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.

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Durability of Immunity Is Low Against Severe Acute Respiratory Syndrome Coronavirus 2 Omicron BA.1, BA.2, and BA.3 Variants After Second and Third Vaccinations in Children and Young Adults With Inflammatory Bowel Disease Receiving Biologics

The continued emergence of Omicron variants during the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has challenged infection control and posed a risk to individuals with inflammatory bowel disease (IBD) despite vaccination. Previous data suggest an attenuated response to vaccination in adult patients with IBD receiving anti–tumor necrosis factor and other immunomodulatory therapy.[1,2] We previously observed a blunted antibody response in children and young adults receiving biologics after SARS-CoV-2 infection.[3]

The Omicron variant (B.1.529.1/BA.1) became the dominant variant of concern as it spreads around the globe in November 2021.[4] Since then, subvariants of Omicron emerged (BA.2 and BA.3), each with its own set of mutations from SARS-CoV-2 infection or vaccination-induced antibodies (Supplementary Table 1).[5,6] Thus far, the BA.2 variant demonstrates higher transmissibility compared with BA.1 and has reached dominance in several countries.[4] Individuals with IBD who are receiving biologic therapies have a blunted antibody response to SARS-CoV-2 infection.[3] However, limited knowledge exists regarding neutralizing antibodies after 2 doses vs 3 doses of mRNA vaccination and their durability against SARS-CoV-2 Omicron lineages in children and young adults with IBD receiving therapeutics.

Antibody assays were performed with approval from the US Food and Drug Administration's Research Involving Human Subjects Committee under exemption protocol 252-Determination-CBER-2020-08-19. All assays performed fell within the permissible usages in the original consent. Study pediatric sites relied on the Connecticut Children's Medical Center Institutional Review Board, and informed consent was obtained from at least 1 parent or legal guardian when possible, or consent was waived for deidentified samples from clinical discards. The protocol was approved by the Institutional Review Board at Connecticut Children's Medical Center (20-073#). The study is registered on Clinicaltrials.gov (NCT04838834).

In this longitudinal study, we evaluated serum samples from SARS-CoV-2 mRNA-vaccinated coronavirus disease 2019 (COVID-19)-naive IBD children and young adults aged $\geq$ 12 years who were receiving biologics (n = 70) vs healthy COVID-19–naive children (n = 30) for durability of the immune response after the second and third SARS-CoV-2 vaccinations (Figure 1*A* and *B*, Supplementary Table 2). Ninety-three percent of the IBD cohort was receiving infliximab and 7% vedolizumab. Virus-neutralizing titers were measured using a qualified pseudovirus neutralization assay (PsVNA) against the SARS-CoV-2 vaccine–homologous WA1 strain and against the Omicron BA.1, BA.2, and BA.3 subvariants (Supplementary Methods) The PsVNA titers correlated well with neutralization titers measured against the authentic SARS-CoV-2 in a plaque reduction neutralization test.[7] A PsVNA50 titer of 1:60 was used as a seropositive cut-off based on current understanding of neutralizing antibody titers as a correlate of protection against COVID-19.[8] All subjects received 2 doses of mRNA vaccine between March and December 2021, mostly Pfizer ($\geq$97%; BNT162b2) or Moderna (mRNA-1273). All subjects received a third (or booster) vaccine dose in December 2021 to February 2022. There were no significant differences between the 2 cohorts in regard to age, sex, race, or vaccine brand (Supplementary Table 2).

Children and young adults with IBD demonstrated peak SARS-CoV-2 neutralization titers at 1 month after the second vaccination (geometric mean titers [GMTs] of 315), which declined by 6-fold at 6 months after vaccination (GMTs of 57) against the vaccine-homologous WA1 strain (Figure 1*C*). Neutralizing antibodies after the second vaccination were minimal (GMTs $<$ 20) against the 3 Omicron subvariants in IBD patients (Supplementary Figure 1). At 6 months after the second vaccination, the neutralizing antibody titers against WA1 and Omicron BA.1, BA.2, or BA.3 subvariants were significantly higher in the healthy children (GMTs of 106–168) compared with the IBD group (GMTs of 11) (Figure 1*D*). Moreover, among the IBD cohort, $<$5% of children had PsVNA50 above 1:60 against Omicron subvariants compared with 64%–71% for the healthy children 6 months after 2 doses of the mRNA vaccination.

Importantly, a third mRNA vaccination was particularly critical to elevate the neutralizing antibodies against Omicron subvariants, especially for the IBD children and young adults (15- to 17-fold increase) (Supplementary Figure 1). At 1 month after 3 mRNA vaccinations, 73%–80% of the IBD patients demonstrated PsVNA50 greater than 1:60 against Omicron BA.1, BA.2, and BA.3 subvariants (GMTs of 168–181) (Supplementary Figure 1). By 3 months, after the third vaccination, Omicron lineage neutralizing titers in the IBD cohort (GMTs of 83–96) were 6 to 8-fold lower compared with healthy children (GMTs of 655–714) (Figure 1*E*). At 3 months after the third mRNA vaccination, 96% of those with

Abbreviations used in this paper: **COVID-19, coronavirus disease 2019; GMT, geometric mean titer; IBD, inflammatory bowel disease; PsVNA, pseudovirus neutralization assay; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.**

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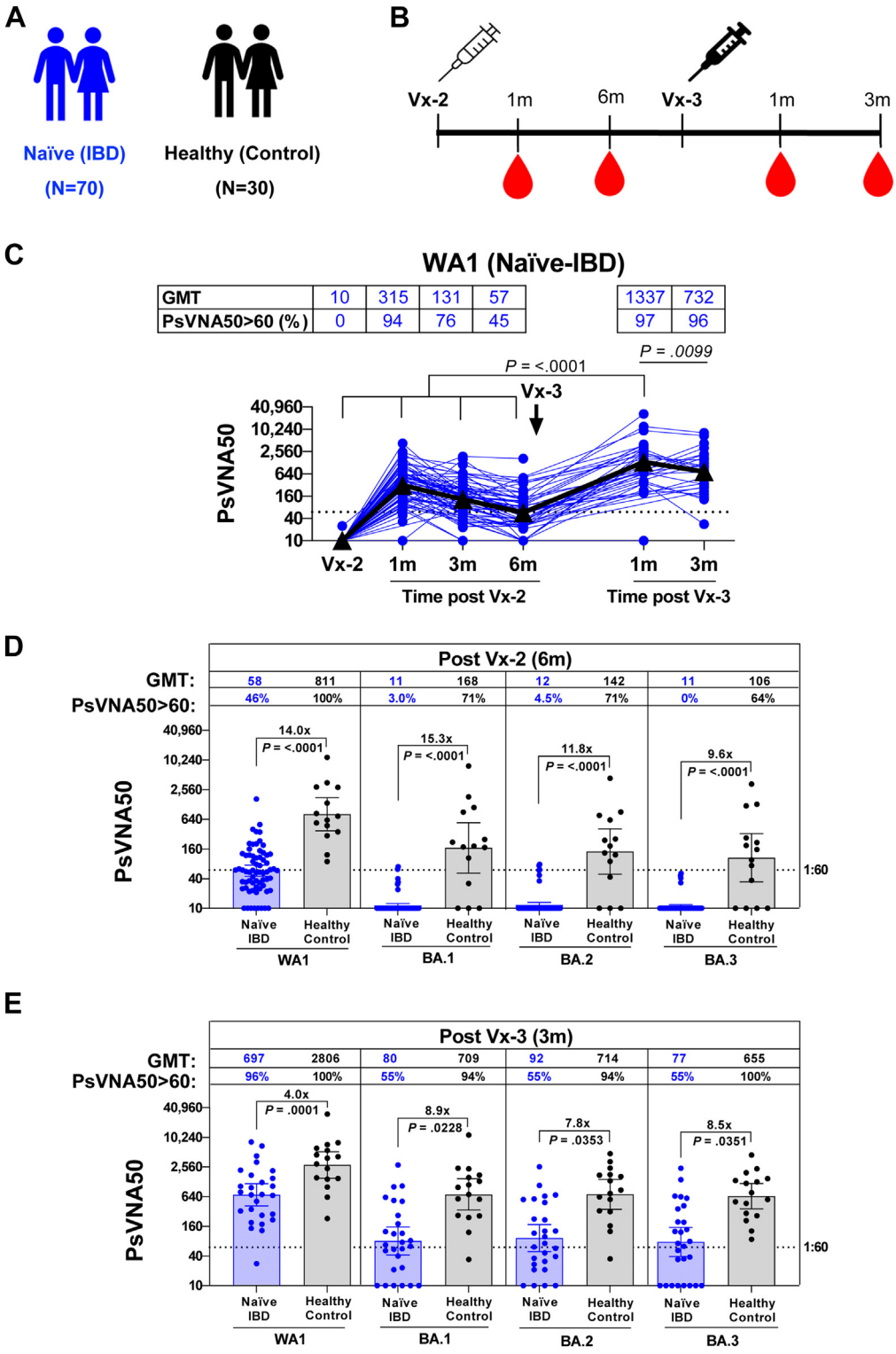
IBD and 100% of healthy children showed PsVNA50 above 1:60 against vaccine-homologous WA1, whereas only 58% of the IBD cohort demonstrated PsVNA50 above 1:60 against Omicron subvariants compared with 94%–100% for the healthy children (Figure 1*E*). This difference in post-vaccination neutralizing antibody response between the 2 cohorts were more apparent in children aged 12–18 years, wherein healthy control subjects demonstrated 25- to 42-fold higher titers (90%–100% of children with PsVNA50 above 1:60) compared with children with IBD (0% of children with IBD with PsVNA50 above 1:60) at 6 months after the second vaccination against Omicron subvariants (Supplementary Figure 2). In children with IBD, the neutralizing antibody titers increased 8- to 10-fold at 1



month after the third vaccination against the Omicron subvariants compared with 1 month after the second vaccination (Supplementary Figure 3). At 3 months after the third vaccination, neutralizing antibody titers were 4- to 6-fold higher in the healthy pediatric control subjects (aged 12–18 years) compared with children with IBD against Omicron subvariants (Supplementary Figure 2).

Our study demonstrates that SARS-CoV-2 mRNA vaccines induce significantly lower short-lived cross-reactive neutralizing antibodies against Omicron lineages BA.1, BA.2, and BA.3 in children and young adults with IBD receiving biologics compared with healthy children after a second or third mRNA vaccination. As new SARS-CoV-2 variants emerge, continued determination of neutralizing antibodies after boosters will be needed in these children. One limitation of our study is the lack of children and young adults with IBD not receiving biologic therapy. Our data suggest that children, adolescents, and young adults with IBD undergoing treatment with biologic agents may benefit from a second booster dose of mRNA vaccines to provide suitable protection against the Omicron subvariants.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org and at https://doi.org/10.1053/j.gastro.2022.08.009.

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Figure 1. Neutralizing antibodies after second and third vaccinations in COVID-19–naive children with IBD or COVID-19–naive healthy children against SARS-CoV-2 WA1 and Omicron subvariants. (*A*) Overview of vaccination cohort, including 70 unexposed COVID-19–naive children with IBD (blue) and 30 COVID-19–naive healthy children (black) receiving second and third mRNA vaccinations. (*B*) Timeline of SARS-CoV-2 vaccination and blood sample collection in the 2 cohorts. Serum samples from healthy children were obtained either 6 months after the second vaccination or 3 months after the third vaccination. (*C–E*) SARS-CoV-2–neutralizing antibody titers in serum of 70 unexposed COVID-19–naive IBD (blue) vs 30 healthy children (black) after the second or third mRNA vaccinations as determined by a qualified PsVNA in 293-angiotensin-converting enzyme 2 (ACE2)-transmembrane protease, serine 2 (TMPRSS2) cells with SARS-CoV-2 WA1 strain and Omicron subvariants BA.1, BA.2, and BA.3 (Supplementary Table S1). (*C*) PsVNA50 (50% neutralization titer) after the second vaccine (Vx-2; at 1 month, 3 months, or 6 months after the second dose) or at 1 month and 3 months after the third dose (Vx-3) in 70 unexposed COVID-19–naive children with IBD against the vaccine-matched WA1 strain. PsVNA50 GMTs are shown as black triangles and are presented for each vaccination time point against the SARS-CoV-2 WA1 on top of the panel. Each data point represents an individual sample (circles). The horizontal dashed line indicates the seropositive cutoff for the neutralization titers (PsVNA50 of 60). Percent seropositivity (PsVNA50 >60) for each time point was calculated as the number of seropositive samples divided by the total number of samples $\times$ 100. (*D* and *E*) Comparisons of PsVNA50 titers against WA1 and Omicron BA.1, BA.2, and BA.3 subvariants for 6 months after the second (*D*) or at 3 months after the third (*E*) mRNA vaccinated serum from 70 unexposed COVID-19–naive IBD (blue) vs 30 healthy children (black). The heights of the bars and the numbers over the bars indicate GMTs, and the whiskers indicate 95% confidence intervals and are color-coded. Percent seropositivity for each variant is color coded for each group matching the colors in the graph. The fold-difference in titers between IBD vs healthy cohorts are shown. The PsVNA is a qualified assay where all samples are run with a set of internal standards in every plate of the neutralization assay, and results conform with assay performance. Differences between the cohorts of IBD and healthy children were analyzed by lme4 and emmeans packages in R using Tukey's pairwise multiple comparison test, which controlled for age and sex as covariates, and the significant *P* values are shown. Nonsignificant *P* values ($P > .05$) are not shown. All PsVNA experiments were performed in duplicate, and the researchers performing the assay were blinded to sample identity. The variations for duplicate runs were $<7\%$. The data shown are average values of 2 experimental runs.

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Conflicts of Interest
The authors disclose no conflicts.

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