

WORKSHOP: Paradox of Immunization and IBD

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Case: What vaccines would you recommend?

A 14-year-old boy is newly diagnosed with moderate-to-severe ileocolonic Crohn's disease. His pediatric gastroenterologist wants to start a course of prednisone as a bridge to anti-TNF therapy. His pre-biologic work-up showed no immunity to measles or hepatitis B. His parents did not vaccinate him for his childhood vaccines, and he has not received a vaccine for COVID-19. They do not want to vaccinate him prior to starting treatment.

CAG CPGs: LIVE AND INACTIVATED VACCINES IN IBD

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 Clinical Guidelines



Clinical Guidelines

Canadian Association of Gastroenterology Clinical Practice Guideline for Immunizations in Patients With Inflammatory Bowel Disease (IBD)—Part 1: Live Vaccines

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 Clinical Guidelines

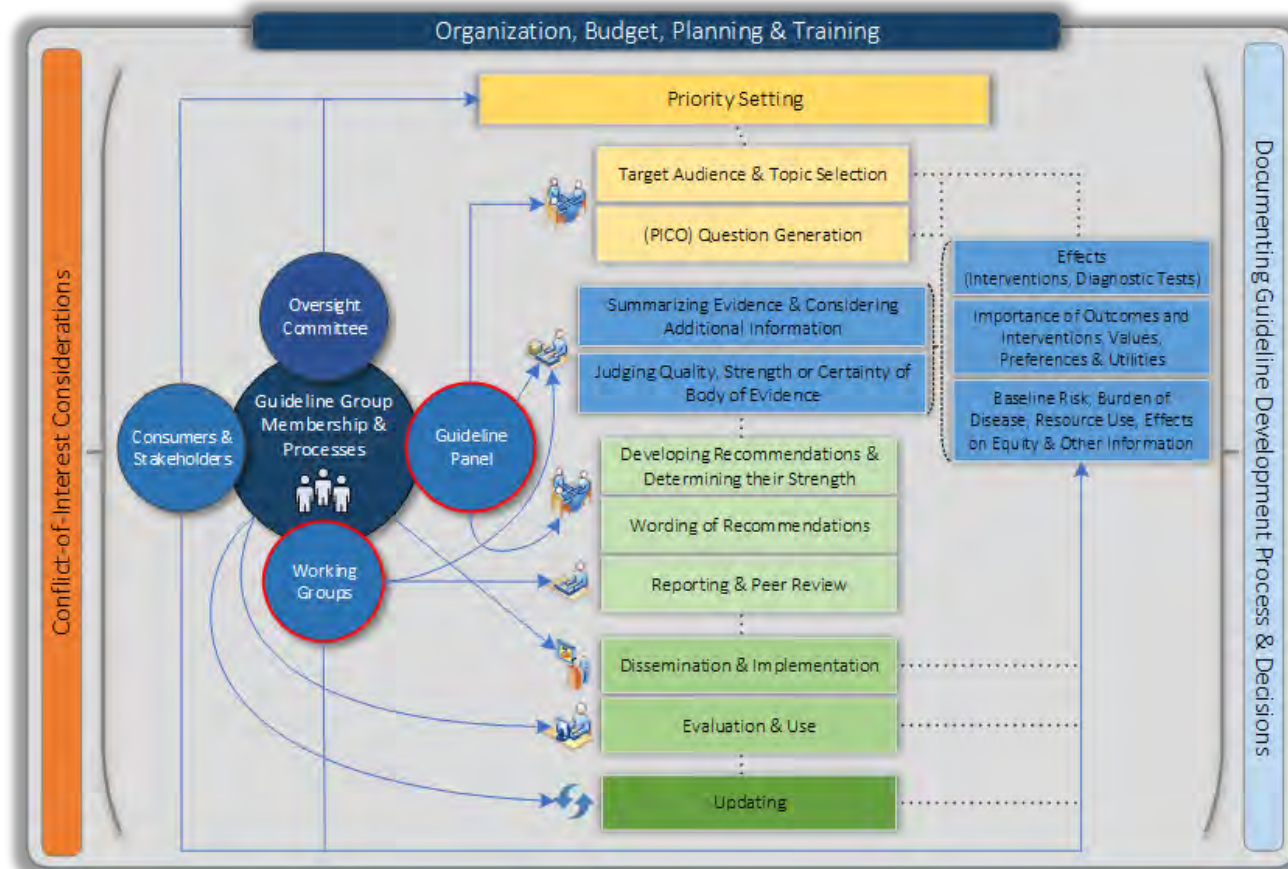


Clinical Guidelines

Canadian Association of Gastroenterology Clinical Practice Guideline for Immunizations in Patients With Inflammatory Bowel Disease (IBD)—Part 2: Inactivated Vaccines

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METHODS - OVERVIEW



cebgrade.mcmaster.ca/guidelinechecklistonline.html

SCOPE

- Common vaccine-preventable diseases (VPDs)
- Live and inactivated vaccines
- Adult and paediatric
- Populations in North American and Europe
- **NOT** special patient subgroups or situations
 - Infantile-onset or monogenic IBD
 - Travellers
 - COVID-19 pandemic

GRADE APPROACH

Certainty of Evidence	Explanation
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain

CONSENSUS MEETING

- Voting panel: 11 adult/paediatric gastroenterologists, ID specialists and vaccinologists from Canada and the United States
- Non-voting: 2 GRADE methodologists, representatives from CAG
- People with direct COI could not vote
- 3 patient representatives involved

- Consensus met with $\geq 75\%$ agreement (yes/no or uncertain/neutral)
- Second vote for strength of recommendation (strong or conditional)
- When low or very low CoE, default was “conditional recommendation”

RECOMMENDATIONS

- **Recommendation 1:** Complete review of patient's immunization history should be performed at diagnosis, and regular intervals by IBD care providers.
- **Recommendation 2:** All appropriate vaccinations should be given ASAP, ideally prior to initiation of immunosuppressive therapy.
- **Recommendation 3:** In patients who require urgent immunosuppressive therapy, treatment should **not be delayed** in order to provide vaccinations.

LIVE VACCINES

- Examples:

- MMR (measles-mumps-rubella)
- Varicella (chicken pox)
- Infant rotavirus vaccine
- Nasal spray influenza vaccine



- **Should be given, unless on immunosuppressive medications**

DEFINITION OF IMMUNOSUPPRESSION

- **No standard definition**
- **CDC and NACI recommend no live vaccine if therapy equivalent to:**
 - Prednisone: ≥ 2 mg/kg/day or 20 mg/day prednisone ≥ 14 days
- **IDSA defines 'low-level' immunosuppression as:**
 - Prednisone < 2 mg/kg/day (max. ≤ 20 mg/day)
 - Methotrexate ≤ 0.4 mg/kg/week
 - Azathioprine ≤ 3 mg/kg/day
 - 6-MP ≤ 1.5 mg/kg/day
- **Live vaccines should not be administered for at least 3 months after immunosuppressive therapy**

Recommendation 4A: In MMR-susceptible pediatric patients with IBD not on immunosuppressive therapy, we recommend **MMR vaccine be given.**

GRADE: Strong recommendation, moderate-certainty of evidence. Vote on PICO question: yes, 100%

Recommendation 4B: In MMR-susceptible pediatric patients with IBD on immunosuppressive therapy, we suggest against giving **MMR vaccine.**

GRADE: Conditional recommendation, very low-certainty of evidence. Vote on PICO question: no, 100%

Recommendation 5A: In MMR-susceptible adult patients with IBD not on immunosuppressive therapy, we recommend **MMR vaccine be given.**

GRADE: Strong recommendation, moderate-certainty of evidence. Vote on PICO question: yes, 100%

Recommendation 5B: In MMR-susceptible adult patients with IBD on immunosuppressive therapy, we suggest against giving **MMR vaccine.**

GRADE: Conditional recommendation, very low-certainty of evidence. Vote on PICO question: no, 100%

Recommendation 6A: In varicella-susceptible pediatric patients with IBD not on immunosuppressive therapy, we recommend **varicella vaccine be given.**

GRADE: Strong recommendation, moderate-certainty of evidence. Vote on PICO question: yes, 100%

Recommendation 6B: In varicella-susceptible pediatric patients with IBD on immunosuppressive therapy, we suggest against giving **varicella vaccine.**

GRADE: Conditional recommendation, very low-certainty of evidence. Vote on PICO question: no, 100%

Recommendation 7A: In varicella-susceptible adult patients with IBD not on immunosuppressive therapy, we suggest **varicella vaccine be given.**

GRADE: Conditional recommendation, very low-certainty of evidence. Vote on PICO question: yes, 100%

Recommendation 7B: In varicella-susceptible adult patients with IBD on immunosuppressive therapy, we suggest against giving **varicella vaccine.** GRADE: Conditional recommendation, very low-certainty of evidence. Vote on PICO question: no, 100%

INACTIVATED VACCINES



Recommendation 8A: In pediatric patients with IBD, 5 years of age and younger, we recommend Hib vaccine be given.

GRADE: Strong recommendation, moderate-certainty of evidence. Vote on PICO question: yes, 100%

Recommendation 8B: In unimmunized pediatric patients with IBD, older than 5 years of age, we suggest Hib vaccine be given.

GRADE: Conditional recommendation, low-certainty of evidence. Vote on PICO question: yes, 100%

Recommendation 15: In pediatric patients with IBD, we recommend age-appropriate pneumococcal vaccines be given.

GRADE: Strong recommendation, moderate-certainty of evidence. Vote on PICO question: yes, 100%

Recommendation 17: In pediatric patients with IBD, we recommend age-appropriate meningococcal vaccine be given.

GRADE: Strong recommendation, moderate-certainty of evidence. Vote on PICO question: yes, 100%

Recommendation 19: In pediatric patients with IBD, we recommend age-appropriate tetanus, diphtheria, and pertussis-containing vaccines be given.

GRADE: Strong recommendation, moderate-certainty of evidence. Vote on PICO question: yes, 100%

INACTIVATED VACCINES

HEPATITIS B

Recommendation 11: In pediatric patients with IBD, we recommend hepatitis B vaccine be given.

- GRADE: Strong recommendation, moderate certainty of evidence. Vote on PICO question: yes, 100%

Recommendation 12a: In unimmunized adult patients with IBD, with a risk factor for hepatitis B infection, we recommend hepatitis B vaccine be given

- GRADE: Strong recommendation, moderate certainty of evidence. Vote on PICO question: yes, 100%

Recommendation 12b: In unimmunized adult patients with IBD, without a risk factor for hepatitis B infection, we recommend hepatitis B vaccine be given

- GRADE: Conditional recommendation, low certainty of evidence. Vote on PICO question: yes, 100%
- Need for booster is uncertain
- If immunocompromised, check anti-HBs serology within 1-6 months of completion

INACTIVATED VACCINES

INFLUENZA

Recommendation 13: In pediatric patients with IBD, we recommend influenza vaccine be given.

- GRADE: Strong recommendation, moderate certainty of evidence. Vote on PICO question: yes, 100%

Recommendation 14: In adult patients with IBD, we recommend influenza vaccine be given.

- GRADE: Strong recommendation, moderate certainty of evidence. Vote on PICO question: yes, 100%

NO recommendation C: In patients with IBD on maintenance biologic therapy, the consensus group could not make a recommendation for or against timing seasonal influenza immunization in relation to the biologic dose.

- GRADE: Low certainty of evidence. Vote on PICO question: uncertain/neutral, 33%; no, 67%

INACTIVATED VACCINES

Herpes Zoster

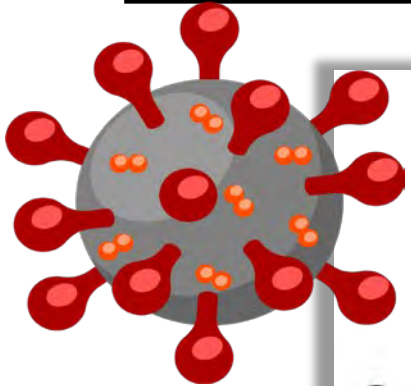
Recommendation 10A: In adult patients 50 years of age and older with IBD, we recommend recombinant zoster vaccine be given.

- GRADE: Strong recommendation, moderate certainty of evidence. Vote on PICO question: yes, 100%

Recommendation 10B: In adult patients with IBD younger than 50 years of age, we suggest recombinant zoster vaccine be given.

- GRADE: Conditional recommendation, low certainty of evidence. Vote on PICO question: yes, 89%; uncertain/neutral, 11%

INACTIVATED VACCINES COVID-19 – NOT ADDRESSED



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doi: 10.1093/jcag/gwaa046

Letter to Editor

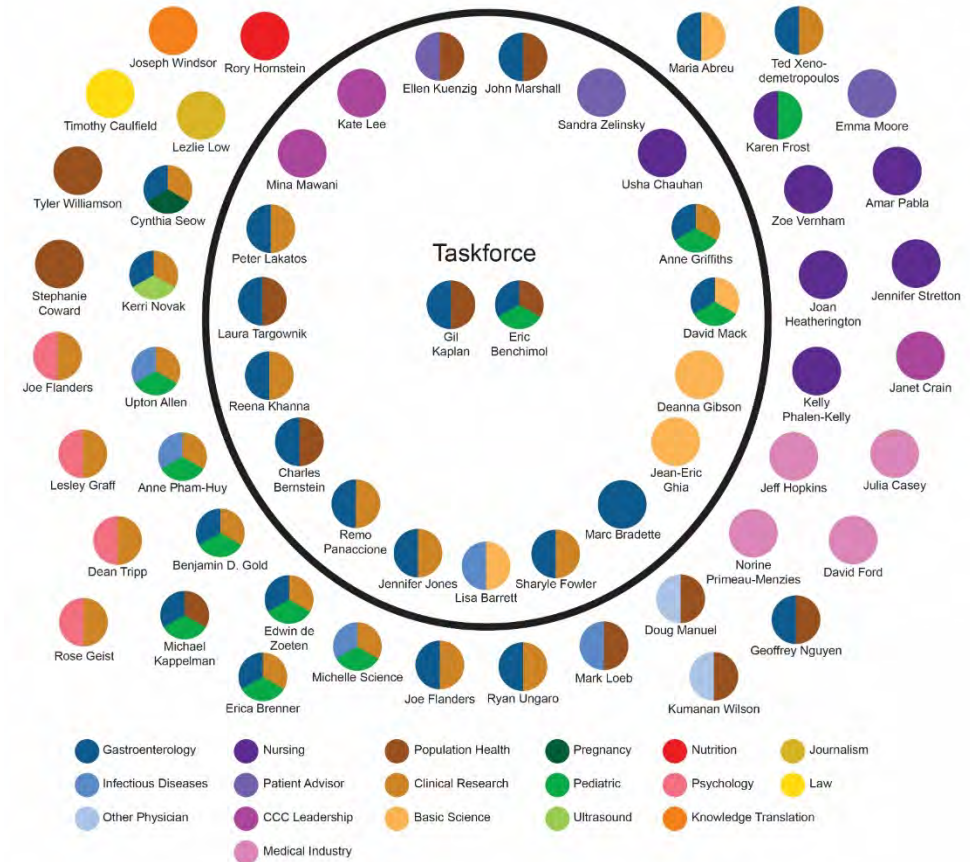
OXFORD

Letter to Editor

COVID-19 Vaccination in Patients With Inflammatory Bowel Disease: Communiqué From the Canadian Association of Gastroenterology

Frances Tse, MD, MPH, FRCPC^{1,2}, Paul Moayyedi, BSc, MB, ChB, PhD, MPH, FRCP, FRCPC, AGAF, FACG CAGF^{1,3,☉}, Kevin A. Waschke, MD, CM, FRCPC, FASGE CAGF^{4,5,☉}, Mark MacMillan, MD, FRCPC^{2,6}, Nauzer Forbes, MD, MSc, FRCPC^{2,7}, Matthew W. Carroll, BSc, BMed(Hons), MHSc, FRACP^{2,8}, Nicholas Carman, BSc, MBBS, FRACP^{2,9}, Grigorios I. Leontiadis, MD, PhD CAGF^{1,2,☉}

Data from national research on those with IBD inform Crohn's and Colitis Canada's COVID-19 & IBD Taskforce



CCC COVID-IBD Taskforce Recommendations:

<https://crohnsandcolitis.ca/About-Crohn-s-Colitis/COVID-19-and-IBD>

Q: How effective is three- or four-dose COVID-19 vaccine regimen in individuals with IBD?

Quan J, Ma C, Panaccione R, Hracs L, Sharifi N, Herauf M, Markovinović A, Coward S, Windsor JW, Caplan L, Ingram RJM, Charlton C, Kanji JN, Tipples G, Holodinsky JK, Bernstein CN, Mahoney DJ, Bernatsky S, Benchimol EI, Kaplan GG; STOP COVID-19 in IBD Research Group. **Serological responses to the first four doses of SARS-CoV-2 vaccine in patients with inflammatory bowel disease.** *Lancet Gastroenterol Hepatol.* 2022

Oct 25:S2468-12

[1253\(22\)00340-5](https://doi.org/10.1016/S2468-2667(22)00340-5)

THE LANCET

Gastroenterology & Hepatology

A: From the first to the fourth dose of a SARS-CoV-2 vaccine, antibody titers increase, decay, and robustly recover

First dose of the vaccine:

81.8% seroconvert; average antibody levels are 276 AU/ml

1 to 8 weeks after 2nd dose:

98.8% seroconvert; average antibody levels are 4,053 AU/ml

8+ weeks after 2nd dose:

95.6% seroconvert; average antibody levels are 1,127 AU/ml

1 to 8 weeks after 3rd dose:

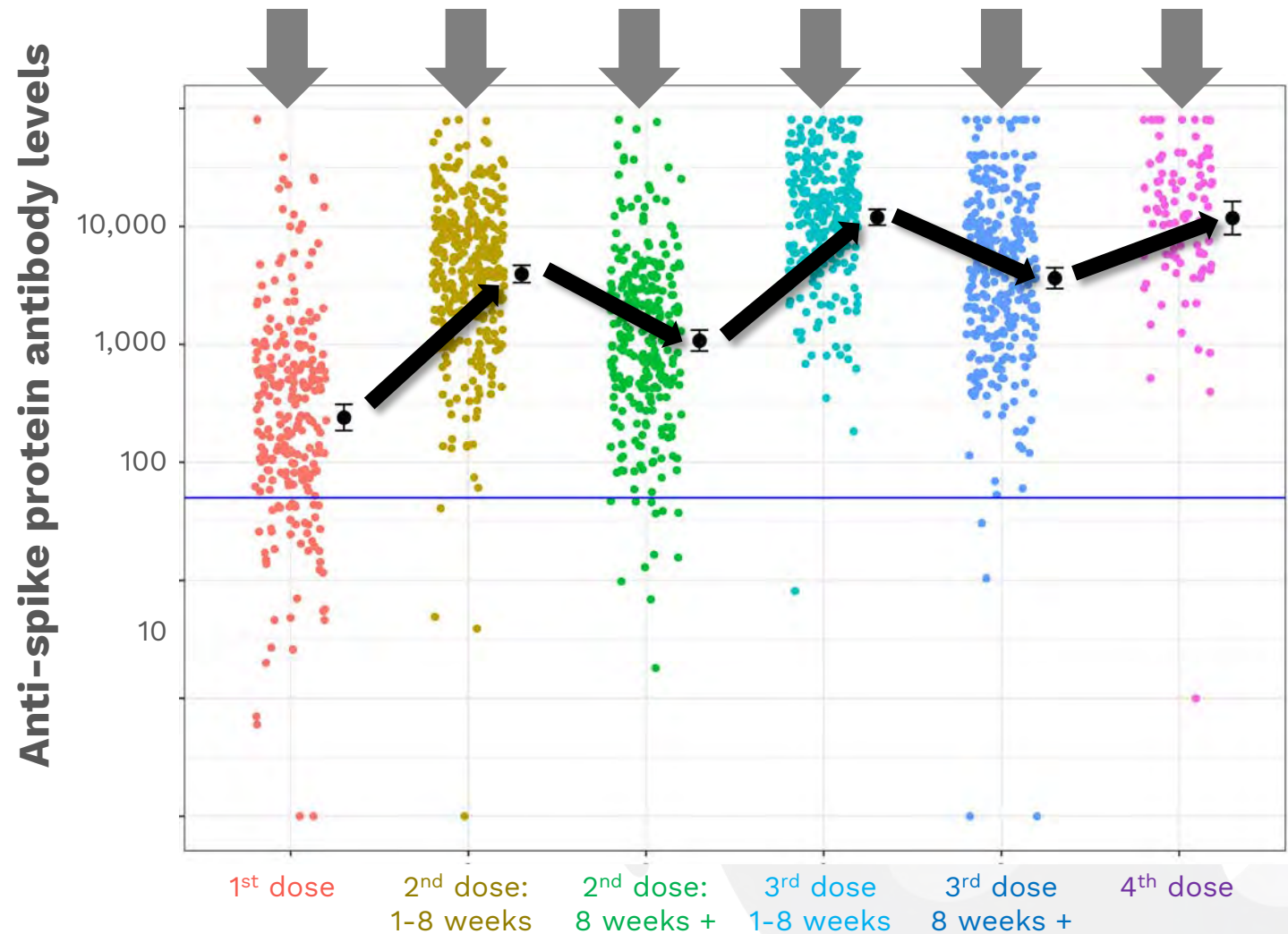
99.6% seroconvert; average antibody levels are 12,016 AU/ml

8+ weeks after 3rd dose:

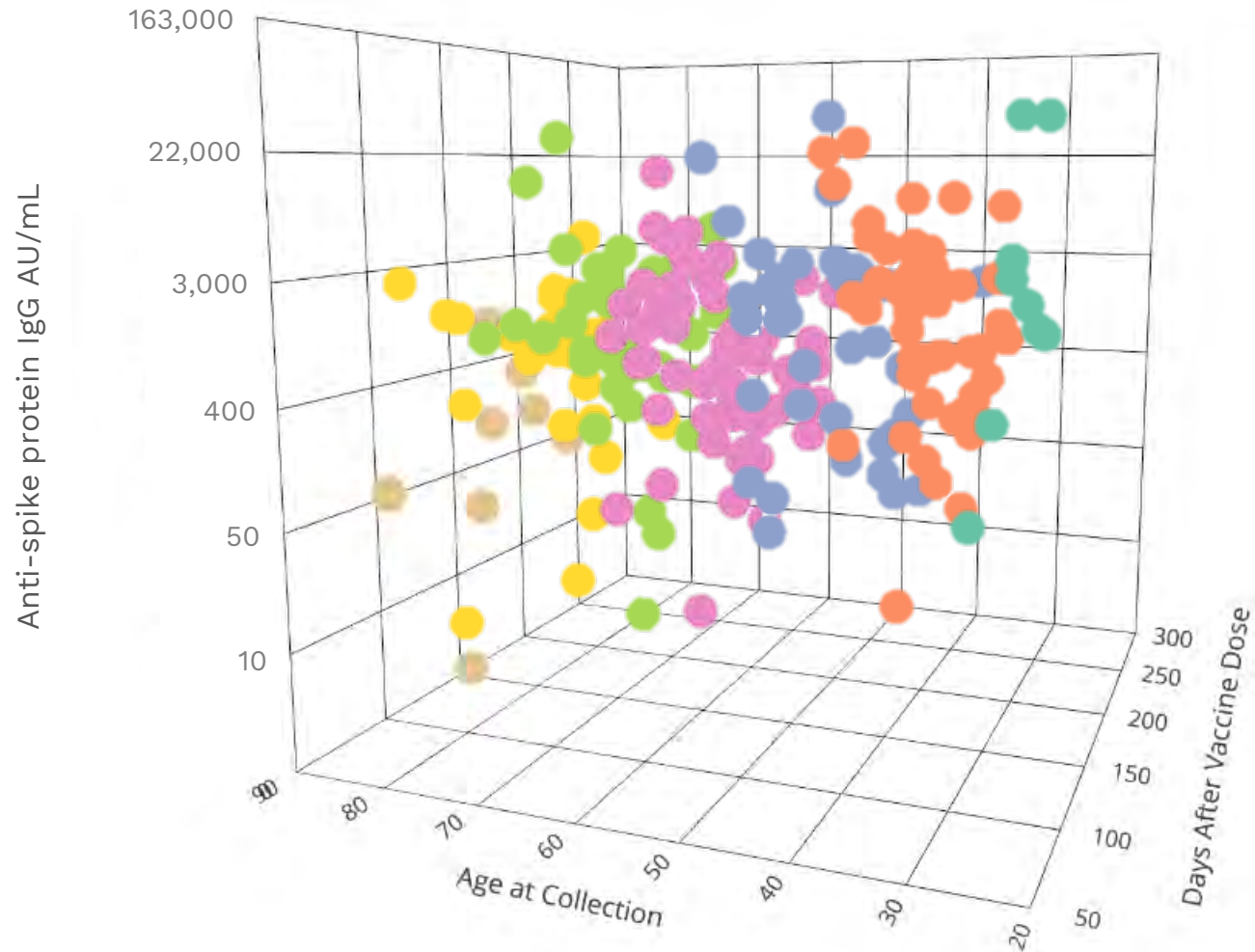
98.8% seroconvert; average antibody levels are 4,247 AU/ml

After 4th dose:

97.4% seroconvert; average antibody levels are 10,405 AU/ml



Antibody levels are higher in younger individuals with IBD

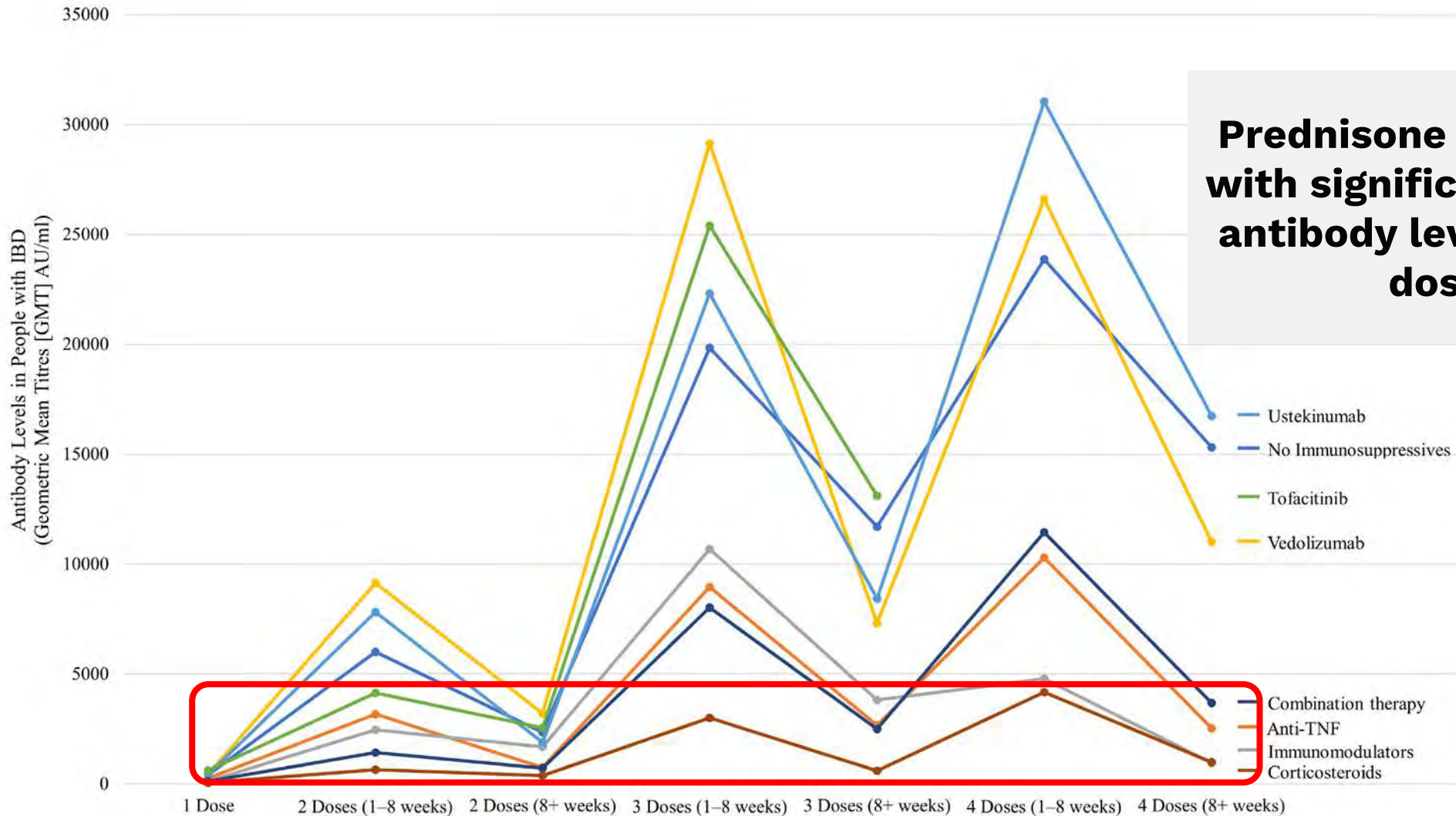


- 20-29yo
- 30-39yo
- 40-49yo
- 50-59yo
- 60-69yo
- 70-79yo
- 80-89yo

For example, after the third dose of a SARS-CoV-2 vaccine, for each decade of increased age antibody levels fell by 12%.

Quan...Kaplan; STOP COVID-19 in IBD Research Group. Serological responses to the first four doses of SARS-CoV-2 vaccine in patients with inflammatory bowel disease. *Lancet Gastroenterol Hepatol.* 2022 Oct 25:S2468-1253(22)00340-5.

Antibody levels recovered after 3rd and 4th vaccine dose Antibody levels were lower for anti-TNF therapy, for all IBD medications, except oral prednisone combination, immunomodulators, and oral prednisone



Prednisone associated with significantly lower antibody levels after 3 doses

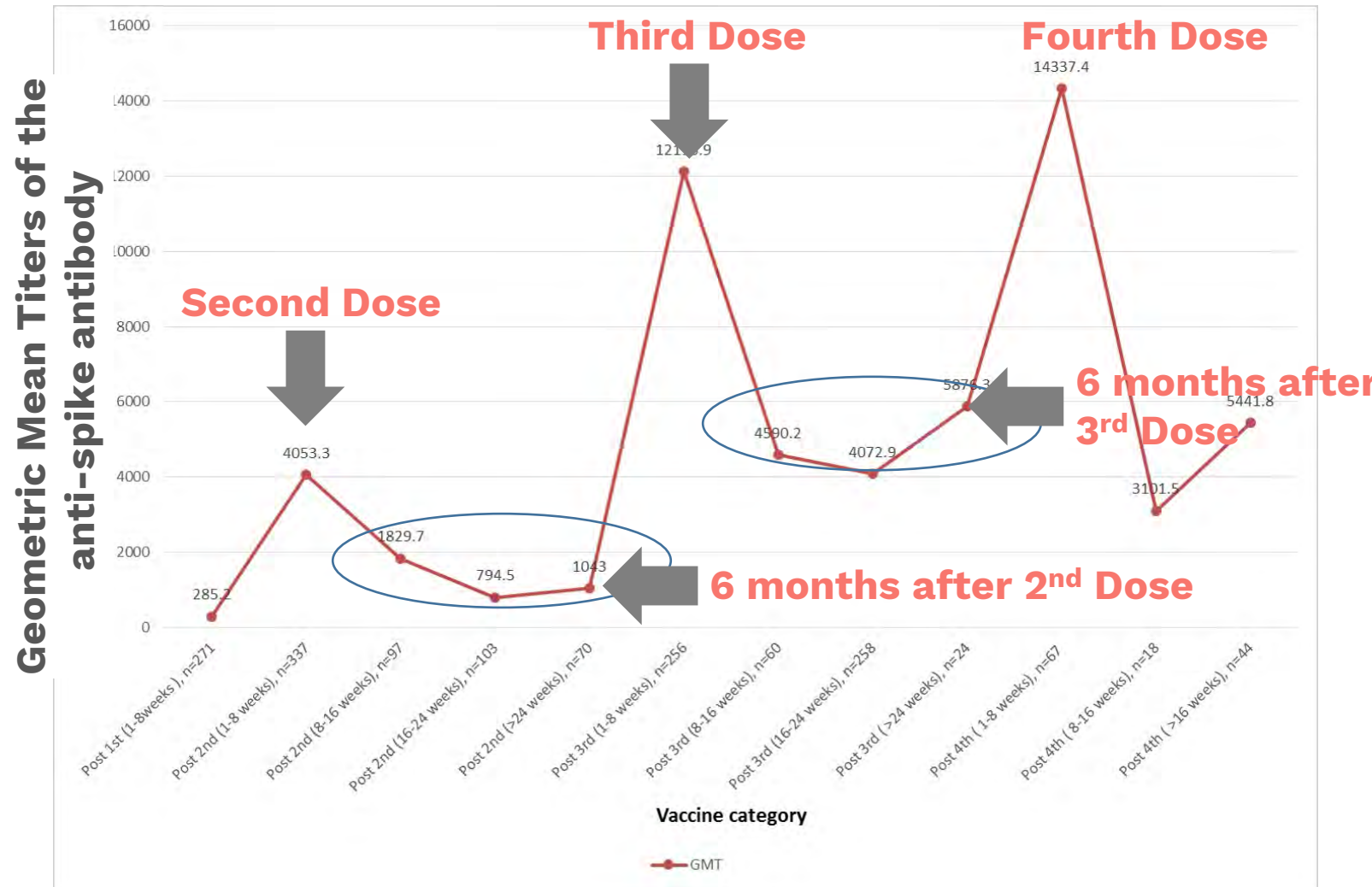
Geometric Meant Titres (GMT) of antibody levels for SARS-CoV-2 vaccines stabilize at 6 months after 2nd and 3rd dose.

Second dose of the vaccine:

GMT stabilize at 6 months at ~1000 AU/ml

Third dose of the vaccine:

GMT stabilize at 6 months at ~5000 AU/ml



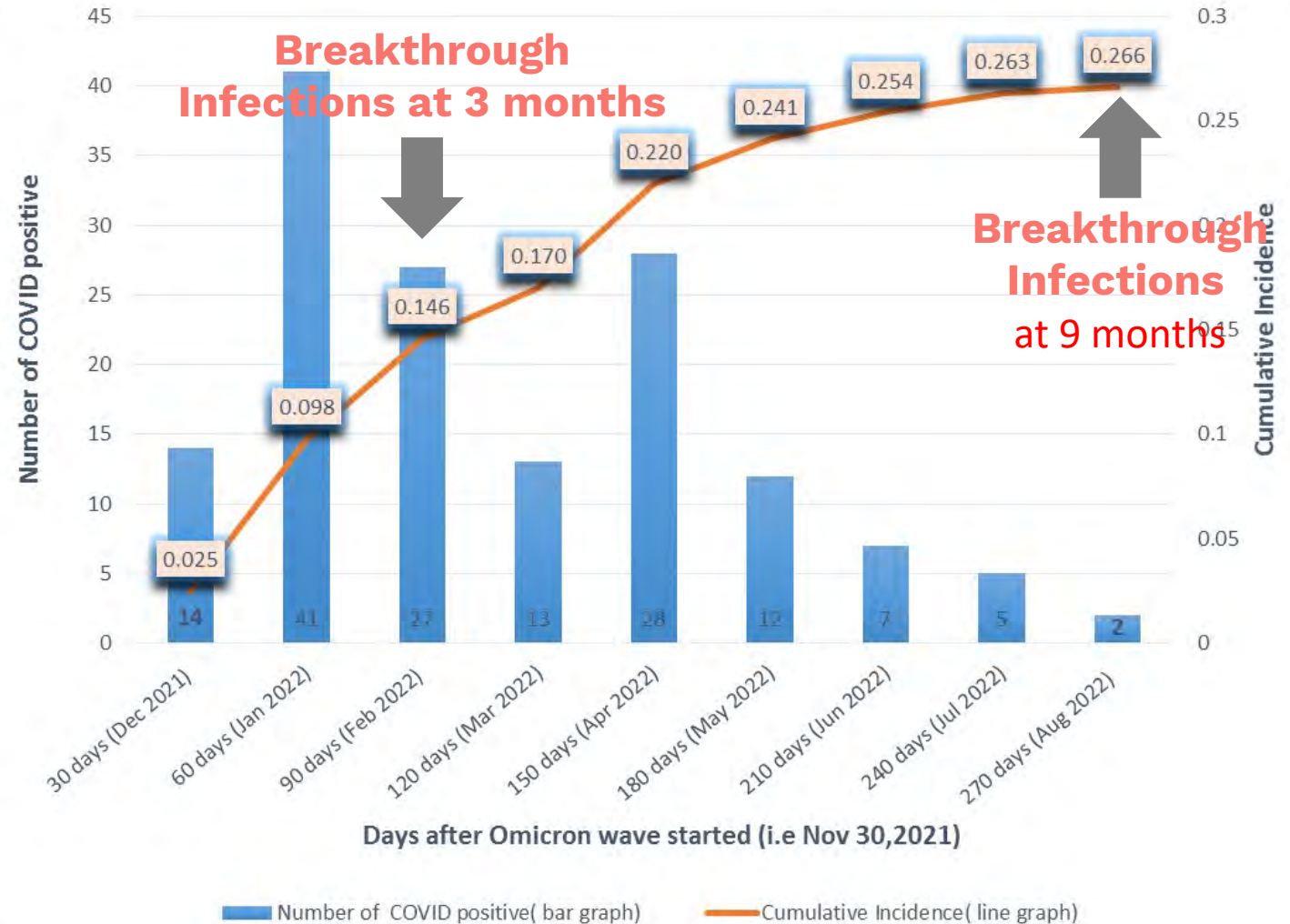
Despite 3rd and 4th dose vaccines, the cumulative risk of breakthrough infections during the omicron era was 15% after 3 months and 27% after 9 months?

Breakthrough Infections:

15% risk at 3 months during the Omicron Wave

Breakthrough Infections:

27% risk at 9 months during the Omicron Wave



Bivalent omicron vaccines have a robust immune response

Bivalent mRNA booster vaccine

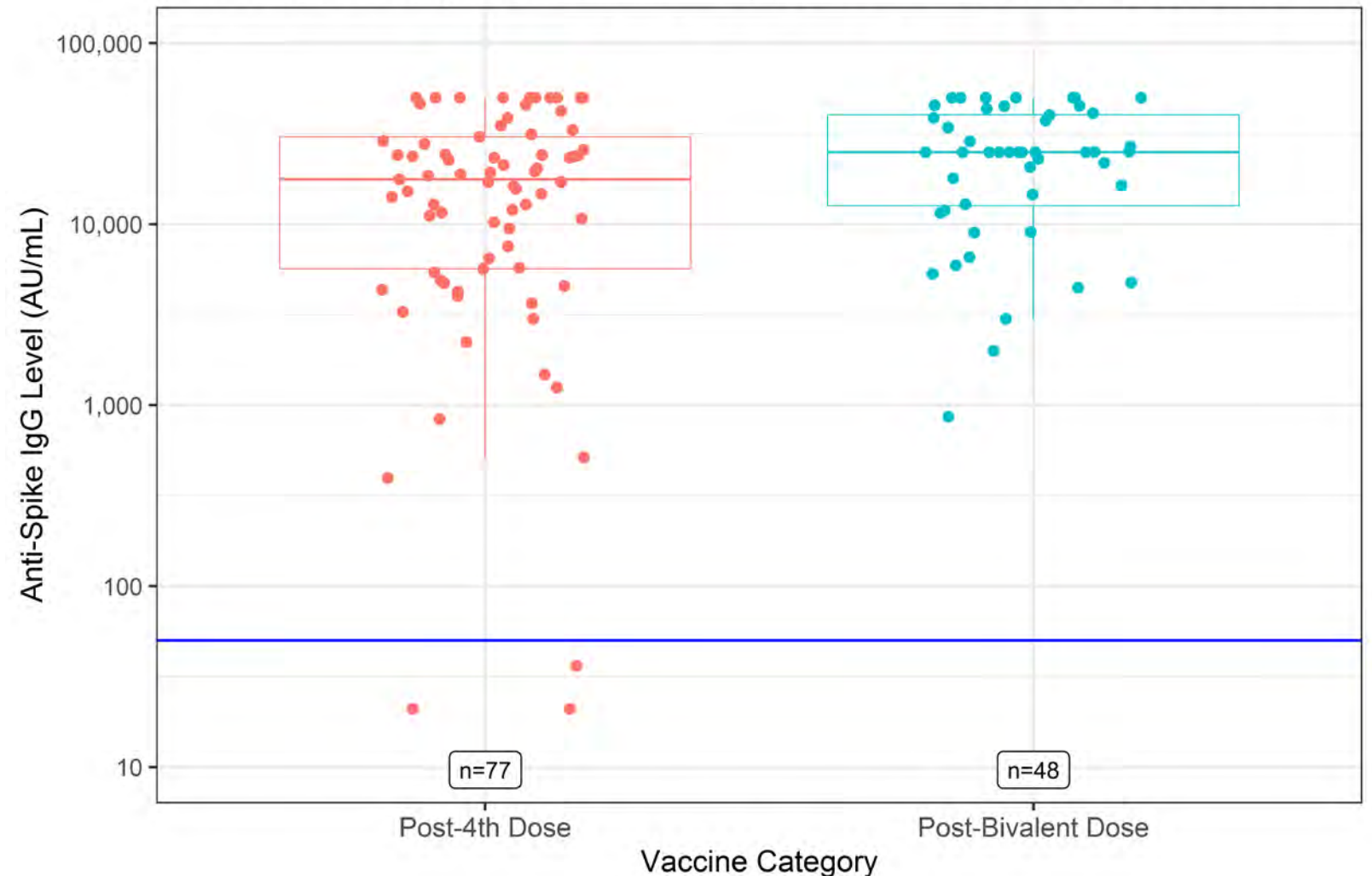
Using existing mRNA technology in use in approved vaccines, the bivalent vaccine contains two mRNA components: One of the originator SARS-CoV-2 strain, and one of the omicron variant.

mRNA vaccine targets Omicron XBB.1.5 subvariant

KRAKEN:

The World Health Organization (WHO) has called XBB.1.5 the most transmissible Omicron strain so far.

Figure 1. Distribution of antibody titres for Post-4th and Post-Bivalent groups with associated boxplots. Solid blue line represents seroconversion threshold.



Vaccine adverse events in those with IBD similar to those in general population: very low risk of triggering a flare

Symptoms post vaccine:

Similar frequency and duration to general population

Adverse events:

Injection site pain, fatigue, & malaise most common
(GI symptoms <12%)

Risk of flare:

No objective flare within 30 days of vaccine across 3rd and 4th doses vaccine

Inflammatory Bowel Diseases, 2022, XX, 1–5
<https://doi.org/10.1093/ibd/izac174>
Advance access publication 23 August 2022
Original Research Articles - Clinical



Postvaccination Symptoms After a Third Dose of mRNA SARS-CoV-2 Vaccination in Patients With Inflammatory Bowel Disease: Results From CORALE-IBD

Dalin Li, PhD,¹ Philip Debbas,² Angela Mujukian, MD,³ Susan Cheng, MD, MS,¹ Jonathan Braun, MD,⁴ Dermot P.B. McGovern, MD, PhD,⁵ Gil Y. Melmed, MD, MS,⁶ and the CORALE-IBD Study Group



Injection site reactions associated with 3-fold **higher levels of antibodies** after 4th dose.

Adverse Events and Serological Responses After SARS-CoV-2 Vaccination in Individuals With Inflammatory Bowel Disease

Ante Markovinić, BA¹, Joshua Quan, MSc¹, Michelle Herauf, MSc¹, Lindsay Hraes, PhD¹, Joseph W. Windsor, PhD¹, Naeem Sharifi, MD¹, Stephanie Coward, PhD¹, Lee Caplan, BHSoc¹, Julia Garsoge, BSc¹, Kenneth Ernest-Suarez, MD¹, Christopher Ma, MD, MPH¹, Remo Panaccone, MD¹, Richard J.M. Ingram, MD, PhD¹, Jamil N. Kanji, MD^{2,3,4}, Graham Tipples, PhD^{2,5}, Jessalyn K. Holdinsky, PhD⁶, Charles N. Bernstein, MD⁷, Douglas J. Mahoney, PhD⁸, Sasha Bernatsky, MD, PhD⁹, Eric I. Benchimol, MD, PhD^{2,11,12}, Gilaad G. Kaplan, MD, MPH, FRCP¹ and on behalf of the STOP COVID-19 in IBD Research Group

Am J Gastroenterol 2023;118:1693–1697.

Case: What are the ethical implications?

A 14-year-old boy is newly diagnosed with moderate-to-severe ileocolonic Crohn's disease. His pediatric gastroenterologist wants to start a course of prednisone as a bridge to anti-TNF therapy. His pre-biologic work-up showed no immunity to measles or hepatitis B. His parents did not vaccinate him for his childhood vaccines, and he has not received a vaccine for COVID-19. They do not want to vaccinate him prior to starting treatment.