# Variation in response to SARS-CoV-2 vaccines in Health Care Workers and people with Immune-mediated diseases

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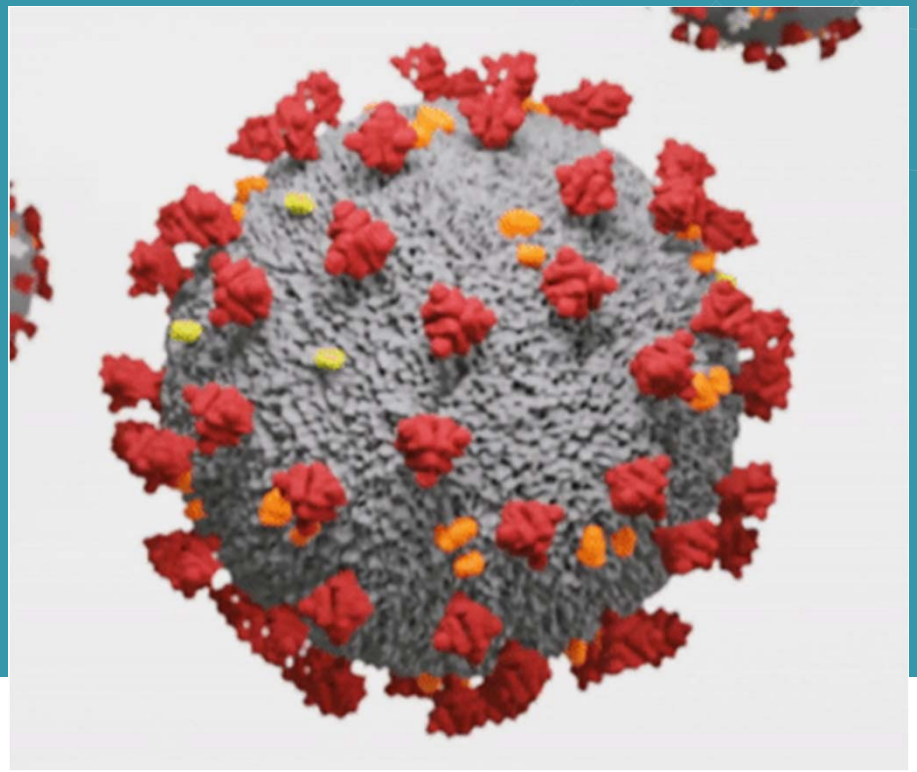
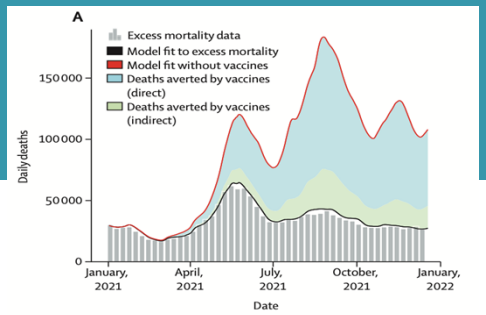
# Anti-SARS-CoV-2 Vaccines



- **Overall Cases / Deaths**
  - Globally: >6M / 524 M
  - US: >83M / >1 M
- **Vaccines against SARS-CoV-2**
  - Prevent infection (humoral)
  - Prevent severe disease and death (cellular immunity)




**'we estimated that vaccinations prevented ……. 19·8 million deaths from COVID-19'**

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https://commons.wikimedia.org/wiki/File:SARS-CoV-2_virion_animation.gif
Hadi Y, et al APT 2022
Watson et al. , Lancet Infectious Diseases, June 2022

Open access Original research

BMJ Open

# Demographic and clinical characteristics associated with variations in antibody response to BNT162b2 COVID-19 vaccination among healthcare workers at an academic medical centre: a longitudinal cohort analysis

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Ebinger JE, *et al. BMJ Open* 2022;**12**:e059994. doi:10.1136/bmjopen-2021-059994

## Aim

**To improve understanding of longitudinal immune responses following initial SARS-CoV-2 Vaccination**

## Overview of Study Design I

- **Academic Medical Center (CSMC)**
- **Longitudinal Study of Healthcare Workers (HCW) who received 2 doses of Pfizer-BioNTech (BNT162b2) mRNA vaccine**
- **Questionnaires about medical history & exposure risk**
- **Dx of COVID-19 based on:**
  - History
  - Medical Records
  - Raised IgG(N)



Ebinger JE, *et al. BMJ Open* 2022;**12**:e059994. doi:10.1136/bmjopen-2021-059994

# Overview of Study Design II

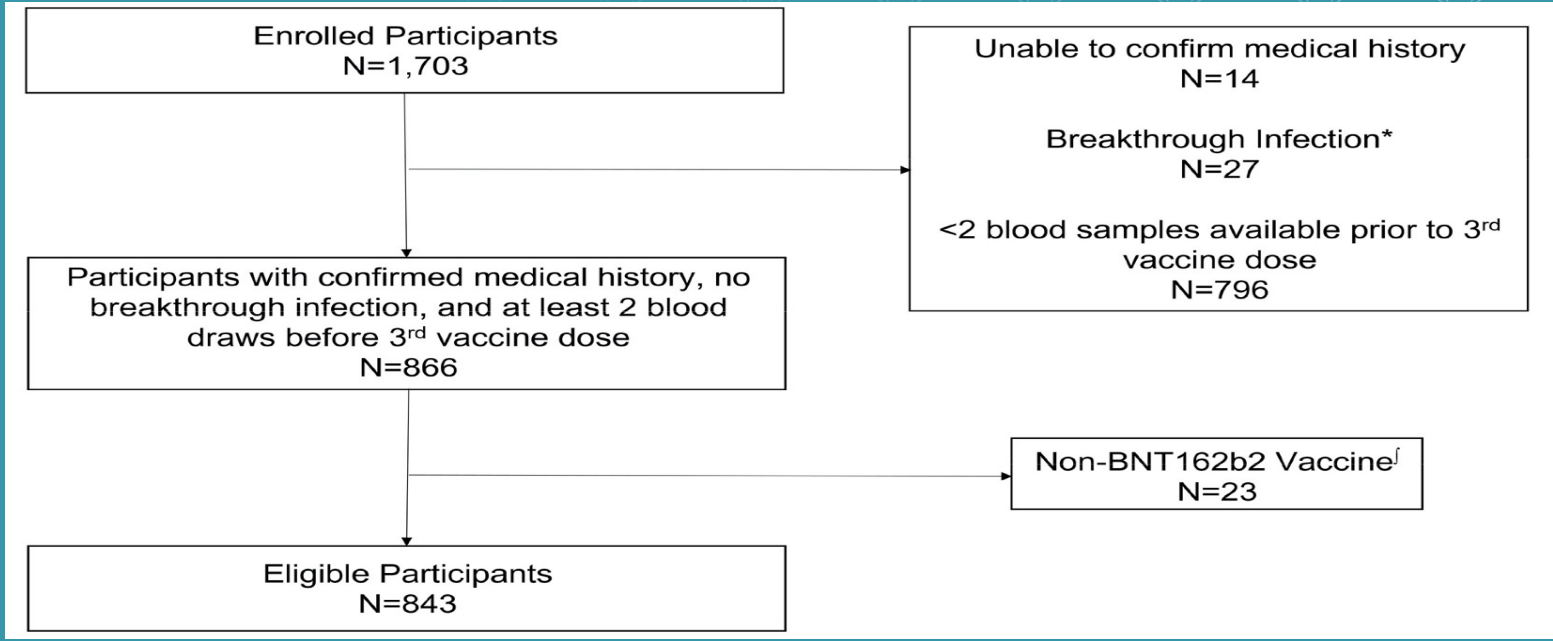
- **Exclusion Criteria**
  - Received other vaccines
  - COVID-19 status not confirmed
  - Developed breakthrough infections
  - Non-compliant with protocol
- **Serology measured** with Abbott SARS-Cov-2 IgG assays for both Spike (S) and Nucleocaspid (N) proteins.
  - Dose 1 and dose 2,
  - Weeks 8, 16, 24, 32, and 40
- **Statistical Analyses**
  - Standard Approaches
    - Differences in variances & Kruskall-Wallis for continuous variables
    - $X^2$ for Categorical Variables
    - Mixed Effects for Longitudinal
  - Analyses adjusted for age, sex, self-identified race and ethnicity, obesity, hypertension, & Charlson Co-morbidity Index

- IgG (N) signal to cut off (S/C) Index of ≥ 1.4 evidence of previous infection



Ebinger JE, *et al. BMJ Open* 2022;**12**:e059994. doi:10.1136/bmjopen-2021-059994

# Results I




*Breakthrough cases defined as IgG(N) ≥1.4 when measured after receiving 2 mRNA vaccine doses and prior to a 3rd dose, with prior IgG(N) <0.4 or no history of prior COVID-19 infection.

∫ Participants who received any vaccine other than BNT162b2.



Ebinger JE, *et al. BMJ Open* 2022;**12**:e059994. doi:10.1136/bmjopen-2021-059994

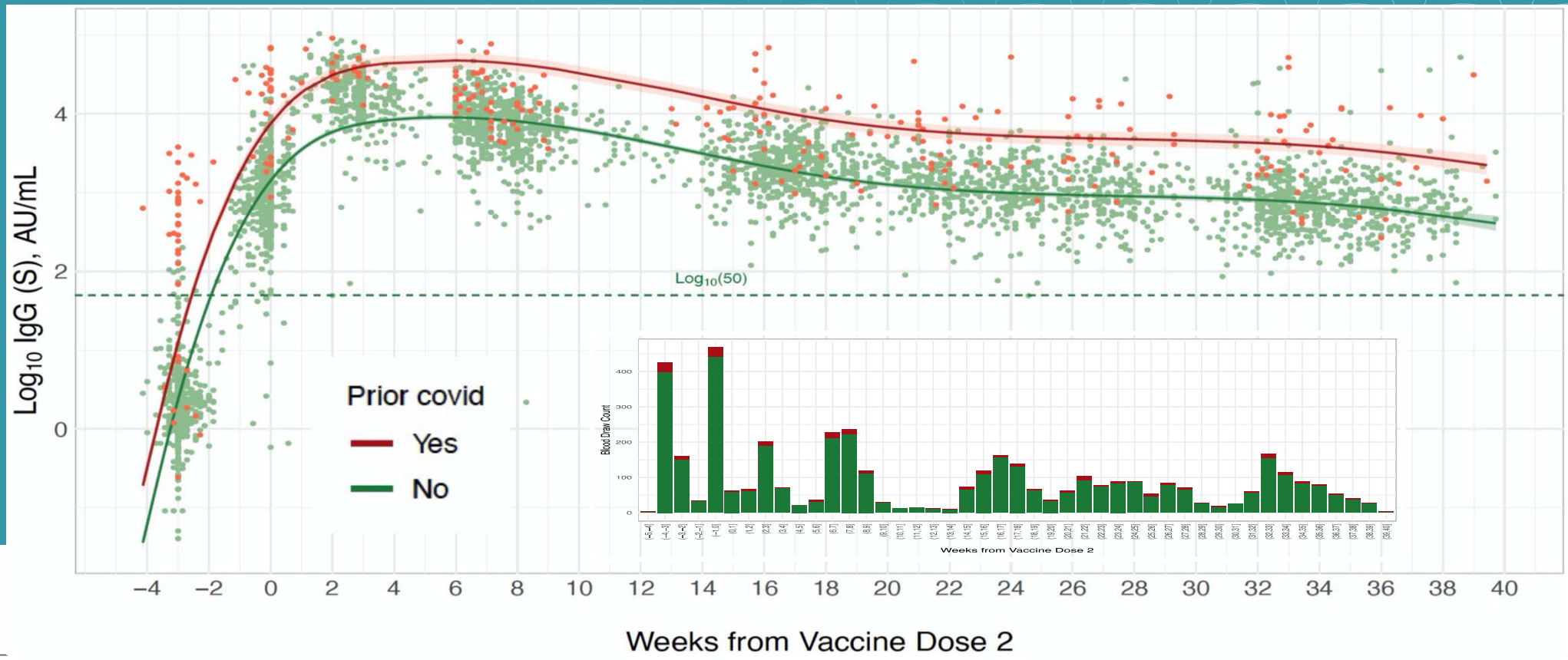
# Results II

| | Total sample | No prior SARS-CoV-2 infection | Prior SARS-CoV-2 infection | P value* |
|---|---|---|---|---|
| n | 843 | 784 | 59 | |
| Age in years, median (IQR) | 41.66 (35.19, 52.80) | 41.89 (35.25, 53.00) | 38.72 (34.93, 49.31) | 0.169 |
| Age in years (range) | 20.37–87.26 | 20.37–87.26 | 23.52–76.87 | |
| Male sex, n (%) | 256 (30.4) | 239 (30.5) | 17 (28.8) | 0.903 |
| Non-white race, n (%) | 405 (48.0) | 372 (47.4) | 33 (55.9) | 0.262 |
| Hispanic ethnicity, n (%) | 86 (10.2) | 73 (9.3) | 13 (22.0) | 0.004 |
| Obesity, n (%) | 103 (12.2) | 92 (11.7) | 11 (18.6) | 0.175 |
| Hypertension, n (%) | 128 (15.2) | 122 (15.6) | 6 (10.2) | 0.355 |
| Charlson Comorbidity Index, median (IQR)† | 0.00 (0.00, 1.00) | 0.00 (0.00, 1.00) | 0.00 (0.00, 1.00) | 0.572 |
| Work environment‡ | | | | |
| ICU, COVID-19 unit | 135 (16.1) | 126 (16.2) | 9 (15.3) | 1.00 |
| ICU, non-COVID-19 unit | 133 (15.9) | 129 (16.5) | 4 (6.8) | 0.073 |
| Ward, COVID-19 unit | 160 (19.1) | 141 (18.1) | 19 (32.2) | 0.013 |
| Ward, non-COVID-19 unit | 204 (24.3) | 193 (24.7) | 11 (18.6) | 0.37 |
| Emergency department /urgent care | 98 (11.7) | 94 (12.1) | 4 (6.8) | 0.315 |
| Outpatient clinic | 215 (25.6) | 206 (26.4) | 9 (15.3) | 0.082 |
| Office | 129 (15.4) | 119 (15.3) | 10 (16.9) | 0.873 |
| Work from home | 61 (7.3) | 57 (7.3) | 4 (6.8) | 1.00 |
| Other | 185 (22.1) | 177 (22.7) | 8 (13.6) | 0.142 |
| Unknown | 74 (8.8) | 71 (9.1) | 3 (5.1) | 0.423 |

*P value comparing those with versus without prior SARS-CoV-2 infection.
†The Charlson Comorbidity Index weights the clinical conditions into a single score to predict 10-year survival: age, myocardial infarction, heart failure, peripheral vascular disease, stroke, dementia, chronic obstructive pulmonary disease, connective tissue disease, peptic ulcer disease, liver disease, diabetes mellitus, hemiplegia, chronic kidney disease, solid tumour, leukaemia, lymphoma and AIDS.
‡Participant-provided work environment. Participants could select multiple environments if they worked in more than one location.
ICU, intensive care unit.


Ebinger JE, *et al. BMJ Open* 2022;**12**:e059994. doi:10.1136/bmjopen-2021-059994

# Results III

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Ebinger JE, *et al. BMJ Open* 2022;**12**:e059994. doi:10.1136/bmjopen-2021-059994

# Results IV

**Table 2** Clinical and demographic correlates of longitudinal anti-spike IgG antibody response following complete initial mRNA vaccination

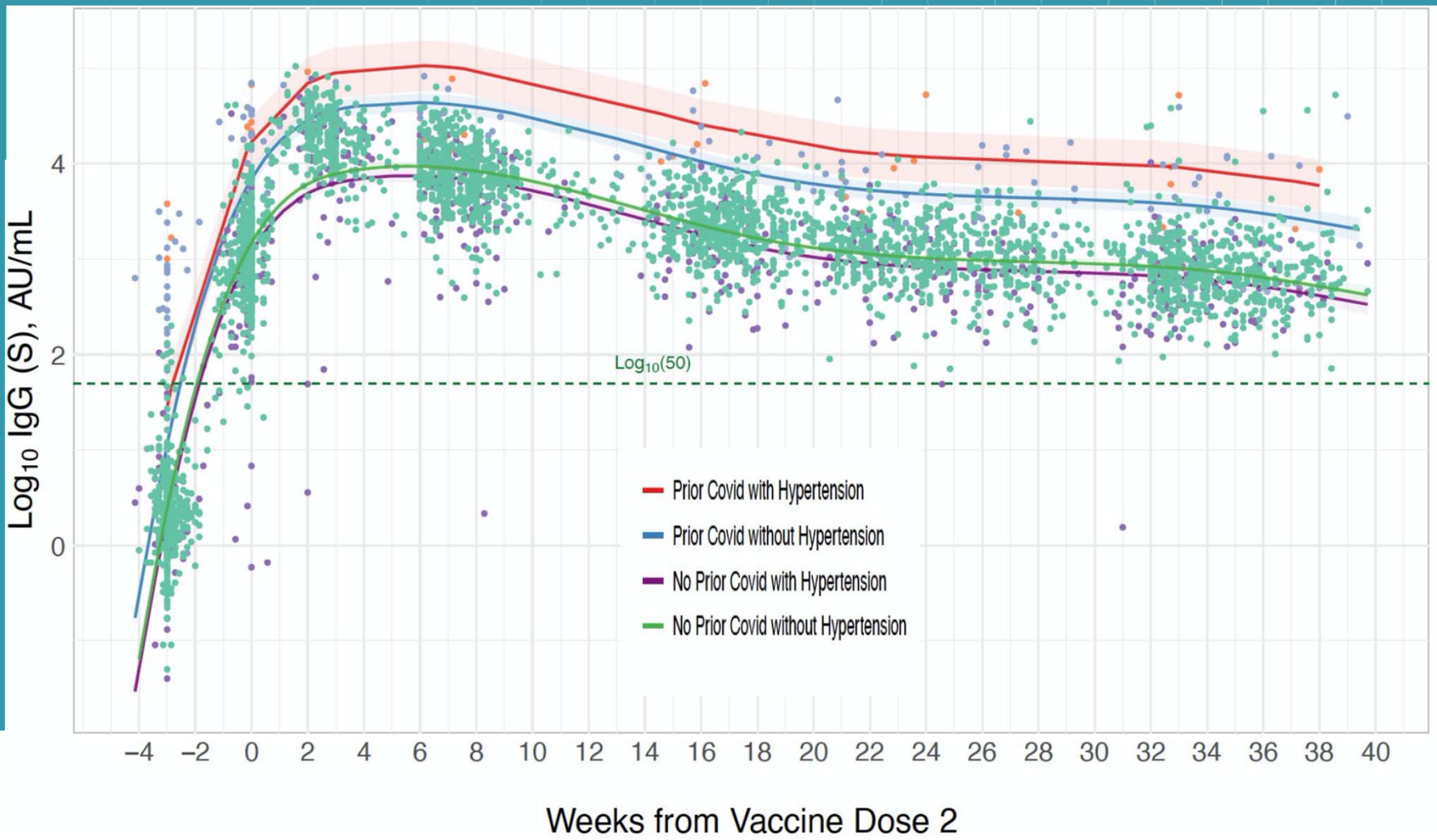
| | Beta* | SE | P value | Partial $R^2$ |
|---|---|---|---|---|
| Prior SARS-CoV-2 infection | 1.74 | 0.11 | <0.001 | 0.134 |
| Age (year) | –0.01 | 0.00 | <0.001 | 0.016 |
| Male sex | –0.27 | 0.06 | <0.001 | 0.013 |
| Non-white race | –0.00 | 0.06 | 0.99 | 0.000 |
| Hispanic ethnicity | 0.02 | 0.10 | 0.80 | 0.000 |
| Obesity | 0.03 | 0.09 | 0.77 | 0.000 |
| Hypertension | –0.17 | 0.08 | 0.041 | 0.003 |
| Charlson Comorbidity Index | –0.02 | 0.03 | 0.56 | 0.000 |

*Beta values represent increase in 1 SD of log(10)IgG-S level per presence (vs absence) of a categorical variable or per unit increment of continuous variable.



Ebinger JE, *et al. BMJ Open* 2022;**12**:e059994. doi:10.1136/bmjopen-2021-059994

# Results V

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Ebinger JE, *et al. BMJ Open* 2022;**12**:e059994. doi:10.1136/bmjopen-2021-059994

# Strengths/Limitations

- BNT162b2 vaccine only
- High # of subjects excluded – but missing had similar characteristics
- Assessment of humoral, but not T-cell mediated responses
- HCW cohort - ? Generalizability – Age, co-morbidities etc
- Some diversity in cohort – more work needed
- ? Generalizability with newer VOCs



Ebinger JE, *et al. BMJ Open* 2022;**12**:e059994. doi:10.1136/bmjopen-2021-059994

# Summary

- Vast majority of adults maintain 'good' IgG-S levels @ 40 weeks post vaccination
  - Levels peak at 2-8 weeks after vaccine and decline slowly to 40 weeks
- Primary differentiator of vaccine response was prior Covid infection
- Elevated humoral response seen in females, younger age & absence of hypertension
- 'Hybrid' immunity benefit persists over duration of study
- Effects of hypertension are 'reversed'
  - High BP – overall lower antibody response
    – prior-infection group - higher antibody response

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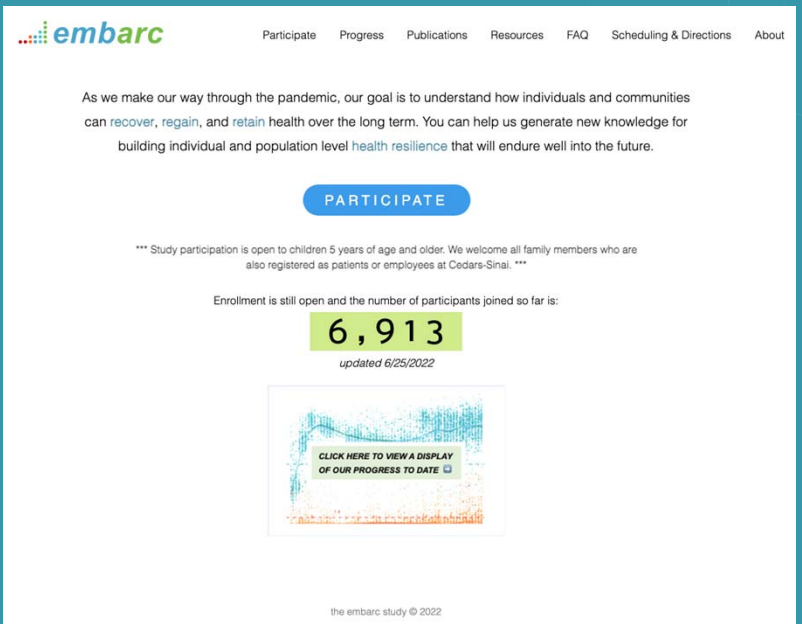
Ebinger JE, *et al. BMJ Open* 2022;**12**:e059994. doi:10.1136/bmjopen-2021-059994

# What are we doing to address these limitations?




| Race/Ethnicity | N (%) |
|---|---|
| American Indian/ Alaska Native | 9 (0.1) |
| Asian | 706 (11.6) |
| Hispanic | 595 (9.8) |
| Native Hawaiian/Pacific Islander | 45 (0.7) |
| Non-Hispanic White | 3906 (64.0) |
| Non-Hispanic Black | 263 (4.3) |
| Multiple | 170 (2.8) |
| Other | 115 (1.9) |
| Unknown | 293 (4.8) |

| Autoimmune Disease | N (%) |
|---|---|
| Current/Past | 977 (16.0) |
| Never | 3913 (64.1) |
| Unknown | 1212 (19.9) |

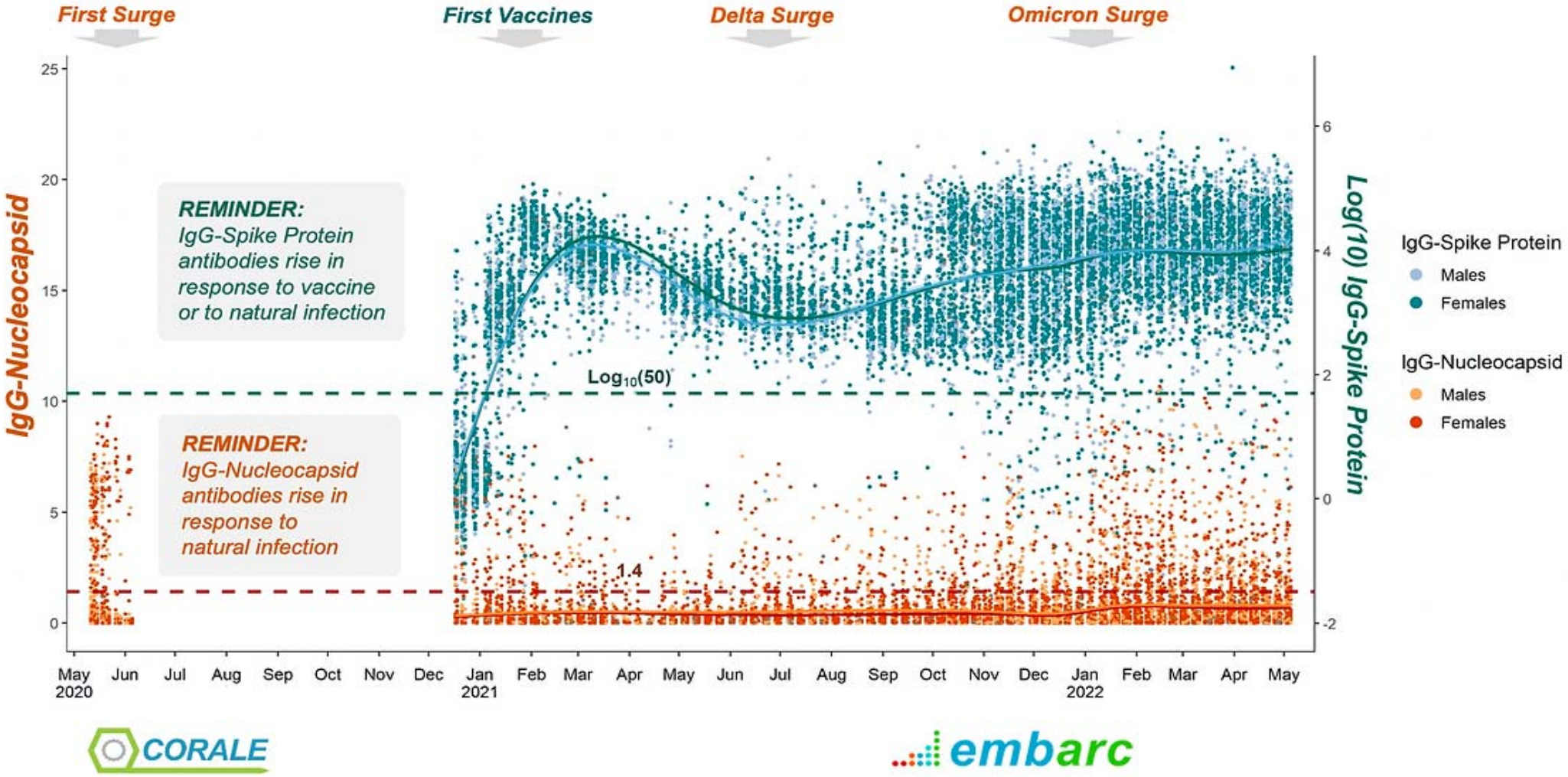
| Organ transplant | N (%) |
|---|---|
| Current/Past | 279 (4.6) |
| Heart | 118 (1.9) |
| Kidney | 136 (2.1) |
| Liver | 41 (0.7) |
| Lung | 10 (0.2) |
| Other | 27 (0.4) |
| Never | 4418 (72.4) |

| Cancer | N (%) |
|---|---|
| Current/Past | 877 (14.4) |
| Breast | 230 (3.9) |
| Prostate | 105 (1.8) |
| Melanoma | 140 (2.3) |
| Lung | 24 (0.4) |
| Liver | 20 (0.3) |
| Colon | 38 (0.6) |
| Other | 452 (7.5) |
| Never | 3839 (62.9) |
| | |

# Vaccination History

| Combinations of vaccine types | N (%) |
|---|---|
| 3 Pfizer | 2121 (34.8) |
| 3 Moderna | 894 (14.7) |
| 2 Pfizer | 714 (11.7) |
| 2 Moderna | 415 (6.8) |
| 4 Pfizer | 397 (6.5) |
| Unknown | 335 (5.5) |
| 4 Moderna | 307 (5.0) |
| 2 Pfizer + 1 Moderna | 179 (2.9) |
| 1 Johnson | 128 (2.1) |
| 3 Pfizer + 1 Moderna | 110 (1.8) |
| 1 Pfizer + 2 Moderna | 102 (1.7) |
| 1 Moderna + 1 Johnson | 77 (1.3) |
| 1 Pfizer + 1 Johnson | 54 (0.9) |

| Combinations of vaccine types | N (%) |
|---|---|
| 2 Pfizer + 2 Moderna | 42 (0.7) |
| 1 Pfizer + 3 Moderna | 35 (0.6) |
| 2 Johnson | 31 (0.5) |
| 1 Pfizer | 29 (0.5) |
| 2 Pfizer + 1 Johnson | 24 (0.4) |
| 2 Moderna + 1 Johnson | 23 (0.4) |
| 1 Moderna | 17 (0.3) |
| 1 Pfizer + 1 Moderna + 1 Johnson | 11 (0.2) |
| 2 Pfizer + 1 Moderna + 1 Johnson | 8 (0.1) |
| 1 Pfizer + 1 Moderna | 7 (0.1) |
| 3 Moderna + 1 Johnson | 6 (0.1) |
| 1 Pfizer + 2 Moderna + 1 Johnson | 5 (0.1) |
| Other combinations | 31 (5.0) |




CORALE

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# COVID-19 and vaccine responses in IBD
# What do we know?

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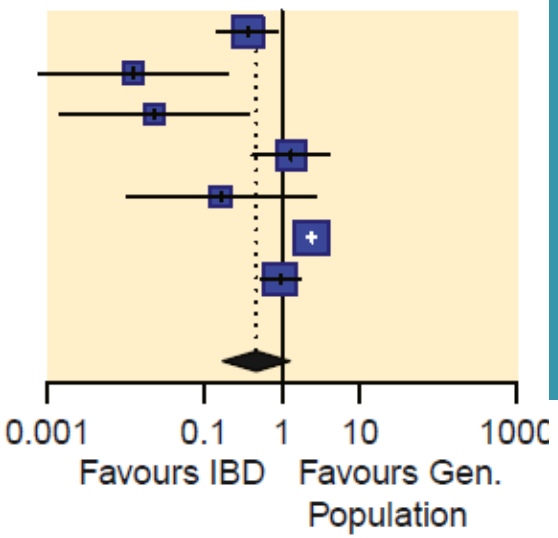
# Prior to vaccination risk of SARS-CoV-2 infection no different from the general population

## Systematic review and meta-analysis

| Study | IBD Events | IBD Total | Gen. Population Events | Gen. Population Total | Weight | Risk Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| Gubatan J et al | 5 | 168 | 1155 | 14067 | 18.3% | 0.36 [0.15; 0.86] |
| Mak JWY et al (1) | 0 | 2954 | 1017 | 75210 | 7.9% | 0.01 [0.00; 0.20] |
| Mak JWY et al (2) | 0 | 3091 | 429 | 60956 | 7.9% | 0.02 [0.00; 0.37] |
| Marafini I et al | 3 | 672 | 205463 | 60317000 | 16.7% | 1.31 [0.42; 4.05] |
| Norsa L et al | 0 | 522 | 6471 | 1114590 | 7.9% | 0.16 [0.01; 2.63] |
| Singh S et al | 232 | 196403 | 19776 | 40000000 | 21.3% | 2.39 [2.10; 2.72] |
| Taxonera C et al | 12 | 1918 | 43877 | 6663394 | 19.9% | 0.95 [0.54; 1.67] |
| **Total (95% CI)** | | **205728** | | **108245217** | **100.0%** | **0.47 [0.18; 1.26]** |

Heterogeneity: $Tau^2 = 1.1859$; $Chi^2 = 54.42$, df = 6 ($P < 0.01$); $I^2 = 89\%$

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*Singh A et al United European Gastroenterol J.* 2021. DOI: 10.1177/2050640620972602

# Prior to vaccination steroids associated with adverse COVID-19 outcomes

| | Hospitalisations | ICU admissions/Severe Covid | Mortality |
|---|---|---|---|
| Systemic steroids | RR 1.99 [95%CI 1.64 - 2.40]* | RR 3.41 [95%CI 2.28 - 5.11]* | RR 2.70 [95%CI 1.61 - 4.55]* |
| Immunomodulators | RR 0.89 [95%CI 0.37 - 2.10] | RR 0.71 [95%CI 0.17 - 3.02] | RR 1.18 [95%CI 0.23 - 6.01] |
| 5-ASA | RR 1.02 [95%CI 0.83 - 1.26] | RR 1.03 [95%CI 0.74 - 1.43] | RR 1.09 [95%CI 0.65 - 1.82] |
| JAK-inhibitors | RR 0.48 [95%CI 0.30 - 0.76]* | RR 0.50 [95%CI 0.14 - 1.86] | RR 0.83 [95%CI 0.10 - 7.11] |
| Anti-TNF | RR 0.58 [95%CI 0.50 - 0.69]* | RR 0.50 [95%CI 0.33 - 0.78]* | RR 0.44 [95%CI 0.26 - 0.76]* |
| Anti-integrin | RR 0.66 [95%CI 0.56 - 0.78]* | RR 0.72 [95%CI 0.42 - 1.24] | RR 0.50 [95%CI 0.32 - 0.78]* |
| IL12/23 inhibitor | RR 0.44 [95%CI 0.36 - 0.54]* | RR 0.43 [95%CI 0.26 - 0.71]* | RR 0.55 [95%CI 0.28 - 1.11] |

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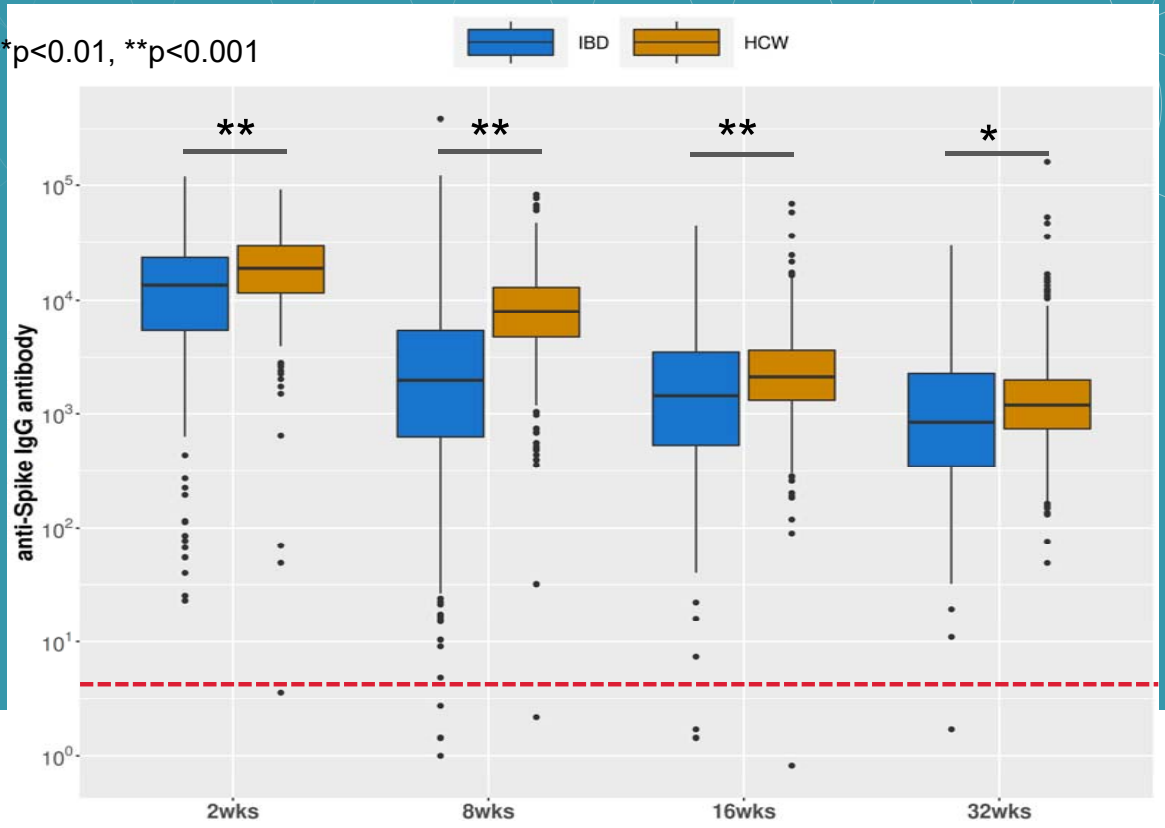
Lin S, et al. Gut 2022;**0**:1–14. doi:10.1136/gutjnl-2021-326784. Figure created from: Ungaro et al Gastroenterology 2022 https://doi.org/10.1053/j.gastro.2021.09.011, *Singh A et al United European Gastroenterol J.* 2021. DOI: 10.1177/2050640620972602

# ‘S’ Antibodies are lower in IBD at each timepoint

- IBD had lower antibody levels than HCW at every timepoint (2w, 8w, 16w, 32w)
- Antibodies decreased after 2w in everyone
- >99% antibodies above “positive” threshold of 50 AU

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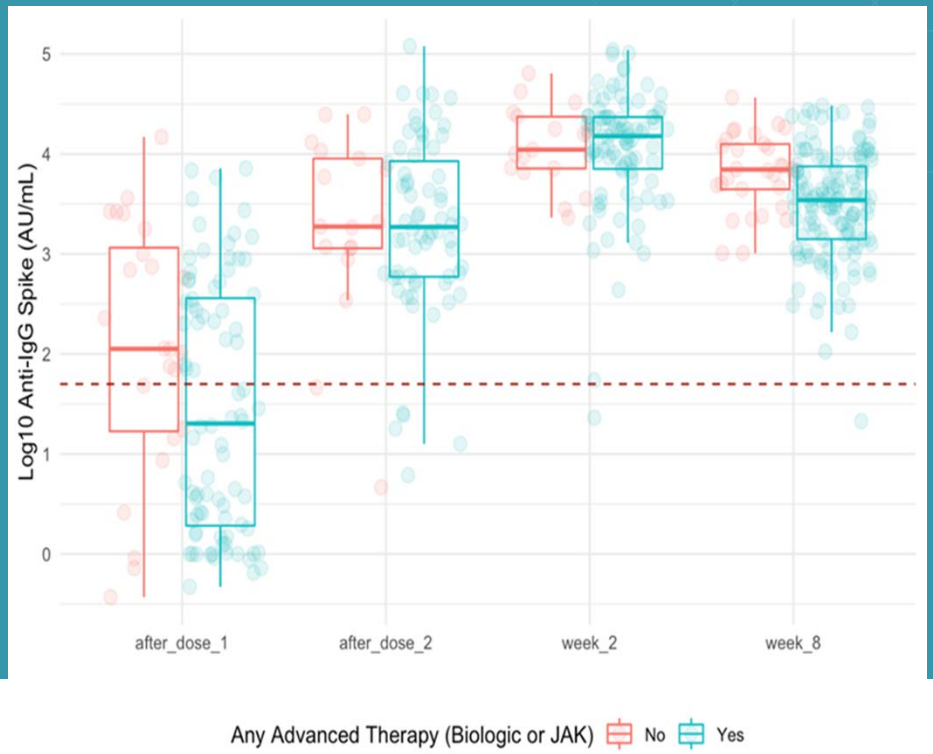
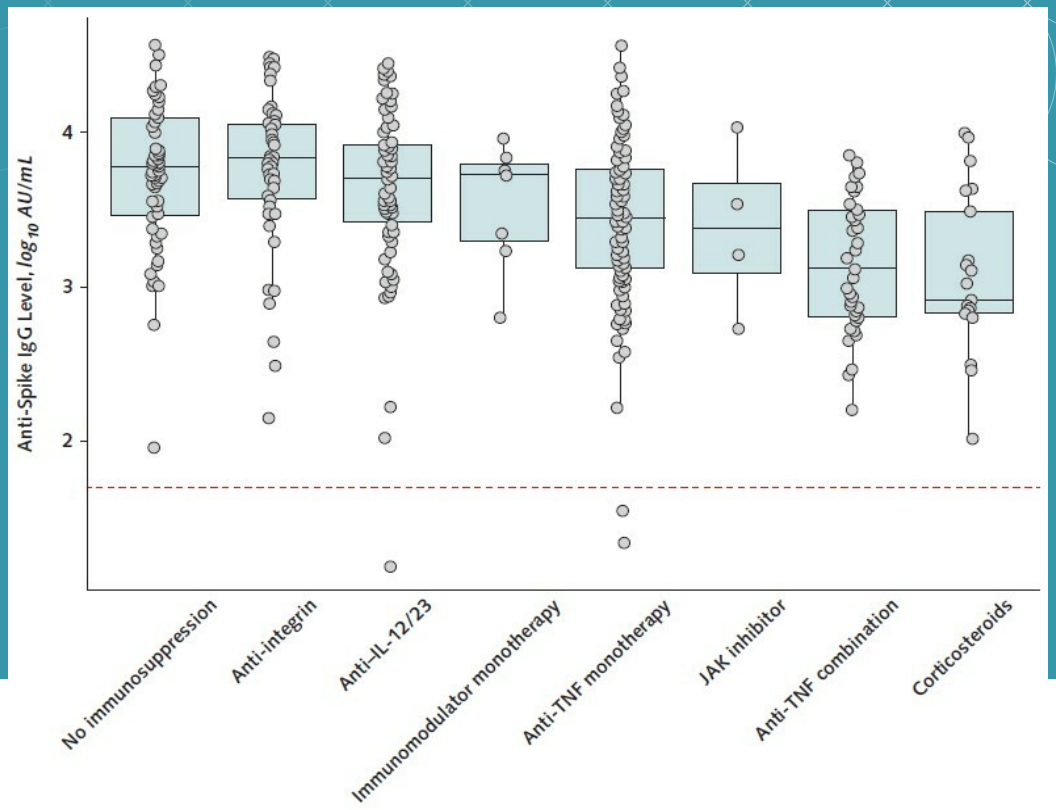
Melmed et al., Presented at DDW May 2022

# Robust Antibody Responses after mRNA vaccination in IBD

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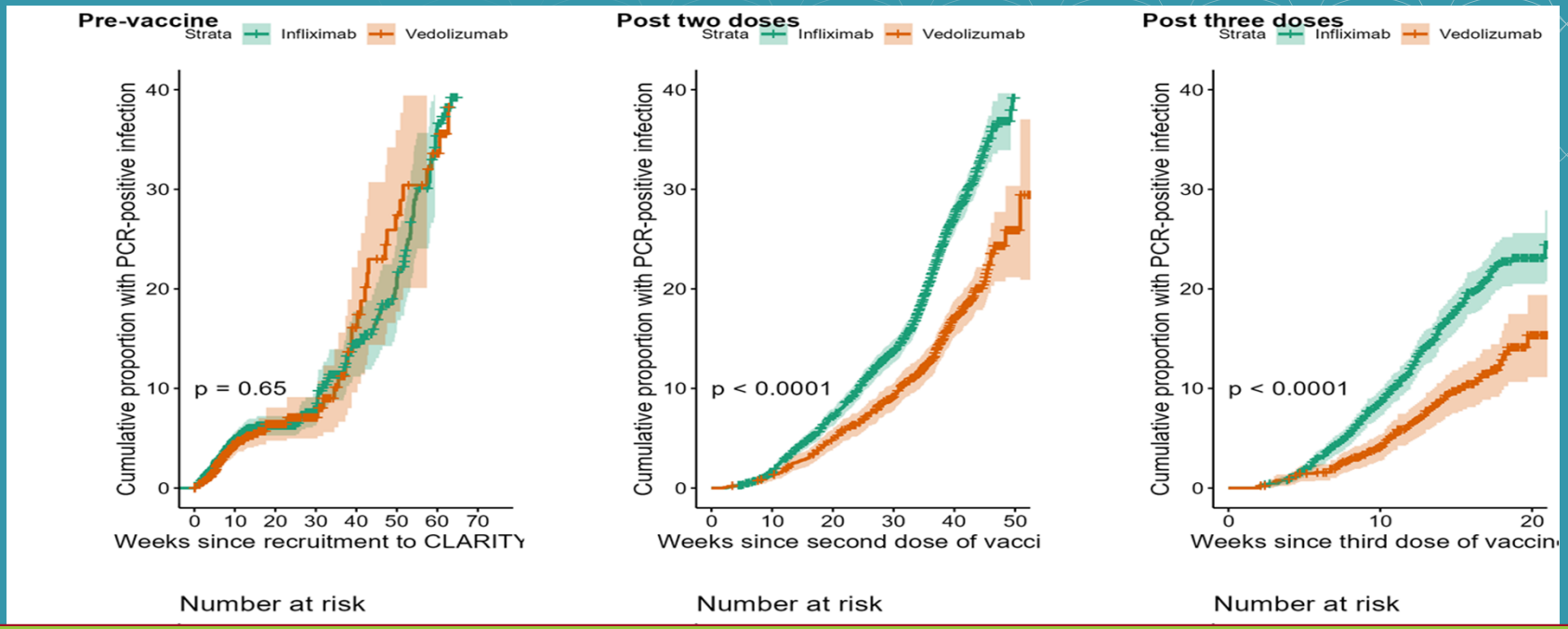
Melmed, Botwin, Sobhani, Li, Prostko, Figueiredo, Cheng, Braun, McGovern. *Annals Internal Medicine*. (Oct, 2021)

# Time to PCR-confirmed SARS-CoV-2 breakthrough infection after 2&3 doses is shorter in infliximab-treated patients




**Anti-S antibody concentration is not associated with shorter time to breakthrough infection**

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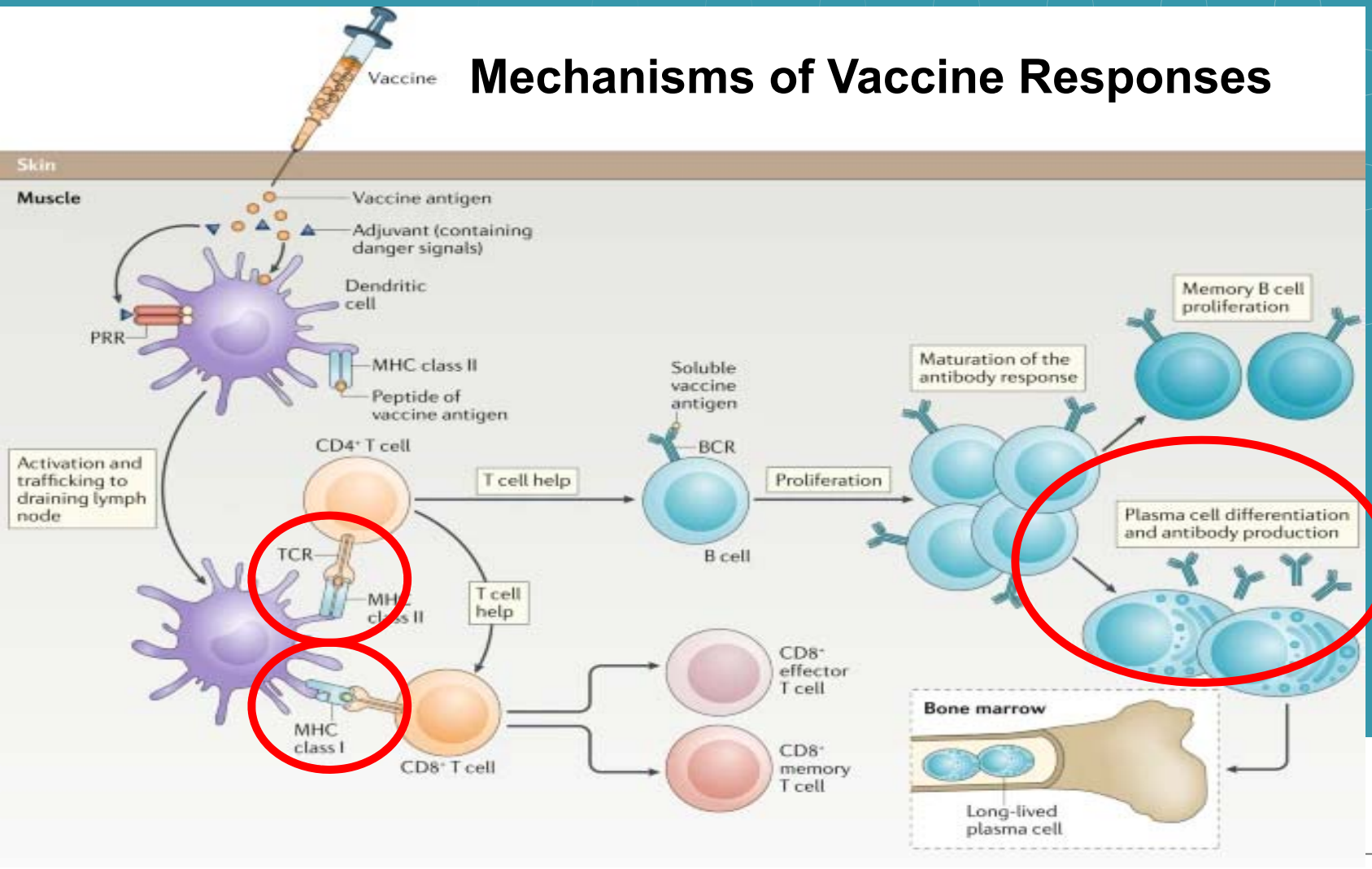
CLARITY study unpublished presented at British Society of Gastro

# Mechanisms of Vaccine Responses




Immune Responses
- Long term
  - Memory B Cells
  - T cells
- Factors
  - Demographics
  - Prior COVID
  - ? Medications

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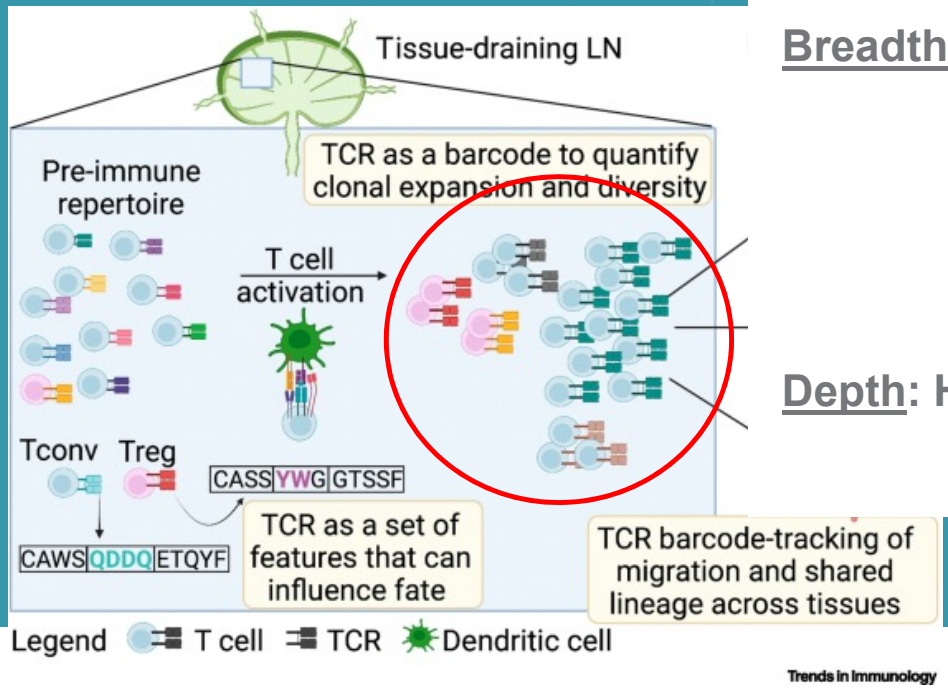
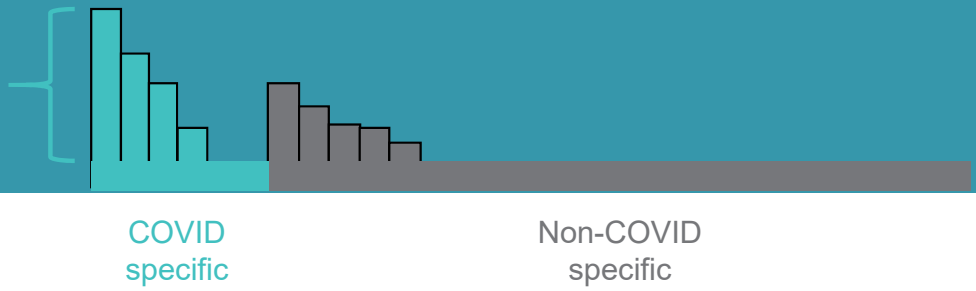
Pollard and Bijker. A Guide to Vaccinology. Nature Rev Imm Dec 2020

# T-Cell clonal expansion – Breadth and Depth




**Breadth**: How many **unique** specific clones are there?


**Depth**: How expanded are the specific clones?





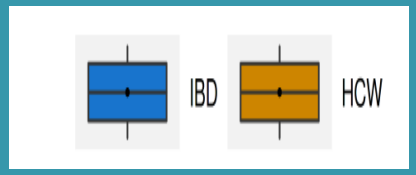

Pauken et al. TCR sequencing: Barcodes and Beyond. Trends in Immunology. March 2022

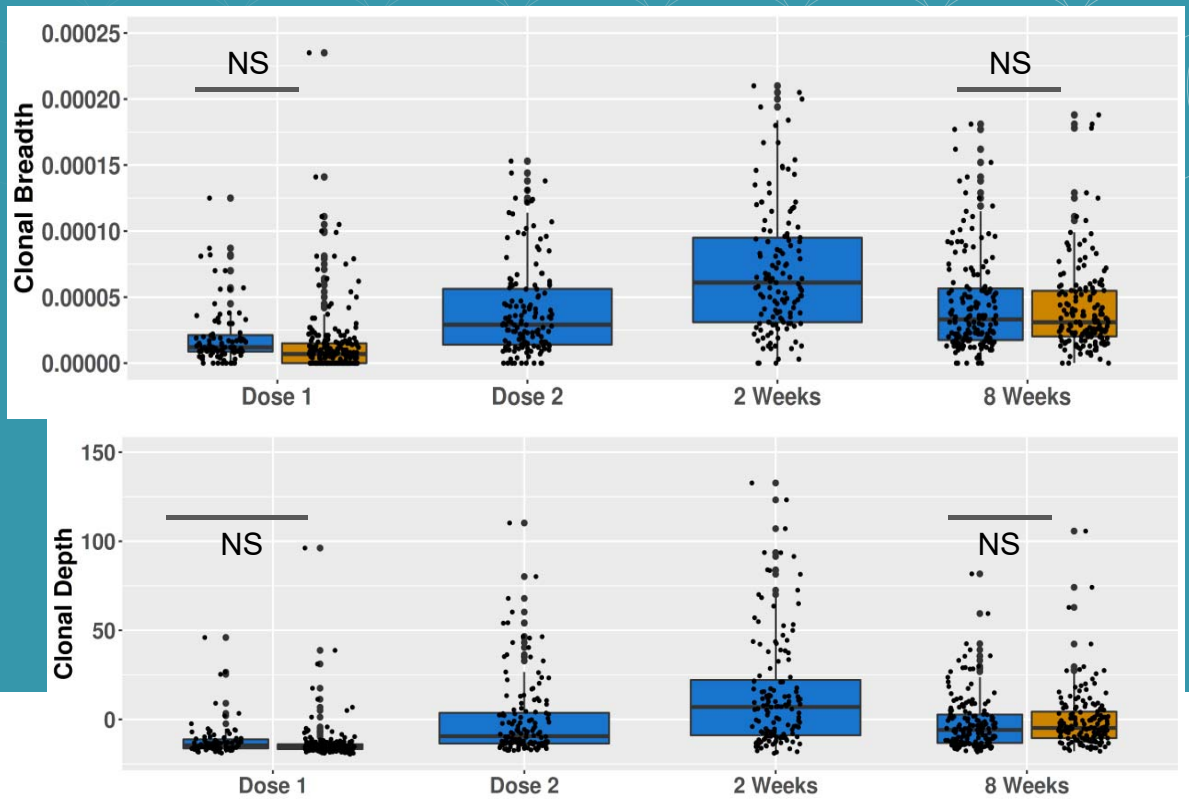
# No Difference in TCR breadth and depth between IBD and HCW

*8 weeks:*

*N=163 (IBD)*

*158 (HCW)*

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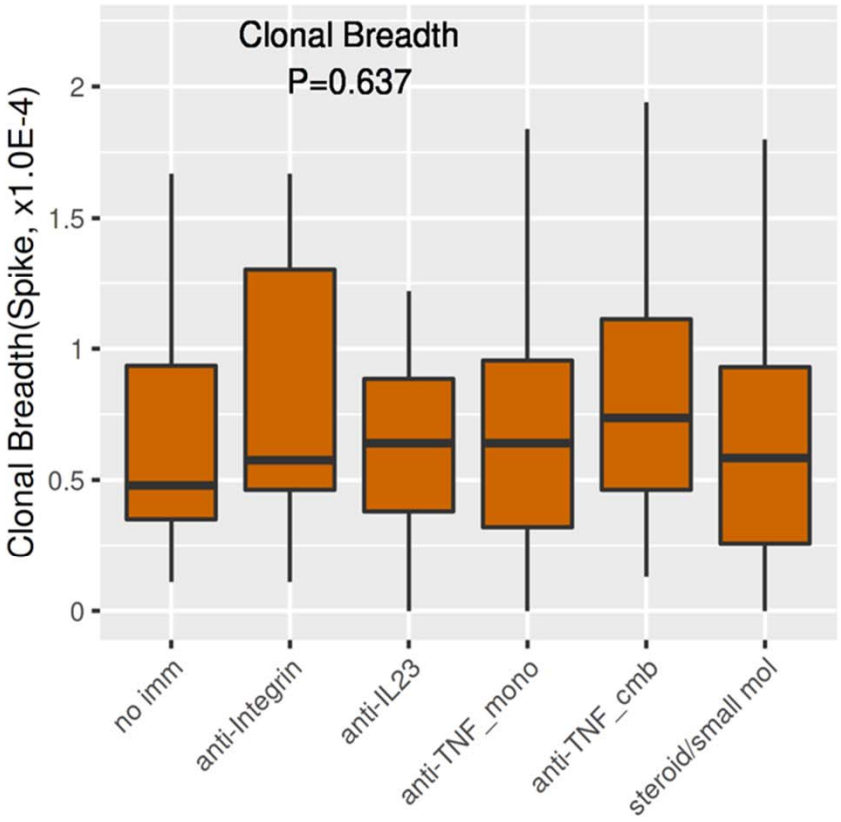
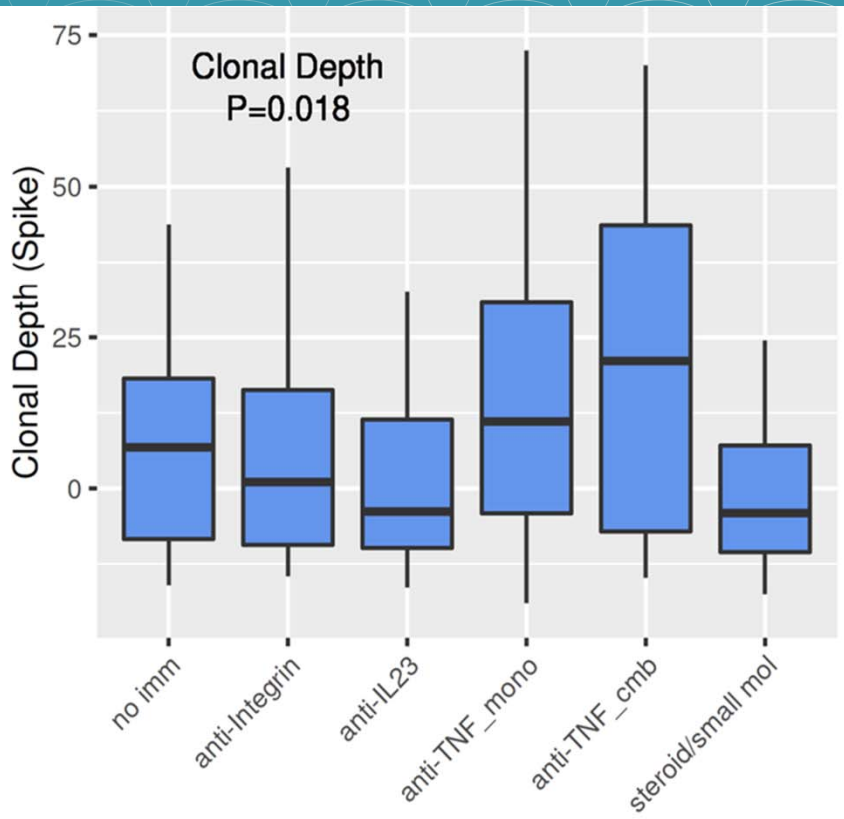
Melmed et al; Presented at DDW, May 2022

# Anti-TNF treatment is associated with clonal depth

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Melmed et al; Presented at DDW, May 2022

## Summary

- Vaccines protect against symptomatic disease, hospitalizations and death in IBD patients. However not all patients are vaccinated.
- anti-TNFs are associated with attenuated antibody responses, breakthrough and re-infections. In the setting of novel VOCs, this might translate to an increased risk of COVID-19.
- In patients treated with anti-TNF therapy additional doses should be considered every 4 to 6 months.
- IBD patients do not show increased risk of adverse reactions to SARS-CoV2 vaccines (data not shown)

# It takes a village!

**Translational**
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**Dermot McGovern**
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# DISCLOSURES

•GYM has consulted for AbbVie, Arena Pharmaceuticals, Boehringer-Ingelheim, Bristol-Meyers Squibb/Celgene, Entasis, Janssen, Medtronic, Pfizer, Samsung Bioepis, Shionogi, Takeda, Techlab, and has received research funding from Pfizer for an unrelated investigator-initiated study.

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•DM: Bridge Biotherapeutics, Gilead, Palatin, Pfizer, Prometheus Biosciences, Prometheus Laboratories, Takeda.

•MC: Abbvie, Arena, Bristol-Meyers Squibb, Janssen, Medtronic, Pfizer, and Takeda.

•EC: Abbvie and Pfizer.

•DF: Pfizer.

•CH: Abbvie, Janssen and Pfizer.

•DL: Abbvie, Janssen and Takeda.

•RM: Abbvie, Pfizer, and Prometheus Bioscience.

•NP: Pfizer.

•DW: Abbvie, Arena, Bristol Meyers Squibb, Corevitas, Janssen, Lilly, Pfizer, and Takeda.

•BM: Abbvie, Bristol Myers Squibb, Janssen, Pfizer and Takeda.

•SG: Abbvie, Janssen, and Takeda.

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•GS: research funding for unrelated investigator study from Pfizer.

•SR: Prometheus Bioscience.