Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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.[2] 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, 0·94–0·97 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, 0·91–0·98; appendix p 13). Sensitivity analyses excluding non-mRNA vaccination and vaccine mixing (ie, different vaccine types across all doses) were similar to the main analyses (appendix p 14). Antibody concentrations are also reported in WHO binding antibody units/mL (appendix p 15).

The data showed a substantial increase in antibody titres after a third dose of vaccine compared with a second dose, similar to studies in the USA and UK.[1,3] Novel data showed a robust antibody response after fourth-dose vaccination analogous in magnitude to third-dose vaccination. Future studies should define the timing of additional doses and quantify rates of decay after fourth-dose vaccination. Current seroconversion thresholds are based on the recommendations of immunoassay manufacturers rather than values correlated with decreased risk of infection. Therefore, understanding the amount of humoral immunity required for protection against SARS-CoV-2 will inform vaccine decision making. This understanding is especially relevant in the context of new SARS-CoV-2 variants, which have been shown to have reduced neutralisation from vaccine-induced antibodies and will therefore require increased amounts of humoral immunity for effective protection.[4]

Lancet Gastroenterol Hepatol 2022

Published **Online** October 25, 2022 https://doi.org/10.1016/S2468-1253(22)00340-5

See **Online** for appendix

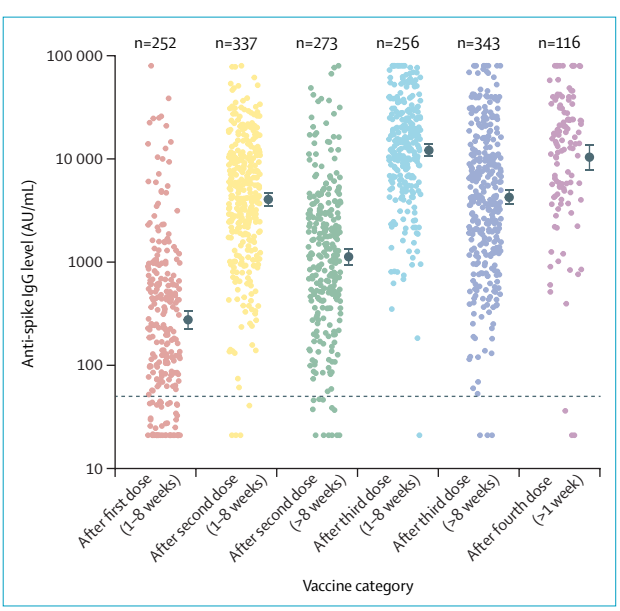

Figure: **Anti-SARS-CoV-2 spike protein antibody concentration per vaccine category**
Black points represent mean antibody titres. Black bars represent bounds of 95% CIs associated with each mean. The dotted line represents the threshold for positive seroconversion (50 AU/mL). AU=arbitrary units. IgG=immunoglobulin G.

We identified several predictors of serological response to vaccination, such as increased age, immunosuppressive 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.[5] 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.[6–8] 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.[6]

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.[9] 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.[10] 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 dose 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.

GGK has received honoraria for speaking from AbbVie, Janssen, Pfizer, Amgen, and Takeda; research support from Ferring, Janssen, AbbVie, GlaxoSmith Kline, Merck, and Shire; and has been a consultant for Gilead. He shares ownership of a patent of treatment of inflammatory disorders, autoimmune disease, and PBC (patent WO2019046959A1, PCT/CA2018/051098). CNB has served on advisory boards for AbbVie Canada, Amgen Canada, Avir Pharmaceuticals, Bristol Myers Squibb Canada, Roche Canada, JAMP Pharmaceuticals Canada, Janssen Canada, Sandoz Canada, Takeda Canada, and Pfizer Canada; is a consultant for Mylan Pharmaceuticals and Takeda; has received educational grants from AbbVie Canada, Pfizer Canada, Takeda Canada, and Janssen Canada; is on the speaker's panel for AbbVie Canada, Janssen Canada, and Takeda Canada; and has received research funding from AbbVie Canada, Amgen Canada, Sandoz Canada, and Pfizer Canada. CM has received consulting fees from AbbVie, Alimentiv, Amgen, Avir Pharmaceuticals, BioJAMP, Bristol Myers Squibb, Celltrion, Ferring, Fresenius Kabi, Janssen, McKesson, Mylan, Takeda, Pendopharm, Pfizer, and Roche; speaker's fees from AbbVie, Amgen, Avir Pharmaceuticals, Alimentiv, Ferring, Janssen, Takeda, and Pfizer; and research support from Ferring and Pfizer. RP has received consulting fees, speaker fees, and research support from AbbVie, Abbott, Alimentiv, Amgen, Arena Pharmaceuticals, AstraZeneca, Bristol Myers Squibb, Boehringer Ingelheim, Celgene, Celltrion, Cosmos Pharmaceuticals, Eisai, Elan, Eli Lilly, Ferring, Fresnius Kabi, Galapagos, Genentech, Gilead Sciences, GlaxoSmithKline, Janssen, Merck, Mylan, Oppilan Pharma, Pandion Pharma, Pfizer, Progenity, Protagonist Therapeutics, Roche, Satisfai Health, Sandoz, Schering-Plough, Shire, Sublimity Therapeutics, Theravance Biopharma, Union Chimique Belge, and Takeda. EIB has been a legal consultant for Hoffman La-Roche and Peabody and Arnold and a consultant for McKesson Canada and the Dairy Farmers of Ontario. All other authors declare no competing interests. The work reported here was funded by the Canadian Institutes of Health Research Operating Grant: COVID-19 Rapid Research Funding Opportunity (VR5–172684), the Crohn's and Colitis Canada COVID-19 and IBD Taskforce, the Public Health Agency of Canada Vaccine Surveillance Reference Group and COVID-19 Immunity Task Force, and The Leona M and Harry B Helmsley Charitable Trust Grant (G-2209–05501).

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