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# Intensity and longevity of SARS-CoV-2 vaccination response in patients with immune-mediated inflammatory disease: a prospective cohort study

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## Summary

**Background** Concerns have been raised about the reduced immunogenicity of vaccines against SARS-CoV-2 in patients with immune-mediated inflammatory diseases and the higher risk of breakthrough infections. The objective of our study was to investigate the intensity and longevity of SARS-CoV-2 vaccination responses in patients with immune-mediated inflammatory diseases, and to assess the effects of diagnosis, treatment, and adapted vaccination schedules.

**Methods** SARS-CoV-2 IgG antibody response after SARS-CoV-2 vaccination was measured over time in a large prospective cohort of healthy controls and participants with immune-mediated inflammatory diseases (attending or admitted to affiliated centres) between Dec 15, 2020, and Dec 1, 2021. Cohort participants with immune-mediated inflammatory diseases and control participants with no diagnosis of immune-mediated inflammatory diseases, were eligible for this analysis. Demographic data and disease-specific data were collected using a questionnaire. Humoral response was compared across treatment and disease groups, and with respect to the receipt of additional vaccinations. SARS-CoV-2 antibody response was measured by ELISA using optical density ratio units and modelled over time with age and sex adjustment using mixed-effects models. Using these models, marginal mean antibody titres and marginal risks of a poor response (optical density ratio <1·1) were calculated for each week starting from week 8 after the first vaccination to week 40.

**Findings** Among 5076 individuals registered, 2535 participants with immune-mediated inflammatory diseases (mean age 55·0 [15·2] years; 1494 [58·9%] women and 1041 [41·1%] men) and 1198 healthy controls (mean age 40·7 [13·5] years; 554 [46·2%] women and 644 [53·8%] men) were included in this analysis. Mean antibody titres were higher in healthy controls compared with people with immune-mediated inflammatory diseases at all timepoints, with a peak antibody response in healthy controls (mean optical density ratio 12·48; 95% CI 11·50–13·53) of more than twice that in participants with immune-mediated inflammatory diseases (5·50; 5·23–5·77; mean difference 6·98; 5·92–8·04). A poor response to vaccination was observed in participants with immune-mediated inflammatory diseases who were taking B-cell inhibitors (peak mean difference from healthy controls 11·68; 10·07–13·29) and T-cell inhibitors (peakmean difference from healthy controls 10·43; 8·33–12·53). Mean differences in antibody responses between different immune-mediated inflammatory diseases were small. Participants with immune-mediated inflammatory diseases who were given a third vaccine dose had higher mean antibody titres than did healthy controls vaccinated with two vaccine doses at 40 weeks after the initial vaccination (mean difference 1·34; 0·01–2·69).

**Interpretation** People with immune-mediated inflammatory diseases show a lower and less durable SARS-CoV-2 vaccination response and are at risk of losing humoral immune protection. Adjusted vaccination schedules with earlier booster doses or more frequent re-doses, or both, could better protect people with immune-mediated inflammatory diseases.

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## Introduction

SARS-CoV-2 is a substantial threat to patients with immune-mediated inflammatory diseases. Because of immune dysfunction and use of immune modulatory drugs in these people, host responses to infection and vaccination are altered and can vary considerably in terms of effectiveness,[1,2] longevity,[3] and protection against poor outcomes.[4–8] From an immunological perspective, the majority of people with immune-mediated inflammatory diseases are able to mount humoral

## Research in context

### Evidence before this study

Although it is known that SARS-CoV-2 vaccination is effective in the general population, few data on the sustained effectiveness of the vaccine in individuals with immune-mediated inflammatory diseases exist at present. Most notably, little is known about whether the immune response against the SARS-CoV-2 vaccine is durable and how it is influenced by immune modulatory therapies. We searched PubMed, medRxiv, bioRxiv, and Google Scholar for articles published from Jan 1, 2020, to April 31, 2022, using the search terms "COVID-19", "SARS-CoV-2", "rheumatic diseases", "rheumatic musculoskeletal diseases", OR "immune mediated inflammatory diseases", "vaccine" OR "vaccination", "response" OR "immunogenicity", "persistence" OR "longevity", "seroconversion", "loss of response", OR "non-response". Finally, we refined the search for studies related to anti-SARS-CoV-2 vaccinations using the search terms "immunosuppressive therapy", "glucocorticoids", "DMARD", "csDMARD", "bDMARD", "biologics", and the comprehended drug classes, "tsDMARD". We limited our search to articles that were published in English.

### Added value of this study

This study shows that the antibody responses of individuals with immune-mediated inflammatory diseases after two doses of SARS-CoV-2 vaccination show both lower intensity and reduced durability compared with healthy controls. In particular, many older individuals with immune-mediated inflammatory diseases lose their humoral response to vaccination over time and are likely to benefit from an additional vaccination. Among all immune modulatory therapies, T-cell-targeted and B-cell-targeted drugs show the strongest inhibitory effect on the immune response to SARS-CoV-2 vaccines.

### Implications of all the available evidence

Our data support the introduction of adjusted vaccination schedules with more frequent booster vaccinations for individuals with immune-mediated inflammatory diseases to ensure effective immunisation to prevent breakthrough infections.

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immune responses after SARS-CoV-2 infection[9,10] and vaccination.[1,2] However, these responses appear to be blunted,[1,2] and the overall prevalence of anti-SARS-CoV-2 antibody positivity due to infection is significantly lower compared with the general population.[11] This low seroprevalence seems to be, at least in part, driven by specific immunomodulatory therapies such as methotrexate,[12,13] mycophenolate mofetil,[14,15] or rituximab.[16,17]

As reports of waning vaccine effectiveness and new virus variants resistant to antibody neutralisation are emerging, the increased susceptibility of people with immune-mediated inflammatory diseases to earlier breakthrough infections is of particular concern.[8,18] To date, the immunogenicity of SARS-CoV-2 vaccines in these individuals has been studied mostly in the first 2–6 weeks after vaccination, whereas extended longitudinal data are scarce. One study suggested a more pronounced decline in the humoral response to vaccination in people with immune-mediated inflammatory diseases than in healthy individuals.[19] Furthermore, a pronounced decrease in the vaccine response rate was observed in a small cohort of people with immune-mediated inflammatory diseases treated with tumour necrosis factor (TNF) inhibitors compared with healthy controls 6 months after vaccination, despite similar responses at previous timepoints.[20] Considering that the titres of anti-SARS-CoV-2 IgG correlate with COVID-19 risk and vaccine effectiveness,[21] this finding might represent a warning signal of waning immunity, especially in subsets of people who are at a high risk. Therefore, there is a need to investigate the long-term course of vaccine response in people with immune-mediated inflammatory diseases to better identify patients at risk of losing protective immunity in the long term, and also to assess the effect of currently recommended vaccine regimens over this time period to inform decisions on vaccination practices and updates to the current vaccination recommendations for people with immune-mediated inflammatory diseases.[22]

To this end, we used data from a dynamic cohort of participants with immune-mediated inflammatory diseases and healthy individuals to assess the time course of antibody response to SARS-CoV-2 vaccination. The primary objective of this study was to characterise the long-term antibody response to two doses of SARS-CoV-2 vaccine in people with immune-mediated inflammatory diseases in comparison with individuals without immune-mediated inflammatory diseases. We also aimed to characterise the variations in the time course of antibody response associated with individual immune-mediated inflammatory disease diagnoses, the use of immune modulators, and additional vaccine doses.

## Methods

### Study design and participants

We did a prospective cohort study, in which participants with immune-mediated inflammatory diseases and healthy controls were recruited from the prospective COVID-19 study programme conducted by the Deutsche Zentrum fuer Immuntherapie, which since February 2020 has collected data at each of its participating centres on respiratory infections including COVID-19, as well as anti-SARS-CoV-2 antibody responses before and after the approval of vaccines against SARS-CoV-2 and exposure risk behaviour over time. Further study details have been described elsewhere.[11] Briefly, patients attending or admitted to affiliated centres (University Clinic Erlangen, Sozialstiftung Bamberg, and rheumatology practices in Erlangen and Bamberg, Germany) who received either no

treatment or treatment with immunomodulatory agents were recruited. Healthy controls included employees of the University Hospital Erlangen, and individuals in Erlangen and Erlangen-Höchstadt (Germany) recruited in several organised field campaigns recruiting personnell at fire and police stations in Erlangen during the pandemic (from February to April 2020, from December 2020, to January 2021, and from November to December 2021). Participants with immune-mediated inflammatory diseases were asked to participate during their routine follow-up visits. A structured questionnaire was used to collect data on demographic characteristics and comorbidities. The study was approved by the Institutional Review Board of Erlangen University Hospital (approval number #157_20.B), and written informed consent was obtained from all study participants.

See Online for appendix

Cohort participants with physician-diagnosed immune-mediated inflammatory diseases, including systemic autoimmune diseases, rheumatoid arthritis, spondyloarthritides (including psoriatic arthritis), vasculitides (excluding cutaneous-limited vasculitis), psoriasis, inflammatory bowel diseases (Crohn's disease and ulcerative colitis), polymyalgia rheumatica, and miscellaneous immune-mediated inflammatory diseases including sarcoidosis, IgG-4-related disease, juvenile idiopathic arthritis, myositis, autoinflammatory syndromes, and inflammatory demyelinating diseases, as well as control participants with no diagnosis of immune-mediated inflammatory diseases, were eligible for this analysis. Participants who were sampled while being evaluated for a possible immune-mediated inflammatory disease but did not receive a clear diagnosis, those with organ-specific autoimmunity (autoimmune thyroiditis and autoimmune liver disease), atopy (urticaria, asthma, and atopic dermatitis), immunodeficiency, malignancy, and those with an uncertain diagnostic status were excluded. Included participants had at least one blood sample available starting from 4 weeks before their first vaccination date.

### Procedures and outcomes

All SARS-CoV-2 vaccines approved in Germany at the time of sampling were allowed, including the mRNA vaccines BNT162b2 (Pfizer–BioNTech) and mRNA-1273 (Moderna), and the viral vector vaccines Ad26.COV2.S (Johnson & Johnson) and ChAdOx1 nCov-19 (Oxford–AstraZeneca). All patients were vaccinated according to the standard vaccination schedules as approved by the European Medicines Agency. That is, two doses 3 weeks apart for BNT162b2, two doses 4 weeks apart for mRNA-1273, a single dose for Ad26.COV2.S, and two doses 4 weeks apart for ChAdOx1 nCov-19. Additional booster vaccinations were administered starting from 6 months after the last administered vaccine dose, according to local regulations, except for patients who did not respond to the standard vaccine regimen (defined as an optical density ratio of <0·8 with the Eurimmune SARS CoV-2 IgG ELISA assay measured at least 4 weeks after the completion of the standard vaccination schedule), who were offered revaccination as early as 2 months after the primary vaccine regimen. Participants were advised to stop taking some immunosuppressive medications before and after vaccination according to local recommendations. Methotrexate and T-cell-targeted drugs, such as abatacept and mycophenolate mofetil, were paused 1 week before and 1 week after vaccination, and Janus kinase inhibitors were withheld 1 day before and 1 day after vaccination. Cytokine blockers were not discontinued. Rituximab was also not discontinued, but SARS-CoV-2 vaccination was given 2–6 weeks before the next scheduled infusion as per routine practice.

This study was undertaken using serum samples obtained between Dec 15, 2020, and Dec 1, 2021. A recruitment per month scheme is shown in the appendix (p 10). The follow-up for each patient started on the date of first vaccination and ended at the last date of sample collection. We estimated the duration of follow-up as the time difference in weeks between the date of first vaccination and last date of sampling, considering samples obtained on or within the 4 weeks before the first vaccination date as baseline. Samples were collected during routine visits for participants with immune-mediated inflammatory diseases, in response to email reminders for participating health-care personnel, and via several recruitment campaigns through advertising and social media by investigators for community-dwelling individuals without immune-mediated inflammatory diseases throughout the post-vaccination period. Serum samples were collected by health-care professionals from the participating centers.

We categorised current immunomodulatory treatments used for immune-mediated inflammatory diseases at each sampling timepoint as either: cytokine inhibitors (eg, TNF, interleukin [IL]-1, IL-5, IL-6, IL-12/23, IL-17, and IL-36), signalling inhibitors (eg, Janus kinase and phosphodiesterase), adhesion molecule inhibitors (eg, integrin), T-cell inhibitors (eg, CD80/86 and calcineurin), B-cell inhibitors (eg, CD20 and B lymphocyte stimulator), conventional immune modulators (eg, methotrexate, azathioprine, leflunomide, mycophenolate mofetil, and cyclophosphamide), or other drugs (eg, hydroxychloroquine and sulfasalazine) as detailed in the appendix (p 1). A primary treatment category was assigned to each patient for each sampling timepoint (patients who provided samples at more than one timepoint would be assigned to the corresponding category on the basis of the treatment currently received at the corresponding timepoint) following the following hierarchy: biological agents (ie, adhesion molecule inhibitors, cytokine inhibitors, B-cell inhibitors, and T-cell inhibitors); signalling inhibitors; conventional immune modulators; other drugs; and glucocorticoids. When a patient was on multiple concomitant treatments, this was indicated as a

combination treatment in a separate variable. This hierarchy was used to designate mutually exclusive treatment categories.

IgG antibodies against the S1 domain of the spike protein of SARS-CoV-2 were measured using the April 2020 version of the commercial ELISA from Euroimmun (Lübeck, Germany) using the Euroimmun Analyzer 1 platform according to the manufacturer's instructions. Optical density ratios were read at 450 nm with a reference wavelength of 630 nm. A density value of between 0·8 and 1·1 (optical density ratio 450 nm) was considered to be borderline and a value of 1·1 or more was considered positive. A density value of less than 0·8 was considered to be negative. Assays were performed in line with the guidelines of the German Medical Association (RiliBAK) with stipulated internal and external quality controls.

We had two primary outcomes in this study: the optical density ratio values representing antibody titres, and a poor vaccine response defined by an optical density ratio value of less than 1·1. There were no other outcomes and the primary outcomes were assessed in healthy controls and patients with immune-mediated inflammatory diseases.

### Statistical analysis

We did not undertake a sample size calculation for this analysis and aimed to include the highest number of participants possible. We used descriptive statistics to summarise the cohort characteristics. Optical density ratio values representing antibody titres were separated into 2–8-week intervals of sample acquisition time after the first vaccination for descriptive purposes and summarised as geometric means and standard deviations as observed.

The time course of SARS-CoV-2 antibody titres was analysed after log-transformation and modelled as a function of time after the first vaccination using mixed-effects linear regression. Because the relationship between time and antibody titres is expected to be curvilinear, we used restricted cubic splines with four degrees of freedom for time in all analyses. We constructed three linear models to compare: (1) healthy controls versus all participants with immune-mediated inflammatory diseases, indicated by a binary variable; (2) healthy controls and immune-mediated inflammatory disease diagnoses indicated by a categorical variable; and (3) healthy controls and primary treatment category classified by mechanism of action. Using these linear models, we estimated the age-adjusted and sex-adjusted marginal geometric mean optic density ratios for each week starting from week 8 after the first vaccination up to week 40. We also estimated the marginal mean between-group differences from these models with multiplicity adjusted 95% CIs at weeks 8–12 to characterise the differences in responses around the peak response to vaccination and at week 40 to characterise the differences in the long term.

We modelled the risk of a poor response to vaccination over time using mixed-effects logistic regression, where an optical density ratio value of less than 1·1 indicated a poor response. Using this logistic regression model, we estimated the marginal risk of a poor response from week 8–40 with 95% CIs. We also obtained odds ratios for the overall association of age and sex with a poor antibody response and estimated the marginal risks of a poor response for patients with immune-mediated inflammatory diseases by age and sex from this model.

In further analyses we aimed to address two potential confounders, the type of vaccination in the primary series and a previous SARS-CoV-2 infection. To address the influence of vaccination type, we repeated the analyses for mean antibody titres and risk of poor response by adding an interaction term between the study group and the vaccine type in the two-dose primary vaccination series. The type of vaccination was classified for this analysis as homologous mRNA, homologous vector, heterologous, and unclear when the type of one or both of the two vaccinations were unknown. From this model we obtained separate marginal mean antibody titres and marginal risks of a poor response for participants with immune-mediated inflammatory diseases and healthy control groups by type of vaccination. In a second sensitivity analysis, we aimed to address potential confounding due to a previous SARS-CoV-2 infection and repeated the analyses for the time course of mean antibody titres after excluding participants who reported a positive PCR test for SARS-CoV-2. Finally, we repeated the analysis for mean antibody titres by the number of vaccine doses received.

All models included age at the time of first vaccination and sex for adjustment, interaction terms between time and grouping variables, and participant identifier entered in the models as a random intercept. Tukey's method was used for multiplicity adjustment of the CIs in pairwise comparisons and 95% CIs of mean differences excluding 0 were considered significant. All analyses were conducted using R (version 4.1.1; R Foundation for Statistical Computing, Vienna, Austria) using the packages lme4 and emmeans. Analyses were done on complete cases without any specific procedure for missing data.

### Role of the funding source

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

## Results

Among the 5076 individuals registered in our cohort, 3733 participants were eligible for this analysis, including 2535 participants with immune-mediated inflammatory diseases and 1198 healthy controls who provided a total of 5564 samples when they were recruited between Dec 15, 2020, and Dec 1, 2021. A flow chart describing

| | Immune-mediated inflammatory diseases (n=2535) | Healthy controls (n=1198) | All (n=3733) |
|---|---|---|---|
| Age | 55·0 (15·2) | 40·7 (13·5) | 50·4 (16·1) |
| Follow-up duration, weeks | | | |
| Median | 19·9 (12·6–27·0) | 31·1 (24·0–36·7) | 23·3 (13·9–30·9) |
| Range | 1·7–46·9 | 1·6–47·3 | 1·6–47·3 |
| Sex | | | |
| Male | 1041 (41·1%) | 644 (53·8%) | 1685 (45·1%) |
| Female | 1494 (58·9%) | 554 (46·2%) | 2048 (54·9%) |
| Vaccine doses | | | |
| One dose | 155 (6·1%) | 57 (4·8%) | 212 (5·7%) |
| Two doses | 2233 (88·1%) | 1047 (87·4%) | 3280 (87·9%) |
| Three doses | 147 (5·8%) | 94 (7·8%) | 241 (6·5%) |
| Vaccination times, weeks | | | |
| First to second dose | 6·0 (5·0–6·1) | 4·7 (3·0–6·0) | 6·0 (3·9–6·0) |
| Second to third dose | 20·3 (12·0–26·7) | 29·6 (26·9–36·1) | 26·3 (16·2–31·8) |
| Number of samples per participant | | | |
| 1 | 1573 (62·1%) | 741 (61·9%) | 2314 (62·0%) |
| 2 | 767 (30·3%) | 327 (27·3%) | 1094 (29·3%) |
| 3 | 143 (5·6%) | 111 (9·3%) | 254 (6·8%) |
| >3 | 52 (2·1%) | 19 (1·6%) | 71 (1·9%) |
| Diagnosis | | | |
| Spondyloarthritis | 824 (32·5%) | NA | NA |
| Rheumatoid arthritis | 581 (22·9%) | NA | NA |
| Systemic autoimmune diseases | 307 (12·1%) | NA | NA |
| Inflammatory bowel diseases | 241 (9·5%) | NA | NA |
| Vasculitis | 184 (7·3%) | NA | NA |
| Psoriasis | 119 (4·7%) | NA | NA |
| Polymyalgia rheumatica | 103 (4·1%) | NA | NA |
| Sarcoidosis* | 53 (2·1%) | NA | NA |
| Autoinflammatory syndromes* | 30 (1·2%) | NA | NA |
| IgG4 related disease* | 30 (1·2%) | NA | NA |
| Myositis* | 26 (1·0%) | NA | NA |
| Juvenile idiopathic arthritis* | 24 (0·9%) | NA | NA |
| Demyelinating disease* | 13 (0·5%) | NA | NA |
| Dominant treatment at time of sampling†‡ | | | |
| Cytokine inhibitors | 1467/3759 (39·0%) | NA | NA |
| No immunomodulation | 717/3759 (19·1%) | NA | NA |
| Conventional immune modulators | 638/3759 (17·0%) | NA | NA |
| Glucocorticoids | 288/3759 (7·7%) | NA | NA |
| Signalling inhibitors | 239/3759 (6·4%) | NA | NA |
| B-cell inhibitors | 197/3759 (5·2%) | NA | NA |
| T-cell inhibitors | 62/3759 (1·6%) | NA | NA |
| Adhesion molecule inhibitors | 45/3759 (1·2%) | NA | NA |
| Other drugs | 106/3759 (2·8%) | NA | NA |
| Combination treatment | 482/3759 (12·8%) | NA | NA |
| Overall glucocorticoid use | 814/3759 (21·7%) | NA | NA |

Data shown as n (%), mean (SD), or median (IQR). NA=not applicable. *Designated as other diagnoses throughout the manuscript. †Detailed list of individual agents per class provided in the appendix (p 1). ‡Counts and percentages based on the number of samples to accommodate treatment switches over the study time window.

***Table 1:*** **Participant characteristics**

cohort selection is in the appendix (p 11). The mean (SD) age of the cohort at the time of first vaccination was 50·4 (16·1) years, 2048 (54·9%) participants were women and 1685 (45·1%) were men. Participants with immune-mediated inflammatory diseases were on average older than the healthy controls, with a mean age of 55·0 (15·2) versus 40·7 (13·5) years, and a greater proportion were women (1494 [58·9%] participants with immune-mediated inflammatory diseases *vs* 554 [46·2%] healthy controls; table 1). The most common diagnoses among patients with immune-mediated inflammatory diseases were spondyloarthritis (including psoriatic arthritis), rheumatoid arthritis, systemic autoimmune diseases (including systemic lupus erythematosus, systemic sclerosis, and primary Sjögren's syndrome), inflammatory bowel diseases, vasculitis, and psoriasis. The distribution of treatments by diagnostic groups is summarised in the appendix (p 2).

A total of 7495 vaccine doses were administered. 3280 (87·9%) participants received two doses, with a median interval time between the first and second doses of 6 weeks (IQR 3·9–6·0 weeks) and 241 (6·5%) participants received a third dose after a median interval of 26·3 (16·2–31·8) after the second dose. Because of the early revaccination policy in non-responders, participants with immune-mediated inflammatory diseases received the third vaccine dose earlier than healthy controls (table 1). The BNT162b2 mRNA vaccine was the most frequently administered vaccine, with 5641 (75·3%) of 7495 doses, followed by the ChAdOx1 nCov-19 viral vector-based vaccine (807 doses [10·8%]). Among the 3280 participants who received two vaccine doses, 2444 (74·5%) received homologous mRNA vaccination, 195 (5·9%) received homologous vector vaccination, and 293 (8·9%) participants received heterologous vaccination. The distribution of vaccine types across all doses were similar between participants with immune-mediated inflammatory diseases and healthy controls, and are summarised in detail in the appendix (p 3). At the time of sample collections, 2141 participants with immune-mediated inflammatory diseases responded to questions on the worsening of their primary disease after vaccination, among whom 100 (4·7%) reported a worsening after one of the vaccine doses, resulting in a physician visit in 32 patients, a treatment dose change in 20 patients, the initiation of a new medication in 15 patients, and hospital admission in seven patients.

Observed geometric mean SARS-CoV-2 IgG antibody titres by periods of follow-up after first vaccination are presented in table 2. The highest optical density ratio values were observed after more than 8–10 weeks after the second vaccination dose in both groups, and antibody titres increased faster in healthy controls compared with participants with immune-mediated inflammatory diseases, and with overall higher mean values. A summary of participant characteristics

across the different periods of follow-up is presented in the appendix (p 4).

Estimated marginal mean antibody titres after adjustment for age and sex (table 3) were higher in the healthy controls compared with participants with immune-mediated inflammatory diseases at all timepoints from 8 weeks post-second vaccination onwards, where the peak marginal mean antibody response in the healthy controls (12·48; 95% CI 11·50–13·53) was more than twice the value estimated for participants with immune-mediated inflammatory diseases (5·50; 5·23–5·77), showing a mean difference of 6·98 (5·92–8·04) at week 10. At week 40, the difference was less pronounced, with a marginal mean antibody titre of 3·31 (3·00–3·64) in healthy controls compared with 2·40 (2·00–2·86) in participants with immune-mediated inflammatory diseases, with a small but significant mean difference of 0·91 (0·38–1·45). The healthy controls showed a biphasic loss of antibodies over time; an initial rapid decline after the peak up to week 20 and a slower decline thereafter until week 40, as opposed to a relatively monophasic loglinear decline after a shallower peak in participants with immune-mediated inflammatory diseases (figure 1A).

The observed proportion of samples showing a poor antibody response after week 8 (an optical density ratio of less than 1·1) ranged from 0 to 2·3% among healthy controls, and from 7·4% to 17·8% among participants with immune-mediated inflammatory diseases, rising steadily after the 8–10-week period after the first vaccination (table 2). The average estimated marginal risk of a poor response adjusted for mean cohort age was higher in participants with immune-mediated inflammatory diseases compared with healthy controls at all timepoints (figure 1B). The estimated marginal risk ranged from 0·24% to 2·87% in healthy controls but was more than 5% at all timepoints in participants with immune-mediated inflammatory diseases, reaching 12·79% (95% CI 10·08–16·10%) at week 32 and 26·08% (15·69–40·08%) at week 40, almost ten times the risk estimated for healthy controls at week 40 (2·87%; 1·34–6·04%; table 3).

Age and sex also had an effect on the risk of a poor response to vaccination. The estimated marginal risk of a poor response at week 40 for participants with immune-mediated inflammatory diseases was 17·87% (95% CI 10·12–29·59%) at 35 years and 35·83% (22·74–51·43%) at 65 years, corresponding to an overall odds ratio of 1·03 (1·02–1·04) per year increase in age across all timepoints.

| | Healthy controls | | | Immune-mediated inflammatory diseases | | |
|---|---|---|---|---|---|---|
| | Samples (N) | Optical density ratio (mean [SD])* | Poor response samples, n (%)* | Samples (N) | Optical density ratio (mean [SD])* | Poor response samples, n (%)* |
| ≤4 weeks | 168 | 0·29 (4·92) | 131 (78·0%) | 266 | 0·43 (5·31) | 175 (65·8%) |
| >4–8 weeks | 270 | 8·44 (1·56) | 3 (1·1%) | 457 | 2·82 (4·04) | 100 (21·9%) |
| >8–10 weeks | 77 | 8·59 (1·19) | 0 | 297 | 5·19 (2·58) | 22 (7·4%) |
| >10–16 weeks | 138 | 7·39 (1·76) | 2 (1·4%) | 879 | 4·13 (3·21) | 92 (10·5%) |
| >16–24 weeks | 207 | 6·10 (1·54) | 1 (0·5%) | 867 | 3·46 (2·87) | 106 (12·2%) |
| >24–32 weeks | 417 | 5·08 (1·67) | 5 (1·2%) | 637 | 2·98 (2·53) | 85 (13·3%) |
| >32 weeks | 431 | 3·87 (1·78) | 10 (2·3%) | 174 | 2·72 (2·77) | 31 (17·8%) |

Number of samples obtained before the third dose of vaccination, observed geometric mean optical density ratio (representing antibody titres), and observed number of samples showing a poor antibody response, by post-vaccination period. *Means and percentages do not take into account multiple samples from singular participants that are expected to be correlated.

***Table 2:*** **Observed geometric mean SARS-CoV-2 IgG antibody titres by periods of follow-up after first vaccination**

| | Healthy controls | | Immune-mediated inflammatory diseases | | Mean difference (optical density ratio [95% CI]) |
|---|---|---|---|---|---|
| | Optical density ratio, mean (95% CI) | Poor response, % (95% CI) | Optical density ratio, mean (95% CI) | Poor response, % (95% CI) | |
| 8 weeks | 10·00 (9·19–10·88) | 0·44% (0·16–1·20%) | 4·35 (4·13–4·59) | 9·77% (8·01–11·88%) | 5·65 (4·77–6·52) |
| 10 weeks | 12·48 (11·50–13·53) | 0·24% (0·09–0·70%) | 5·50 (5·23–5·77) | 7·02% (5·76–8·53%) | 6·98 (5·92–8·04) |
| 16 weeks | 6·22 (5·62–6·89) | 0·48% (0·10–2·21%) | 4·50 (4·28–4·74) | 7·58% (6·12–9·35%) | 1·72 (1·04–2·40) |
| 24 weeks | 4·16 (3·85–4·50) | 1·27% (0·49–3·27%) | 3·49 (3·32–3·66) | 9·24% (7·64–11·15%) | 0·67 (0·30–1·05) |
| 32 weeks | 4·32 (4·03–4·64) | 1·84% (0·96–3·49%) | 3·12 (2·92–3·33) | 12·79% (10·08–16·10%) | 1·21 (0·83–1·58) |
| 40 weeks | 3·31 (3·00–3·64) | 2·87% (1·34–6·04%) | 2·40 (2·00–2·86) | 26·08% (15·69–40·08%) | 0·91 (0·38–1·45) |

Estimated marginal mean antibody titres and estimated risk of a poor antibody response with 95% CIs when adjusted for mean cohort age and sex, at specific timepoints after the first vaccination.

***Table 3:*** **Estimated marginal mean antibody titers and estimated risk of poor response after adjustment for age and sex**

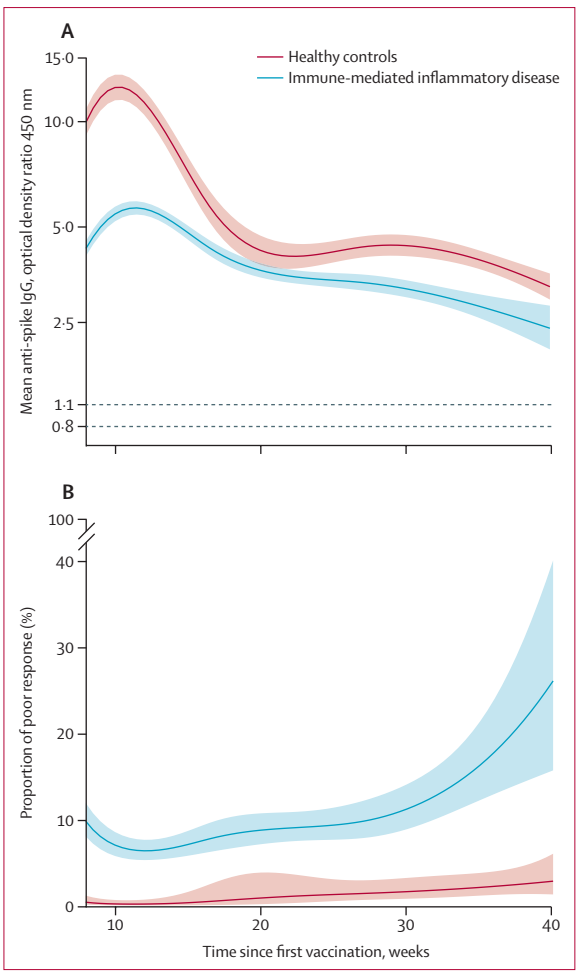


***Figure 1:*** **Estimated marginal mean anti-spike IgG titres (A) and estimated risks of a poor antibody response (B) between 8 to 40 weeks after first vaccination**

The bands represent the 95% CIs. The dashed lines mark negative (0·8) and borderline (1·1) optical density ratio thresholds. Estimated risk of poor response is the estimated percentage of participants that would have a poor vaccine response at a given timepoint on the x axis.

Male participants were slightly more likely to have a poor response at week 40, showing an estimated risk of a poor response at 28·62% (17·23–43·56%) in male participants with immune-mediated inflammatory diseases compared with 23·69% (14·05–37·09%) in female participants with immune-mediated inflammatory diseases, corresponding to an overall odds ratio of 1·29 (1·02–1·63) across all timepoints.

Age-adjusted and sex-adjusted marginal mean antibody titres by diagnosis showed an overall blunted peak immune response in participants with immune-mediated inflammatory diseases compared with healthy controls (appendix p 5; figure 2). Of note, peak responses were also lower in untreated participants with immune-mediated inflammatory diseases with no immunomodulation than in healthy controls (appendix p 5; figure 3). The largest adjusted mean differences between healthy controls and participants with an immune-mediated inflammatory disease diagnosis were observed at week 10, ranging from 5·62 (95% CI 2·75–8·50) for psoriasis to 8·69 (6·74–10·64) for other diagnoses (appendix pp 6–7). Lowest responses were found in patients with rheumatoid arthritis, vasculitis, and other diagnoses. Within immune-mediated inflammatory disease groups, the marginal mean antibody titres at peak were significantly lower in vasculitis and other diagnoses in comparison with those with systemic autoimmune diseases, inflammatory bowel diseases, polymyalgia rheumatica, psoriasis, and spondyloarthritis, with the largest absolute marginal mean differences ranging between 1·57 (0·00–3·15) for systemic autoimmune diseases versus vasculitis and 3·10 (0·53–5·67) for psoriasis versus other diagnoses. The peak marginal mean antibody titres for rheumatoid arthritis were significantly lower than only that of psoriasis among all immune-mediated inflammatory disease groups, with a mean difference of 2·57 (0·09–5·06; appendix pp 6–7). At week 40, the mean differences in antibody titres between the healthy controls and individual immune-mediated inflammatory disease groups were mostly small and imprecise, except for rheumatoid arthritis with a mean difference of 1·50 (0·38–2·61), and spondyloarthritis with a mean difference of 1·44 (0·26–2·62). All pairwise mean differences between diagnoses are presented in the appendix (p 6–7).

The overall course of marginal mean antibody titres was not different in untreated participants with immune-mediated inflammatory diseases from those on antimalarials or sulfasalazine (other drugs) or those on glucocorticoid monotherapy (mostly low doses; appendix p 5; figure 3). In contrast, mean antibody titres were low throughout follow-up in patients on T-cell and B-cell inhibitors. At their peak, the largest mean differences between the healthy controls and treatment groups were observed at week 10, and among them, the largest absolute difference was with B-cell inhibitors (11·68, 95% CI 10·07–13·29) followed by T cell inhibitors (10·43; 95% CI 8·33–12·53; appendix p 8). In paired comparisons between treatment groups for peak vaccine responses, B-cell inhibitors showed lower mean antibody titres in comparison to all other treatment groups, except for T-cell inhibitors. The absolute mean optical density ratio difference between B-cell inhibitors and signalling inhibitors was 3·66 (2·45 to 4·87) and between B-cell inhibitors and other drugs (hydroxychloroquine or sulfasalazine) was 6·60 (3·57 to 9·63). Peak responses with T-cell inhibitors were also lower than those observed with cytokine and signalling inhibitors as well as conventional immune modulators and other drugs, with absolute mean differences ranging between 2·41 (0·76 to 4·07) with signalling inhibitors and 5·36 (2·12 to 8·59) with other drugs. Post-hoc analyses also showed that patients receiving mycophenolate mofetil

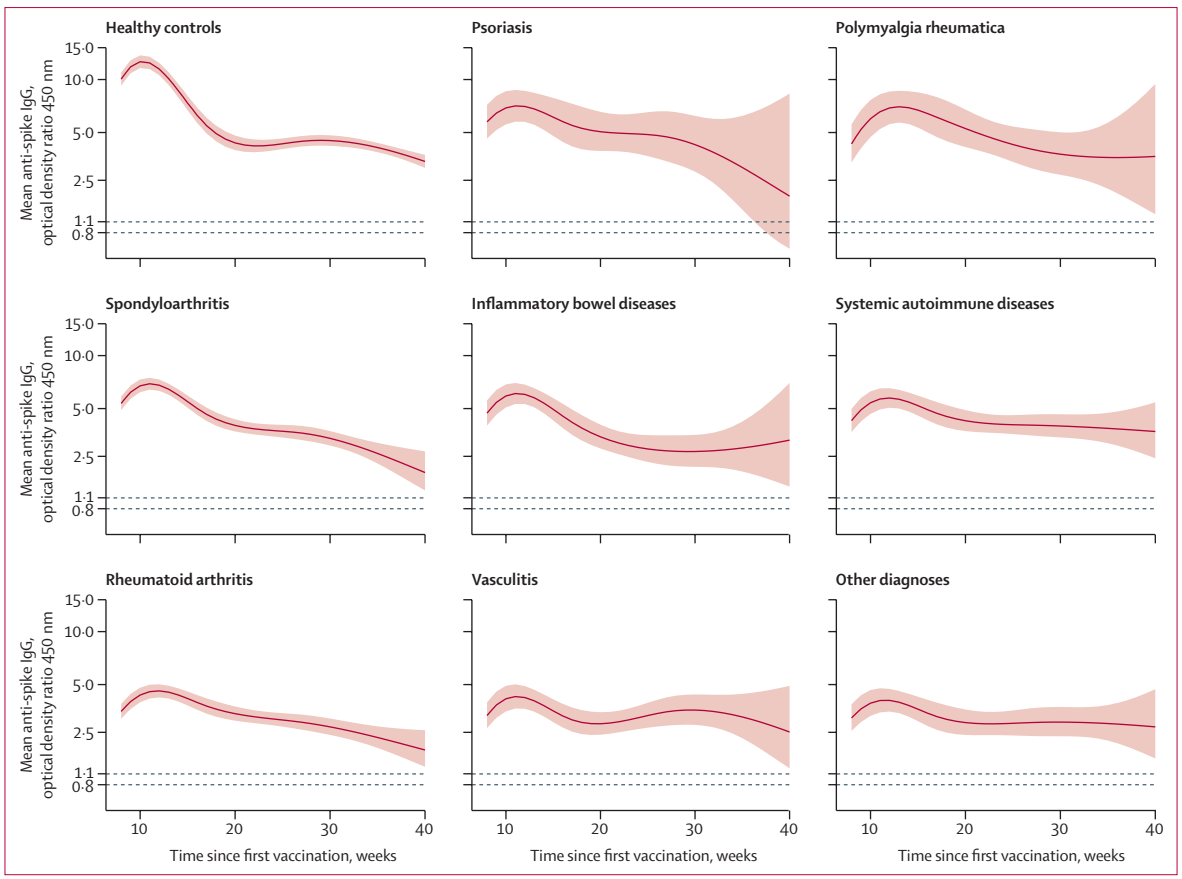


***Figure 2:*** **Age-adjusted and sex-adjusted estimated marginal mean anti-spike IgG titres at 8–40 weeks after first vaccination by immune-mediated inflammatory disease diagnosis**

The bands represent the 95% CIs. The panels are ordered by peak mean value from highest to lowest. The dashed lines mark negative (0·8) and borderline (1·1) optical density ratio thresholds.

doses of more than 1500 mg per day had slightly lower antibody responses than those receiving less than 1500 mg per day (appendix p 12). All pairwise differences between treatment types are presented in the appendix (pp 8–9).

At week 40, the marginal mean antibody titres in healthy controls were significantly higher compared with conventional immune modulators, cytokine inhibitors, and B-cell and T-cell inhibitors. Adjusted absolute mean differences ranged between 1·36 (95% CI 0·05–2·67) for conventional immune modulators and 2·32 (0·50–4·13) for T-cell inhibitors. Other pairwise comparisons between healthy controls and immune-mediated inflammatory disease treatment groups were not significant. Among the immune-mediated inflammatory disease treatment groups, untreated participants showed higher mean antibody titres compared with cytokine inhibitors (absolute mean difference 2·48; 0·01–4·94), B-cell inhibitors (absolute mean difference 3·01; 0·19–5·82) and T-cell inhibitors (3·05; 0·15–5·95). Although the responses in participants taking T-cell and B-cell inhibitors were low throughout the observation period, the responses in participants taking cytokine inhibitors were gradually lost over time.

When combination treatment status was added to the model, monotherapy with cytokine inhibitors, T-cell inhibitors, and conventional immune modulators was associated with higher mean antibody titres compared with combination therapy. This finding was most clearly observed with cytokine inhibitors, early in the time course after vaccination and up to 30 weeks (appendix p 13).

We also analysed the differences in vaccination responses between the type of vaccination classified as homologous mRNA, homologous vector, and heterologous vaccinations. Although heterologous vaccinations and homologous mRNA vaccinations showed similar patterns with better results in healthy controls than in participants with immune-mediated inflammatory diseases, homologous vector immunisations yielded overall lower IgG responses than the two other vaccination types. Again, however, healthy controls showed better responses than participants with immune-mediated inflammatory diseases (appendix p 14). In addition, we performed sensitivity analyses by excluding 277 participants who had a positive PCR test for SARS-CoV-2. No differences in the results were observed when PCR-positive patients were excluded from the analysis (appendix p 15).

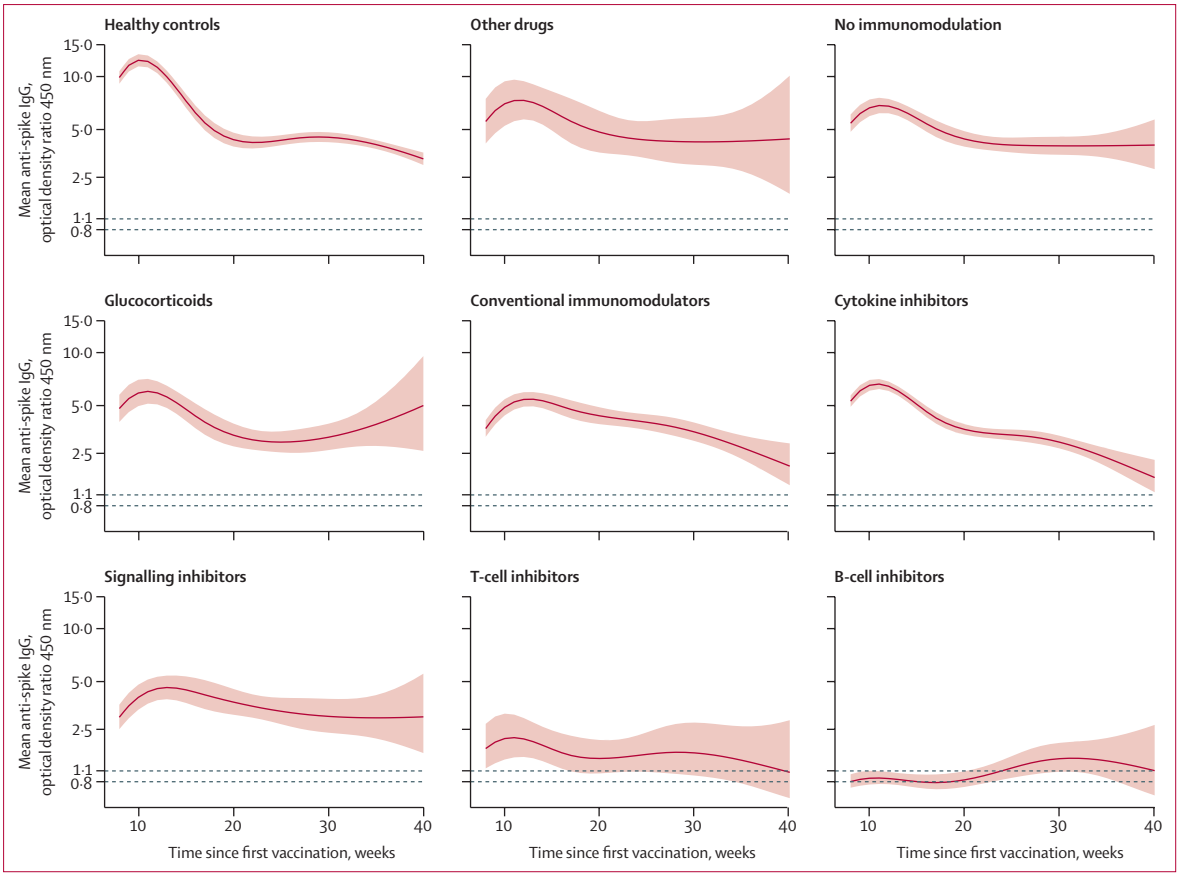


***Figure 3:*** **Age-adjusted and sex-adjusted estimated marginal mean anti-spike IgG titres at 8–40 weeks after first vaccination by type of treatments used for immune-mediated inflammatory diseases**

The bands represent the 95% CIs. The panels are ordered by the mean of the estimated mean values at all timepoints from highest to lowest. The dashed lines mark negative (0·8) and borderline (1·1) optical density ratio thresholds. A list of individual drugs per class are provided in the appendix (p 1).

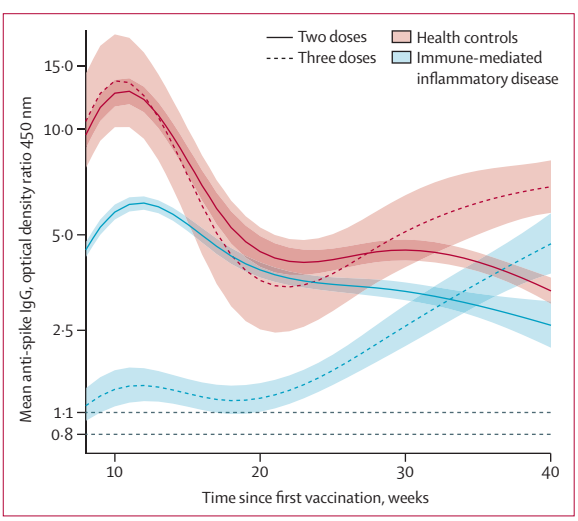


***Figure 4:*** **Age-adjusted and sex-adjusted estimated marginal mean anti-spike antibody titres in healthy controls and participants with immune-mediated inflammatory diseases receiving two or three doses of COVID-19 vaccine**

The bands represent the 95% CIs. The grey dashed lines at the bottom mark negative (0·8) and borderline (1·1) optical density ratio thresholds.

241 (6·5%) participants had a third vaccine dose (table 1). Figure 4 depicts the time course of age-adjusted and sex-adjusted marginal mean antibody titres among participants with immune-mediated inflammatory diseases and healthy controls by the overall number of vaccine doses received. This figure shows the selective application of a third vaccine dose in patients with immune-mediated inflammatory diseases, who showed an early poor response to two doses of vaccine as depicted by the lower mean optic density ratio values up to week 30. Over the long term (ie, at 40 weeks), the marginal mean antibody titres in participants with immune-mediated inflammatory diseases who received a third vaccine dose (4·68; 95% CI 3·80 to 5·76) were higher than those in participants with immune-mediated inflammatory diseases who received two doses (2·57; 2·13 to 3·09), with a mean difference of 2·12 (–0·70 to 3·54); and also healthy controls who received two doses (3·34; 3·03 to 3·68) by a mean difference of 1·34 (0·01 to 2·69; data not shown). Descriptive plots of individual antibody titres in participants with immune-mediated inflammatory diseases and healthy controls who have received a third dose of vaccine are presented in the appendix (p 16).

## Discussion

This large prospective cohort study shows the lower intensity and reduced longevity of the antibody response to two doses of SARS-CoV-2 vaccination in participants with immune-mediated inflammatory diseases than in healthy controls. The peak response in participants with immune-mediated inflammatory diseases was less than half of that observed in healthy controls after adjustment for age and sex. Furthermore, participants with immune-mediated inflammatory diseases showed lower mean antibody titres over the entire course of follow-up, losing humoral immunity more frequently than healthy controls. Of note, a fifth of younger participants (35 years) and a third of older participants (65 years) with immune-mediated inflammatory diseases lose humoral responses 40 weeks after two-dose immunisation. This finding confirms previous observations made on shorter follow-up periods, in which humoral responses in participants with immune-mediated inflammatory diseases appeared blunted[1,2] and with higher rates of seroreversion.[3,19] Our results also provide useful insights on the course of vaccine response in various treatment groups, with particularly poor responses observed in patients administered B-cell and T-cell inhibitors. This finding is particularly notable, since B-cell and T-cell interaction is a key step for the formation of memory B cells, which in turn result in the longevity of antibody responses and their effectiveness upon infection. Furthermore, although participants with immune-mediated inflammatory diseases administered cytokine inhibitors showed peak responses similar to untreated participants with immune-mediated inflammatory diseases, the durability of the response over time was not as good, and declined to lower levels compared with participants with immune-mediated inflammatory diseases who were untreated. This finding is in line with a previous report on a smaller cohort of participants with immune-mediated inflammatory diseases, in which TNF inhibitors were associated with a steep decline in humoral responses starting from the sixth month after vaccination, but not earlier.[20] Notably, patients administered TNF inhibitors also showed the most rapid decline in neutralising capacity compared with other treatments in another report, declining to less than the protective threshold within 5 months of vaccination.[23]

To ensure sufficient protection, the earlier administration of booster doses might be crucial in participants with immune-mediated inflammatory diseases. We had previously shown that participants with immune-mediated inflammatory diseases who did not develop antibodies after two doses of SARS-CoV-2 vaccination were likely to develop antibodies after a third dose.[24] In this study, we show that, at 40 weeks after the first vaccination, participants with immune-mediated inflammatory diseases who received a third vaccine dose could produce anti-SARS-CoV-2 IgG titres higher than healthy controls who did not receive a third vaccine dose. In addition, given the observation that peak antibody titres at 10 weeks after the first vaccination in participants with immune-mediated inflammatory diseases are similar to titres at 16–24 weeks after the first vaccination in healthy controls, it might be reasonable to administer the third dose within the 3–4 months of the first dose for those with immune-mediated inflammatory diseases. It should also be emphasised that protective antibody responses against neutralisation-resistant SARS-CoV-2 strains, such as the currently dominant omicron variant, are not as durable compared with those against previous strains.[25,26] Therefore a third vaccination might still be inadequate to offer sufficient protection against the omicron variant in patients with immune-mediated inflammatory diseases.

Our study has strengths and several limitations. The large sample size and long follow-up duration are the main strengths of the study. Furthermore, to our knowledge, this is the first study that compares the influence of different vaccine schedules on humoral responses in participants with immune-mediated inflammatory diseases as well as healthy controls over an extended period, and also the first study to report the risk of a poor vaccine response in participants with immune-mediated inflammatory diseases over time.

We collected serum samples in an unscheduled manner during the routine care of participants with immune-mediated inflammatory diseases, which might have resulted in more frequent or diligent sampling in participants who visited the clinic more frequently. To mitigate this potential bias, we used regression methods that accounted for within-patient correlations using random effects. However, most participants provided a single sample. On the one hand, samples from participants with immune-mediated inflammatory diseases were obtained predominantly during cytokine blocking treatments, therefore the overall between-group comparisons should reflect the weight of this treatment class, which affects the generalisability of our results. On the other hand, we also observed similar differences between participants with immune-mediated inflammatory diseases not receiving any immunomodulating treatment and healthy controls. We did not attempt to separate the effects of treatments independent of diseases or antibody responses across disease activity states, therefore the antibody titres reported here could be the result of the average effect of treatments combined with the variety of diseases they are used for, or similarly the average effects of diagnoses combined with their routine treatment patterns. Although we collected data on the use of corticosteroids, this was only categorical, and data on the dose used was not collected; however, higher doses of corticosteroid treatments are usually given in combination with cytotoxic agents for remission induction in conditions such as lupus nephritis or antineutrophil cytoplasmic antibody-associated vasculitis. Therefore, their effects could be considered as embedded within those

treatment categories and participants using only corticosteroid treatment would more likely be on lower maintenance doses, which might explain the relatively favourable antibody course with corticosteroids in comparison with cytotoxic or anti-cytokine treatments. We did not collect data regarding symptomatic SARS-CoV-2 infections, but we addressed this issue in a sensitivity analysis excluding cohort participants who reported a positive SARS-CoV-2 test. No changes in the results were observed. Although there was an age and sex difference between the immune-mediated inflammatory disease and healthy controls groups that could influence the humoral responses differentially, we addressed this issue through regression adjustments. The third dose grouping in our analyses was not time varying (ie, patients who received a third dose were classified as such from baseline onwards). Our findings on the third dose of vaccine should therefore be interpreted with caution. Finally, we evaluated only one aspect of the humoral immune response and did not assess the neutralising capacity of the antibodies nor the cellular immune responses in this study.

In conclusion, these data support the concept that participants with immune-mediated inflammatory diseases are at risk of losing their protective humoral response after SARS-CoV-2 vaccination, an occurrence that has also been observed after SARS-CoV-2 infection.[3,11] Considering that anti-SARS-CoV-2 IgG are a good indicator of protection against COVID-19,[27] and the absence of antibodies also reflects a higher susceptibility to breakthrough infections,[8] adapted vaccination schedules that include earlier booster vaccinations should be implemented to sustain adequate protection in participants with immune-mediated inflammatory diseases. We hope that these findings will be of use to policy makers responsible for disease control and prevention, and that they reconsider current recommendations.

#### Contributors

DS, FF, AK, CM, PD, TO, JM, JT, JK, SKe, A-ML, VS, DB, FH, ML AR, MP, FS, MR, SKl, AJH, KM, BM, RA, and IM collected the samples. KT, DS, and GS designed the study. KT, GK, LS, and MYM did the experiments and the data analysis. DS, KT, and GS created the tables and figures. KT, DS, CB, MS, AK, MFN, and GS interpreted the data. KT, DS, FF, MFN, and GS wrote the manuscript. All authors critically proofread the manuscript. KT and DS accessed and verified the data. KT, DS, and GS were responsible for the decision to submit the manuscript for publication.

#### Declaration of interests

CB reports honorarium for lectures from Almirall Hermal, LEO Pharma, and Novartis Pharma; and participation on a data safety monitoring board or advisory board for Almirall Hermal and Novartis Pharma. MS reports royalties from Becton Dickinson and BioRad; honorarium for lectures from Abbvie, Amgen, Boehringer Ingelheim, Celgene, Janssen-Cilag, Leo, Pfizer, Merck Sharpe & Dohme, and Novartis; and participation on a data safety monitoring board or advisory board for Abbvie, Amgen, Celgene, Janssen-Cilag, Lilly, Pfizer, Merck Sharpe & Dohme, Novartis, Leo, Sanofi, and Union Chimique Belge. MFN reports consultancy fees from the British Medical Association house, Janssen-Cilag, Pentax, and S Karger; and honorarium for lectures from Asian Organisation for Crohn's and Colitis, Falk foundation, Janssen-Cilag, Lilly Deutschland, Medi K, Northwell Foundation, Scherl-Roberts, Skaggs School of Pharmacy and Pharmaceutical sciences, and Takeda Pharmaceuticals International. All other authors declare no competing interests.

#### Data sharing

All data relevant to the study are included in the Article or uploaded in the appendix.

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