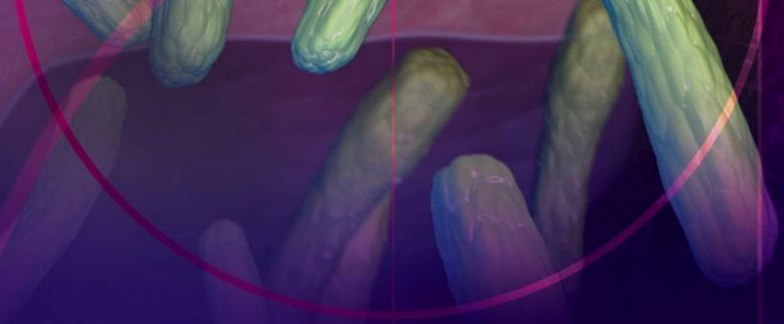

Vaccines for the Rheumatic Disease Patient

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Disclosures

- Research funding from Pfizer, BMS
- Scientific consultant work for Amgen, Abbvie, Pfizer, UCB, Genentech, BMS, Lilly
- Data safety monitoring boards for RCTs conducted by UCB, Roche, Astellas, Lilly, Janssen, Galapagos, Sanofi, Regeneron

Vaccine Development

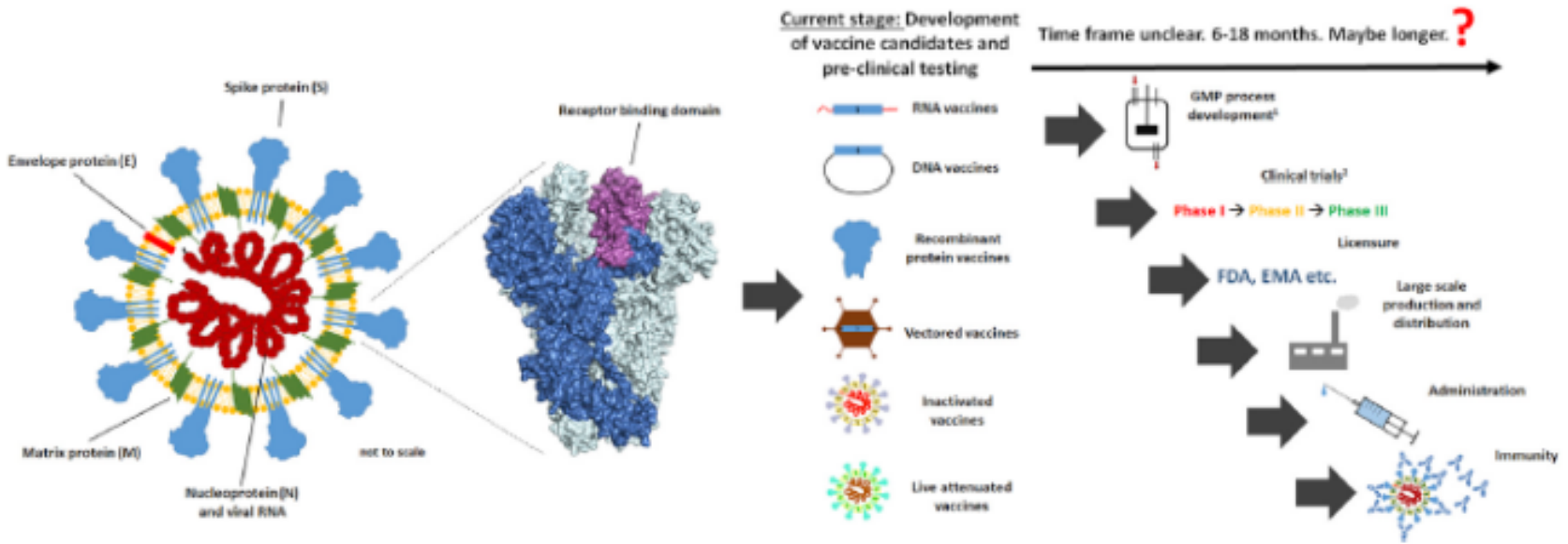


Figure 1. Overview of Potential SARS-CoV-2 Vaccine Platforms

The structure of a coronavirus particle is depicted on the left, with the different viral proteins indicated. The S protein is the major target for vaccine development. The spike structure shown is based on the trimeric SARS-CoV-1 spike (PDB: 5XL3). One trimer is shown in dark blue, and the receptor binding domain, a main target of neutralizing antibodies, is highlighted in purple. The other two trimers are shown in light blue. SARS-CoV-2 vaccine candidates based on different vaccine platforms have been developed, and for some of them, pre-clinical experiments have been initiated. For one mRNA-based candidate, a clinical trial recently started to enroll volunteers shortly (ClinicalTrials.gov: NCT04283461). However, many additional steps are needed before these vaccines can be used in the population, and this process might take months, if not years. [1]For some candidates, cGMP processes have already been established. [2]Clinical trial design might be altered to move vaccines through clinical testing quicker.

Amanat F et al. Immunity 2020

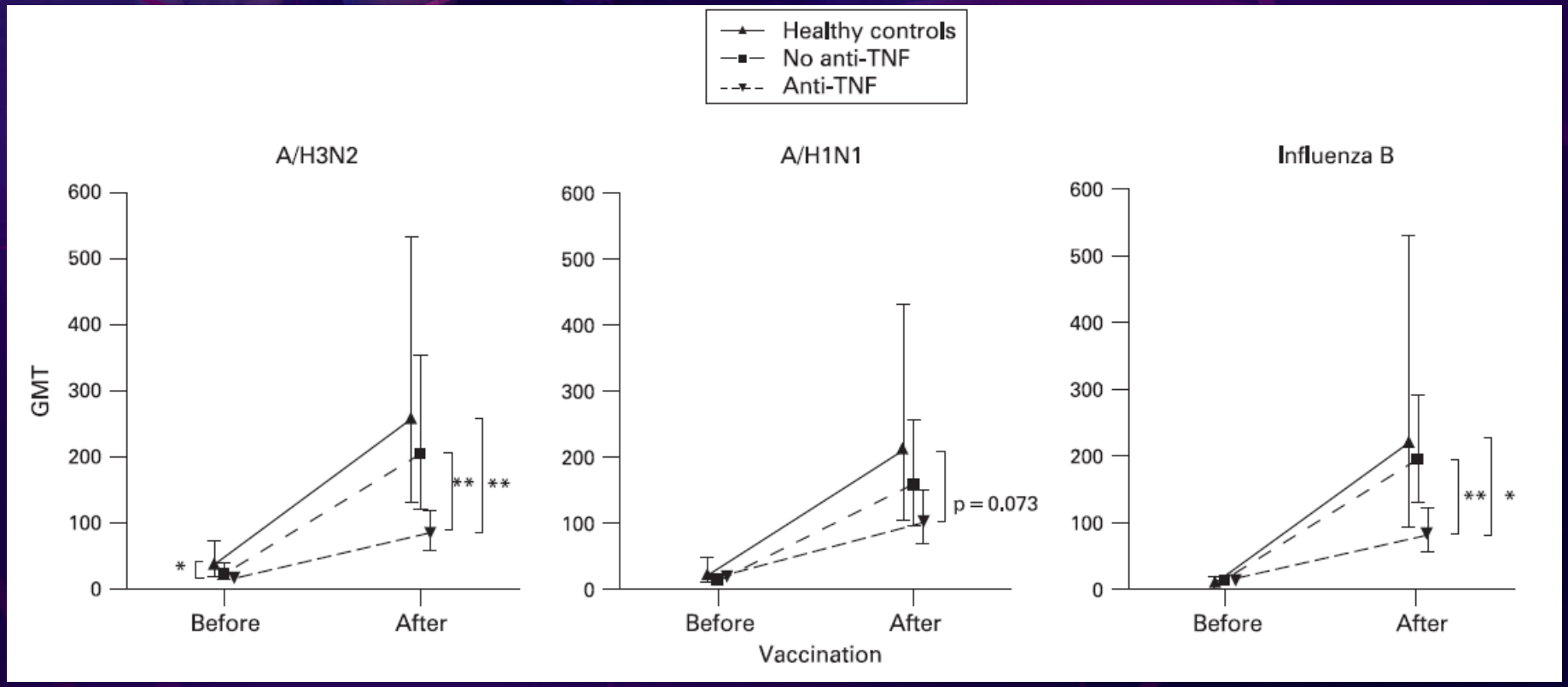
Table 1: Impact of disease modifying antirheumatic drugs on vaccine immunogenicity:

	Influenza	Pneumococcal	Herpes Zoster	Hepatitis B	Human papilloma virus	Tetanus	SARS-CoV-2 (mRNA)
Methotrexate	↓[14 22 24]	↓[49 50]	OK (ZVL)[51]		OK [113 128 129]	↓[117]	↓[78 80 81]
TNF-inhibitors	OK[14 16 20 27 28]	OK[14 55]	OK (ZVL) [60]	↓[99-101]	OK [113 128]	OK[117 120*]	OK [80 81 84]
Rituximab	↓↓[14-17 19-21 24 130]	↓↓[14 18 44-46]	OK T-cell response (RZV)[61]			↓[18 117]	↓↓[77 78-80]
Abatacept	↓[24 26]	↓[44 45]				OK (SQ) [118] ↓(IV)[119]	↓[80]
JAK-inhibitor	OK[30]	↓[30]				OK (tofacitinib)[116] ↓(baricitinib)[52]	↓[78 80]
IL-6R inhibitor	OK[31]	OK[31]				OK[121]	OK[80]
IL-12/23 inhibitor	OK[32]	OK[53]		↓[101]		OK[53]	OK [78]
IL-17 inhibitor	OK[33-35]	OK[54]				OK[54]	OK[80]

OK: No significant/meaningful effect on vaccine immunogenicity (may include reduction in absolute post-vaccination titers if rates of protective titers are unchanged.) ↓: Reduces vaccine immunogenicity. ↓↓: Significantly reduces vaccine immunogenicity. For OK, ↓, and ↓↓: if no control group is available, data are compared to expected vaccine responses in the general population.
Empty cells indicate a lack of data.
TNF = tumor necrosis factor, JAK = Janus kinase, IL = interleukin, ZVL = zoster vaccine live, RZV = recombinant zoster vaccine, SQ = subcutaneous

Friedman M et al. ARD In Press

Diminished quantitative responses with anti-TNF



- **Proportion reaching HI titer >1:40 was no different between groups**

Gelinck et al. *Ann Rheum Dis* 2008

Hepatitis B Vaccine (HBV)

Efficacy and safety of hepatitis B-vaccination in AIIRD-patients.

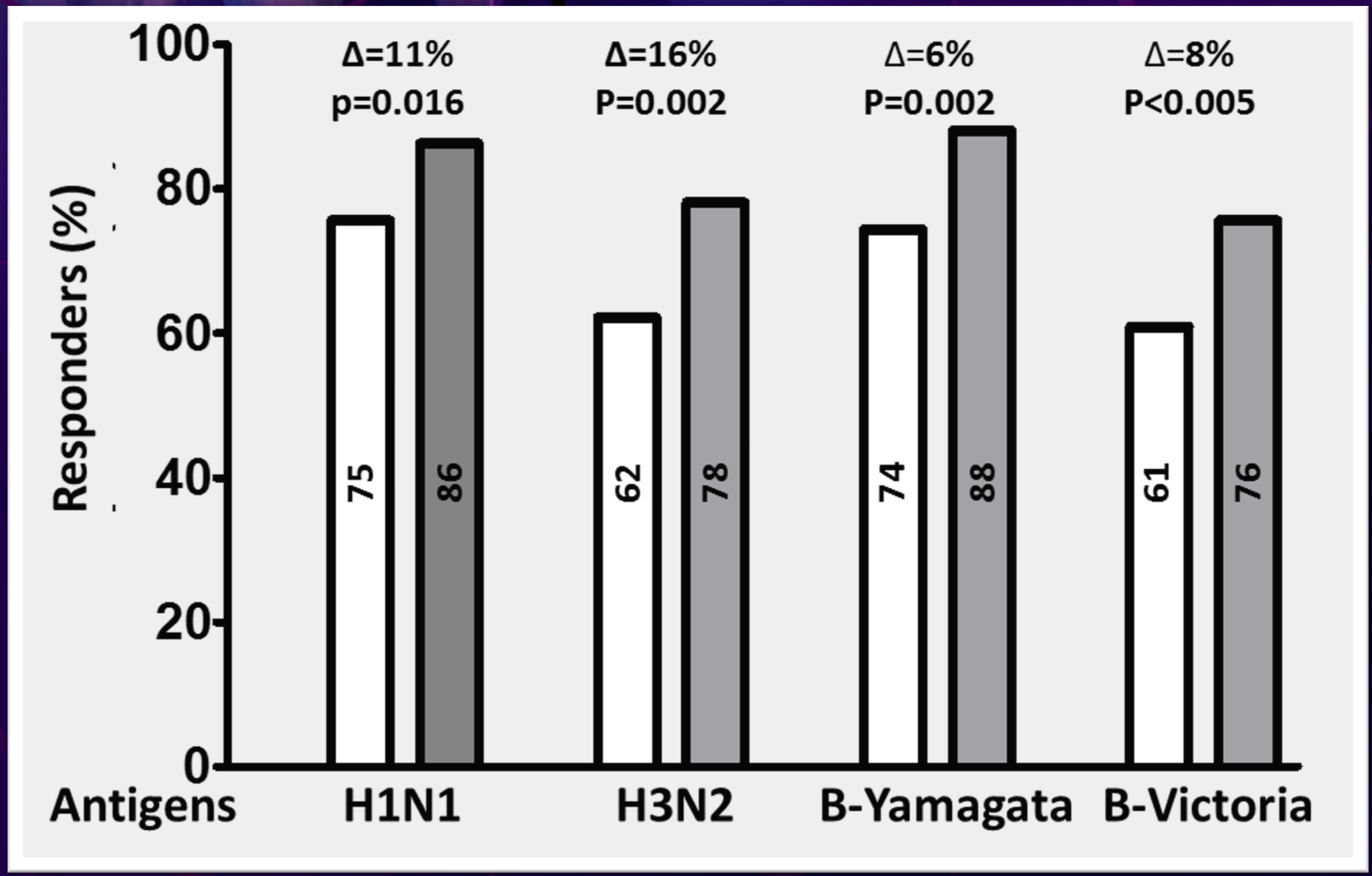
Hepatitis B vaccination						
Author	Year	Study design	No. cases	Efficacy	Influence of IS on efficacy	Safety
Elkayam [151]	2002	Controlled	22 RA 22 RA-DC	68% protection	No	No flares
Kuruma [152]	2007	Uncontrolled	28 SLE	93% protection	NA	11% flares
Franco Salinas [148]	2009	Controlled	20 SpA-anti-TNF 10 SpA-DC	Reduced in SpA-anti-TNF	Reduced on anti-TNF	NA
Erkek [153]	2005	Controlled	13 Behçet 15 HC	No difference	NA	No

Abbreviations: IS: immunosuppressive drugs, LoE: level of evidence, HC: healthy controls, DC: disease-control, NA: not addressed.

- IBD literature with decreased responses in those on TNFi
  - Protein vaccine (T-cell dependent)
  - Older age problematic
- Double dose vaccine improves response rate

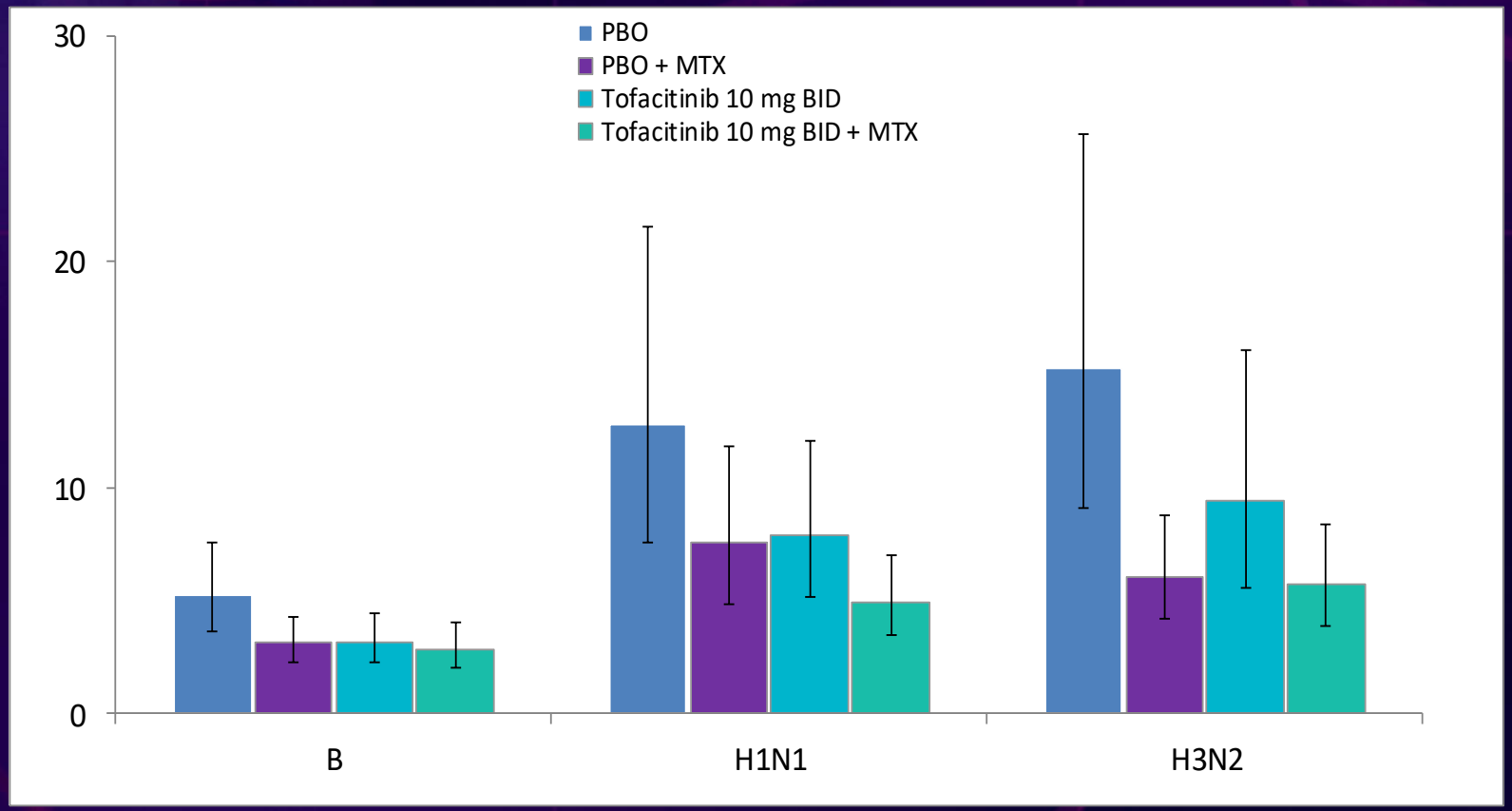
Van Assen et al. *Autoimmunity Reviews* 2011; Gisbert JP et al Ailment Pharmacol Ther 2012; Gisbert JP et al. Am J Gastro 2012

Holding MTX and Seroprotection



Park JW et al. ARD (In Press)

Tofacitinib and HI Titer Rise

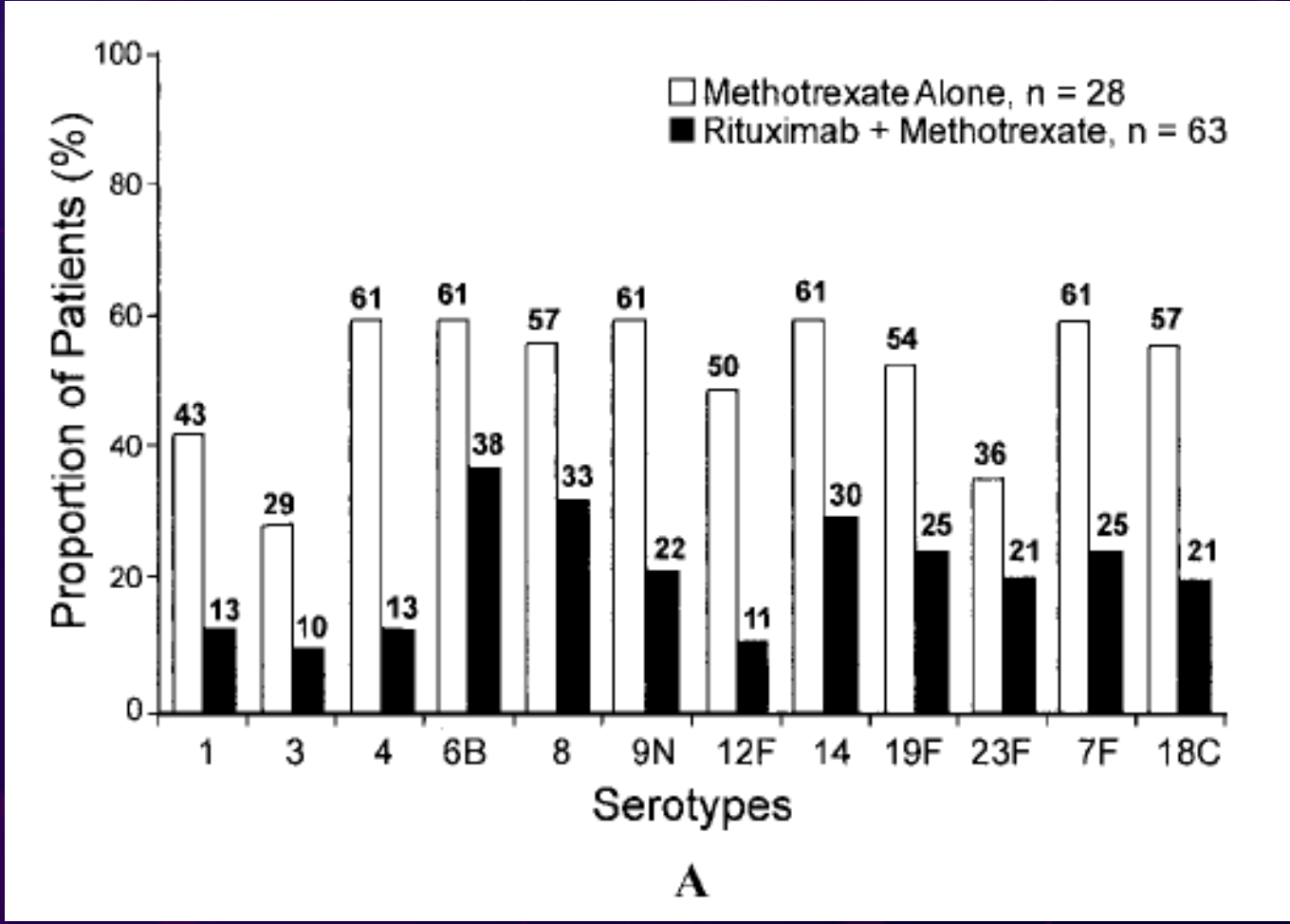


Influenza antibody GMFR 95% CI

Influenza vaccine serotype

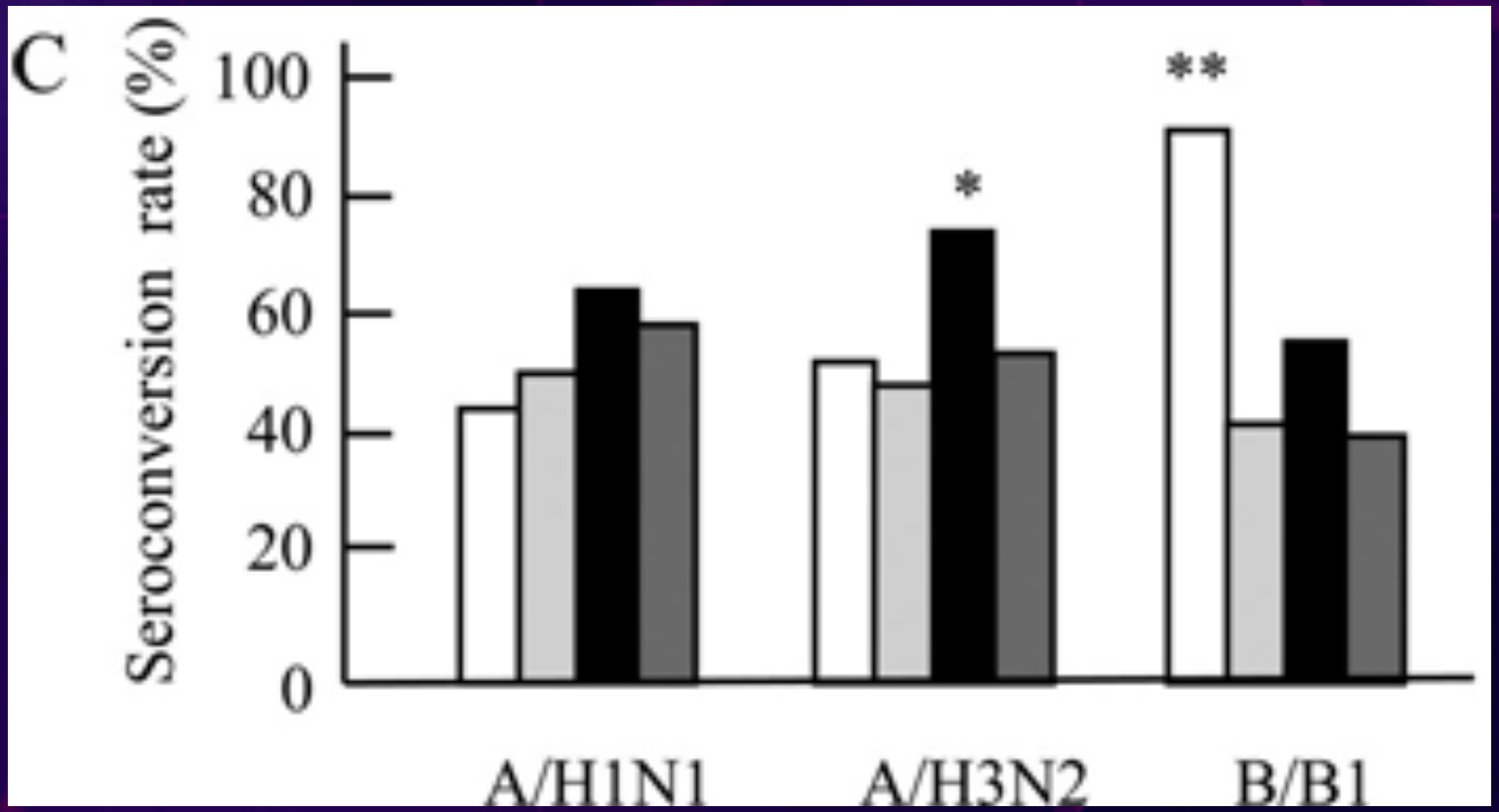
Winthrop K et al. ARD 2015

Diminished humoral responses to PPSV-23 with Rituximab



Bingham C. et al. Arthritis & Rheumatism 2010

Tocilizumab and Trivalent Influenza



Mori et al. *Ann Rheum Dis* 2012

Anti-IL-17 and influenza (Secukinumab in Healthy Controls)

TABLE 4 Proportion of subjects showing ≥4-fold increase in titer at 4 weeks after vaccination for meningitis and in at least 2 of 3 serotypes for influenza virus[a]

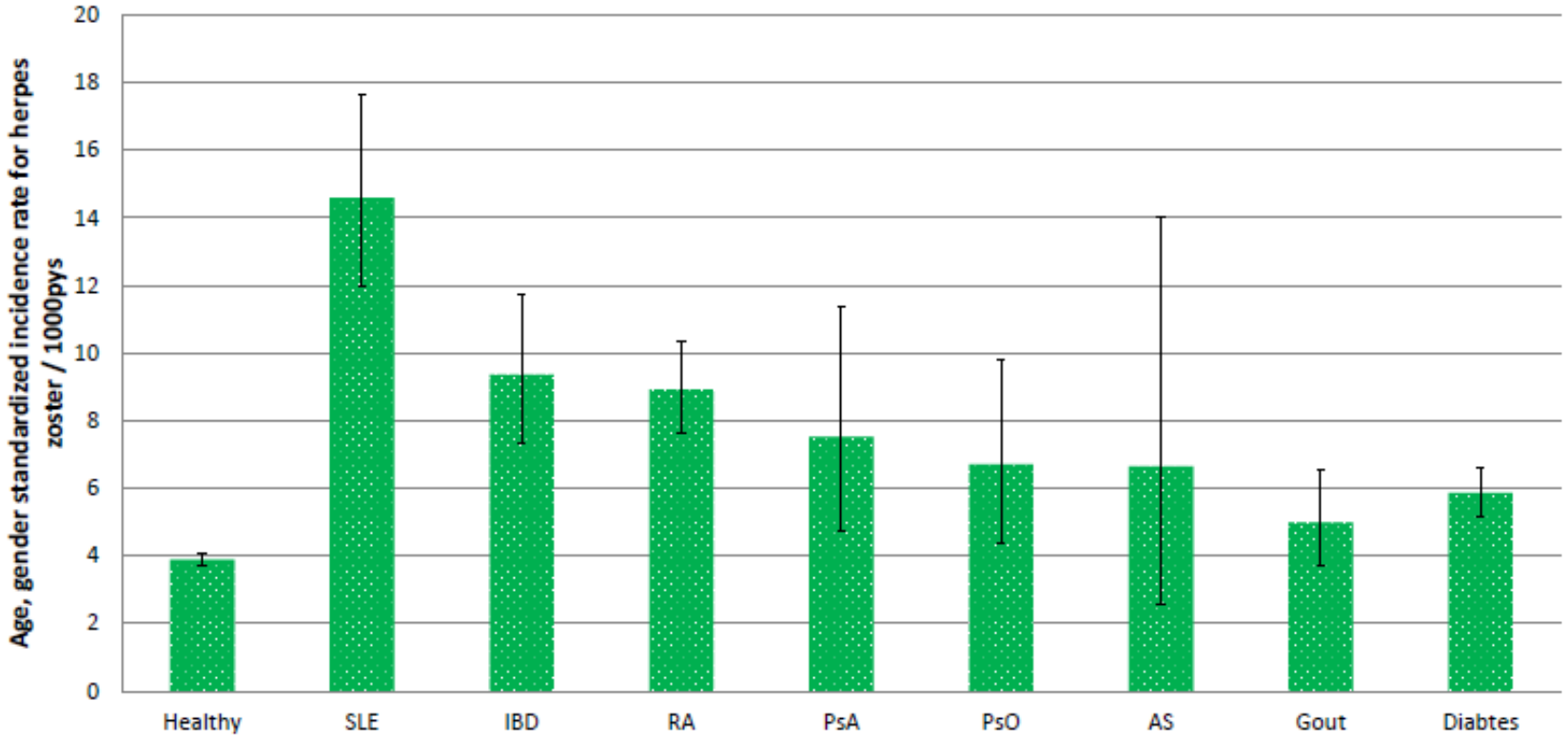
Vaccination	No. (%) of subjects showing ≥4-fold increase in titer		Difference in proportions (90% CI)
	Secukinumab ($n = 25$)	Control ($n = 25$)	
TIV	20 (80.0)	20 (80.0)	0.00 (−0.19, 0.19)
MenC	19 (76.0)	18 (72.0)	0.04 (−0.16, 0.24)

[a] CI, confidence interval; TIV, trivalent inactivated influenza vaccine.

Chioato A et al. Clin and Vacc Immunol 2012

Herpes Zoster (Shingles)

Figure: Age standardized incidence rate for herpes zoster per 1000pys (standardized to the U.S. 2010 census)



Curtis J et al, EULAR abstract 2014

VERVE Trial

- All active anti-TNF users (most RA)
  - N=617
- 1:1 live shingles vaccine versus placebo
- Results
  - Immunogenicity diminished as expected
  - Safety---No cases of vaccine HZ in 42 days post-vaccination

Curtis J et al. Ann Int Met 2021

Table 2. GMFR in VZV-Specific IgG and IFNg levels from baseline at 6 weeks

		GMF Week 6 / Baseline	95% CI	Ratio Active / Placebo (95% CI)	p-value*
IgG	Active (262)	1.33	1.18, 1.51	1.31 (1.11, 1.55)	0.0017
	Placebo (278)	1.02	0.91, 1.14		
IFNg	Active (266)	1.49	1.14, 1.94	1.30 (0.90, 1.90)	0.16
	Placebo (280)	1.14	0.87, 1.48		

Two-Group t-test, using Satterthwaite method allowing for unequal coefficient of variation
y treatment arms.

GMFR= geometric mean fold rise; VZV = varicella zoster virus; IgG = immunoglobulin; IFNg
= interferon gamma; CI = confidence interval

Curtis J et al. Ann Int Met 2021

Quillaja saponaria

1. Rationale

IMID patients / IMID treatments = higher risk of zoster
Recombinant Zoster Vaccine: available, high efficacy, new adjuvant
Adjuvant → **Theoretical risk of flares after vaccine**

Are rheumatology patients at **higher risk of flares** after RZV?

2. Study

Retrospective single-center study (Rheumatology, CCF, USA)
Inclusion: ≥1 RZV dose between Feb. 2018 and May 2020
Data extracted from Electronic Medical Records

- **Flares in the 12-week period after each dose? Risk factors?**
- **Adverse events? Zoster outbreak?**

3. Results

n=622 rheumatology patients
n=359 IMID patients

67% female
Median age 67 yo
77% received 2 doses
8.7% adverse events
Median f/u = 36 weeks

Which IMID/treatment? Flared after RZV?

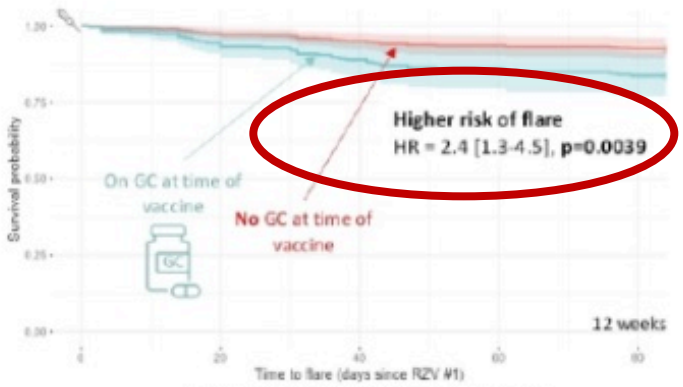
Description

IMID subgroups	Total from IMID (n=359)	On GC n=125 (35%)	≥1 Flare n=59 (16%)
RA	88 (25%)	37 (42%)	21 (24%)
Vasculitis	50 (14%)	23 (46%)	5 (10%)
PMR	29 (8%)	21 (72%)	5 (17%)
Gout	28 (8%)	3 (11%)	5 (18%)
SLE	24 (7%)	10 (42%)	4 (17%)

Flares: n=59
A change in IS treatment was needed in 25%

Logistic regression

Risk factor	No flare (n=300)	Flare (n=59)	Univariate p-value	Multivariate OR [IC95]	p-value
RA	67 (22%)	21 (36%)	**0.030**	1.57 [0.8-3]	0.173
GC	31%	53%	**0.002**	2.31 [1.3-4]	**0.004**
Jak-i	4%	10%	**0.032**	2.09 [0.6-6]	0.203



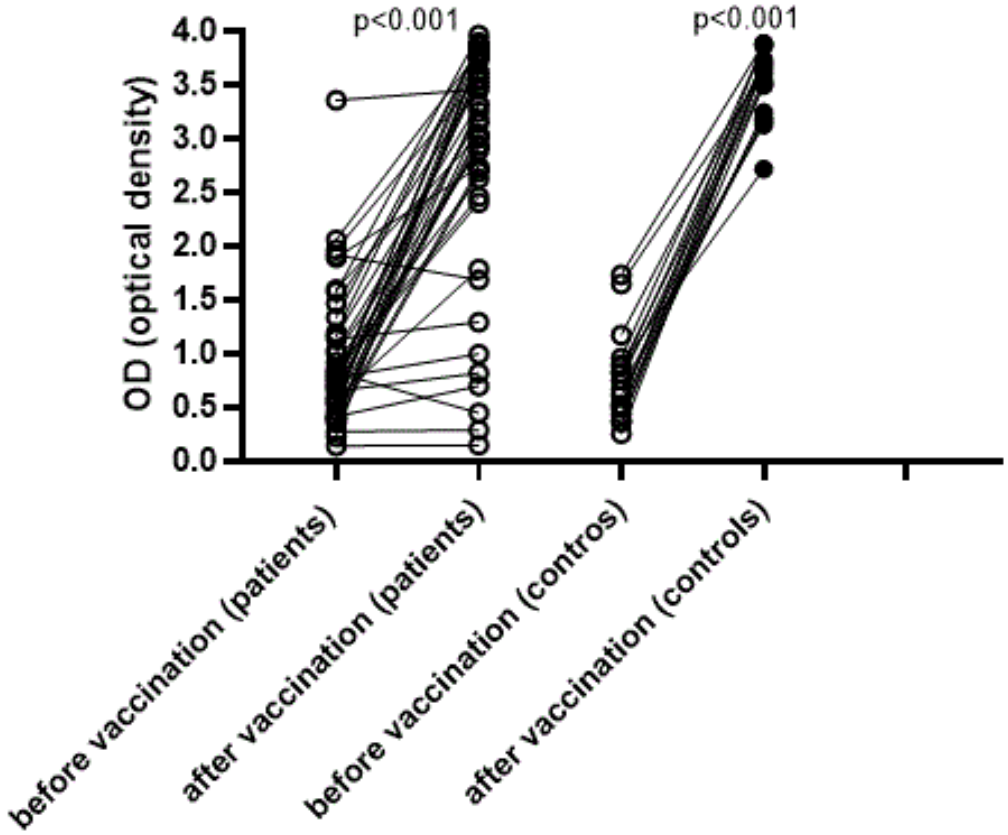
Survival analysis (multivariate Cox-model)

Key messages

- ✓ RZV appears safe in IMID patients
- ✓ GC at time of vaccine = higher risk of flare
- ✓ Patient + Provider discussion
- ✓ Informed consent
- ✓ Benefits / Risks Balance

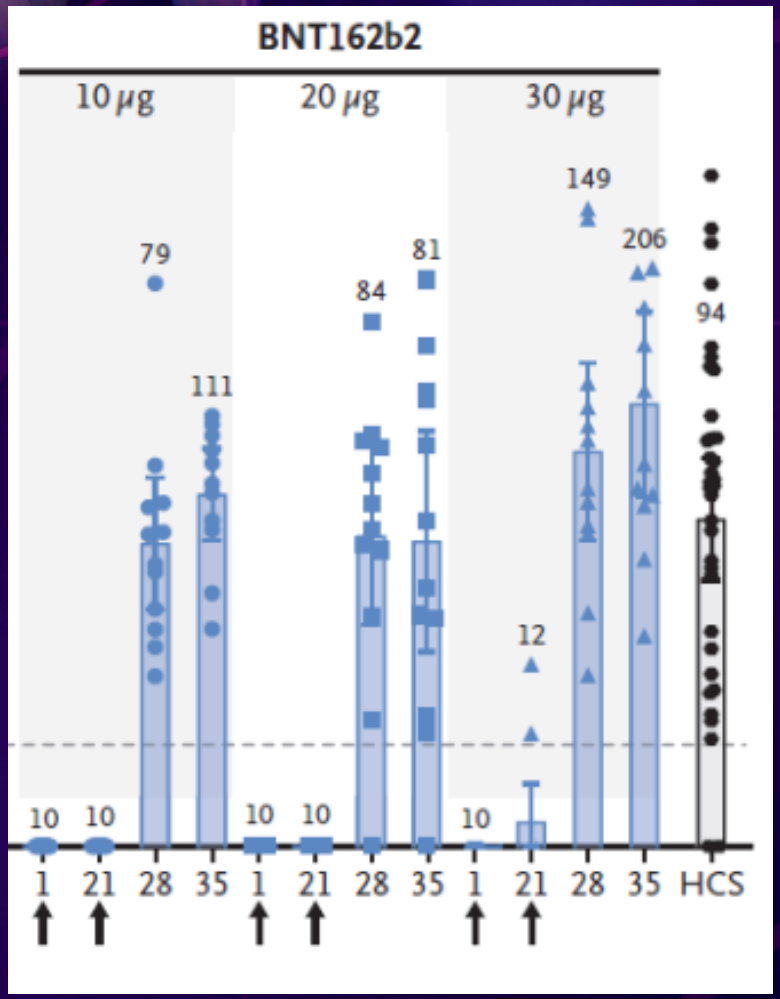
Lenfant T t al. Rheum 2021

Optical density before and after vacciantion with subunit herpes zoster vaccine in sera of patients with rheumatoid arthritis treated with JAK-inhibitors and healthy controls



Källmark H et al. ACR abstract 2020

Pfizer mRNA vaccine (BNT162b2)

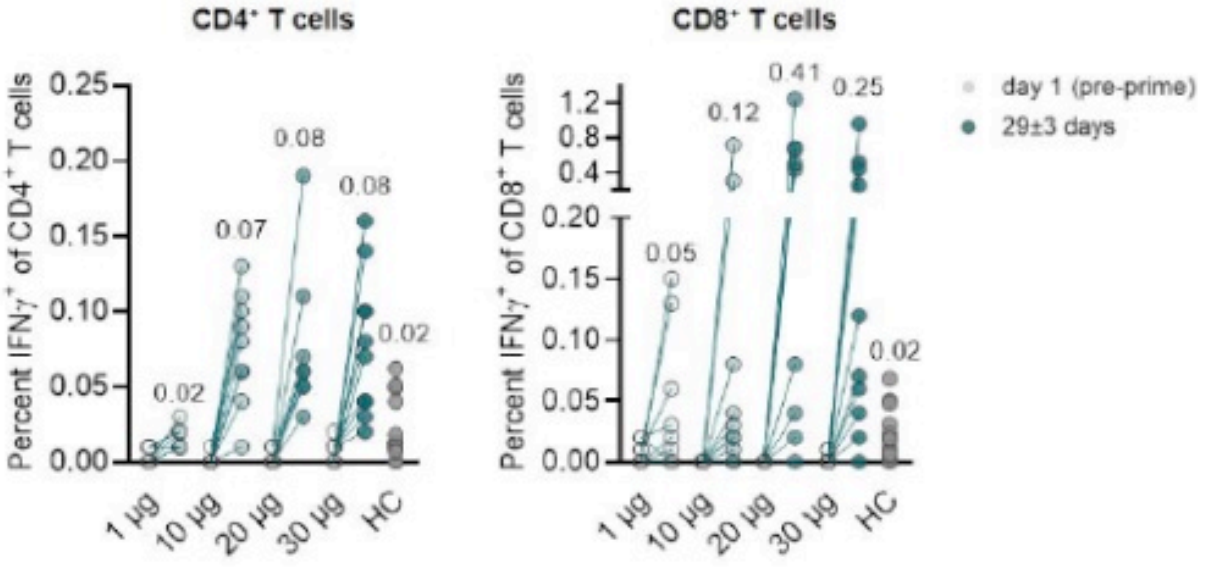


65-85 years old

Walsh E et al NEJM 2020

Cell-mediated Responses

Figure 2. Frequency and Magnitude of BNT162b2-induced CD4⁺ and CD8⁺ T Cell Responses



PBMCs of BNT162b2-immunized participants were obtained on Day 1 (pre-prime) and on Day 29 (7 days post dose 2) (cohorts 1 µg, n=8; 10 and 30 µg, n=10; 20 µg, n=9) and COVID-19-recovered human convalescent donors (HC, n=18) were stimulated overnight with an overlapping peptide pool representing the N-terminal portion of the wild-type sequence of SARS-CoV-2 S protein (S pool 1 [aa 1-643]) and were analyzed by intracellular cytokine staining flow cytometry analysis. Frequency of S-specific CD4+ and CD8+ T cells producing IFNγ in response to S pool 1 as a fraction of total circulating CD4 and CD8 T cells are shown. Numbers indicated in the graphs are the arithmetic mean fractions.

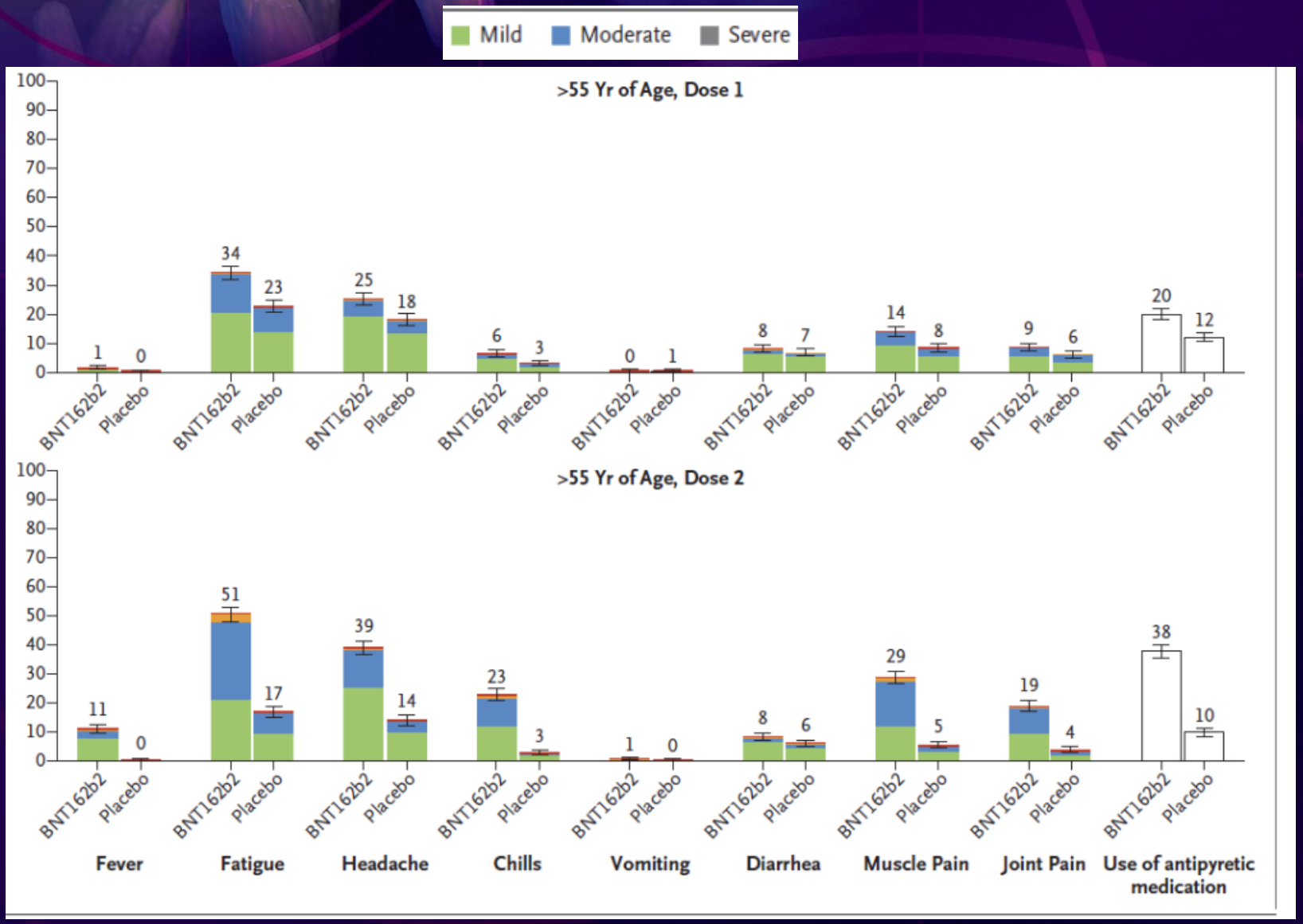
(https://www.fda.gov/media/144246/download).

Phase 3 "Data"

- Pfizer (BNT162b2) mRNA vaccine
  - 38,955 with two doses (21 days apart)
  - Interim analyses at 94 cases (of 164 anticipated) = 90% efficacy
- Moderna mRNA vaccine
  - 25,645 with two doses (28 days apart)
  - Interim analyses at 95 cases = 94% efficacy
- AZ adenoviral vaccine
  - UK trial with 2,700+ with two doses (28 days apart) of 12,000+ planned
  - Half dose/full dose (mistake) = 90% efficacy
  - 8,900 + vaccinated correctly in Brazil = 62% efficacy
  - US phase 3 interim results = 76% efficacy

https://www.idsociety.org/covid-19-real-time-learning-network/vaccines/vaccines/#Phase3

Pfizer mRNA vaccine (BNT162b2)



Polack F et al NEJM 2020

Chimp Adenoviral vaccine ChAdOx1 nCoV-19

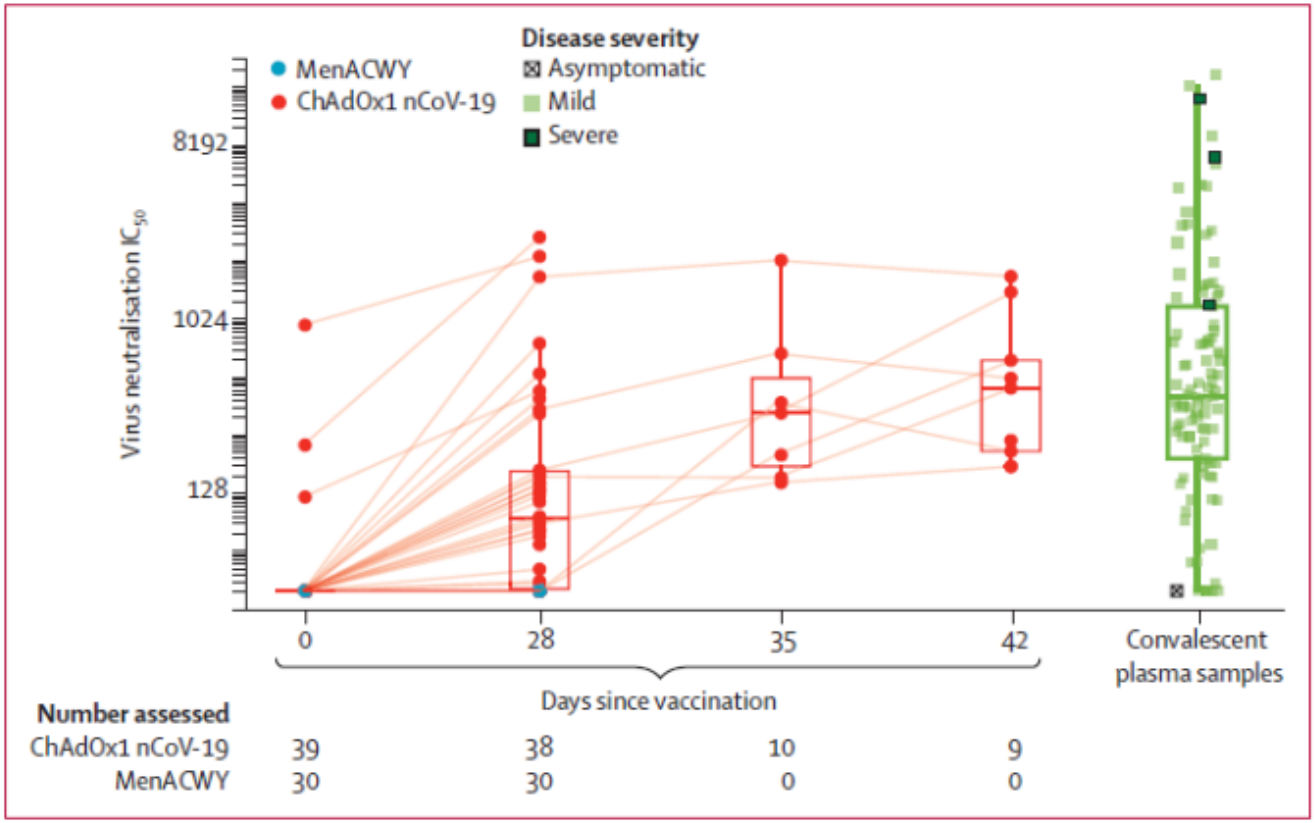


Figure 5: **PseudoNA results in trial participants and in convalescent plasma samples from 146 patients with PCR-confirmed COVID-19 and 24 asymptomatic health-care workers**

Solid lines connect samples from the same participant. Boxes show median (IQR). Results for days 35 and 42 are samples from participants who received a booster dose at day 28. IC=inhibitory concentration. MenACWY=meningococcal group A, C, W-135, and Y conjugate vaccine.

Folgatti P et al Lancet 2020

Chimp Adenoviral vaccine ChAdOx1 nCoV-19c

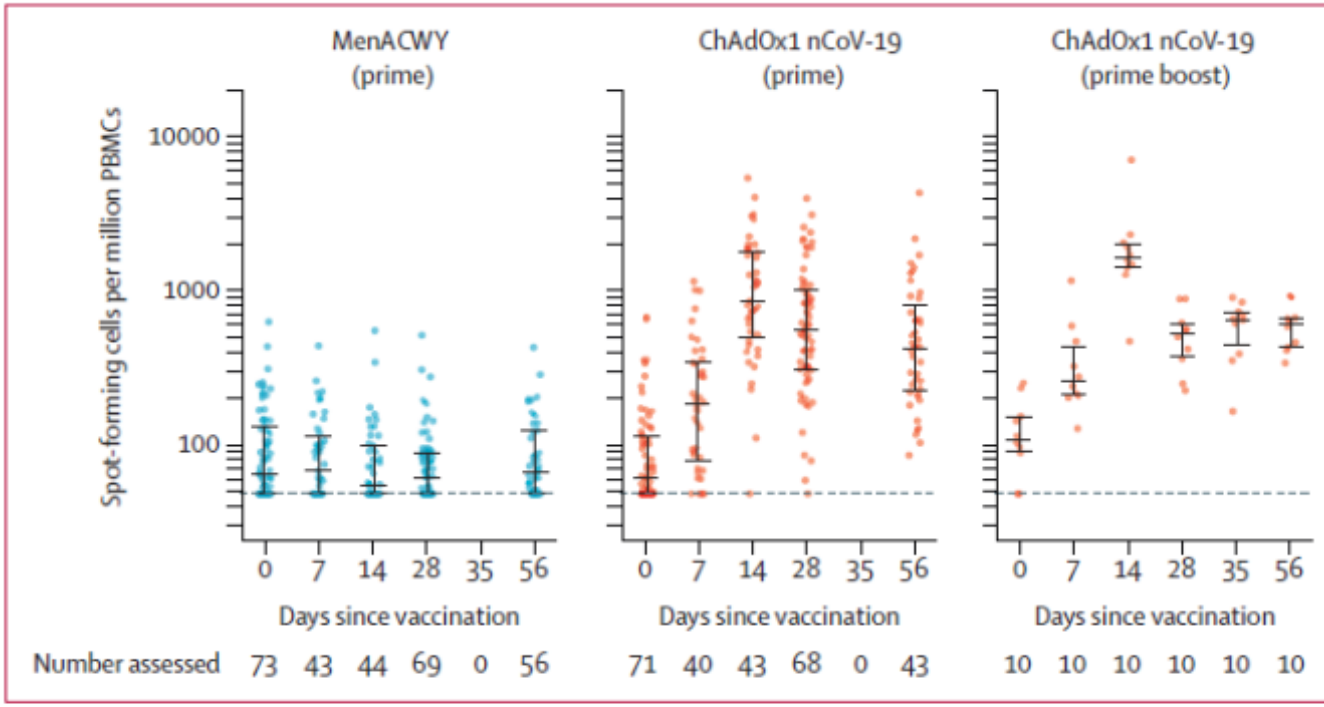
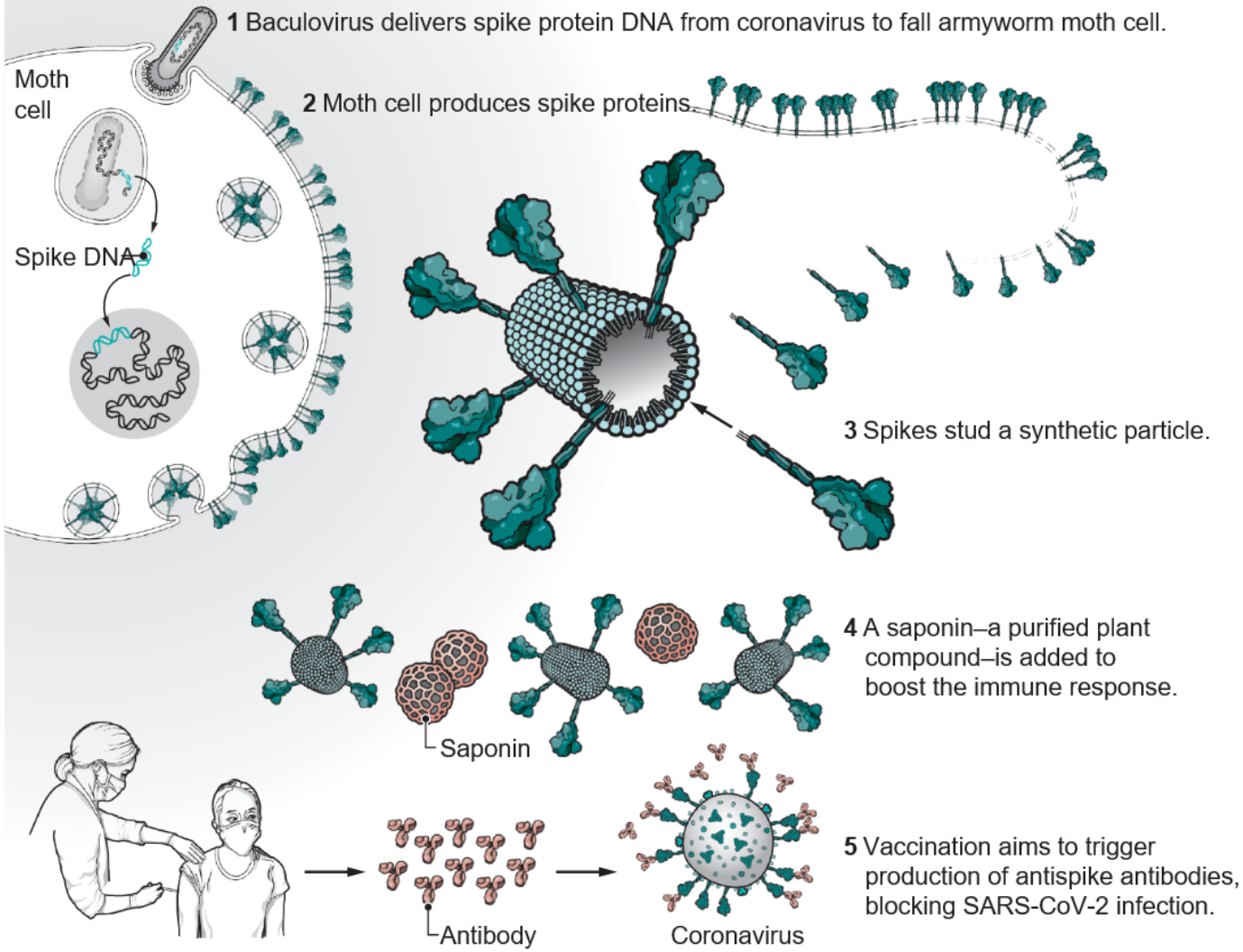


Figure 6: **Interferon-γ ELISpot response to peptides spanning the SARS-CoV-2 spike vaccine insert**
Error bars show median (IQR). The lower limit of detection, indicated with the dotted line, is 48 spot-forming cells per million PBMCs. PBMC=peripheral blood mononuclear cell. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. ELISpot=enzyme linked immunospot. MenACWY=meningococcal group A, C, W-135, and Y conjugate vaccine.

Folgatti P et al Lancet 2020

What Moth Cells are Good For?



https://www.sciencemag.org/news/2020/11/will-small-long-shot-us-company-end-producing-best-coronavirus-vaccine

Protein-based Vaccine (Saponin adjuvant)

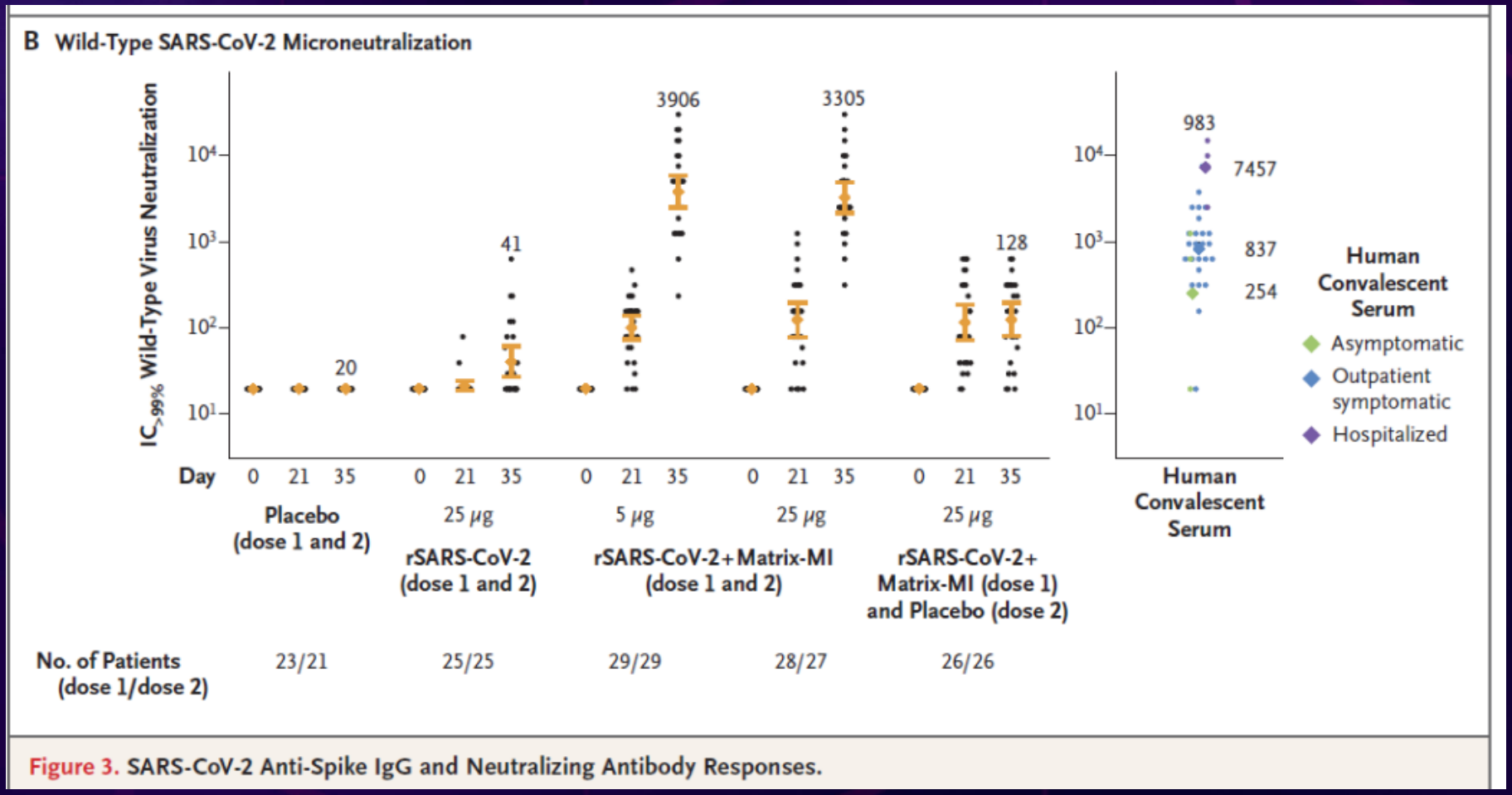


Figure 3. SARS-CoV-2 Anti-Spike IgG and Neutralizing Antibody Responses.

Polack F et al NEJM 2020

Phase 3 results

- **JnJ Adenoviral vaccine** (Ad26.COV2.S)
  - **One shot, no deep freeze**
  - **72% efficacy US, 57% S. Africa**
- **Novavax (NVX-CoV2373)**
  - **Protein conjugate, no deep freeze, two shot (21 days apart)**
  - **89% efficacy UK, 60% S. Africa**

Vaccine Induced Immune Thrombotic Thrombocytopenia

ORIGINAL ARTICLE

Pathologic Antibodies to Platelet Factor 4 after ChAdOx1 nCoV-19 Vaccination

Marie Scully, M.D., Deepak Singh, B.Sc., Robert Lown, M.D., Anthony Poles, M.D., Thomas Solomon, M.D., Marcel Levi, M.D., David Goldblatt, M.D., Ph.D., Pavel Kotoucek, M.D., William Thomas, M.D., and William Lester, M.D.

Risk 1/100,000 with AZ, mostly female, under age 60
Risk 1/1,000,000 with JnJ vaccine, female, young

Centers for Disease Control and Prevention

Clinical Considerations: Myocarditis and Pericarditis after Receipt of mRNA COVID-19 Vaccines Among Adolescents and Young Adults

- **393 cases in US in 306,000,000 doses**
  - **Mostly younger males**
  - **Almost all self-limited**
  - **Pericarditis also reported**

https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/adverse-events.html

Myocarditis/pericarditis incidence in VSD in 21-day risk interval, ages 16-39 years old (data thru May 29, 2021)

Vaccine(s) (dose #)	Cases	Doses admin	Rate per million doses (95% CI)
mRNA (both doses)	22	2,546,874	8.6 (5.4–13.1)
mRNA (dose 1)	4	1,428,872	2.8 (0.8–7.2)
mRNA (dose 2)	18	1,118,002	16.1 (9.5–25.4)
Pfizer-BioNTech (dose 1)	1	846,765	1.2 (0.0–6.6)
Pfizer-BioNTech (dose 2)	7	671,899	10.4 (4.2–21.5)
Moderna (dose 1)	3	582,107	5.2 (1.1–15.1)
Moderna (dose 2)	11	446,103	24.7 (12.3–44.1)

https://www.fda.gov/media/150054/download

COVAX EULAR

- 1,519 Rheumatic Disease Patients
  - 51% inflammatory joint disease
  - 36% taking biologics, MTX 29%
- 31% with reactogenicity within 7 days
  - 19% injection site pain, 11% fatigue, 7% HA
- Flares post-vaccination were rare
  - 5% flare (almost all were arthritis/arthralgia)
- 0.1% SAE

Ann Rheum Dis, volume 80, supplement 1, year 2021, page 19

HZ with COVID-19 and mRNA Vaccine

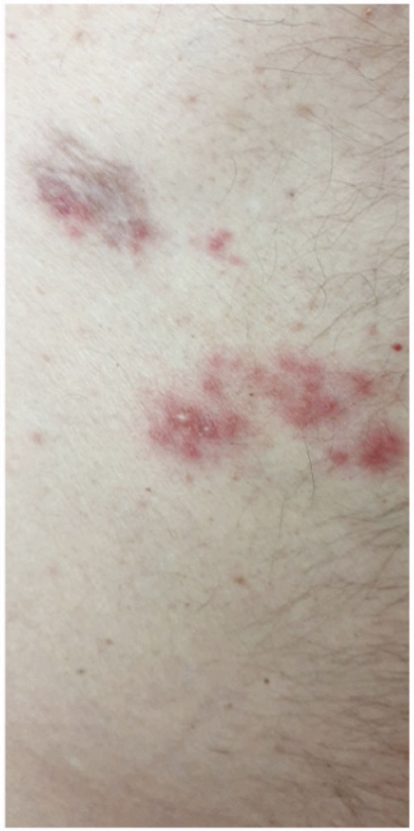


Figure 1 Grouped vesicles on the dorsum over an erythematous background

Methods:

The safety of the BNT162b2 mRNA vaccination was assessed in an observational study monitoring post-vaccination adverse effects in patients with AIIRD (n=491) and controls (n=99), conducted in two Rheumatology Departments in Israel.

Results:

The prevalence of HZ was 1.2% (n=6) in patients with AIIRD compared to none in controls. Six female patients aged 49±11 years with stable AIIRD: rheumatoid arthritis (n=4), Sjogren's syndrome (n=1), and undifferentiated connective disease (n=1), developed the first in a lifetime event of HZ within a short time after the first vaccine dose in 5 cases and after the second vaccine dose in one

Tartari F et a. Int J of Derm 2020; Furer V et al. Rheum 2021

Variant Strains

- B.1.1.7, UK (alpha)
- CAL.20C, California
- B.1.351 South Africa (beta)
- P1 Brazil (gamma)
- Many, many others
  - B.1.617.22 India (delta)

- More transmissible?
  - Escape Ab, vaccine, pcr tests?

Wibner KC et al. Med Rx 2021

Neutralizing activity of BNT162b2 against Variants

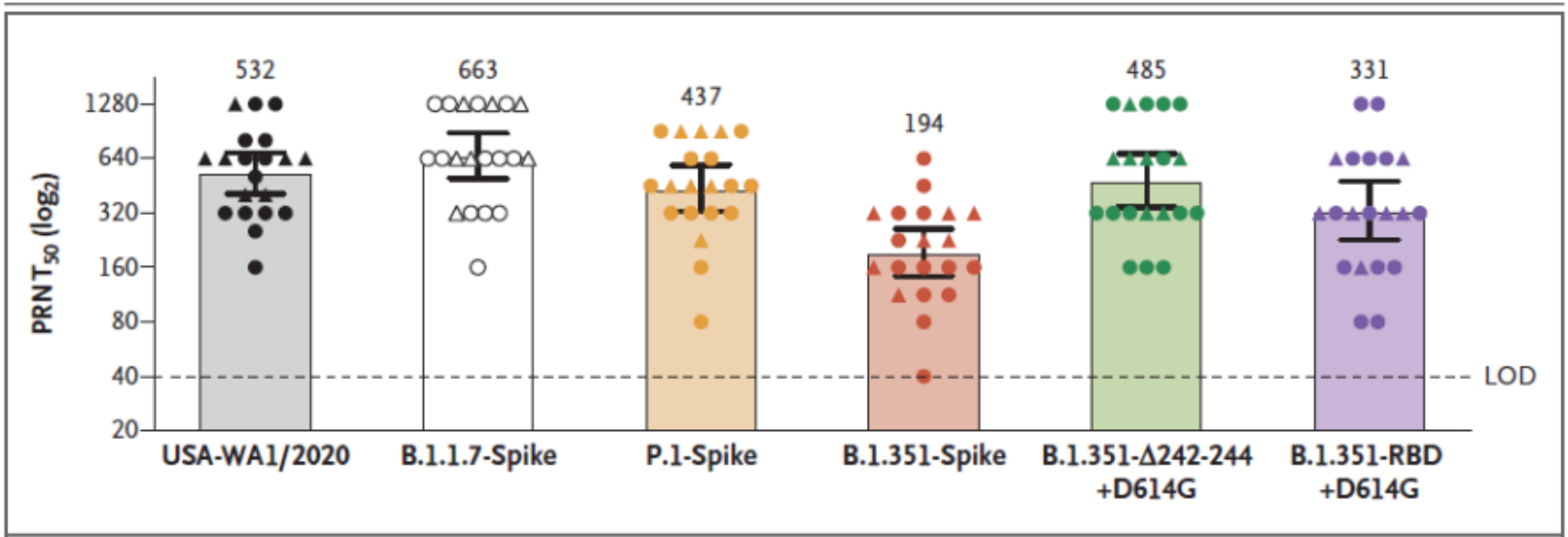
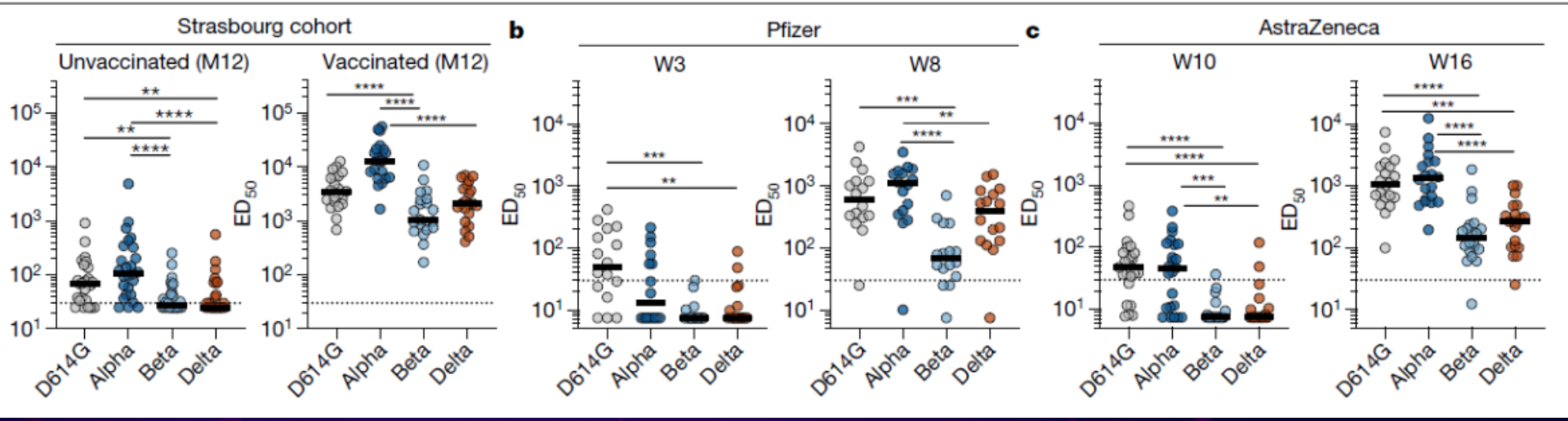


Figure 1. Serum Neutralization of Variant Strains of SARS-CoV-2 after the Second Dose of BNT162b2 Vaccine.

Liu Y et al. NEM 2021

Delta: Natural versus Vaccine



Planas D et al. Nature 2021

Monoclonals Vs Variants

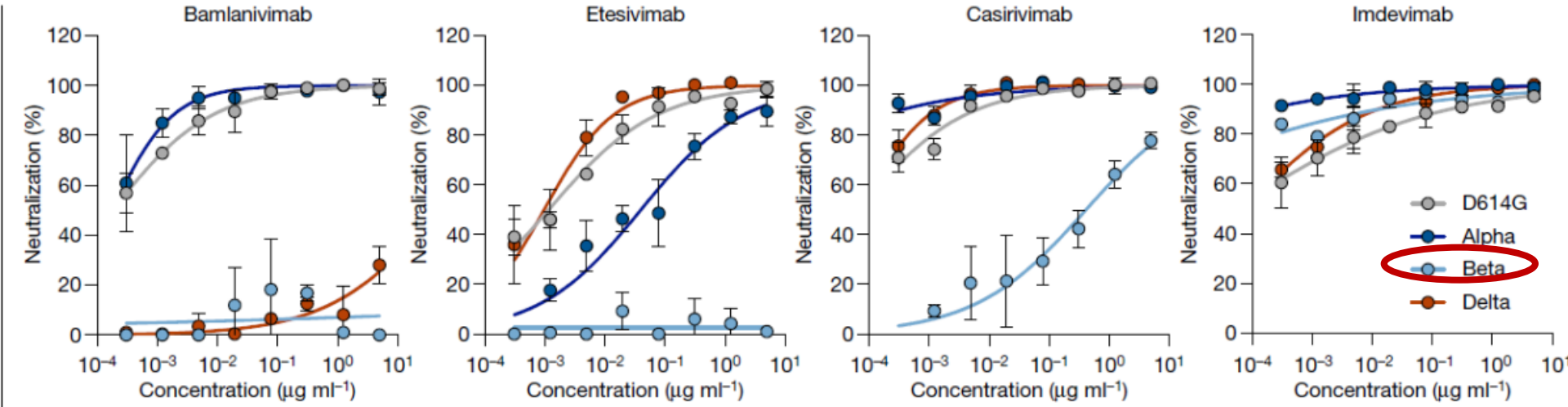


Fig. 1 | Neutralization of the SARS-CoV-2 variants D614G, Alpha, Beta and Delta by therapeutic monoclonal antibodies. Neutralization curves of monoclonal antibodies. Dose–response analysis of neutralization of the D614G strain and the Alpha, Beta and Delta variants by four therapeutic monoclonal antibodies (bamlanivimab, etesivimab, casirivimab and imdevimab). Data are mean ± s.d. of four independent experiments.

Planas D et al. Nature 2021

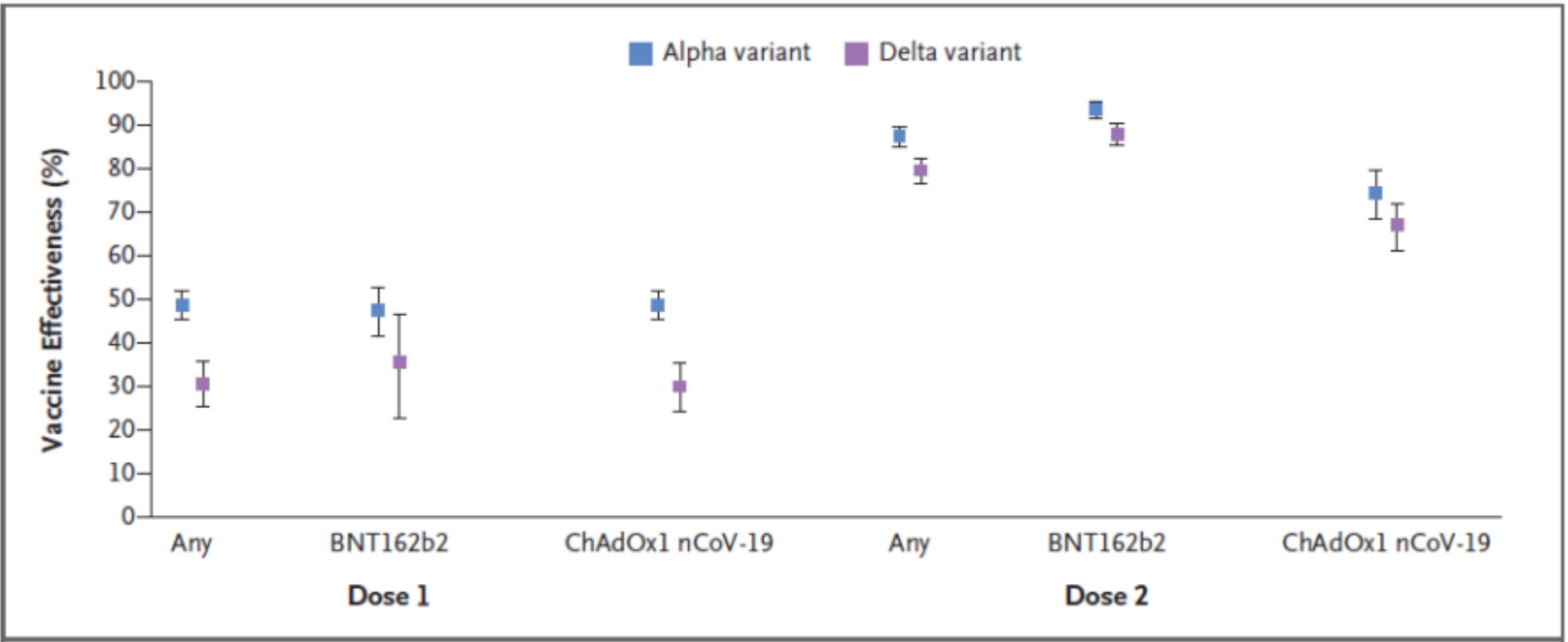


Figure 1. Vaccine Effectiveness against the Alpha and Delta Variants, According to Dose and Vaccine Type.

Shown is the effectiveness of one dose and two doses of the BNT162b2 and ChAdOx1 nCoV-19 vaccines, or either vaccine ("any"), against symptomatic disease with the B.1.1.7 (alpha) or B.1.617.2 (delta) variant of the severe acute respiratory syndrome coronavirus 2. I bars indicate 95% confidence intervals.

Bernal JL et al NEJM 2021

FIGURE 1. Whole genome sequencing lineage determination among adults hospitalized with COVID-19 — 21 academic medical centers in 18 states,*,† March–July 2021

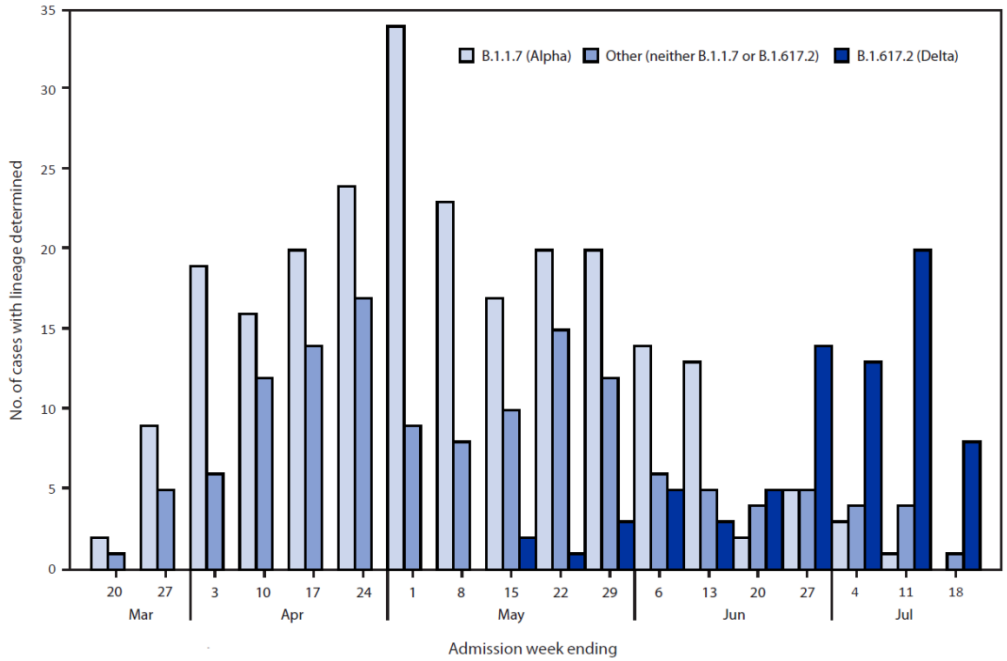
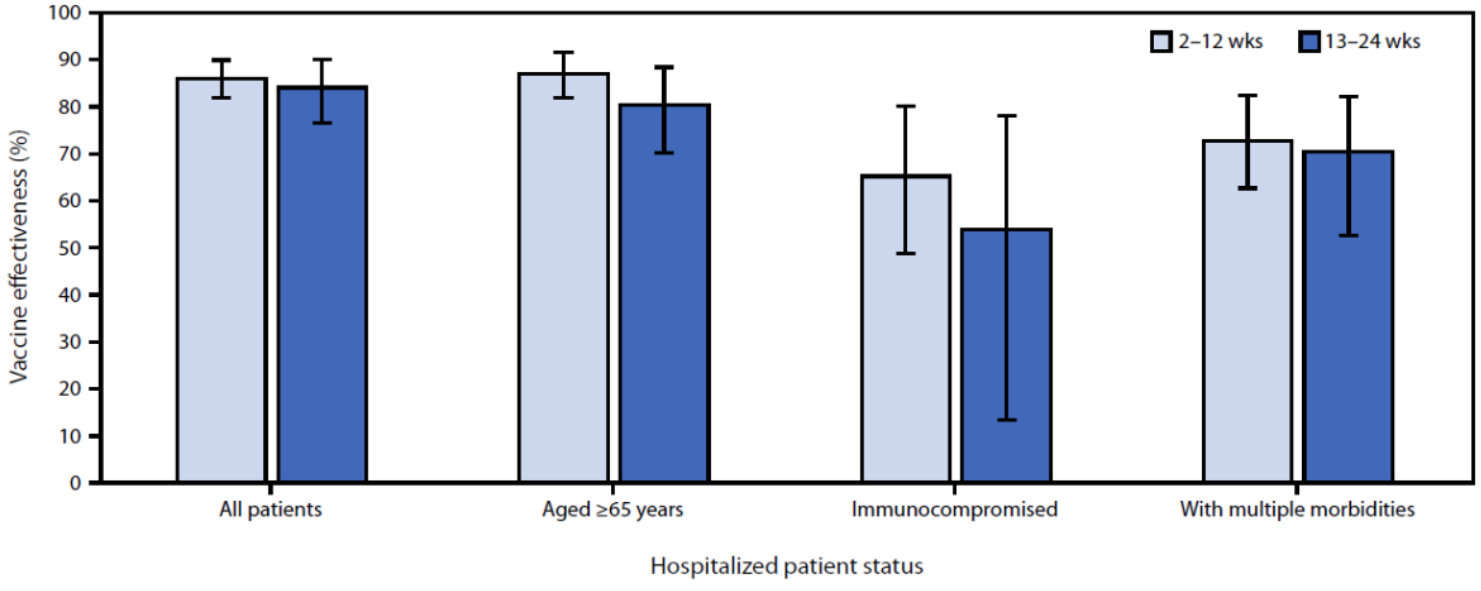
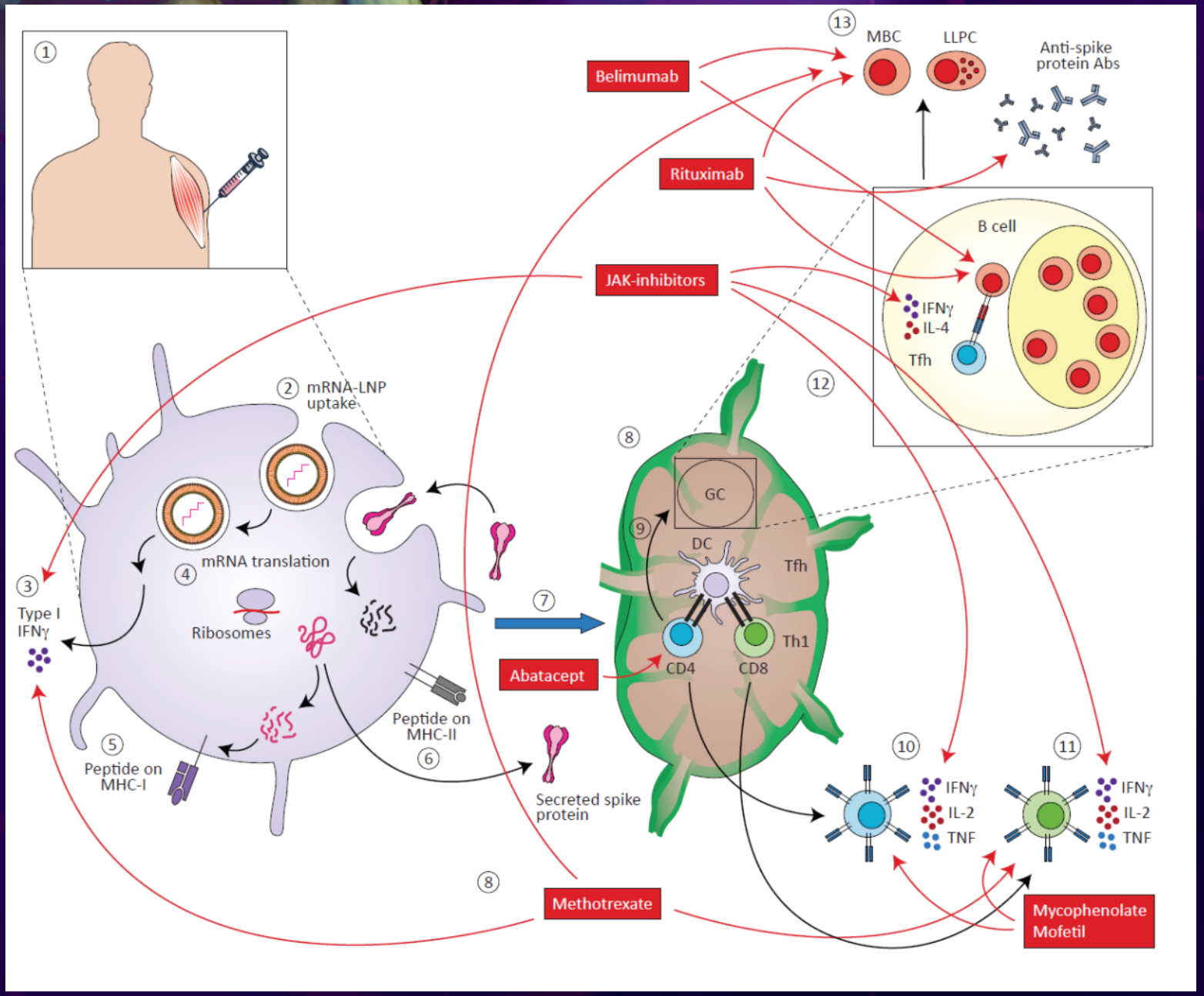


FIGURE 2. Sustained vaccine effectiveness* against COVID-19 among hospitalized adults, by patient status†,§ and interval since vaccination — 21 medical centers in 18 states,¶ March–July 2021



Tenforde MW et al. MMWR 2021



Friedman M et al. ARD In Press

Infliximab and Diminished Ab Response to Infection?

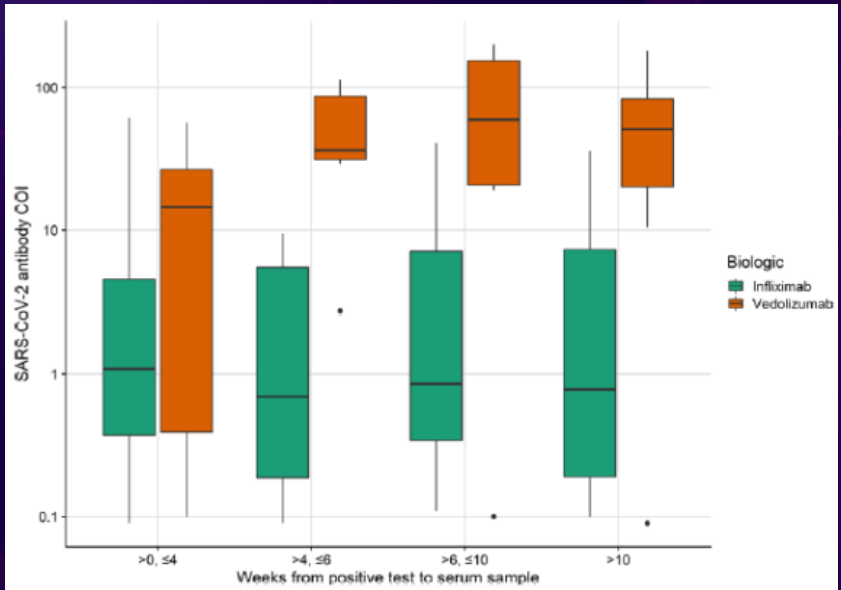


Figure 3 Boxplot of the magnitude of anti-SARS-CoV-2 antibody reactivity stratified by biological therapy and time since prior positive PCR test. COI, cut-off index.

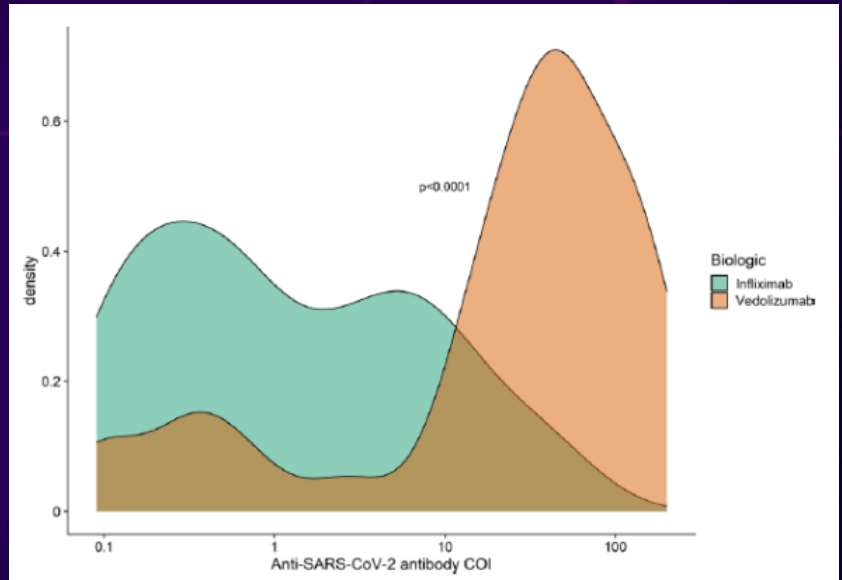


Figure 2 Density plot of the magnitude of anti-SARS-CoV-2 antibody reactivity stratified by biological therapy among participants who had a positive PCR to anti-SARS-CoV-2 at least 2 weeks prior to their serology sample. COI, cut-off index.

Kennedy NA et al. Gut 2021

mRNA Vaccine and Transplant

Table 2: Baseline characteristics of study HTx patients stratified by their S-IgG immunogenicity to a 2-dose (prime-boost) BNT162b2 mRNA vaccine

	Non-responders (n=19)	**Responders** (n=18)	**p-value**
Age (years)	68 (59, 70)	46 (34, 63)	0.034
Time from HTx (months)	119 (13, 162)	84 (32, 174)	0.891
Gender (male)	17 (89)	14 (78)	0.402
HTx indication, ischemic	11 (58)	6 (33)	0.156
Immunosuppressive drugs			
Calcineurin inhibitors	14 (74)	16 (89)	0.233
mTOR inhibitors	7 (37)	13 (72)	0.045
Oral steroids	14 (74)	13 (72)	0.923
Anti-metabolites*	16 (84)	5 (28)	0.010
Immunosuppressive drug protocol **			
CNI-based	12 (63)	6 (33)	0.089
CNI-reduced	2 (11)	10 (56)	0.011
CNI-free	5 (26)	2 (11)	0.305
Anti-metabolites-based protocol	17 (89)	8 (44)	0.011
Immunosuppression drug levels			
Tacrolimus level (ng/ml)	6.1 (5.9, 9.5)	4.2 (3.7, 5.5)	0.044
Cyclosporine level (ng/ml)	157 (60, 172)	81 (81, 81)	1.000
Everolimus level (ng/ml)	5 (4, 5.6)	3.6 (3.0, 5.3)	0.163

MMF

Data are presented as median (25^{th}, 75^{th} quartiles) or as percentages, as appropriate.

Abbreviations: CNI, calcineurin inhibitors; HTx, heart transplantation; mTOR, mammalian target of rapamycin

Itzhaki Ben Zadok O et al. Transplant 2021

mRNA Response by DMARD

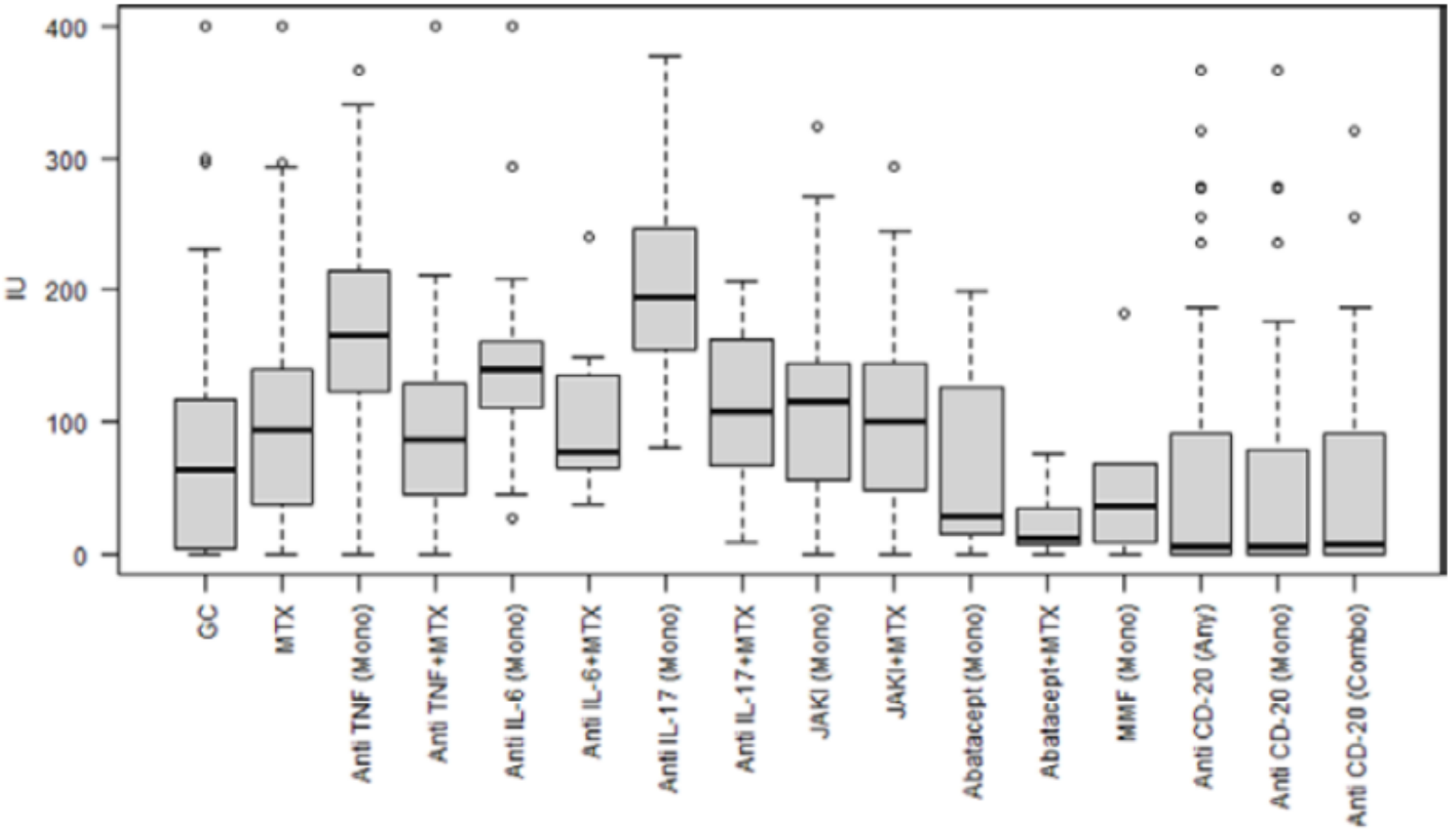


Figure 1. Seropositivity rate by immunosuppressive treatment.

Furer V et al. EULAR abstract 2021

Table 5 Unadjusted and adjusted logistic regression models examining the factors associated with seropositivity

	Seropositivity rate, n (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	P value
Age >65 years, n=246	195 (79.27)	0.33 (0.22 to 0.52)	0.43 (0.25 to 0.75)	**0.002**
AIIRD diagnosis				
PsA, n=165	160 (96.97)	Reference	Reference	
RA, n=263	216 (82.13)	0.14 (0.06 to 0.37)	0.31 (0.11 to 0.82)	**0.02**
AxSpA, n=68	67 (98.53)	2.09 (0.24 to 18.26)	2.01 (0.23 to 17.72)	0.52
SLE, n=101	93 (92.08)	0.36 (0.12 to 1.14)	0.35 (0.11 to 1.16)	0.08
IIM, n=19	7 (36.84)	0.02 (0.01 to 0.07)	0.06 (0.02 to 0.27)	**<0.001**
LVV, n=21	20 (95.24)	0.63 (0.07 to 5.63)	0.82 (0.09 to 7.54)	0.86
AAV, n=26	8 (30.77)	0.01 (0.004 to 0.05)	0.04 (0.01 to 0.17)	**<0.001**
Other vasculitis, n=23	19 (82.61)	0.15 (0.04 to 0.6)	0.26 (0.06 to 1.22)	0.09
AIIRD treatments				
Anti-CD20, n=87	36 (41.38)	0.05 (0.03 to 0.08)	0.13 (0.07 to 0.24)	**<0.001**
Anti-CD20 monotherapy, n=28	11 (39.29)	0.07 (0.03 to 0.16)	0.92 (0.33 to 2.57)	0.87
Anti-CD20 +MTX, n=14	5 (35.71)	0.07 (0.02 to 0.21)	0.94 (0.23 to 3.89)	0.93
MTX, n=176	148 (84.09)	0.64 (0.4 to 1.03)	0.58 (0.31 to 1.07)	0.08
MTX monotherapy, n=41	38 (92.68)	1.75 (0.53 to 5.79)	1.84 (0.5 to 6.74)	0.36
GC, n=130	86 (66.15%)	0.16 (0.1 to 0.29)	0.48 (0.26 to 0.87)	**0.02**
TNFi, n=172	167 (97.09)	5.6 (2.24 to 14.0)	1.89 (0.68 to 5.24)	0.22
TNFi monotherapy, n=121	119 (98.35)	9.46 (2.3 to 38.87)	2.58 (0.56 to 11.94)	0.22
TNFi +MTX, n=29	27 (93.1)	1.86 (0.44 to 7.94)	1.46 (0.31 to 6.91)	0.63
IL6i, n=37	37 (100)	NA	NA	NA
IL6i monotherapy, n=19	19 (100)	NA	NA	NA
IL6i+MTX, n=7	7 (100)	NA	NA	NA
IL17i, n=48	47 (97.92)	6.73 (0.92 to 49.32)	1.42 (0.16 to 12.83)	0.75
IL17 monotherapy, n=37	37 (100)	NA	NA	NA
IL17 +MTX, n=7	6 (85.71)	0.81 (0.1 to 6.8)	0.25 (0.02 to 2.7)	0.25
Abatacept, n=16	10 (62.5)	0.21 (0.08 to 0.6)	0.14 (0.04 to 0.43)	**<0.001**
Abatacept monotherapy, n=7	5 (71.43)	0.33 (0.06 to 1.74)	0.2 (0.033 to 1.16)	0.073
Abatacept+MTX, n=5	2 (40)	0.09 (0.01 to 0.53)	0.07 (0.01 to 0.48)	**0.007**
JAKi monotherapy, n=21	19 (90.48)	1.29 (0.3 to 5.63)	0.72 (0.15 to 3.48)	0.68
JAKi+MTX, n=24	22 (91.67)	1.5 (0.35 to 6.48)	1.78 (0.38 to 8.35)	0.46
MMF, n=28	18 (64.29)	0.22 (0.1 to 0.5)	0.1 (0.03 to 0.34)	**0.0013**
MMF monotherapy, n=5	3 (60)	0.2 (0.03 to 1.21)	0.11 (0.02 to 0.83)	**0.03**

AAV, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis; AIIRD, autoimmune inflammatory rheumatic diseases; anti-CD20, CD20 inhibitors; AxSpA, axial spondyloarthritis; GC, glucocorticoids; IIM, idiopathic inflammatory myositis; IL6i, interleukin 6 inhibitors; IL17i, interleukin 17 inhibitors; JAKi, Janus kinase inhibitors; LVV, large vessel vasculitis; MMF, mycophenolate mofetil; MTX, methotrexate; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; TNFi, tumour necrosis factor inhibitors.

RTX and Dosing Interval

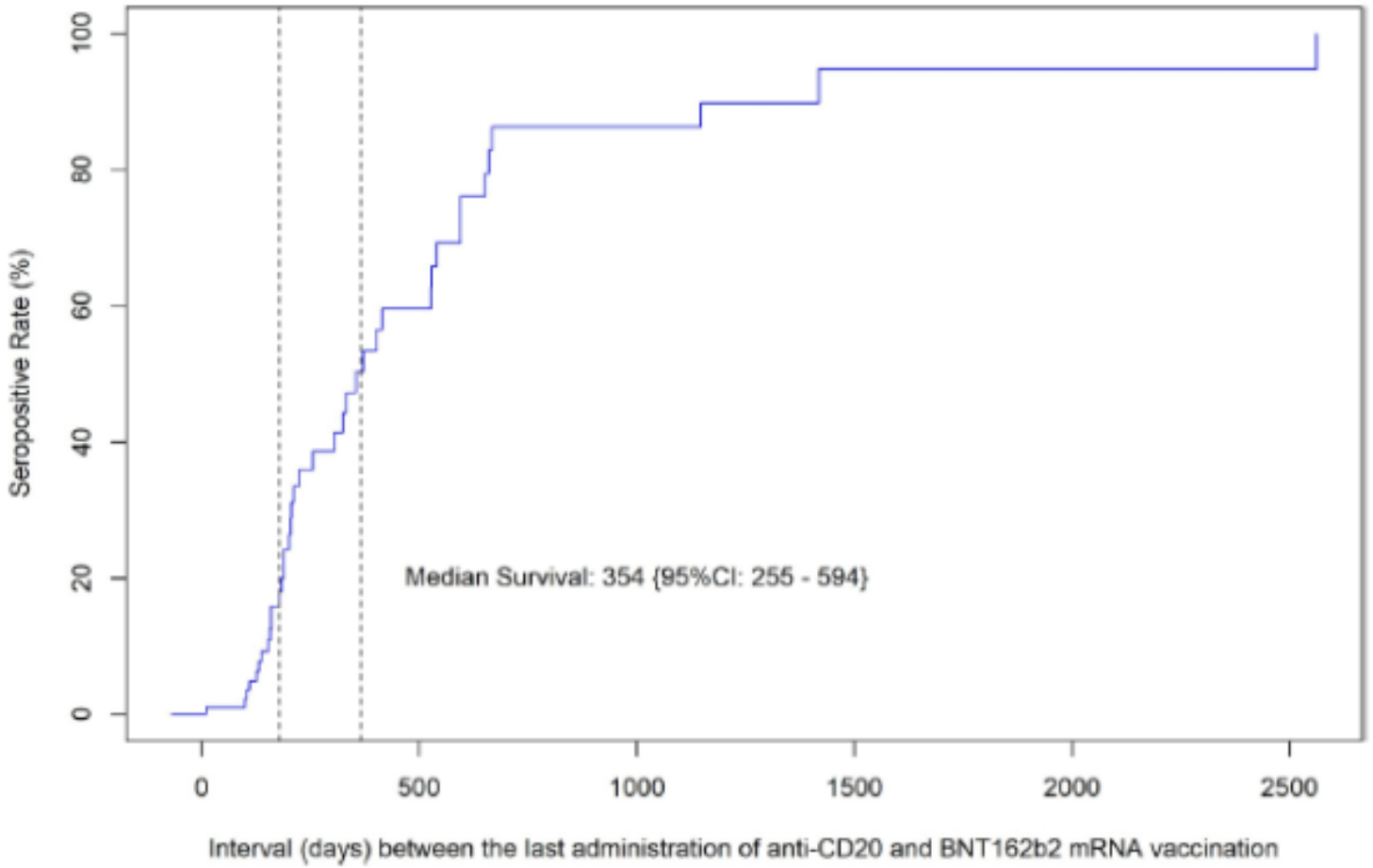
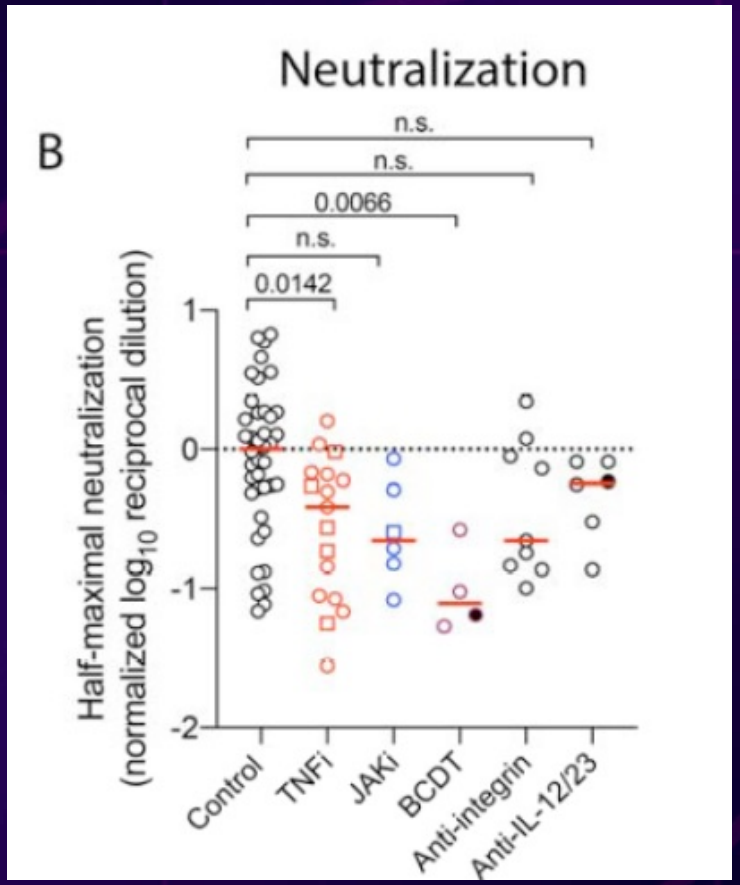


Figure 1 Cumulative seropositive rate according to the interval (days) between the last course of rituximab administration and BNT162b vaccination. mRNA, messenger RNA.

Furer V et al. ARD 2021

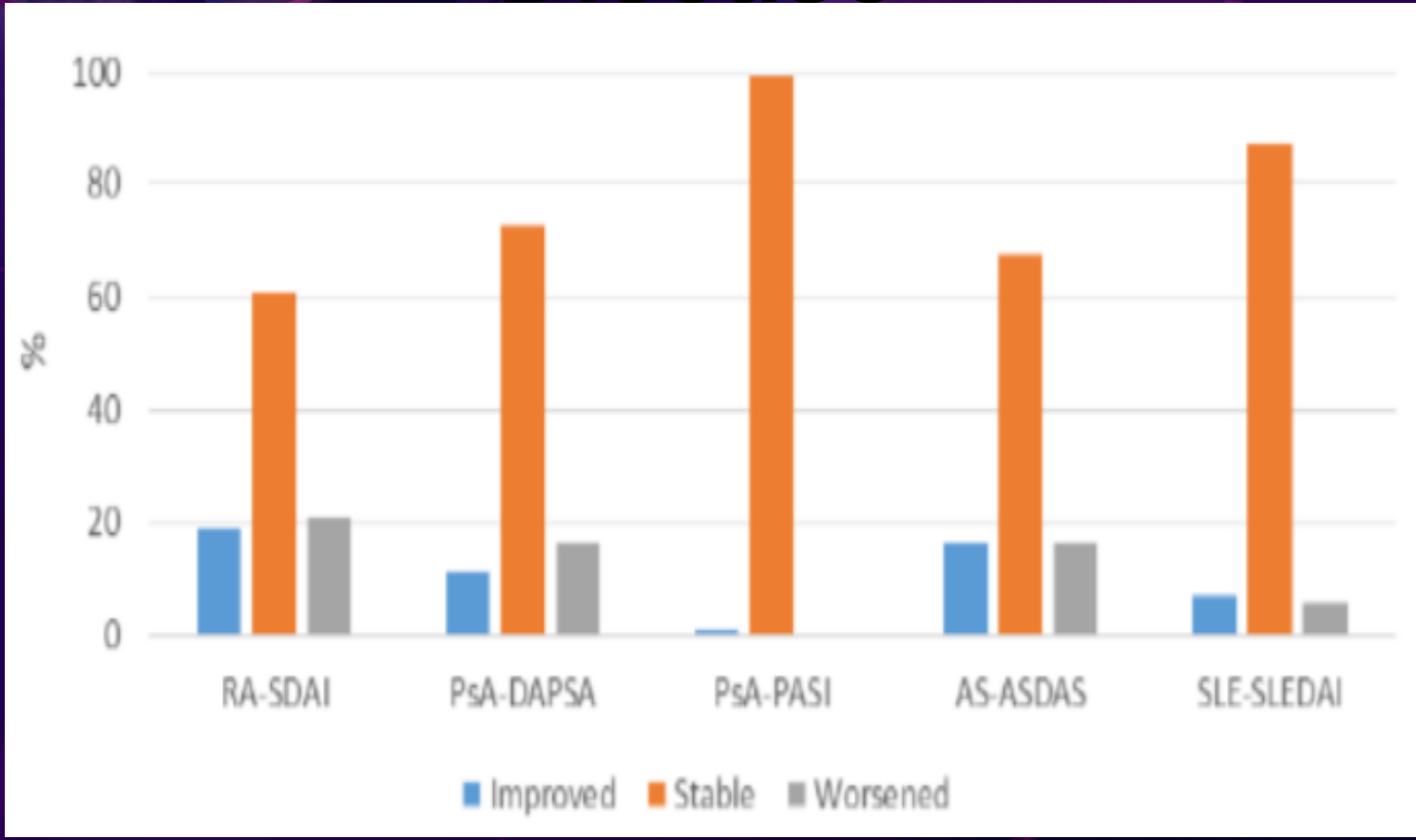
Effects of DMARDs on mRNA Vaccine Response



Mixed IMID, low numbers of disease and therapy groups

Deepak P et al. MedRxiv 2021 pre-print non-peer reviewed

Vaccine Effect on Rheumatic Disease



Change in disease activity score following vaccination

Furer V. Ann Rheum Dis. 2021 Jun 14; Epub ahead of print.

Table 3: Guidance Related to the Use and Timing of Vaccination and Immunomodulatory Therapies in Relation to COVID-19 Vaccination in RMD Patients*

Medication	Timing Considerations for Immunomodulatory Therapy and Vaccination*	Level of Task Force Consensus
Hydroxychloroquine; apremilast; IVIG; glucocorticoids, prednisone-equivalent dose <20mg/day	No modifications to either immunomodulatory therapy or vaccination timing	Strong-Moderate
Sulfasalazine; Leflunomide; Azathioprine; Cyclophosphamide (oral); TNFi; IL-6R; IL-1; IL-17; IL-12/23; IL-23; Belimumab; Glucocorticoids, prednisone-equivalent dose ≥ 20mg/day†	No modifications to either immunomodulatory therapy or vaccination timing	Moderate
Mycophenolate; **oral calcineurin inhibitors**	Assuming that disease is stable, hold for 1 week following each vaccination	Moderate
Methotrexate	Hold MTX for 1 week after each of the 2mRNA vaccine doses, for those with well-controlled disease; no modifications to vaccination timing	Moderate
Methotrexate	Hold MTX for 2 weeks after single-dose COVID vaccination, for those with well-controlled disease	Moderate
JAKi	Hold JAKi for 1 week after each vaccine dose; no modification to vaccination timing	Moderate
Abatacept SQ	Hold SQ abatacept both one week prior to and one week after the first COVID-19 vaccine dose (only); no interruption around the second vaccine dose	Moderate
Abatacept IV	Time vaccine administration so that the first vaccination will occur four weeks after abatacept infusion (i.e., the entire dosing interval), and postpone the subsequent abatacept infusion by one week (i.e., a 5-week gap in total); no medication adjustment for the second vaccine dose	Moderate
Cyclophosphamide IV	Time CYC administration so that it will occur approximately 1 week after each vaccine dose, when feasible	Moderate
Rituximab	Assuming that patient's COVID-19 risk is low or is able to be mitigated by preventive health measures (e.g., self-isolation), schedule vaccination so that the vaccine series is initiated approximately 4 weeks prior to next scheduled rituximab cycle; after vaccination, delay RTX 2-4 weeks after final vaccine dose, if disease activity allows	Moderate
Acetaminophen, NSAIDs	Assuming that disease is stable, hold for 24 hours prior to vaccination (no restrictions on use post vaccination to treat symptoms)	Moderate
Supplemental Dosing (i.e., booster dose)		
All immunomodulatory or immunosuppressive therapies‡	**Except for glucocorticoids and anti-cytokine therapies (see footnote), hold all immunomodulatory or immunosuppressive medications for 1-2 weeks after booster vaccination, assuming disease activity allows.**	**Moderate**
Rituximab§	**Patients on rituximab or other anti-CD20 medications should discuss the optimal timing with their rheumatology provider before proceeding with booster vaccination.**	**Strong**

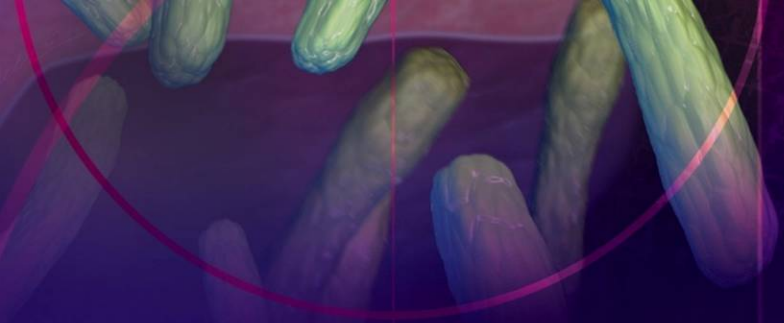
https://www.rheumatology.org/Portals/0/Files/COVID-19-Vaccine-Clinical-Guidance-Rheumatic-Diseases-Summary.pdf

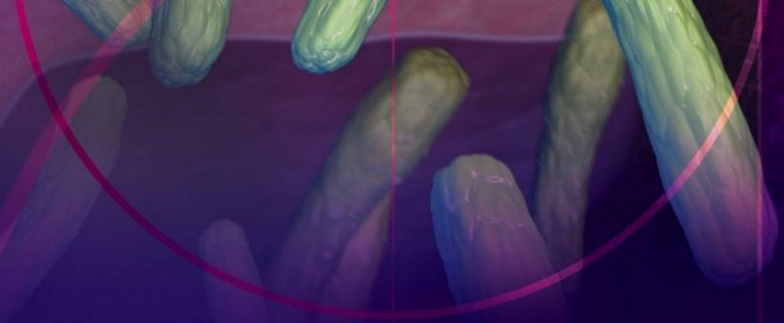
Considerations for Rheum Patients

- B cell depletion therapies and COVID vaccination
  - Time to hold the next dose?
- Needed studies
  - Vaccine responses modified by DMARDs?
  - Length of vaccine protection?
  - Co-Administration studies
- How long for mask wearing and avoidance?
  - 2022 looks to be full of travel (maybe)

Acknowledgements

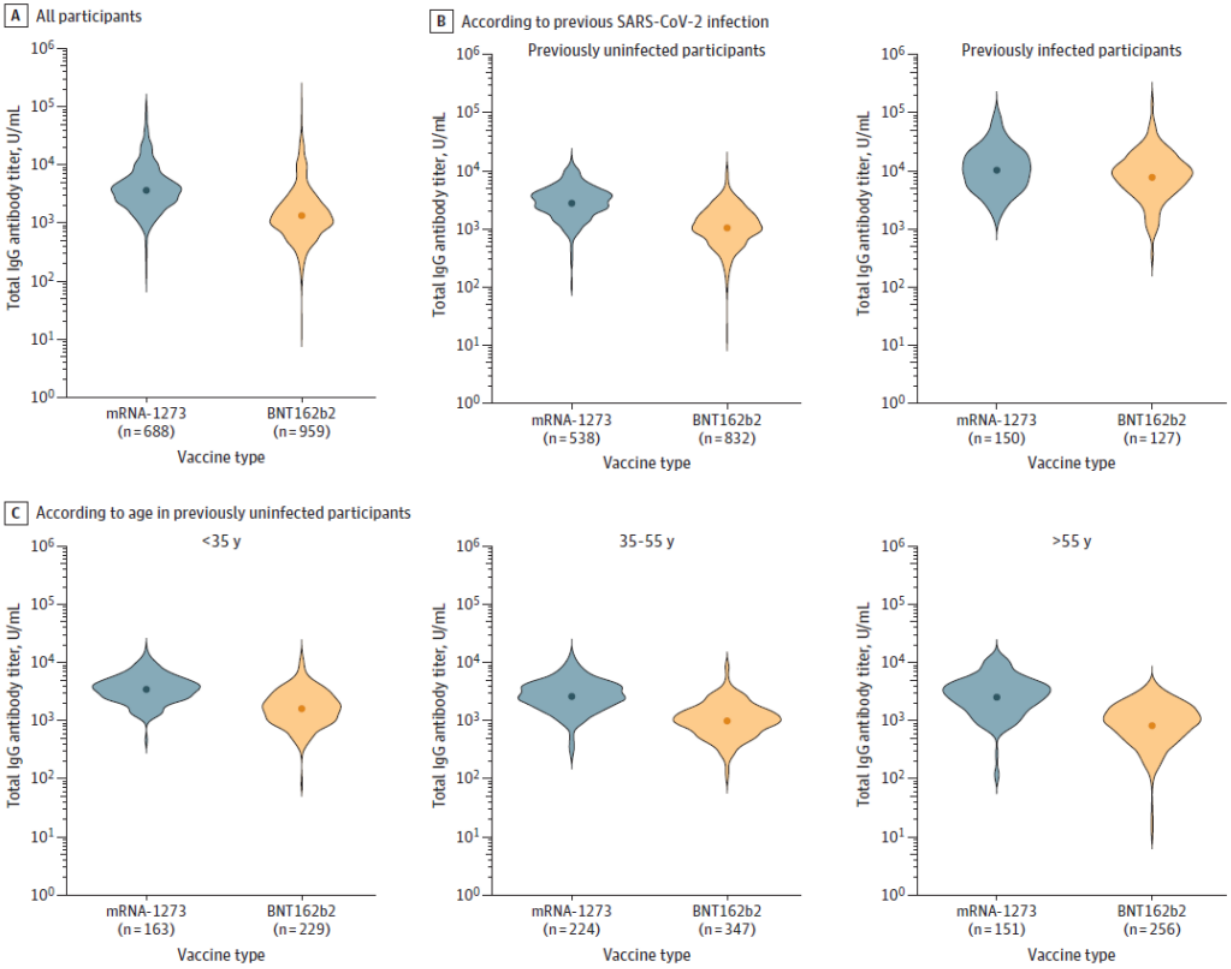
- UAB colleagues
- ACR and EULAR colleagues
- Oregon Health Authority colleagues
- CDC colleagues





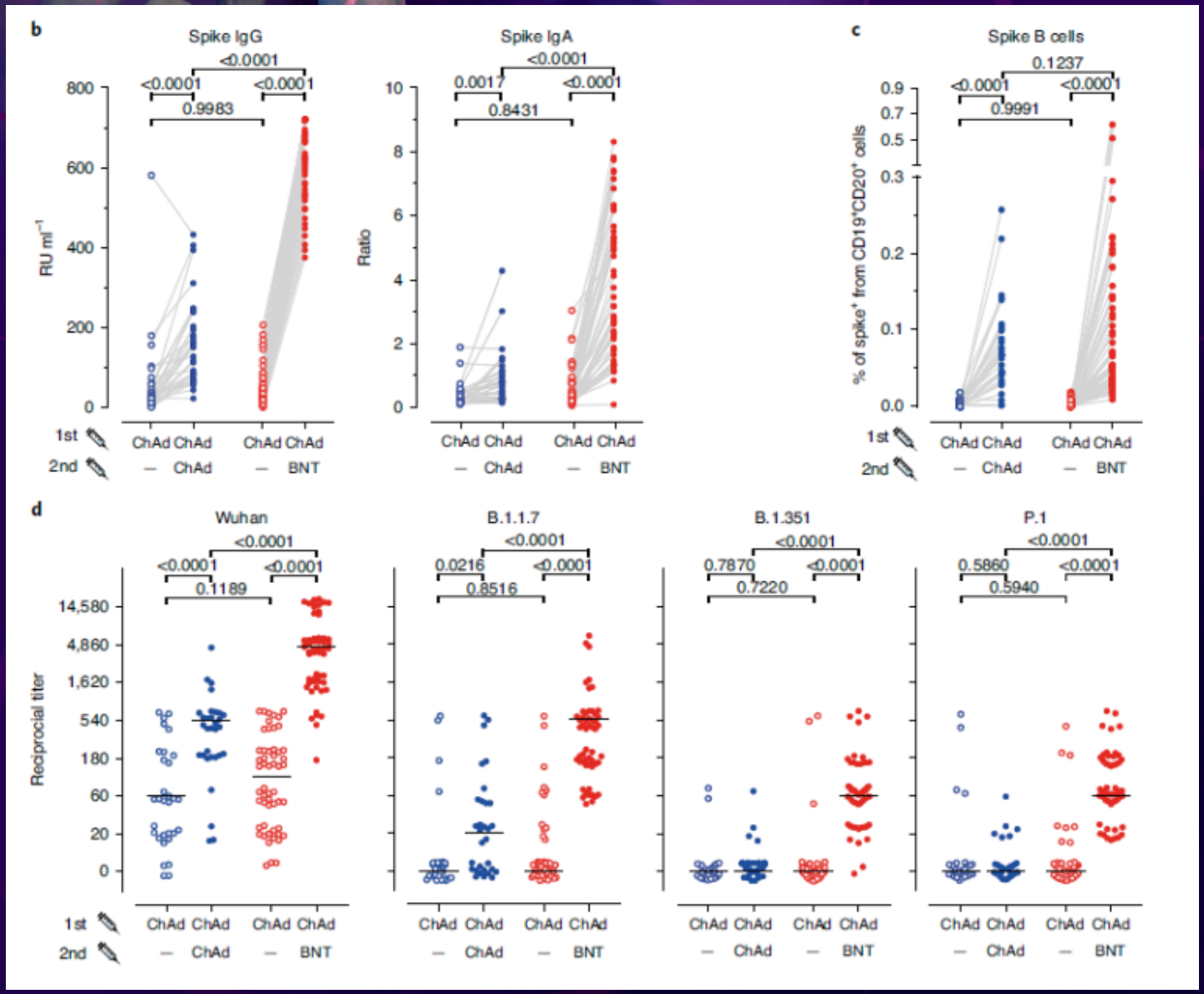
Moderna versus Pfizer

Figure. Humoral Immune Response Following SARS-CoV-2 mRNA Vaccination



Steensels D et al. JAMA 2021

mRNA Boost of Adeno Primary



Barrios-Martins J et al. Nat Med 2021

Annals of Internal Medicine

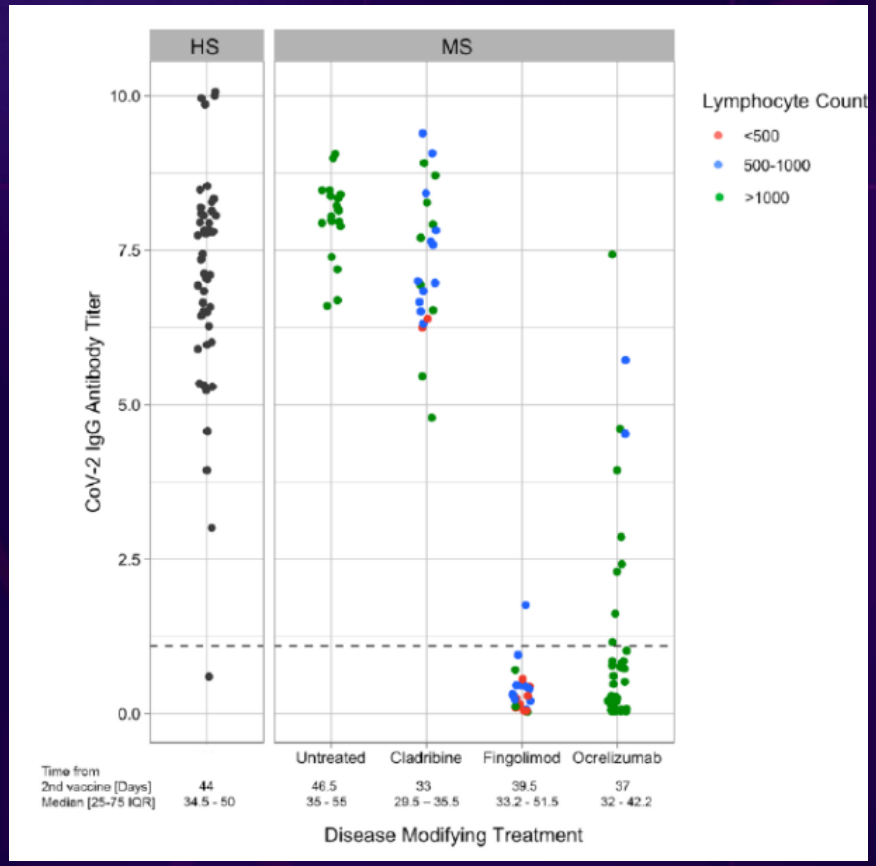
OBSERVATIONS: CASE REPORTS

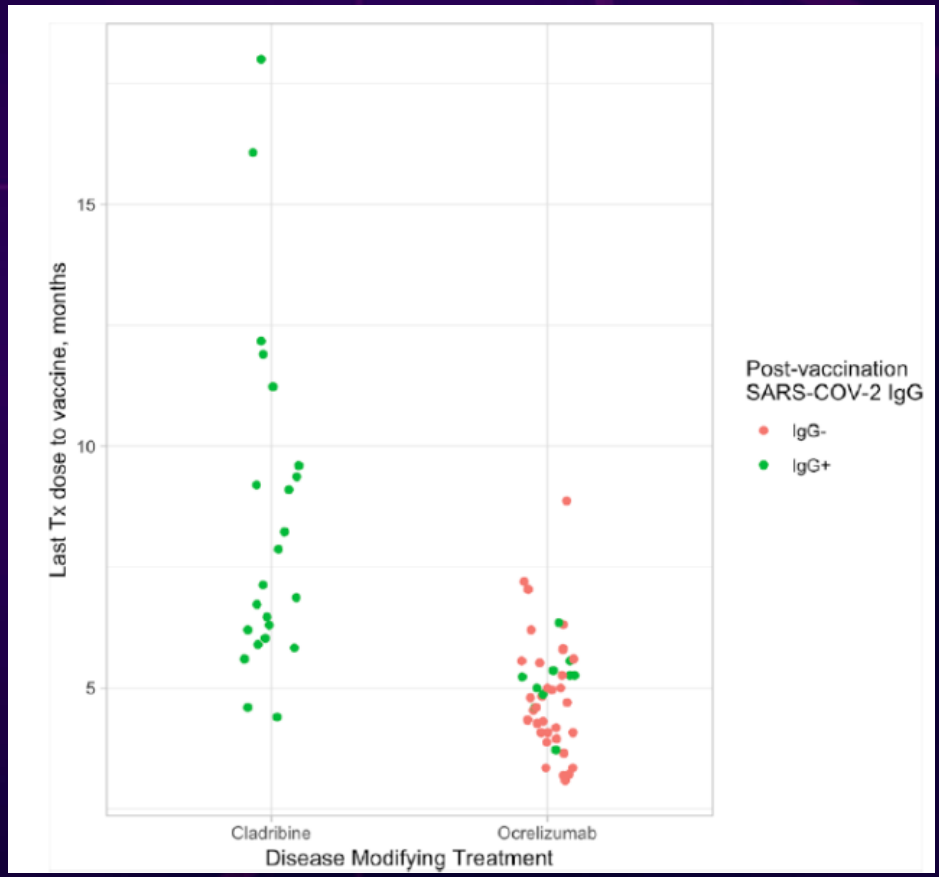
Safety and Immunogenicity of a Third Dose of SARS-CoV-2 Vaccine in Solid Organ Transplant Recipients: A Case Series

We repeated antibody testing a median of 14 days (IQR, 14 to 17 days) after the third dose of vaccine. Of the 6 patients with low-positive antibody titers before the third dose, all had high-positive antibody titers after the third dose. In contrast, of the 24 patients with negative antibody titers before the third dose, only 6 (25%) had high-positive antibody titers after the third dose. Two (8%) had low-positive antibody titers, and 16 (67%) remained negative.

Werbel WA et al. Ann Int Med 2021

Fingolomod and Ocre Decrease mRNA response in MS





Achiron A et al. Ther Adv Neurol Disord 2021

JnJ Vs mRNA in RMD

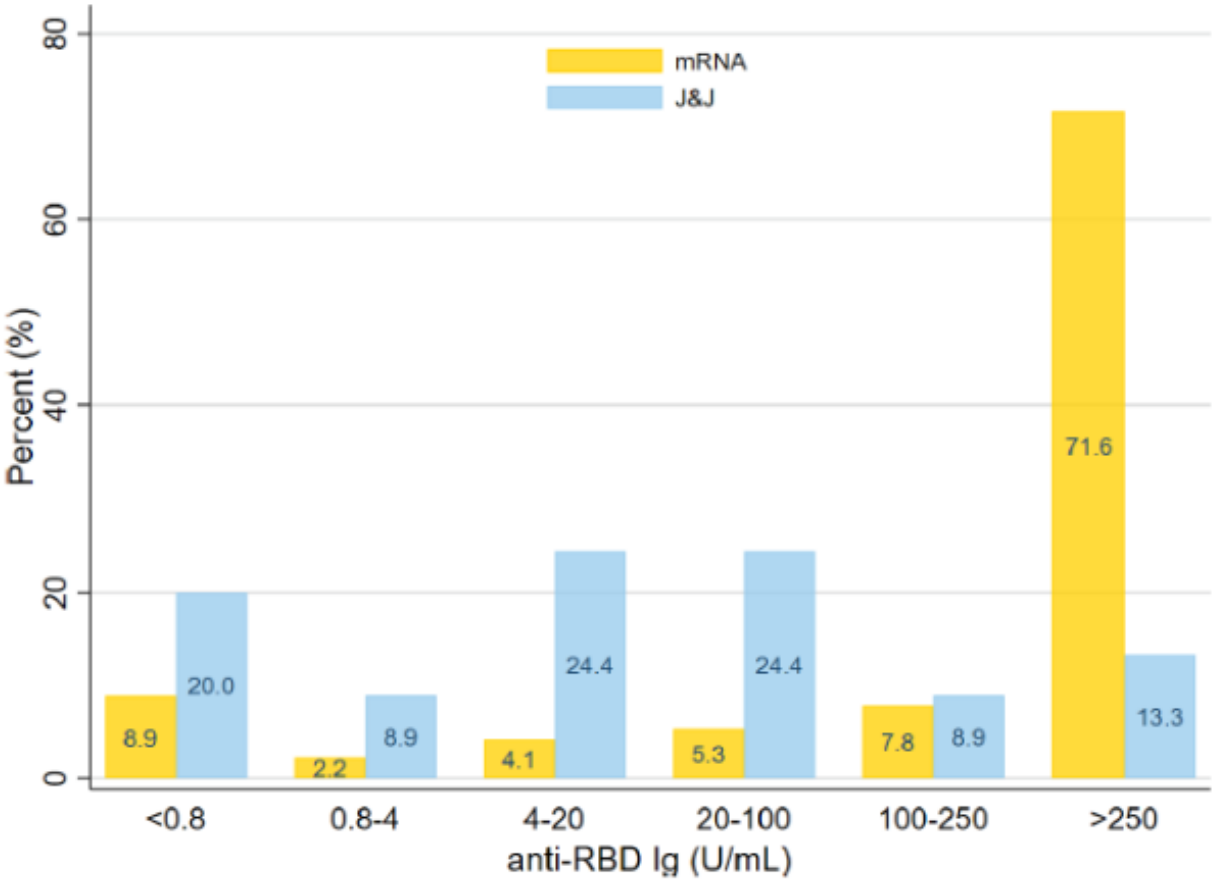
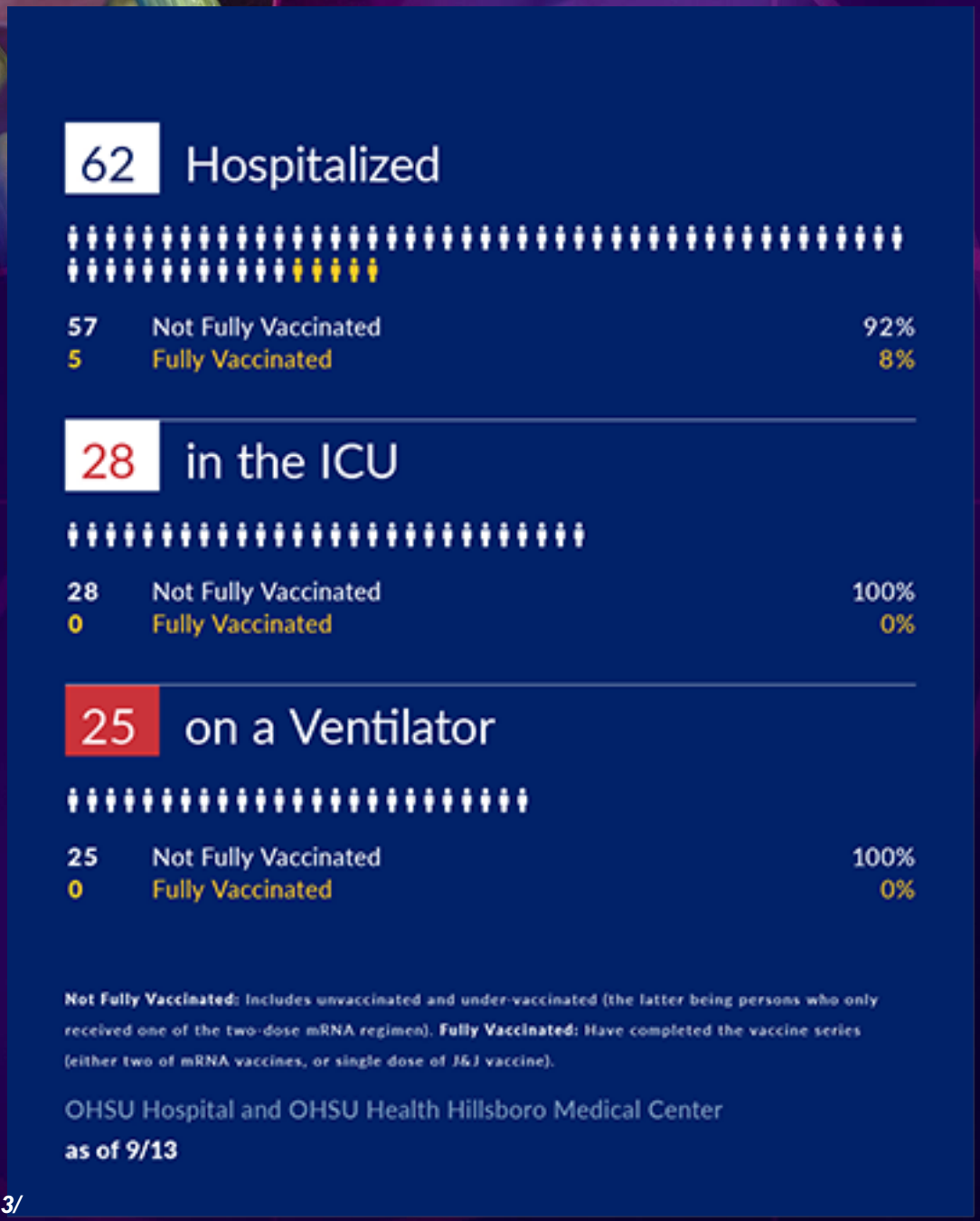
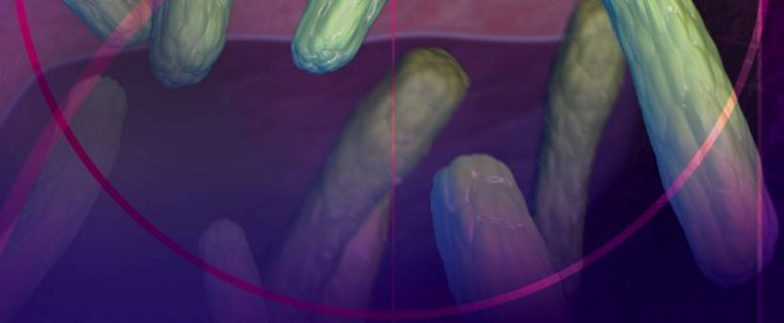


Figure 1 SARS-CoV-2 anti-RBD antibody titres among recipients of mRNA vs J&J vaccine. Titres could range from <0.4 U/mL to >250 U/mL. Positive antibody is defined as an anti-SARS-CoV-2 RBD antibody titre >0.79 U/mL. Ig, immunoglobulin; J&J, Johnson & Johnson; RBD, receptor binding domain.

Po-Yu Chiang et al. ARD 2021



https://news.ohsu.edu/2020/07/13/preparing-for-the-novel-coronavirus-at-ohsu



Short-term Protection from Natural Infection

Table 1: Comparison of infection rates during the Spring 2021 semester (12/28/20 to 5/1/21) among students with and without previous infections during the Fall 2020 semester.

	Spring 2021					
	Population (N)	**Infections (N)**	**Percent infected**	**Testing compliance[a]**	**Relative risk (95% CI)[b]**	**Estimated Protection (95% CI)[b]**
Main analysis						
Fall 2020 positive	2,021	44	2.2%	10 (83%)	0.16 (0.12 – 0.22)	84% (78% - 88%)
...confirmed reinfections[c]	2,010	33	1.6%	10 (83%)	0.12 (0.09 – 0.17)	88% (83% – 91%)
Fall 2020 negative	14,080	1,697	12.1%	10 (83%)	1 *(reference)*	-

Clemson University

Rennert L et al. CID 2021

One Dose Good Enough Post-Infection

NATURE MEDICINE

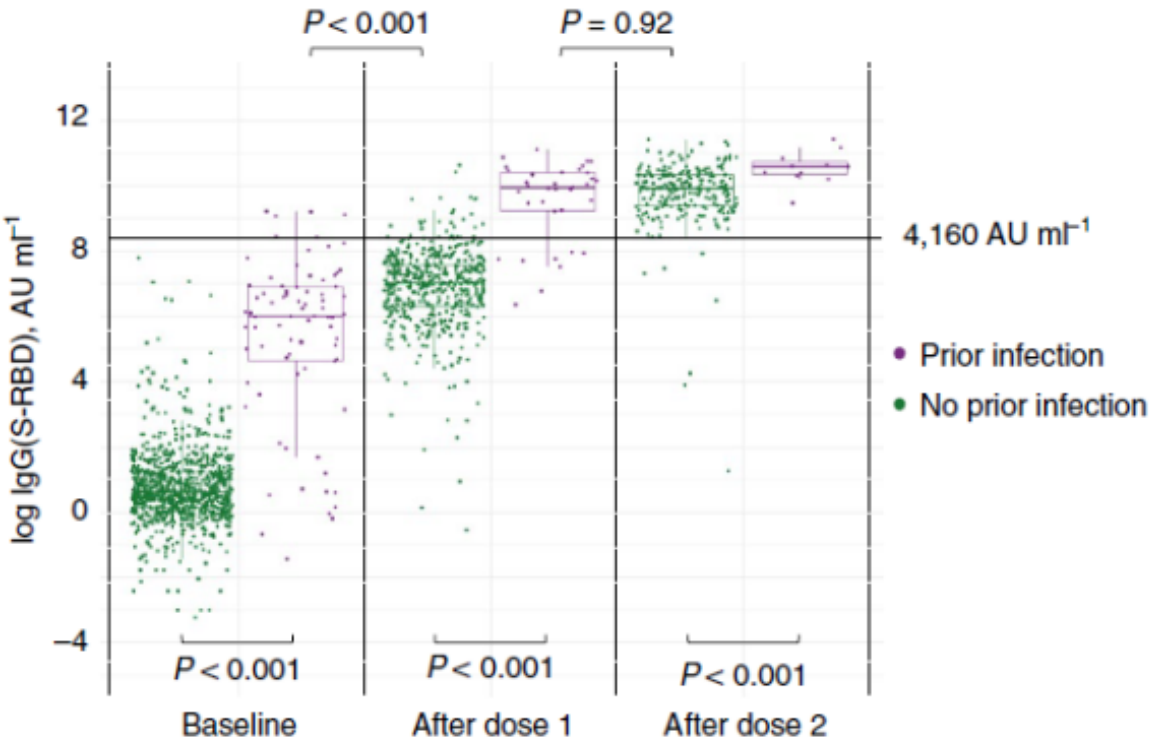


Fig. 1 | IgG(S-RBD) antibody response to mRNA SARS-CoV-2 vaccination in individuals with and without prior SARS-CoV-2 infection. Box plots

Ebinger JE et al. Nat Med 2021

mRNA Vaccine Real World Efficacy

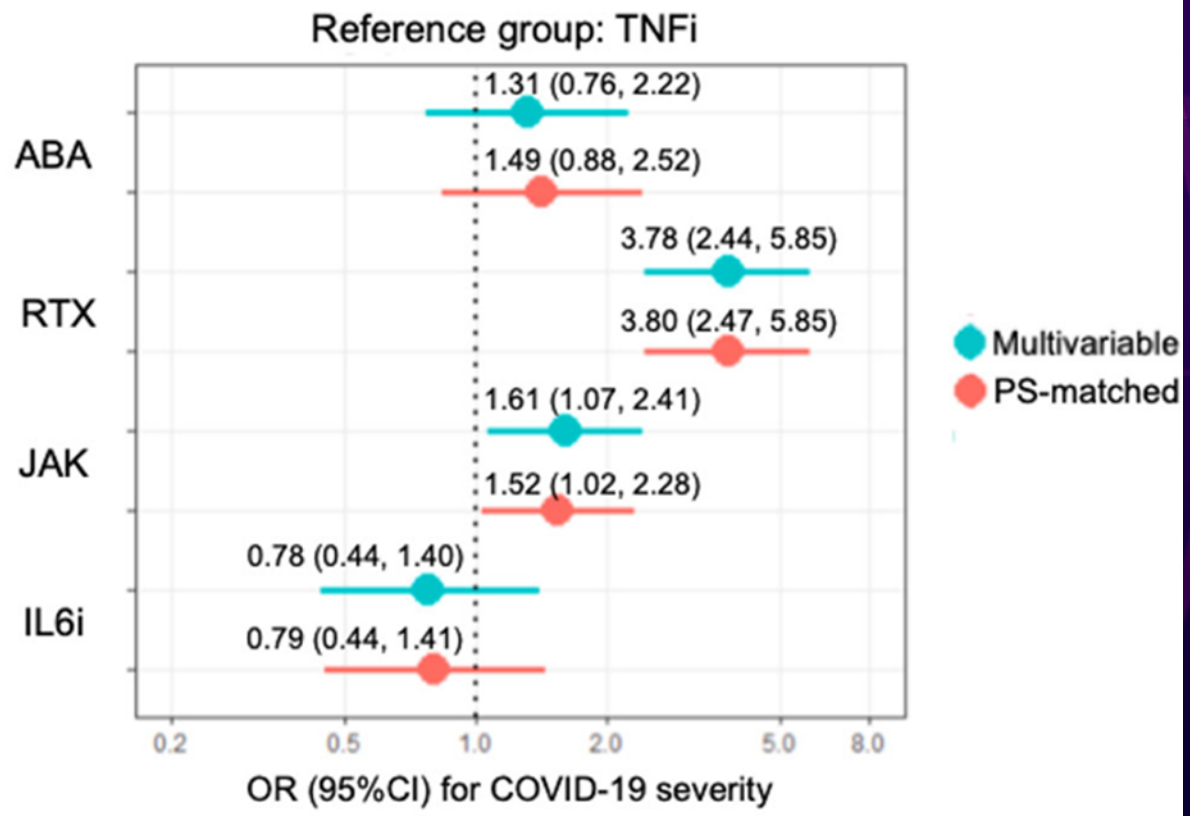
TABLE 2. Person-days, SARS-CoV-2 infections, and vaccine effectiveness among health care personnel, first responders, and other essential and frontline workers, by messenger RNA immunization status — eight U.S. locations, December 14, 2020–March 13, 2021

		SARS-CoV-2 infections		Unadjusted vaccine effectiveness*	Adjusted vaccine effectiveness*,†
COVID-19 immunization status	Person-days	No.	Incidence rate per 1,000 person-days	% (95% CI)	% (95% CI)
Unvaccinated	116,657	161	1.38	N/A	N/A
Partially immunized	41,856	8	0.19	82 (62–91)	80 (59–90)
≥14 days after receiving first dose only§	15,868	5	0.32		
≥14 days after first dose through receipt of second dose	25,988	3	0.12		
Fully immunized					
≥14 days after second dose	78,902	3	0.04	91 (73–97)	90 (68–97)

Abbreviations: CI = confidence interval; N/A = not applicable.
* Vaccine effectiveness was estimated using a Cox proportional hazards model accounting for time-varying immunization status.
† Hazard ratio is adjusted for study site.
§ Participants received first dose but had not received second dose by the end of the study period.

https://www.cdc.gov/mmwr/volumes/70/wr/mm7013e3.htm?s_cid=mm7013e3_x

Figure. Odds ratios for the ordinal COVID-19 severity outcome for patients with RA on biologic or targeted synthetic DMARDs (n=1673).



The effect size is the odds of being one level higher on the ordinal scale than the reference group.

n for propensity score (PS)-matched analyses: 98 ABA and 525 TNFi; 127 RTX and 520 TNFi; 198 JAK and 527 TNFi; 107 IL6i and 525 TNFi.

Multivariable covariates and propensity score included age, sex, region, season, smoking, obesity, RA disease activity, interstitial lung disease, cancer, comorbidity count, concomitant non-biologic DMARD use, and glucocorticoid use/dose.

DMTs and COVID-19 Severity

Table 2. Multivariable Multinomial Logistic Regression Model for the Clinical Severity Outcome

Risk factor	COVID-19 clinical course outcome level[a]					
	Hospitalization only, OR (95% CI)	*P* value	ICU and/or required ventilator support, OR (95% CI)	*P* value	Death, OR (95% CI)	*P* value
Age (every 10-y increase)	1.32 (1.12-1.56)	<.001	1.29 (0.99-1.67)	.06	1.77 (1.20-2.59)	.004
Sex (male vs female)	1.41 (0.98-2.03)	.06	1.00 (0.54-1.83)	.99	3.12 (1.46-6.65)	.003
Disease-modifying therapy						
None	1 [Reference]	NA[b]	1 [Reference]	NA[b]	1 [Reference]	NA[b]
Fumarates	0.99 (0.52-1.88)	.90	0.26 (0.08-0.82)	.98	0.40 (0.09-1.70)	.30
S1PR	0.65 (0.26-1.61)	.23	0.77 (0.28-2.14)	.94	0.86 (0.15-4.93)	.89
Glatiramer acetate	1.15 (0.51-2.61)	.73	NA[b]	.96	0.86 (0.16-4.56)	.89
Interferons	0.35 (0.08-1.57)	.11	0.29 (0.04-2.32)	.98	0.56 (0.06-5.49)	.75
Natalizumab	0.67 (0.31-1.45)	.18	0.09 (0.01-0.73)	.98	0.80 (0.19-3.44)	.96
Ocrelizumab	1.63 (0.98-2.72)	.009	0.91 (0.46-1.80)	.94	0.47 (0.17-1.30)	.25
[illegible]	1.21 (0.45-3.24)	.70	0.50 (0.10-2.38)	.96	0.91 (0.18-4.73)	.83
Rituximab	4.56 (2.10-9.90)	<.001	1.92 (0.61-6.07)	.91	2.81 (0.45-17.70)	.11
Teriflunomide	0.83 (0.34-2.02)	.58	0.30 (0.06-1.37)	.98	0.48 (0.08-3.04)	.57
Glucocorticoid use in past 2 mo						
No	1 [Reference]	NA[b]	1 [Reference]	NA[b]	1 [Reference]	NA[b]
Unknown	0.94 (0.46-1.92)	.16	0.44 (0.10-1.94)	.19	2.13 (0.68-6.72)	.95
Yes	2.62 (1.33-5.17)	.009	1.57 (0.49-4.97)	.21	4.17 (1.13-15.4)	.13

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Italian MS Cohort

TABLE 4. Univariate, Multivariate, and PS-Weighted Ordinal Logistic Regression Models Evaluating Risk Factors for Severe Coronavirus Disease 2019[a]

	Univariate Analysis, n = 844[b]		Multivariate Analysis, n = 844[b]		PS Analysis, n = 844[b]	
Variable	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Age, yr	1.06 (1.04–1.08)	<0.001	1.06 (1.03–1.08)	<0.001	1.06 (1.03–1.10)	0.001
Sex, F vs M	0.64 (0.40–1.03)	0.068	0.69 (0.45–1.04)	0.076	0.83 (0.50–1.39)	0.49
Progressive vs RRMS	4.14 (2.70–6.35)	<0.001	1.59 (0.81–3.01)	0.18	1.76 (0.70–4.40)	0.23
Methylprednisolone[c]	3.38 (1.49–7.67)	0.004	5.24 (2.20–12.53)	0.001	2.51 (0.99–6.44)	0.05
DMT						
No therapy[d]	1 (ref)		1 (ref)		1 (ref)	
Interferon	0.35 (0.15–0.79)	0.012	0.67 (0.28–1.65)	0.39	0.71 (0.29–1.78)	0.48
Glatiramer-acetate	0.34 (0.14–0.81)	0.015	0.77 (0.29–2.00)	0.59	1.19 (0.30–4.87)	0.80
Teriflunomide	0.48 (0.21–1.07)	0.07	0.86 (0.36–2.08)	0.74	1.17 (0.41–3.63)	0.76
Dimethyl fumarate	0.38 (0.20–0.70)	0.002	1.12 (0.55–2.30)	0.75	1.29 (0.58–2.87)	0.62
Natalizumab	0.35 (0.16–0.76)	0.009	1.30 (0.53–3.22)	0.57	1.77 (0.61–5.07)	0.29
Fingolimod	0.50 (0.26–0.98)	0.04	1.19 (0.57–2.52)	0.64	1.48 (0.66–3.34)	0.34
Anti-CD20[e]	0.94 (0.52–1.08)	0.85	2.37 (1.18–4.74)	0.015	3.91 (1.71–8.91)	0.001

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