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Serological responses to the first four doses of SARS-CoV-2 vaccine in patients with inflammatory bowel disease

Three-dose SARS-CoV-2 vaccine regimens have been recommended for people with inflammatory bowel disease (IBD), with studies of third-dose vaccination indicating favourable outcomes, including for those who did not attain seroconversion after two doses.1 We examined serological response after the first, second, third, and fourth doses of SARS-CoV-2 vaccines in people with IBD; the decay of antibodies for extended periods of time; and the factors, including medications, associated with antibody titres in people with IBD.

STOP COVID-19 in IBD is a prospective, observational cohort study of adults with IBD who have been vaccinated against SARS-CoV-2.3 Serum samples were assessed for immunoglobulin G (IgG) antibodies to the spike protein of SARS-CoV-2 (anti-S) with the Abbott Architect SARS-CoV-2 IgG II Quant assay. Serum samples were taken for assessment of anti-S antibodies after vaccination against SARS-CoV-2 in multiple groups based on availability of serum samples. The groups were 1–8 weeks after the first dose of the vaccine, 1–8 weeks after the second dose of the vaccine, more than 8 weeks after the second dose of the vaccine, 1–8 weeks after the third dose of the vaccine, more than 8 weeks after the third dose of the vaccine, and more than 1 week after the fourth dose of the vaccine.

Our primary outcome was geometric mean titres of anti-S antibodies. We also reported the proportion of individuals with positive anti-S seroconversion. Full details of methods and statistical analyses are shown in the appendix (pp 2–6); the distribution of demographic, disease-related, and vaccine-related characteristics alongside seroconversion and geometric mean titres stratified by previous SARS-CoV-2 infection is also shown in the appendix (p 7).

Geometric mean titres consecutively increased significantly from the first to the fourth dose (figure). Paired analysis of within-individual changes in antibody titres indicated congruent trends with geometric mean titres (appendix p 8).

Multivariable linear regression models showed significantly decreased log-transformed anti-S concentration per decade increase in age for all vaccine dose groups (eg, 1–8 weeks after second dose geometric mean ratio: 0.83 per decade, 95% CI 0.75–0.91; appendix p 9). Corticosteroid use was associated with the lowest geometric mean titre values across all medication classes (appendix pp 10–11). Compared with individuals with no immunosuppressive medication, several medication classes, including anti-TNF monotherapy, combination therapy, and corticosteroid use, were associated with diminished log anti-S concentration. Previous SARS-CoV-2 infection was significantly associated with increased log anti-S concentration. Antibodies decayed during an extended time period after the second dose (>8 weeks geometric mean ratio: 0.96, 94–0.97 per week) and after the third dose (1–8 weeks geometric mean ratio: 0.87, 0.80–0.94 per week; appendix pp 9, 12). A non-significant geometric mean ratio was observed for decay more than 8 weeks after the third dose (0.97, 0.94–1.00 per week). However, sensitivity analyses excluding people with previous SARS-CoV-2 infection indicated antibody decline by 5% per week (>8 weeks after the third dose geometric mean ratio: 0.95, 0.92–0.98 per week).
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9 We identified several predictors of serological response to vaccination, such as increased age, immune-suppressive therapies, previous SARS-CoV-2 infection, and vaccine timing. Our models indicate decreased antibody titres per decade of increased age. For example, each decade of increased age is associated with a 12% decrease in antibody titres after third-dose vaccination. These data highlight that with advancing age the serological response to SARS-CoV-2 decreases; this shows the importance of additional doses for sufficient immune protection in this population, especially considering their high susceptibility to severe COVID-19. In addition, our data are similar to previous studies showing diminished antibody responses after two doses of a SARS-CoV-2 vaccine for patients on anti-TNF therapy, combination immunosuppressive therapies, and corticosteroids. The data also indicate comparatively diminished titres after third-dose vaccination. People with IBD who are taking these medications still show a significantly increased geometric mean titre after third-dose and fourth-dose vaccination compared with second-dose vaccination, indicating a robust response to additional doses. Similar to previous literature, antibodies were increased for individuals with previous SARS-CoV-2 infection, with the strongest association for first-dose antibody responses and the weakest for third-dose antibody responses.

Several limitations of our work should be considered. We were unable to assess if antibody titres were associated with breakthrough infections (ie, SARS-CoV-2 infection after vaccination). In addition, we did not assess other immune responses to SARS-CoV-2 vaccination, including neutralising antibodies or T-cell immunity. We did not compare people with IBD to healthy individuals. However, a 2022 prospective cohort study of the general population within the same jurisdiction and with the same assay showed higher antibodies than our IBD population after first and second doses of the vaccine. Residual confounding from omitted risk factors, such as smoking, should be considered. Findings across medication class should be interpreted cautiously as small sample size reduces the precision of estimates. Furthermore, we did not analyse drug dosage or duration before vaccination.

Our data show novel findings about antibody responses to third-dose and fourth-dose vaccination, which indicate the importance of additional doses in maintaining humoral immunity. Considering the significant decay of antibodies after a two-dose regimen and robust response after the third dose, health-care providers and public health officials should prioritise communication of the necessity of a three-dose vaccine regimen to ensure sufficient serological protection for people with IBD. Our data highlight that antibodies decay after third-dose vaccination but are recovered by a fourth dose of the vaccine. Individuals older than 65 years with IBD; people who require prednisone, anti-TNF, or combination therapies; and people with no previous SARS-CoV-2 infection have attenuated antibody responses after third-dose vaccination and are therefore most likely to benefit from fourth-dose vaccination.

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