay [22]. Serum or dried blood samples [22] were tested for the presence of anti-spike glycoprotein antibodies (The Binding Site, Birmingham, UK). Results are reported as an IgGAM ratio (optical density compared with calibrator) and results > 1.0 are defined as seropositive. The ratio provides a semi-quantitative assessment of the magnitude of the antibody responses [23]. Serum samples were also assessed for neutralising capacity using an in-house live virus neutralisation assay. T cell responses were assessed using the T-SPOT®.COVID assay (Oxford Immunotec, Abingdon, UK), an ELISPOT based IFN-gamma release assays utilising peptide pools derived from the SARS-CoV-2 spike and nucleocapsid proteins; 0–4 spots per well is considered negative, 5–7 spots per cell, borderline and greater than 7 spots per well a positive response. Detailed descriptions of the methods are available in the Supplementary Methods.

Results

The results of 320 participants in the COV-AD study were available for interim analysis (Table 1). The median age of participants was 58.5 years and 40% (n = 128/320) were male. The median interval between the first and second vaccine dose was 76 days; 42.1% (n = 135/320) of participants

### Table 1 Demographics of COV-AD study participants

|                          | 320       |
|--------------------------|-----------|
| N                        | 320       |
| Age (y)                  | 58.5 (43.0–68.8) |
| Sex (male) n, %          | 128 (40.0) |
| Vaccination              |           |
| Pfizer BioNTech 162b2    | 135 (42.1) |
| AstraZeneca ChAdOx1 nCoV-19 | 176 (55.0)* |
| Unvaccinated             | 2 (0.63)  |
| Unknown                  | 7 (2.2)   |
| Vaccine dosing interval (d) | 76 (70–78) |
| Diagnosis                |           |
| Primary immunodeficiency | 228 (71.3) |
| Common variable immunodeficiency disorder | 139 (43.4) |
| Other primary antibody deficiency | 38 (11.8) |
| Specific polysaccharide antibody deficiency | 17 (5.3) |
| X-linked agammaglobulinemia | 9 (2.8) |
| Hyper IgM syndrome       | 6 (1.9)   |
| Undefined combined immunodeficiency | 4 (1.3) |
| Thymoma with immunodeficiency | 3 (0.9) |
| Other                    | 12 (3.8)  |
| Secondary immunodeficiency | 90 (28.1) |
| Haematological cause     | 62 (19.3) |
| Rheumatological cause    | 18 (5.6)  |
| Other cause              | 10 (3.1)  |
| Unknown                  | 2 (0.6)   |
| Immunoglobulin product   |           |
| Intravenous immunoglobulin | 167 (52.2) |
| Subcutaneous immunoglobulin | 133 (41.6) |
| Prophylactic antibiotics only | 16 (5.0) |
| Unknown                  | 4 (1.3)   |
| Immunoglobulin level     |           |
| Pre-treatment IgG (g/L)  | 3.65 (1.73–4.92) |
| Trough IgG (g/L)         | 9.46 (8.20–11.06) |
| IgA (g/L)                | 0.16 (0.05–0.61) |
| IgM (g/L)                | 0.3 (0.10–0.68) |
| SARS-CoV-2 PCR status at study entry |         |
| Positive                 | 1 (0.31)  |
| Negative                 | 283 (88.4) |
| Unknown                  | 36 (11.3) |

*One participant in both the AZ and Pfizer vaccine group had only received one vaccine dose during study follow up to 31/10/21. Both unvaccinated participants had previously recovered from prior PCR + SARS-CoV-2 infection.
received the Pfizer BioNTech 162b2 vaccine and 55.0% 
(n=176/320) the AstraZeneca ChAdOx1 nCoV-19 vaccine.

Eighteen participants (n=18/320, 5.6%) had suf-
ffered PCR-proven SARS-CoV-2 infection prior to study 
entry; these participants were significantly younger (52.0 
vs. 59.0 years, p=0.02) than individuals who remained 
SARS-CoV-2 infection-naive (Table 2). Only one partici-
 pant remained SARS-CoV-2 PCR positive on study entry. 
Eleven participants (n=11/18, 61.1%) returned negative 
asopharyngeal swabs at the time of study entry and six 
participants declined further investigation. No specific 
immunological characteristics defined the population with 
apparent viral clearance: 4 patients had CVID, 2 other pri-
mary antibody deficiencies, 1 Good’s syndrome, 1 XLA and 
3 secondary immunodeficiencies; 54.4% (n=6/11) made 
no persistent serological response to infection (measured 
at study enrollment) and 36.4% (n=4/11) no serological 
response to subsequent vaccination. T cell responses 
were assessed in five of the six seronegative individuals by inter-
feron-gamma ELISPOT: 100% (n=5/5, median spots/10^6 
cell = 158) mounted responses against spike peptide pools 
and 60% (n=3/5, median spots/10^6 cells = 45) to the nucle-
ocapsid peptide pools demonstrating T cell immunity may 
compensate for the absence of humoral immunity under 
some circumstances.

One hundred and sixty-eight participants were sampled 1 
to 2 months after their second vaccine dose using venous 
or DBS collection. The overall seropositivity following vacci-
nation in this cohort was 54.8% (n=92/168) and the median 
IgGAM ratio of seropositive individuals was 2.81 (positive 
defined as ratio > 1.0), with comparable results in groups 
sampled by DBS and venous blood (Fig. 1A). By compari-
son, overall seropositivity in 205 healthy participants from 
the COCO study was 100.0% with a median IgGAM ratio of 
5.51. There was no significant difference in the percentage 
of individuals who were seropositive, or the magnitude of the 
response between participants who had previously 
had SARS-CoV-2 infection and those who were infection 
naive (Fig. 1B). The Pfizer BioNTech 162b2 vaccine was 
associated with significantly greater seroconversion (65.7% 
vs. 48.0%, p=0.03) and antibody responses (IgGAM ratio 
3.73 vs. 2.39, p=0.0003) in comparison to the AstraZen-
eca ChAdOx1 nCoV-19 vaccine (Fig. 1C). Serological 
responses from both vaccines display significant waning 
over time (2-way ANOVA, p=0.001) but recipients of the 
Pfizer BioNTech vaccine displayed better preservation of 
antibody responses (2-way ANOVA, p<0.0001) (Fig. 1D). 
Age did not significantly affect the magnitude of antibody 
responses or seroconversion following vaccination (Fig. 1E).

Humoral responses following vaccination were variable 
amongst participants with a range of immunodeficiencies 
(Fig. 1F). As expected, serological responses were not 
detected in patients with X-linked agammaglobulinaemia 
(XLA); however, 52.2% of individuals with common vari-
able immunodeficiency mounted a serological response to 
vaccination. Seropositivity was 75.0% in individuals with 
other primary antibody deficiencies (excluding XLA and 
CVID) and 100.0% in individuals with specific polysac-
charide antibody deficiency. Variability was also observed 
amongst individuals with secondary immunodeficiencies 
regardless of aetiology. Thirty-one participants were sam-
ped before and after their second immunisation permitting 
comparison of pre and post vaccine responses (Fig. 1G); 
seropositivity increased from 29.0% following the first dose 
to 61.2% following the second dose; both vaccines increased 
the magnitude of the antibody response.

T cell responses to vaccination were studied in 91 infec-
tion-naive individuals following their second vaccine dose 
and 12 individuals with a history of PCR + proven SARS-
CoV-2 infection (Fig. 2A). In responses to a peptide pool 
derived from the SARS-CoV-2 spike protein, 46.2% of 
infection-naïve participants (n=42/91) mounted a positive 
T cell response and a further 11.0% (n=10/91) mounted a 
borderline response. In contrast, 91.7% (n=11/12) of indi-
viduals with prior PCR positive infection mounted a positive 
T cell response to pooled spike peptides and 8.3% (n=1/12) 
mounted a borderline response, as defined by this assay. In 
response to the SARS-CoV-2 nucleocapsid peptide pool, 
8.8% (n=8/91) of infection-naïve participants demonstrated 
a detectable T cell response and 1.1% (n=1/91) mounted a 
borderline response compared to 66.7% (n=8/12) and 
8.3% (n=1/12) respectively, in the prior-infection group. 
Individuals who had suffered previous PCR + SARS-CoV-2 
infestation mounted a significantly greater post-vaccination T 
cell response to the spike protein than those who were infec-
tion naïve; no significant difference was observed for the 
nucleocapsid protein (Fig. 2A). All eight individuals with 
no prior history of PCR-proven SARS-CoV-2 infection who 
had positive T cell responses to nucleocapsid peptides also 
mounted above average responses to the spike peptide pools 
(>100 spot forming units/10^6 PRMC) suggesting a minority 
of individuals may have had asymptomatic infection, or mild 
symptomatic COVID-19 that was incorrectly attributed to 
other causes.

T cell responses directed towards the spike protein 
were comparable between the Pfizer BioNTech 162b2

| Table 2 | Comparison of participants in Arm 1 vs Arm 2 of the COV-
AD study |
|----------------------------------|----------------------------------|----------------------------------|
| Prior PCR + SARS-
CoV-2 infection | No known PCR + SARS-CoV-2 infection | p |
| N | 18 | 302 | - |
| Age (y) | 52.0 (30.3–61.5) | 59.0 (44.0–69.0) | 0.02 |
| Sex (male) n, % | 7 (38.9) | 121 (40.3) | NS |
and AstraZeneca ChAdOx1 nCoV-19 following the second dose of either vaccine (Fig. 2B) and persisted as time passed following vaccination (Fig. 2C). Participant age did not significantly influence the percentage of participants mounting a T cell response to the spike protein; a trend was observed towards greater magnitude responses in younger participants (Fig. 2D). A total of 57.9% of participants with common variable immunodeficiency disorder mounted a T cell response to the SARS-CoV-2 spike protein following vaccination with a wide range of responses detected in other primary and secondary immunodeficiencies (Fig. 2E). Both the Pfizer and AstraZeneca vaccines induced incremental T cell responses following the second vaccine doses in the majority of participants (Fig. 2F). A detectable T cell response was associated with significantly greater seropositivity following vaccination (79.5% vs. 53.8%, $p = 0.009$) and antibody responses of significantly greater magnitude (IgGAM ratio 3.08 vs. 2.14, $p = 0.03$) (Fig. 2G); however, no significant relationship was observed between the T cell response and peripheral CD19+B cell numbers (Supplementary Fig. 2). Participants that were seropositive post-vaccination had significantly greater serum IgM concentrations (Fig. 3A) and significantly larger numbers of CD19+ peripheral B cells (Fig. 3B) compared to those who were seronegative. There was no direct relationship between CD19 B cell numbers and IgM concentration ($r^2 = 0.001$, $p = 0.53$). Serum concentrations of both IgA and IgM were positively correlated with the magnitude of the antibody response following vaccination (Supplementary Fig. 1).

The functionality of antibodies was studied using in vitro, live virus neutralisation assays. Only 37% of participants with CVID ($p = 0.0001$) and 16% with primary antibody deficiency ($p = 0.0003$) displayed 50% viral neutralising activity or greater, compared to 100% of healthy controls (Fig. 4A). Neutralising capacity was not significantly impacted by prior SARS-CoV-2 infection status (Fig. 4B), type of vaccination received (Fig. 4C) or by participants’ age (Fig. 4D). The capacity of vaccine induced anti-spike IgG antibodies to bind the SARS-CoV-2 delta variant was significantly reduced compared to original Victoria strain (Normalised signal:noise ratio: 1.26 vs. 1.41, $p < 0.0001$).
Fig. 2 Cellular responses to SARS-CoV-2 vaccination in individuals with antibody deficiency. Comparison of cellular responses following SARS-CoV-2 vaccination in COV-AD participants using an IFN-gamma-release assay. A Comparison of T cell responses to spike and nucleocapsid peptide pools in individuals with prior PCR proven SARS-CoV-2 infection and those who were infection naive, in participants sampled 1–2 m post second vaccine dose. B Comparison of cellular responses to spike peptide pools between the Pfizer and AstraZeneca vaccines in participants sampled 1–2 m post second vaccine dose. C Comparison of the cellular responses to spike peptide pools over time. D Comparison of the cellular responses to spike peptide pools by age in participants sampled 1–2 m post second vaccine dose. E Comparison of the cellular responses to spike peptide pools by underlying immunodeficiency in participants sampled 1–2 m post second vaccine dose. F Dynamic changes in cellular response to spike peptide pools before and after the second vaccine dose. G Relationship between the T cell response to spike peptide pools and the magnitude of the anti-spike antibody response in participants sampled 1–2 m post second vaccine dose. Results are presented as the number of IFN-gamma producing spots per 10^6 cells. Dark grey shaded areas represent no response, light grey shaded areas represent borderline response, as per the manufacturers’ instructions.

A total of 39.4% of individuals with detectable IgG responses against the Victoria strain fell below the threshold for positivity when the delta variant was substituted into the ELISA assay (Fig. 4E). Vaccine-induced IgG antibody binding was also significantly reduced to the Omicron variant of concern compared to original virus (Normalised signal:noise ratio 7.66 vs. 10.32, p < 0.0001) (Fig. 4F); however, no participants fell below the threshold for positivity.

Ten vaccine-breakthrough, PCR-proven infections have occurred this cohort up to 31/10/21 (median time from 2nd vaccine dose: 197 day); a further individual was infected between their first and second vaccine dose on the background of prior COVID-19 (Table 3). Eight participants reported new symptoms associated with acute COVID-19 above and beyond any chronic symptoms secondary to their immunodeficiency. A total of 90.0% (n = 9/10) of vaccine-breakthrough infections occurred in recipients of the AstraZeneca vaccine at a median interval of 120 days post second-dose and 70.0% occurred in individual who made no detectable humoral response to vaccination. One participant died of COVID-19, 3 months after receiving their second vaccine dose. This participant had a 31-year history of seropositive rheumatoid arthritis and secondary antibody deficiency (nadir IgG prior to immunoglobulin replacement: 0.97 g/L). Prior treatments for the underlying rheumatoid arthritis included oral corticosteroids, methotrexate, hydroxychloroquine and abatacept. At the time of SARS-CoV-2 infection, this participant was receiving daily oral prednisolone (9.5 mg/day) and had received rituximab 84 days prior to their first vaccine dose and 41 days after their second vaccine dose. No serological or cellular response to vaccination was detected in this participant at study enrolment.

**Discussion**

Understanding the immunogenicity and efficacy of vaccinations is essential to guide global vaccination strategies and when to deploy non-pharmacological countermeasures.
to protect the immunologically vulnerable [19, 20]. Herein, we report the immunogenicity of the AstraZeneca ChAdOx1 nCoV-19 and Pfizer BioNTech 162b2 vaccinations in patients with antibody deficiency, a cohort who have historically responded poorly to vaccinations [24–26].

Overall, seropositivity following vaccination was 54.8%, significantly lower than healthy controls; comparable seropositivity was observed in the two largest subgroups of patients, common variable immunodeficiency (52.1%) and secondary immunodeficiency arising from haematological cause (55.8%). However, less than 10% of individuals with primary or secondary antibody deficiency made a neutralising antibody response equivalent to that of healthy controls following two doses of a SARS-CoV-2 vaccine. Furthermore, in individuals demonstrating a vaccine response, anti-spike IgG binding was significantly reduced against both the Delta and Omicron SARS-CoV-2 variants of concerns which are in widespread global circulation as of December 2021. Evidence suggests antibody binding is strongly associated with neutralising capacity [27]. These data suggest that vaccine-induced antibody responses are inadequate in the majority of individuals with antibody deficiency and additional strategies such as the use of prophylactic monoclonal antibodies to provide passive protection and antivirals are likely to be necessary to prevent severe disease.

T cell responses to vaccination displayed significant heterogeneity in this cohort as has been found in similar studies using identical laboratory methods [28]. The interferon-gamma release assay was originally validated to study T cell responses following natural infection, where it displays 98% sensitivity [29]. A total of 46.2% of infection-naïve COVAD participants and 91.7% of individuals with prior PCR-proven infection mounted a detectable T cell response following vaccination using this assay, compared to 54% of healthy individuals [30]. T cell responses in patients with evidence of previous SARS-CoV-2 infection were significantly greater than those detected following vaccination in infection-naïve participants. The discordance between the detection of vaccine- and infection-induced T cell responses may arise from the duration, anatomy and magnitude of antigen exposure, differences in the immunological environment when antigen was presented, or assay-specific factors including differences in MHC restriction to the constituents of the peptide pool and the antigen-specific T cell repertoire in each circumstance.

Fig. 3 Correlates of seropositivity following SARS-CoV-2 vaccination in individuals with antibody deficiency. Comparison of pre-vaccination immunological parameters between seropositive and seronegative participants sampled 1–2 months following their second vaccine dose: A Pre-treatment serum IgG concentration and current serum IgA and IgM concentration. B Total lymphocyte count and lymphocyte subset enumeration.
In the cohort, there were no differences between the magnitude of the T cell response in individuals with or without a detectable peripheral B cell population. The clinical correlates of infection- or vaccine-induced T cell responses in patients with antibody deficiency, in particular, in the absence of humoral immunity remain uncertain. The absence of humoral immunity is a characteristic feature of individuals with prolonged SARS-CoV-2 infection [7]; however, robust T cell responses can limit the severity of disease in some individuals in the absence of humoral immunity as has been shown previously in patients with haematological malignancy [31]. Further studies are necessary to characterise the quality and breadth of T cell responses and its relationship to the development of effective humoral immunity following infection and vaccination in more detail.

With respect to vaccination strategies, we have shown that the Pfizer BioNTech 162b2 vaccine demonstrated significantly greater humoral immunogenicity in patients with antibody deficiency than the AstraZeneca ChAdOx1 nCoV-19 vaccine, a finding consistent with larger studies in healthy individuals [13, 32] and renal transplant recipients [28]. Furthermore, over 90% of vaccine breakthrough infections occurred in recipients of the AstraZeneca vaccine, 60.0% of whom made no serological response to the initial 2-dose vaccine schedule. Studies in the general population have suggested adenoviral-vectored vaccines demonstrate reduced vaccine-efficacy against severe disease when directly compared to mRNA vaccines (https://www.cdc.gov/mmwr/volumes/70/wr/mm7038e1.htm). These observations support the use of mRNA vaccines in patients with antibody deficiency.

It could be argued that the deployment of a 3rd dose of vaccination in individuals that have not responded to a first dose is futile. However, we have found that serological and cellular responses to the SARS-CoV-2 spike protein were positively incremented by the second vaccine dose,
Table 3 Vaccine breakthrough infections in COV-AD participants

| Patient | Age  | Sex | Diagnosis            | Prior COVID Symptoms and severity  | Duration of positivity (d) | Time from second vaccine dose to infection (d) | Vaccine | Seropositive post vaccination IgGAM ratio | B cell count (×10^9/L) | Outcome |
|---------|------|-----|-----------------------|------------------------------------|---------------------------|-----------------------------------------------|---------|------------------------------------------|------------------------|---------|
| 1       | 54   | F   | Undefined CID         | Y - mild, non-hospitalised, no specific treatment | Not known -declined swabs | 1 dose only AZ Y                              | 5.41    | 4.59                                     | Alive                  |
| 2       | 68   | F   | Secondary—rheumatology | N Y - hospitalised, COVID pneumonia treated with dexamethasone and remdesivir | 29                         | 94 AZ N                                      | 0.25    | Undetectable                             | Deceased               |
| 3       | 38   | M   | CVID                  | N Y - mild, non-hospitalised, no specific treatment | 28                         | 116 AZ Y                                     | 2.47    | 0.17                                     | Alive                  |
| 4       | 38   | F   | Primary antibody deficiency | Y - mild, non-hospitalised, antibiotics for secondary infection | 22                         | 143 AZ N                                     | 0.63    | n/a                                      | Alive                  |
| 5       | 37   | F   | CVID                  | N Y - mild, non-hospitalised, antibiotics for secondary infection | Not known -declined swabs | 138 AZ N                                     | 0.27    | 0.01                                     | Alive                  |
| 6       | 60   | M   | CVID                  | Unknown Y - hospitalised, no specific treatment | 80 Y                       | 92 Pfizer N                                  | 0.19    | 0.03                                     | Alive                  |
| 7       | 61   | F   | Secondary—haematological | Unknown Y - hospitalised, no specific treatment | 11 Y                       | 181 AZ Y                                     | 1.59    | 0.13                                     | Alive                  |
| 8       | 45   | F   | CVID                  | N Y - mild, non-hospitalised, antibiotics for secondary infection | 63                         | 61 AZ N                                      | 0.18    | 0.01                                     | Alive                  |
| 9       | 44   | M   | CVID                  | N Y - mild, non-hospitalised, no specific treatment | 16                         | 111 AZ N                                     | 0.48    | 0.01                                     | Alive                  |
| 10      | 50   | F   | Secondary—haematological | Y - mild, non-hospitalised, antibiotics for secondary infection | 24 Y                       | 199 AZ N                                     | 0.62    | 0.45                                     | Alive                  |
| 11      | 61   | M   | CVID                  | Unknown Y - hospitalised, no specific treatment | 10                         | 120 AZ Y                                     | 2.26    | 0.24                                     | Alive                  |

*Received Casirivimab/imdevimab prior to viral clearance. $Ongoing infection at time of publication. Acronyms: Y Yes, N No, AZ AstraZeneca ChAdOx1 nCoV-19, CID combined immunodeficiency disorder, CVID common variable immunodeficiency disorder, Pfizer Pfizer BioNTech 162b
in keeping with previous studies in patients with inborn errors of immunity [16] suggesting potential benefit from further doses. Our group have demonstrated the effectiveness of a 3rd primary immunisation in raising antibody levels against the delta and omicron variants of concern in a cohort of immunocompromised renal dialysis patients and provide preliminary evidence of the benefit of a heterogeneous vaccination strategy on serological responses to vaccination [33]. Further studies will be necessary to explore whether different vaccination combinations (homologous/heterologous) or dosing schedules may improve responses and efficacy in patients with primary and secondary humoral immunodeficiencies.

Existing studies have reported wide variation in the serological response to vaccination in patients with immunodeficiency: post-vaccine seroprevalence have ranged from 20.0 to 80.0% [14–18]. The COVAD study is the largest reported study of patients with antibody deficiency and finds a seropositivity rate of 54.8% overall. At a cohort level, total B cell numbers were the principal determinate of serological response to vaccination, also in keeping with other SARS-CoV-2 vaccine studies [17]. Additional correlates of vaccine responsiveness remain to be elucidated: Salinas et al. demonstrated patients with CVID have a relative paucity of receptor-binding domain-specific, demonstrated patients with CVID have a relative paucity of receptor-binding domain-specific, B cells compared to healthy controls [18] and Hagine et al. were unable to demonstrate a common T-cell immunophenotype in vaccine non-responders beyond an inverted CD4/CD8 ratio [17]. Future work in COV-AD will employ detailed phenotypic and functional profiling to investigate potential correlates of vaccine immunogenicity and efficacy within this heterogeneous cohort.

This is a large study in a rare disease cohort and, although heterogeneous, we have had the opportunity to compare the immunogenicity of an mRNA and adenoviral-vectored vaccine in an immunodeficient cohort. To some extent, the generalisability of our study to the wider world is confounded by the extended UK vaccine schedule, which has not yet been widely adopted elsewhere. On the one hand, extension of the interval between first and second doses has been associated with greater neutralising antibody responses and enrichment of virus specific CD4 + T cells in healthy individuals [34], but shorter dosing intervals were associated with better humoral responses in a smaller study of patients vaccinated following treatment with B cell depleting agents [35]. There is an urgent need for further studies that explore how to maximise vaccine immunogenicity and efficacy in larger and heterogeneous cohorts of immune deficient patients.

In conclusion, we demonstrate profound impairment of serological responses following SARS-CoV-2 vaccination in patients with antibody deficiency and evidence of the superior immunogenicity of the Pfizer BioNTech 162b2 vaccine. These data highlight the ongoing risk of SARS-CoV-2 infection in antibody deficiency patients and should inform public health policy on vaccination strategies and other treatments to prevent morbidity and mortality.

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COV-AD Consortium
Zahra Ahmed1
Hollie Bancroft2
Michelle Bates2
Hayley Clifford2
Georgina Davis3
Joanne Dasgip1
Mohammad Dinally1
Fatima Dhallia4
Elena Elfathithou1
Shuaib Elkhafifa5
Mark Gompels6
Dan Hartland7
Madeeha Hoque1
Emily Heritage5
Deborah Hughes9
Ann Ivory9
Rashmi Jain1
Sinead Kelly10
Theresa McCarthy1
Christopher McGece1
Daniel Mullan1
Hadeil Morsi1
Eileen O’Grady11
Shannon Page1
Nicholas Peters1
Timothy Plant1
Archanal Shajidevadas12
Malgorzata Slowinska5
Zebra Suleiman1
Neil Townsend1
Charlotte Trinham1
Stuart Wareham3
Sinead Walder1
Consortium Affiliations
1Clinical Immunology Service, Institute for Immunology and Immunotherapy, University of Birmingham, UK
2University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK
3Department of Immunology and Allergy, University Hospital Plymouth NHS Trust, Plymouth, UK
4Department of Clinical Immunology, Oxford University Hospitals NHS Foundation Trust, Oxford, UK
5Department of Immunology, Salford Royal NHS Foundation Trust, Salford, UK
6Department of Immunology, North Bristol NHS Trust, Bristol, UK
7Saving Lives Charity, MIDRU Building, Heartlands Hospital, Birmingham, UK
8Institute of Translational Medicine, University of Birmingham, Birmingham, UK
Author Contribution  AMS, SOB and AGR designed and supervised the study. SEF, HHJ, SAT, CT, FA and ZS undertook experimental work and analysis for the study. SW, FM, NV, SG, SJ, AH, CB, SE, DML, SYP, SS, AMS, SOB and AGR recruited patients to the study and acted as local site principal investigators. HW, GH and NC provided administrative and database support for the study and facilitated patient recruitment to the study. PK, JEDT, SOB and AGR provided senior leadership and strategic oversight for the study. AMS analysed the data, wrote the first draft of the manuscript and revised the manuscript. All authors contributed the revision of the manuscript and read and approved the final version.

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Data Availability  The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Code Availability  Not applicable.

Declarations

Ethics Approval  This study was approved by the London — Dulwich Research Ethics Committee (REC reference: 21/LO/0162) and funded by the UK Research and Innovation (MR/W002663/1). Serological responses from healthy individuals are from participants recruited to the COVID-19 convalescent (COCO) immunity study (REC reference 20/HRA/1817). All participants provided written informed consent prior to participation in this study.

Consent to Participate  All participants provided written informed consent prior to participation in the COV-AD study.

Consent for Publication  Not applicable.

Competing Interests  The authors declare no competing interests.

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Authors and Affiliations

Adrian M. Shields¹,² · Sian E. Faustini³ · Harriet J. Hill³ · Saly Al-Taei³ · Chloe Tanner¹ · Fiona Ashford¹ · Sarita Workman⁴ · Fernando Moreira⁴ · Nisha Verma⁴ · Hollie Wagg⁵ · Gail Heritage⁶ · Naomi Campton⁵ · Zania Stamataki³ · Paul Klienerman⁶ · James E. D. Thaventhiran⁷ · Sarah Goddard⁸ · Sarah Johnston⁹ · Aarnoud Huissoon² · Claire Bethune¹⁰ · Suzanne Elcombe¹¹ · David M. Lowe⁴,¹² · Smita Patel⁶,¹³ · Sinisa Savic¹⁴ · Siobhan O. Burns⁴,¹² · Alex G. Richter¹², on behalf of the COV-AD consortium

¹ Clinical Immunology Service, Institute of Immunology and Immunotherapy, University of Birmingham, Birmingham, UK
² University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK
³ Institute of Immunology and Immunotherapy, University of Birmingham, Birmingham, UK
⁴ Department of Immunology, Royal Free London NHS Foundation Trust, London, UK
⁵ Institute of Translational Medicine, University of Birmingham, Birmingham, UK
⁶ Nuffield Department of Medicine, University of Oxford, Oxford, UK
⁷ Medical Research Council Toxicology Unit, University of Cambridge, Glueson Building, Tennis Court Road, Cambridge CB2 1QW, UK
⁸ Department of Clinical Immunology, University Hospitals North Midlands, Stoke-on-Trent, UK
⁹ Department of Clinical Immunology, North Bristol NHS Trust, Bristol, UK
¹⁰ Department of Allergy and Clinical Immunology, University Hospitals Plymouth NHS Trust, Plymouth, UK
¹¹ Department of Allergy and Clinical Immunology, Newcastle Upon Tyne Hospitals NHS Foundation Trust, Newcastle, UK
¹² Institute of Immunity and Transplantation, University College London, London, UK
¹³ NIHR BRC Oxford Biomedical Centre, University of Oxford, Oxford, UK
¹⁴ Department of Allergy and Clinical Immunology, Leeds Teaching Hospitals NHS Trust, Leeds, UK