When expectations are not met: Immune responses to SARS-CoV-2 vaccination in the immunosuppressed

Michigan Rheumatism Society
Annual Meeting
17 July 2022

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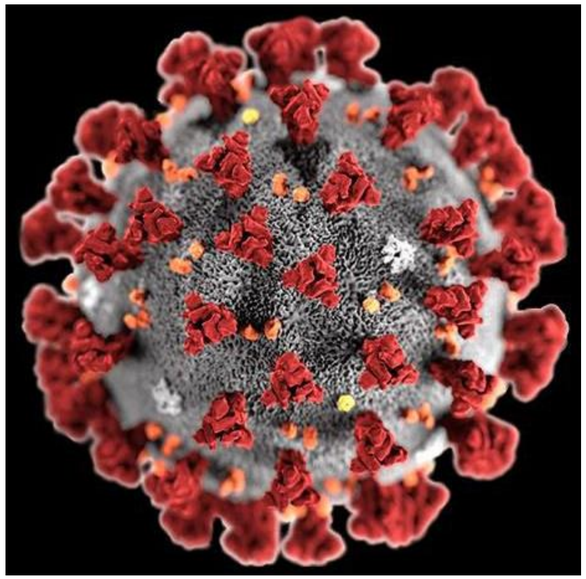
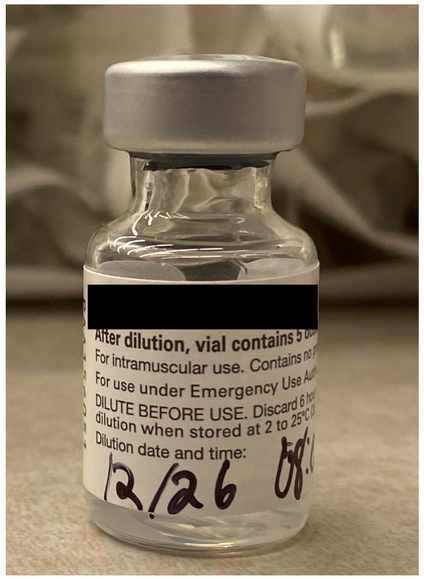
Washington University School of Medicine

@alhkim





Disclosures: Alfred H.J. Kim, MD, PhD

I have no related financial interests to disclose

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  - Foghorn Therapeutics
- Research grants
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  - Multiple Sclerosis Society
  - Helmsley Charitable Trust
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- Consulting/Speaker
  - Alexion Pharmaceuticals
  - AstraZeneca
  - Aurinia Pharmaceuticals
  - Exagen Diagnostics
  - GlaxoSmithKline
  - Kypha, Inc.
  - Pfizer, Inc.
- Royalties/Patent Beneficiary
  - Kypha, Inc. (US Patent 11029318B2)

Health

Coronavirus vaccines may not work in some people. It's because of their underlying conditions.

Early research shows that 15 to 80 percent of people with certain medical conditions, such as specific blood cancers or organ transplants, are generating few antibodies after receiving coronavirus vaccines.

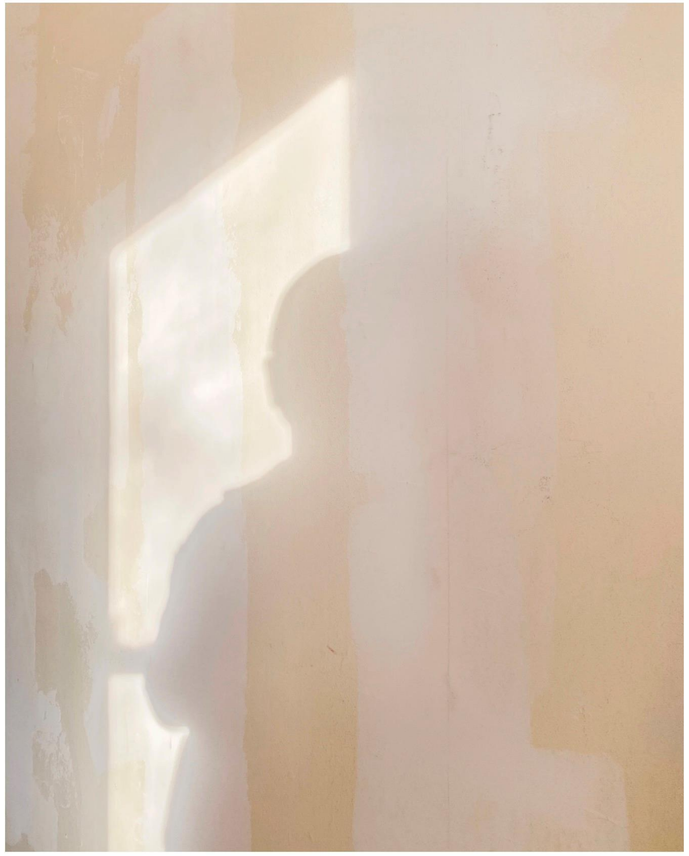
"Risk is very different for people in my situation," said Maria Hoffman, a kidney transplant patient who works for the Medical University of South Carolina. (Brett Lemmo for The Washington Post)

By Ariana Eunjung Cha

Add to list

May 18, 2021 at 7:00 a.m. CDT

Maria Hoffman feels as though she has been left behind. Her adopted hometown of Charleston, S.C., is hopping — with restaurants and bars fully open, park concerts in full swing and maskless friends



John Stanmeyer / VII / Redux

HEALTH

THE MILLIONS OF PEOPLE STUCK IN PANDEMIC LIMBO

What does society owe immunocompromised people?

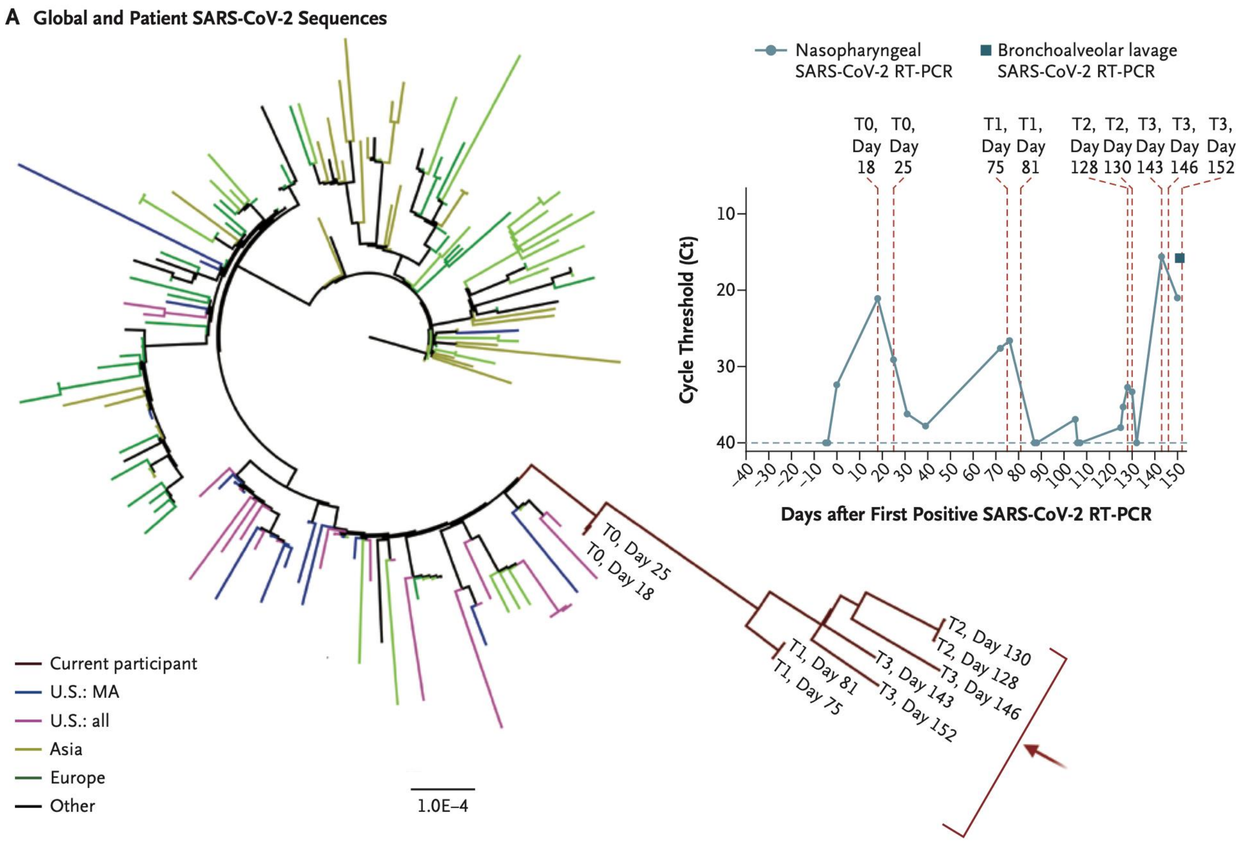
By Ed Yong

FEBRUARY 16, 2022, 10:22 AM ET

SHARE

Protecting the immunosuppressed against COVID-19

- Immunosuppression increases risk of severe COVID-19, including death
  - BCDT, increased disease activity/PDN, JAKi, polytherapy including TNFi
- Variants emerge from patients with prolonged SARS-CoV-2 infection (>3 months)
  - Immunosuppression major risk factor in this scenario



Immunosuppression & COVID-19 severity
Gianfrancesco *et al*, *Ann Rheum Dis*, 2020
Schäfer *et al, Ann Rheum Dis,* 2021
Strangfeld *et al, Ann Rheum Dis,* 2021
Sparks *et al, Ann Rheum Dis,* 2021

Variant emergence in the immunosuppressed
Avanzato *et al*, *Cell*, 2020
Choi *et al*, *New Engl J Med,* 2020/Clark *et al, Cell*, 2021
Kemp *et al, Nature,* 2021
Troung *et al, eBioMedicine*, 2021
Corey *et al*, *New Engl J Med*, 2021

Outline

- Exploration of the types of immune responses induced by vaccination
  - The Spike protein: the target for protective immunity
  - Focus on B cell responses: how immunizing with one variant can protect against other variants

- The impact of immunosuppression on vaccine-induced immunity
  - Associations of specific MOAs on humoral responses
  - Nuances in antibody quality: lessons from TNF inhibition
  - Impact of holding medications: lessons from MTX
  - Role of providing additional doses: lessons from solid organ transplant pts and on BCDT

- Pre-exposure prophylaxis: monoclonal antibodies (tixgevimab/cilgavimab)
  - Discussion on protection against variants of concern
  - Early data on preventing severe infection

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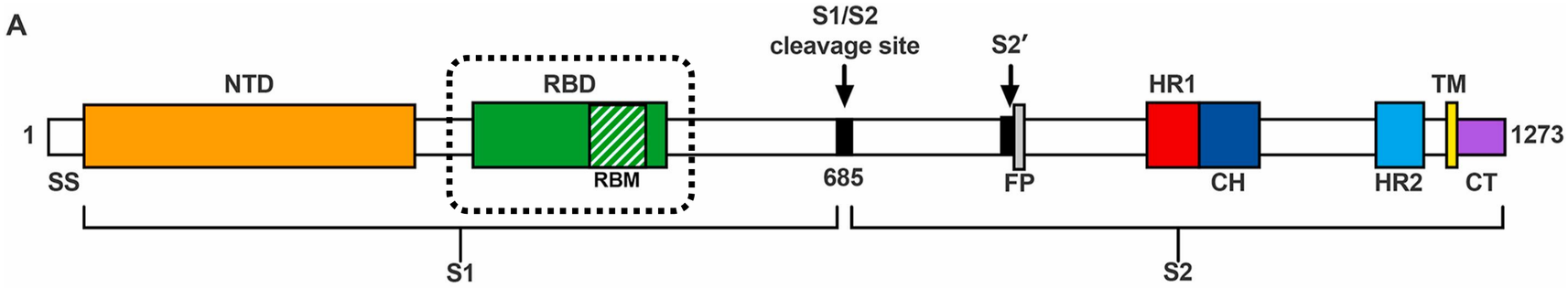
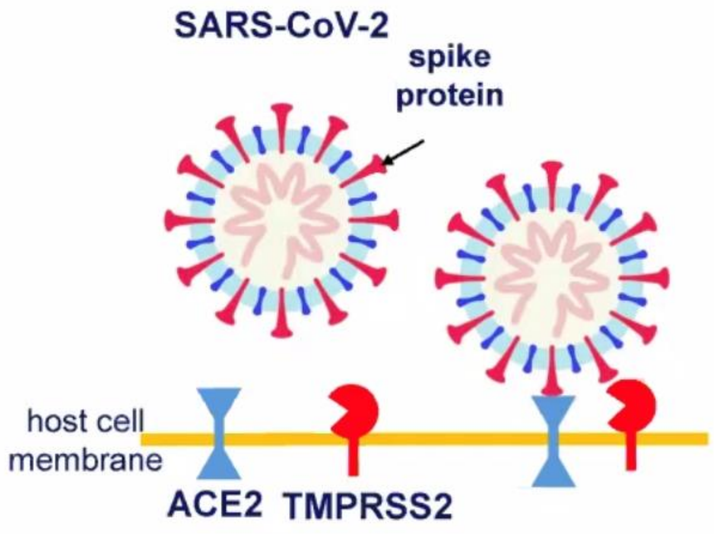
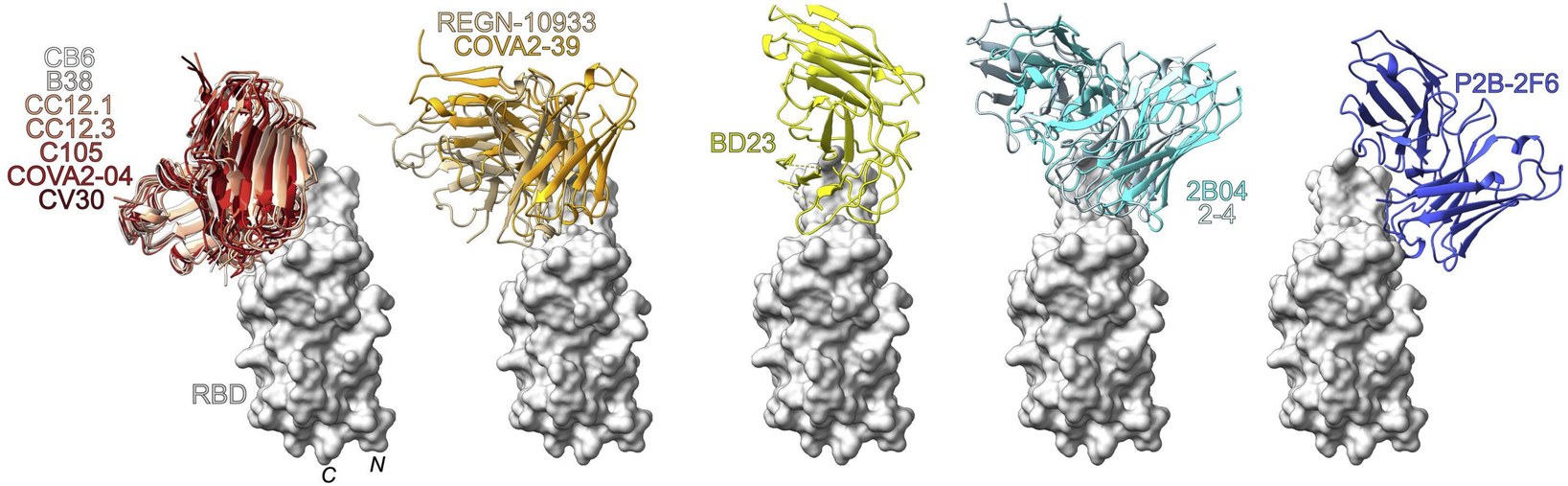
SARS-CoV-2: Spike protein key to vaccine protection

Most potently neutralizing mAbs recognize the RBD of Spike

RBD: receptor binding domain
RBM: receptor binding motif



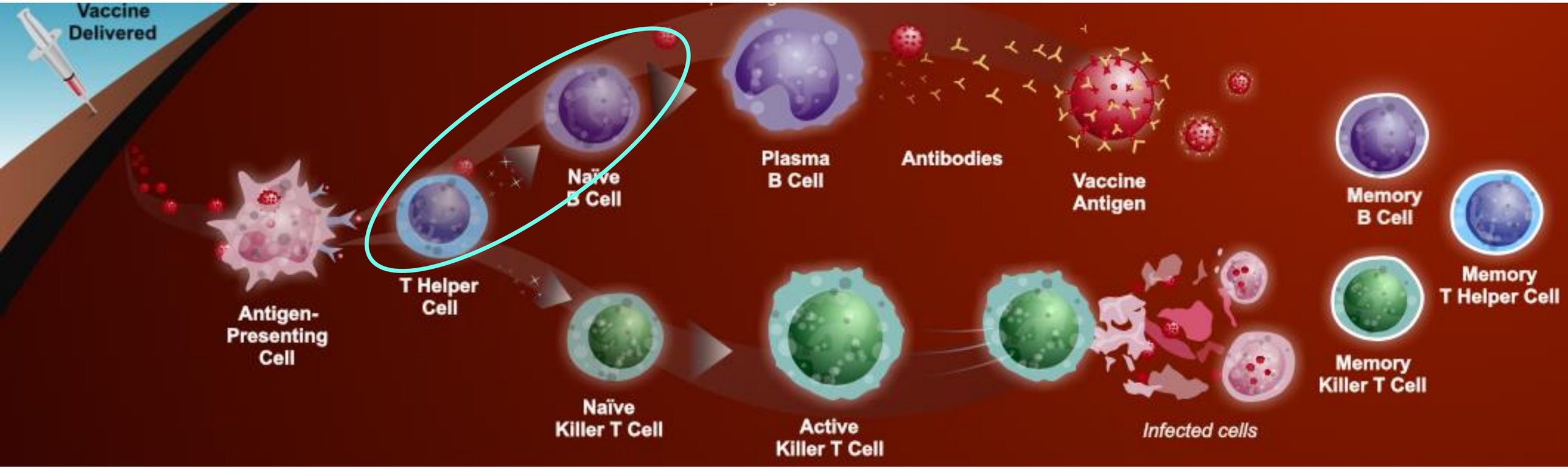




Case *et al., Virology*, 2020
Errico *et al., Cell Reports,* 2021

Simple view of how vaccines works

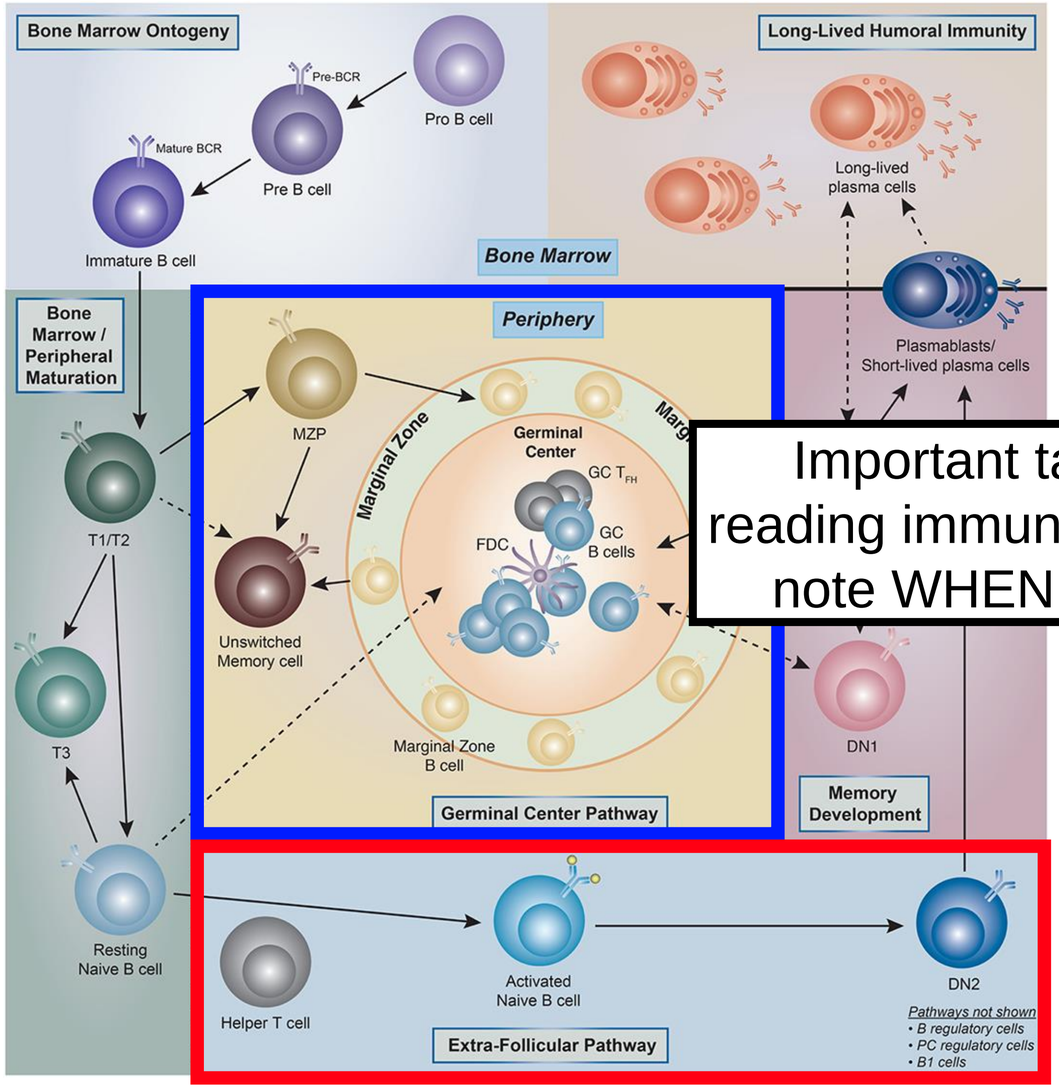
Successful immune responses due to vaccination includes production of protective antibodies and generation of memory cells



The College of Physicians of Philadelphia (https://www.historyofvaccines.org/content/how-vaccines-work)

How does immunizing against one variant protect us from several variants?

Role of the germinal center



- The role of the germinal center reaction for high-quality antibody production
  - Somatic hypermutation (SHM): this is good to enhance antibody diversity
  - Affinity maturation: this is good to increase antibody binding to antigen
  - Isotype switching: this is good to help with antibody
  - cells
  - a couple weeks to mature

Important take-home point: when reading immunogenicity papers, need to note WHEN the samples are taken

- But what about this extrafollicular pathway?
  - Rapid onset of activity (within days)
  - Disadvantages
    - Attenuated proliferation: reduced SHM potential, reduced Ab diversity and binding strength
    - Minimal memory B cell formation

Sanz *et al., Front Immunol*, 2019

Germinal centers persist after SARS-CoV-2 mRNA vaccination for months

Likely >7 months

SARS-CoV-2 mRNA vaccines induce persistent human germinal centre responses

Nature | Vol 596 | 5 August 2021 | 109

https://doi.org/10.1038/s41586-021-03738-2

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Jackson S. Turner[1,12], Jane A. O'Halloran[2,12], Elizaveta Kalaidina[3], Wooseob Kim[1], Aaron J. Schm… James Brett Ca… Michael K. Kle… Florian Kramm… Ali H. Ellebedy…

nature

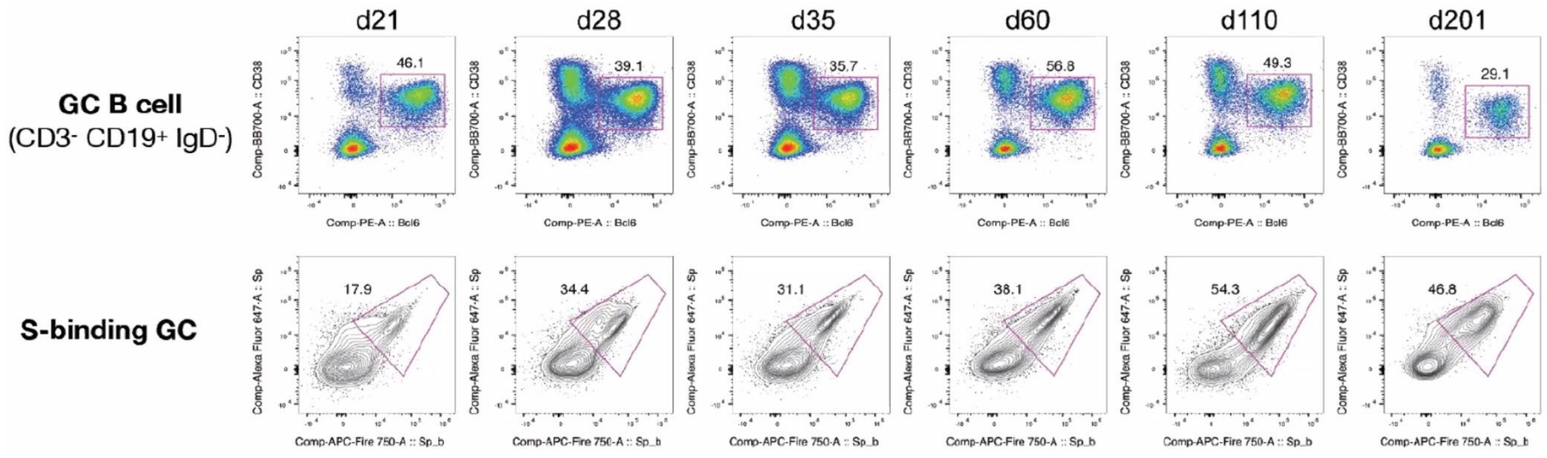
https://doi.org/10.1038/s41586-022-04527-1

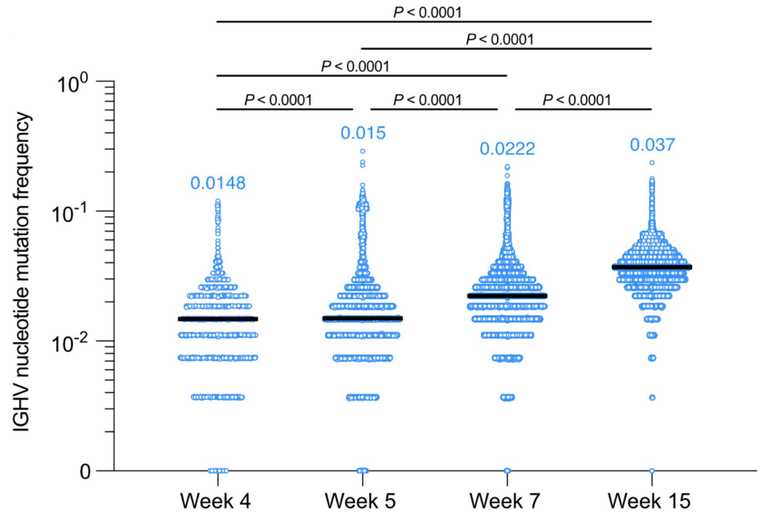
Accelerated Article Preview

Germinal centre-driven maturation of B cell response to mRNA vaccination

…ou, Stephen C. Horvath, Aaron J. Schmitz, Alexandria J. Sturtz, …, Elizaveta Kalaidina, Mahima Thapa, Wafaa B. Alsoussi, …bert, Teresa Suessen, Luis Parra-Rodriguez, Philip A. Mudd, …D. Middleton, Sharlene A. Teefey, Iskra Pusic, Jane A. O'Halloran, …S. Turner & Ali H. Ellebedy

Long duration of GC responses likely has major implications on reintroducing immunosuppressive medications





Influenza vax: Turner *et al*, *Nature*, 2020

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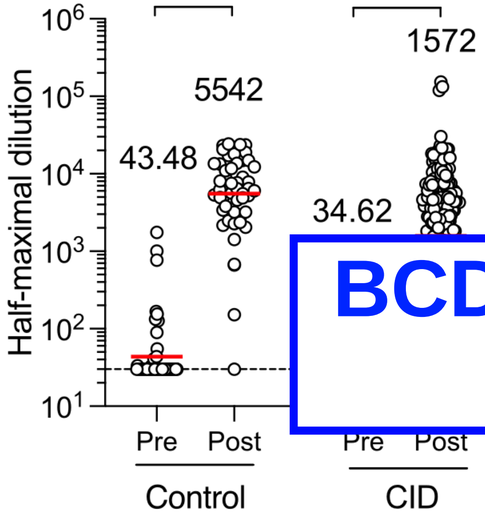
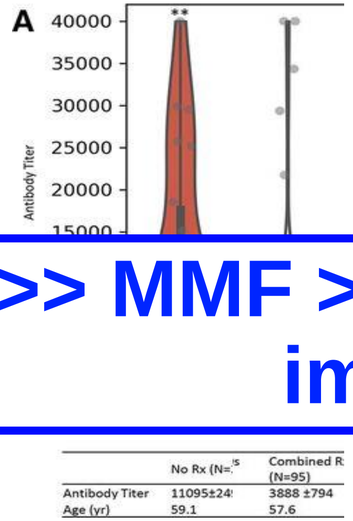
Antibody responses in the immunosuppressed with IMIDs

Consensus: most can generate responses *immediately* after full series of vaccine

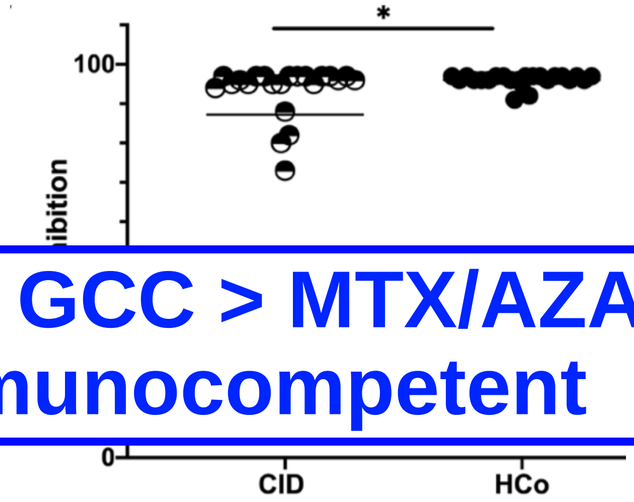
BCDT >> MMF >> GCC > MTX/AZA/JAKi/TNFi > immunocompetent



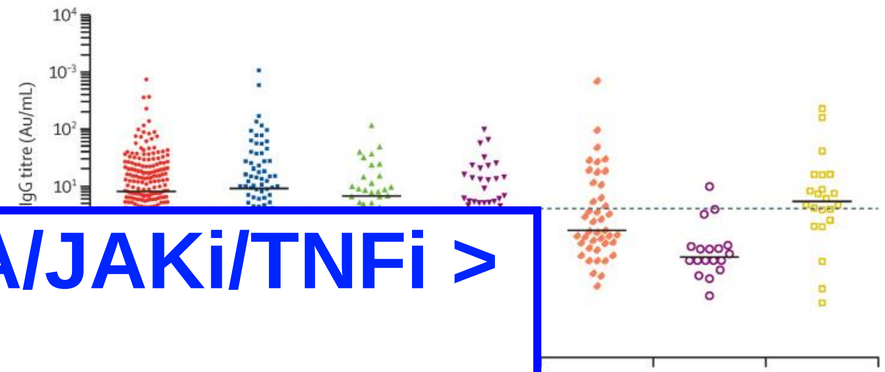
COVaRiPAD
(WashU/UCSF)



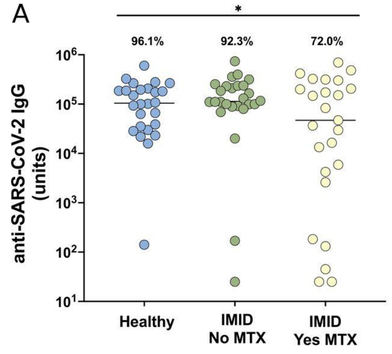
Israel
(Haifa)



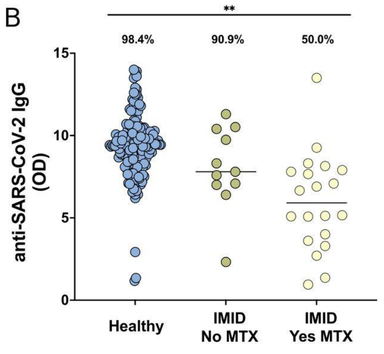
Germany
(Schleswig-Holstein)



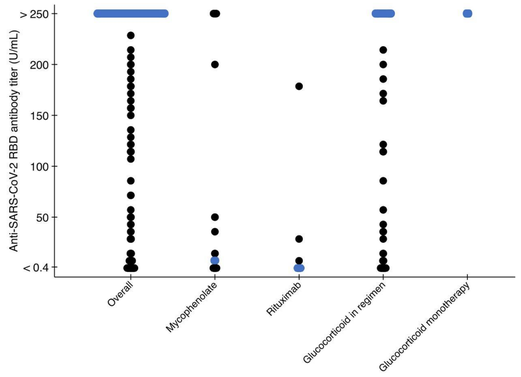
Netherlands



SAGA
(NYU)



Germany
(Erlangen)



Johns Hopkins

Study participants, n	Seropositivity rate, n (% of total)	Serum anti-S1/S2 IgG titre, mean±SD, BAU/mL
Controls, n=121	121 (100)	218.6±82.06
Patients with AIIRD, n=686	590 (86.0)*	132.9±91.7*
RA, n=263	216 (82.1)	108.7±84.7
PsA, n=165	160 (96.9)	162.0±71.7
AxSpA, n=68	67 (98.5)	173.1±90.1
SLE, n=101	93 (92.1)	161.9±105.2
IIM, n=19	7 (36.8)	42.9±62.6
LVV, n=21	20 (95.2)	143.3±84.6
AAV, n=26	8 (30.8)	40.3±73.2
Other vasculitis, n=23	19 (86.6)	122.7±87.9

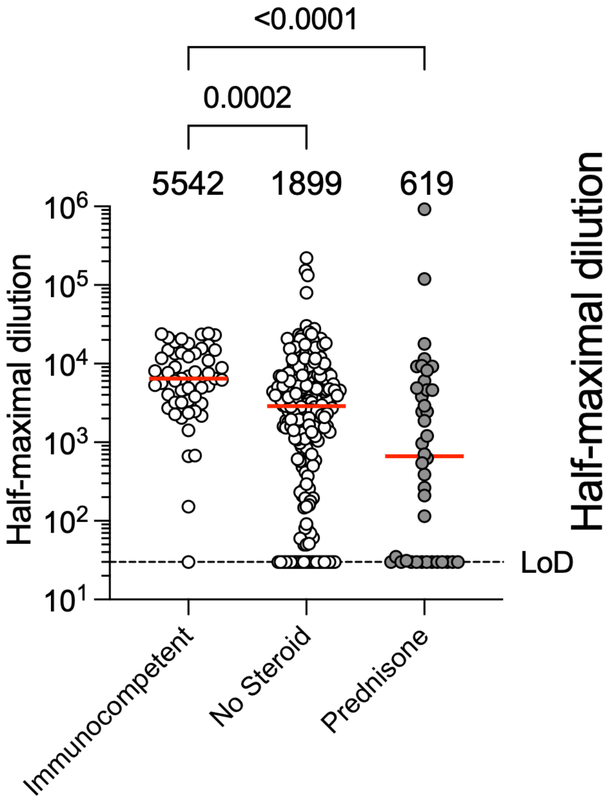
Israel
(Tel Aviv)

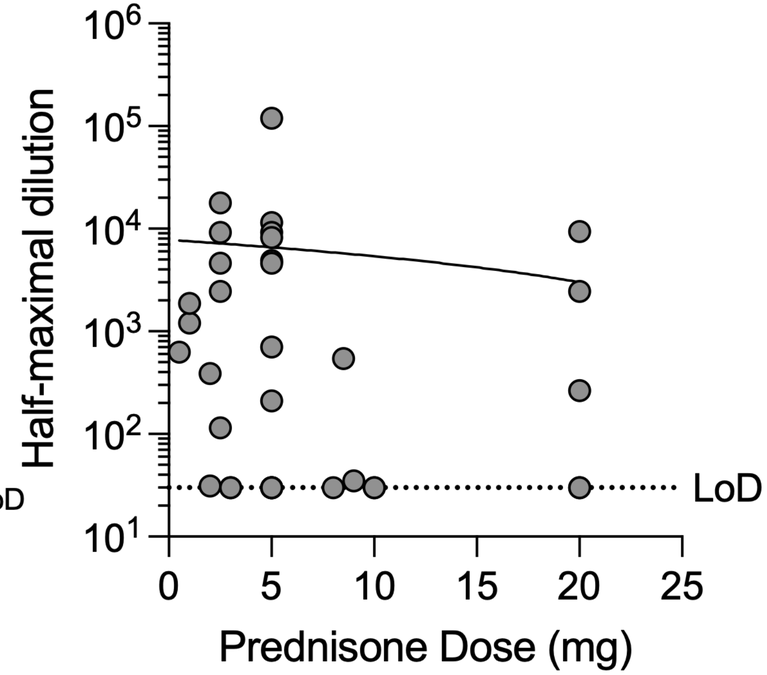
Boekel *et al*, *Lancet Rheumatol*, 2021
Braun-Moscovici *et al*, *Ann Rheum Dis*, 2021
Connolly *et al*, *Ann Intern Med*, 2021
Deepak *et al*, *Ann Intern Med*, 2021
Furer *et al*, *Ann Rheum Dis*, 2021
Geisen *et al*, *Ann Rheum Dis*, 2021
Haberman *et al*, *Ann Rheum Dis,* 2021
Mahil *et al*, *Lancet Rheumatol*, 2021
Prendecki *et al, Ann Rheum Dis*, 2021
Ruddy *et al*, *Ann Rheum Dis,* 2021
Simon *et al*, *Ann Rheum Dis*, 2021

Glucocorticoid immunogenicity

Dose-dependence unclear

- 9-fold reduction (n=40) compared to immunocompetent
- Even some on low-dose (≤ 5 mg/day PDN equivalent) mounted very poor responses
  - May be confounded by concomitant medication use
    - Boekel *et al, Lancet Rheumatol*, 2021
    - Ruddy *et al, Ann Rheum Dis*, 2021





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Boekel *et al*, *Lancet Rheumatol*, 2021
Haberman *et al*, *Ann Rheum Dis,* 2021

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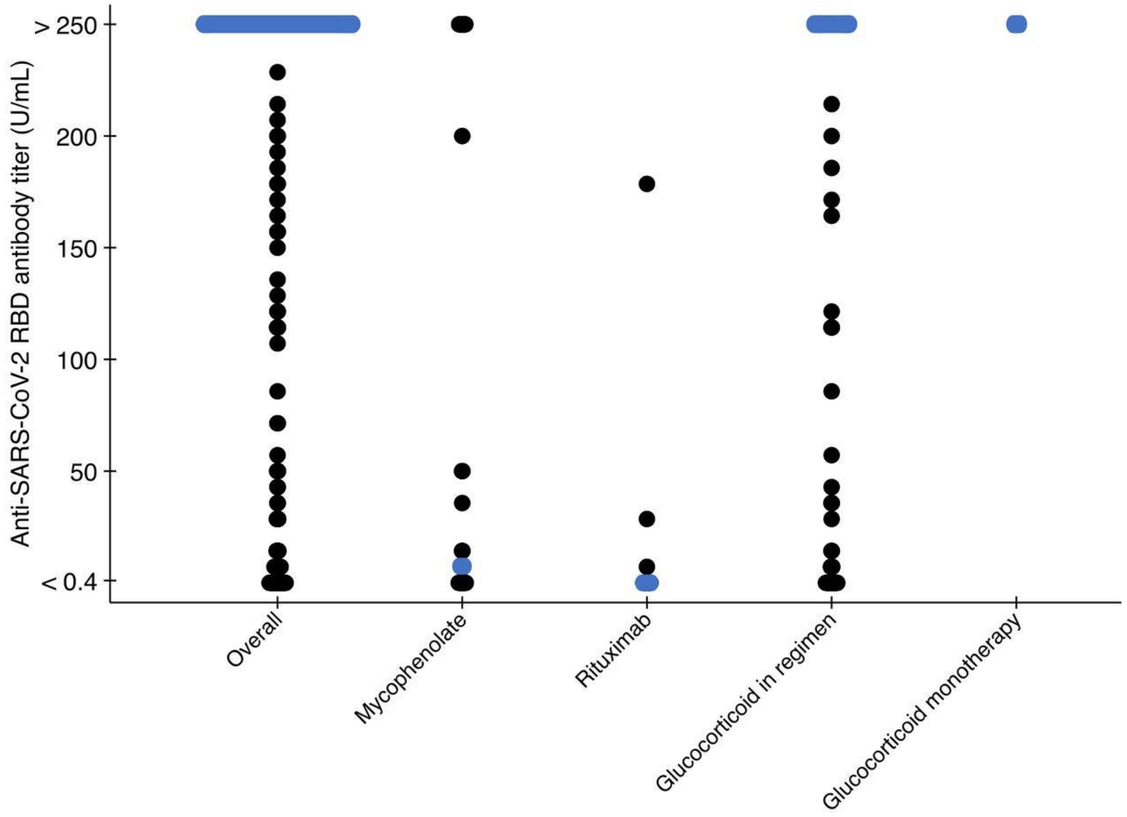
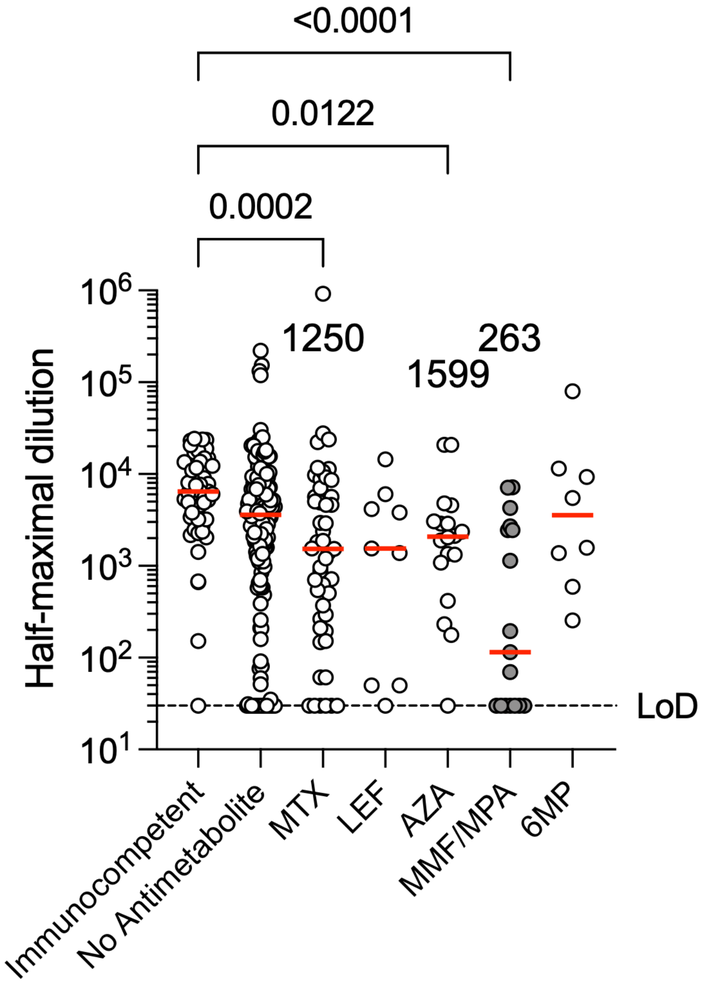


Ruddy *et al*, *Ann Rheum Dis,* 2021

Antimetabolite immunogenicity

MMF/MPA greatly blunts humoral responses

- Compared to immunocompetent:
  - MMF/MPA (n=17): 21-fold reduction
  - MTX (n=51): 4.4-fold reduction
  - AZA (n=18): 3.5-fold reduction



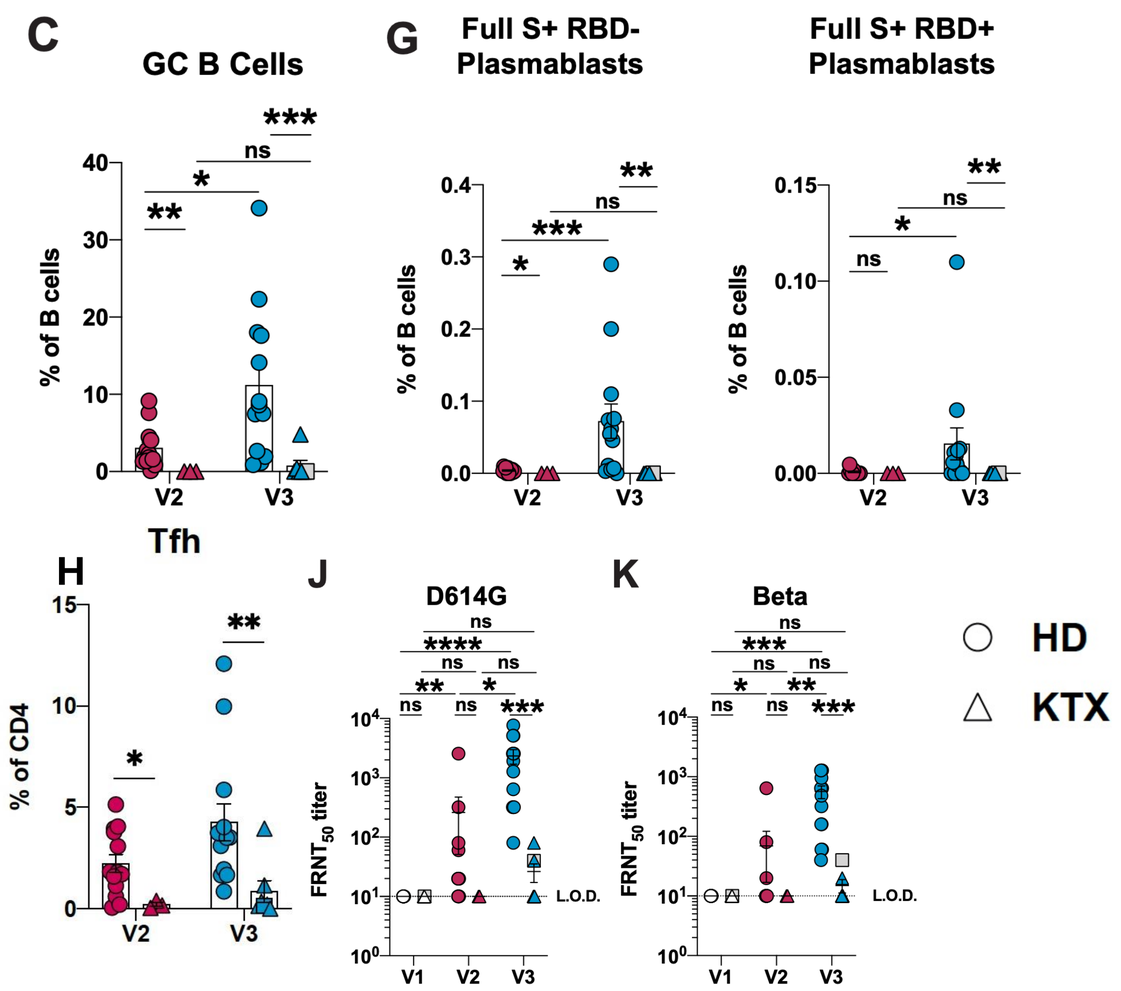
Deepak *et al, Ann Int Med,* 2021
Boekel *et al*, *Lancet Rheumatol*, 2021
Haberman *et al*, *Ann Rheum Dis,* 2021

Antimetabolite immunogenicity

GC machinery virtually absent in kidney transplant patients

- Major GC issues in kidney transplant patients after vaccination (likely similar to MMF patients):
  - No GC B cells (C)
  - No antibody producing cells to Spike (G)
  - Greatly reduced Tfh cells (H)
  - No neutralizing antibodies (J and K)

  - V1: prevax, V2: after 1st dose, V3: after 2nd dose

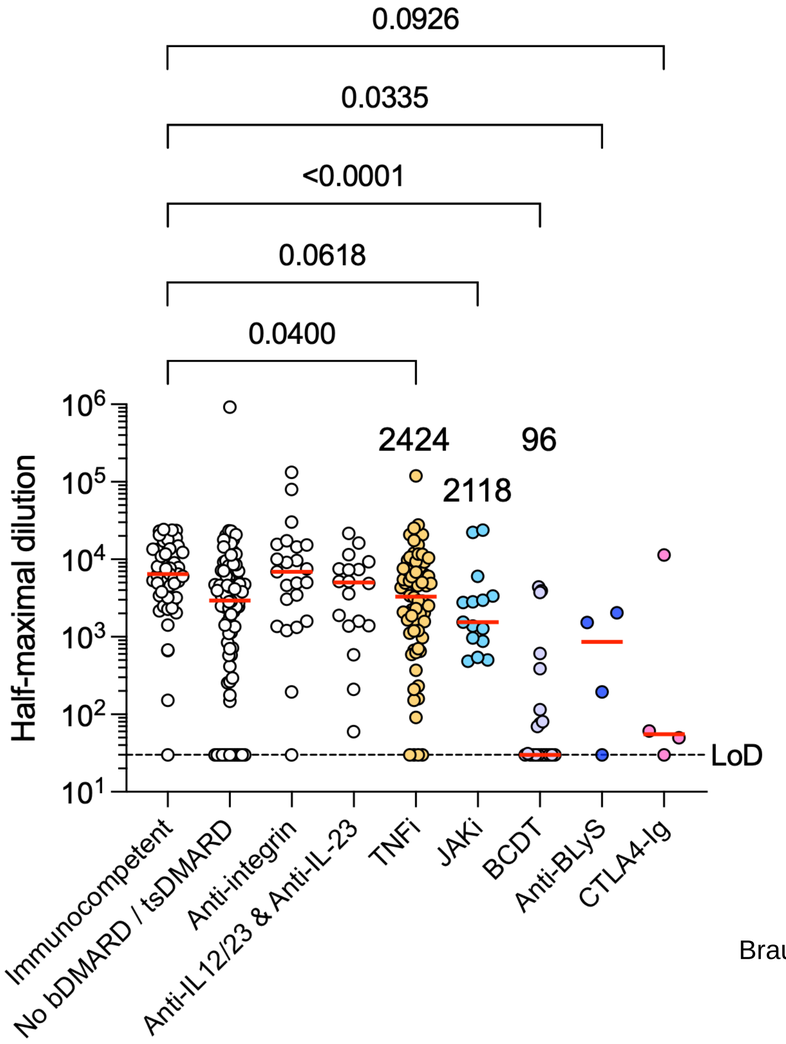


Lederer *et al, Cell*, 2022

bDMARD/tsDMARD immunogenicity

BCDT virtually eliminates humoral responses

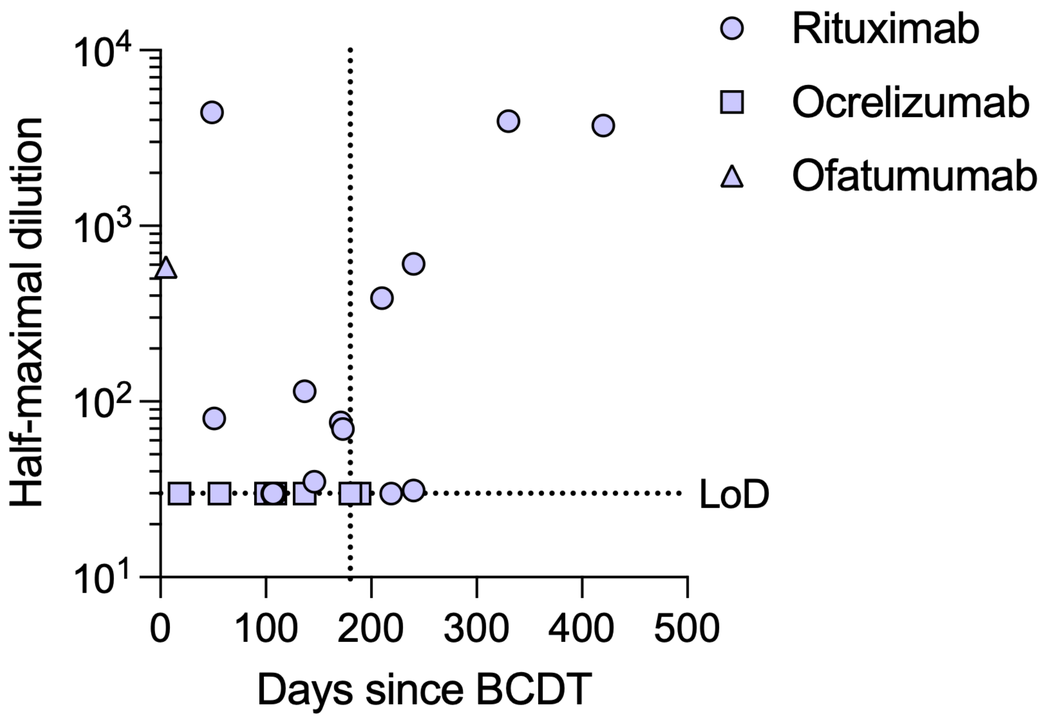
- Compared to immunocompetent:
  - BCDT (n=21): 57.7-fold reduction
  - JAKi (n=15): 8.6-fold reduction
  - *TNFi (n=68): 2.3-fold reduction (we'll come back to TNFi later…)*

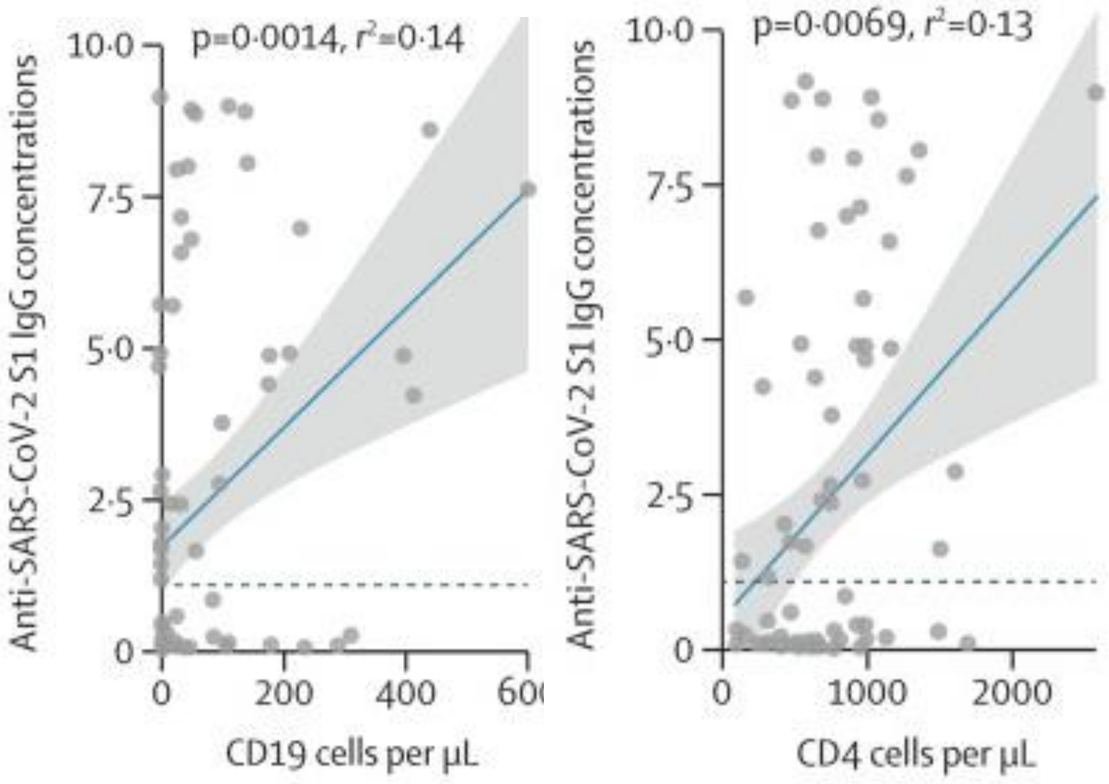


Boekel et al, Lancet Rheumatol, 2021
Braun-Moscovici et al, Ann Rheum Dis, 2021
Deepak et al, Ann Intern Med, 2021
Furer et al, Ann Rheum Dis, 2021
Haberman et al, Ann Rheum Dis, 2021
Mahil et al, Lancet Rheumatol, 2021

BCDT immunogenicity

Timing may be important (6-9 months?)



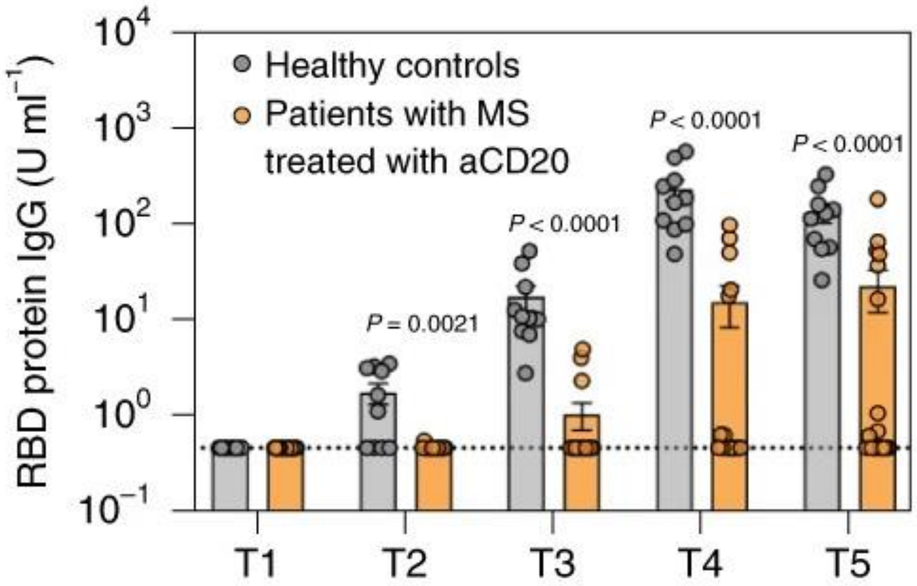


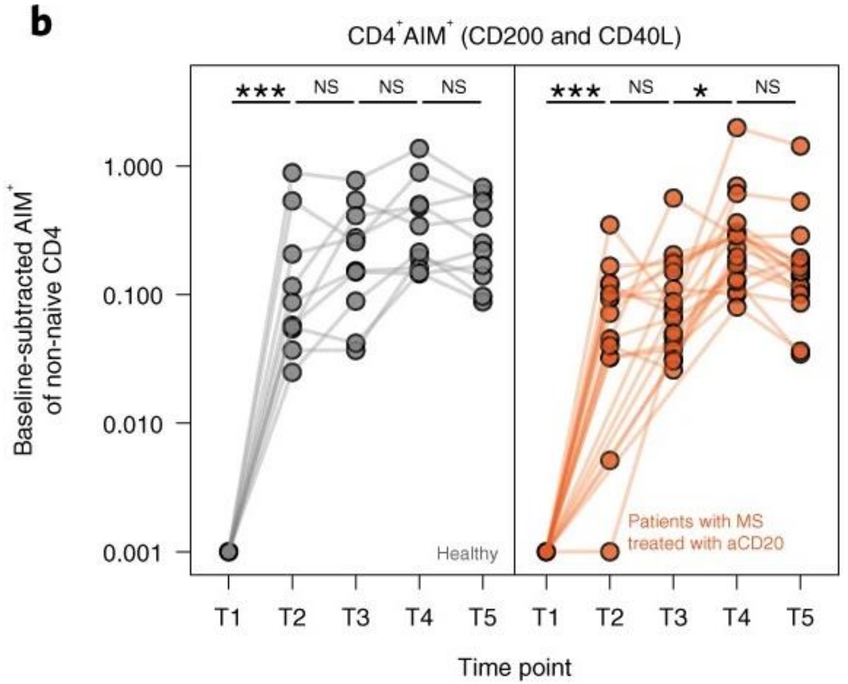
Humoral responses somewhat associate with presence of peripheral B and T cells in other studies

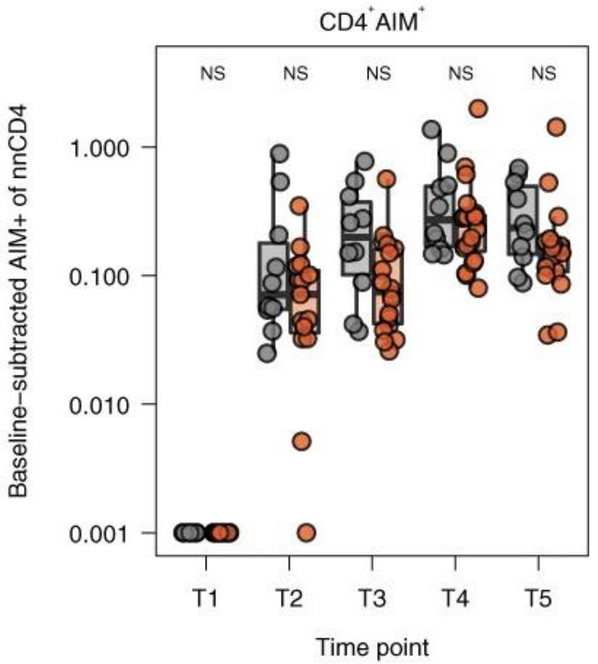
Moor *et al, Lancet Rheumatol*, 2021
Stefanski *et al, Arthritis Rheumatol*, 2021
Schulz *et al, Front Immunol,* 2021

BCDT immunogenicity

Reductions in circulating memory B cells, Tfh cells (albeit modest)







Apostolidis *et al, Nat Med,* 2021, PMID: 34522051

Breakthrough infections

Delta predominance correlated with increased rate of breakthrough infections

Table 2. COVID-19 Breakthrough Infection Among Patients With Immune Dysfunction

Patient group	Pre-Delta variant period			Post-Delta variant period		
	Total person-months	No. of breakthrough infection cases	Incidence rate per 1000 person-months (95% CI)[a]	Total person-months	No. of breakthrough infection cases	Incidence rate per 1000 person-months (95% CI)[a]
Partial vaccination						
Overall	553 478	2165	2.9 (2.9-2.9)	218 443	1562	9.6 (9.5-9.7)
No immune dysfunction	524 821	2007	2.8 (2.8-2.9)	205 139	1433	9.3 (9.2-9.4)
HIV infection	7010	37	3.6 (3.6-3.7)	3354	26	11.9 (11.4-12.4)
MS	2418	<20[b]	3.5 (3.5-3.6)	954	<20[b]	11.6 (10.8-12.4)
RA	10 718	46	3.7 (3.7-3.8)	4003	27	12.2 (11.8-12.6)
SOT	7007	66	6.3 (6.2-6.4)	4164	55	20.6 (19.4-21.8)
BMT	1503	<20[b]	3.4 (3.3-3.5)	829	<20[b]	11.2 (10.3-12.2)
Full vaccination						
Overall	1 501 418	2808	2.2 (2.2-2.2)	2 162 800	16 382	7.3 (7.3-7.4)
No immune dysfunction	1 423 568	2484	2.2 (2.2-2.2)	2 053 050	15 255	7.1 (7.1-7.2)
HIV infection	17 336	45	2.8 (2.8-2.8)	26 844	250	9.1 (8.8-9.4)
MS	6568	<20[b]	2.7 (2.7-2.8)	9644	85	8.9 (8.4-9.3)
RA	32 847	103	2.8 (2.8-2.9)	43 044	408	9.3 (9.1-9.6)
SOT	17 314	137	4.8 (4.7-4.9)	24 647	343	15.7 (15.1-16.4)
BMT	3786	21	2.6 (2.6-2.7)	5581	41	8.6 (8.0-9.1)

Abbreviations: BMT, bone marrow transplantation; MS, multiple sclerosis; N3C, National COVID Cohort Collaborative; RA, rheumatoid arthritis; SOT, solid organ transplant.

[a] Estimated incidence rate was based on unadjusted Poisson regression model.

[b] N3C policy requires all cells that contain fewer than 20 persons to be reported as <20.

Sun *et al.*, *JAMA Int Med*, 2022, PMID: 34962505

Breakthrough infections

Increased rate of associated with low Ab responses

	Patients with immune-mediate inflammatory diseases on immunosuppressants (n= 3207)	Patients with immune-mediate inflammatory diseases not on immunosuppressants (n=985)	Healthy controls (n=822)
SARS-CoV-2 breakthrough infection			
Cumulative incidence	148 (5%)	52 (5%)	33 (4%)
Incidence rate, events per 1000 person-months	8·0	9·2	6·6

	Odds ratio (95% CI)	p value
Humoral determinants analyses (T2B! cohort only)		
Multivariable model (N=2225; 108 events)‡		
No seroconversion after full vaccination	1·00 (ref)	..
Seroconversion after full vaccination	0·58 (0·34–0·98)	0·044
Multivariable model (N=1983; 90 events)‡		
Anti-RBD titre in AU/mL		
4·000 to <53·025	0·97 (0·50–1·88)	0·93
53·025 to <126·250	1·55 (0·88–2·73)	0·13
126·250 to <249·750§	1·00 (ref)	..
≥249·750	0·57 (0·28–1·16)	0·12

Boeckel *et al.*, *Lancet Rheumatol*, 2022

Breakthrough infections

Pre-Omicron, vaccine effectiveness very high among immunosuppressed

Rheumatoid arthritis		
SARS-CoV-2 positive (n=2127)	SARS-CoV-2 negative (n=34 018)	5.9%

Ankylosing spondylitis		
SARS-CoV-2 positive (n=476)	SARS-CoV-2 negative (n=7387)	6.1%

Psoriasis		
SARS-CoV-2 positive (n=3089)	SARS-CoV-2 negative (n=44 110)	6.5%

Inflammatory bowel disease		
SARS-CoV-2 positive (n=1702)	SARS-CoV-2 negative (n=29 609)	5.4%

	Test-positive cases	Test-negative controls	Unadjusted vaccine effectiveness (95% CI)	Adjusted vaccine effectiveness (95% CI)*
Severe outcomes				
Rheumatoid arthritis				
First dose ≥14 days	53/305 (17·4%)	6005/17 393 (34·5%)	60% (46–70)	74% (63–81)
Second dose ≥7 days	35/287 (12·2%)	14 330/25 718 (55·7%)	89% (84–92)	92% (88–95)
Third dose ≥7 days	<6/254 (<2·4%)	453/11 841 (3·8%)	NR	88% (48–97)
Ankylosing spondylitis				
First dose ≥14 days	6/46 (13·0%)	1074/3902 (27·5%)	61% (7–83)	76% (35–91)
Second dose ≥7 days	<6/42 (<14·3%)	2876/5704 (50·4%)	NR	97% (83–99)
Third dose ≥7 days	<6/41 (<14·6%)	89/2917 (3·1%)	NR	NR†
Psoriasis				
First dose ≥14 days	37/269 (13·8%)	6548/23 586 (27·8%)	59% (41–71)	72% (59–82)
Second dose ≥7 days	25/257 (9·7%)	17 230/34 268 (50·3%)	89% (84–93)	92% (86–95)
Third dose ≥7 days	<6/232 (<2·6%)	245/17 283 (1·4%)	NR	NR†
Inflammatory bowel disease				
First dose ≥14 days	30/173 (17·3%)	4570/15 907 (28·7%)	48% (23–65)	65% (44–78)
Second dose ≥7 days	14/157 (8·9%)	11 560/22 897 (50·5%)	90% (83–94)	94% (88–97)
Third dose ≥7 days	<6/145 (<4·1%)	300/11 637 (2·6%)	NR	NR†

Widdifield *et al.*, *Lancet Rheumatol*, 2022, PMID: 35441151

Outline

- Exploration of the types of immune responses induced by vaccination
  - The Spike protein: the target for protective immunity
  - Focus on B cell responses: how immunizing with one variant can protect against other variants

- The impact of immunosuppression on vaccine-induced immunity
  - Associations of specific MOAs on humoral responses
  - Nuances in antibody quality: lessons from TNF inhibition
  - Role of providing additional doses: lessons from solid organ transplant pts and on BCDT
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So you have antibodies: are you protected?

Lessons from TNFi users

	No. (%) 3 months after second vaccination below NT_{50} of 1/50				No. (%) 5[a] or 6[b] months after second vaccination below NT_{50} of 1/50			
Class	Total	WA1/2020 D614G	Wash-B.1.351	B.1.617.2	Total	WA1/2020 D614G	Wash-B.1.351	B.1.617.2
Immunocompetent volunteers	25	0 (0)	4 (16)	2 (8)	24	0 (0)	5 (22)	4 (17)
Individuals with CID	75	14 (19)	26 (35)	27 (36)	43	14 (33)	24 (56)	25 (58)
TNFi	12	3 (27)	8 (67)	8 (67)	7	5 (71)	6 (86)	7 (100)
Antimetabolites	12	2 (17)	5 (42)	4 (33)	5	2 (40)	2 (40)	2 (40)
Antimalarials	8	0 (0)	1 (12.5)	3 (37.5)	7	1 (14)	4 (57)	3 (43)
Anti-integrin	9	0 (0)	1 (11)	0 (0)	3	0 (0)	0 (0)	1 (33)
NSAIDs	9	1 (11)	1 (11)	1 (11)	5	1 (20)	2 (40)	2 (40)
Anti-IL-23	9	1 (11)	2 (22)	2 (22)	3	0 (0)	1 (33)	1 (33)

[a]Samples from individuals with CID were collected 5 months after completion of vaccination.

[b]Immunocompetent volunteer samples were collected 6 months after completion of vaccination.

Immunosuppression generally reduced cross-variant neutralization titers, but those on TNFi had substantial issues

Chen *et al, Med,* 2021, PMID: 34812429

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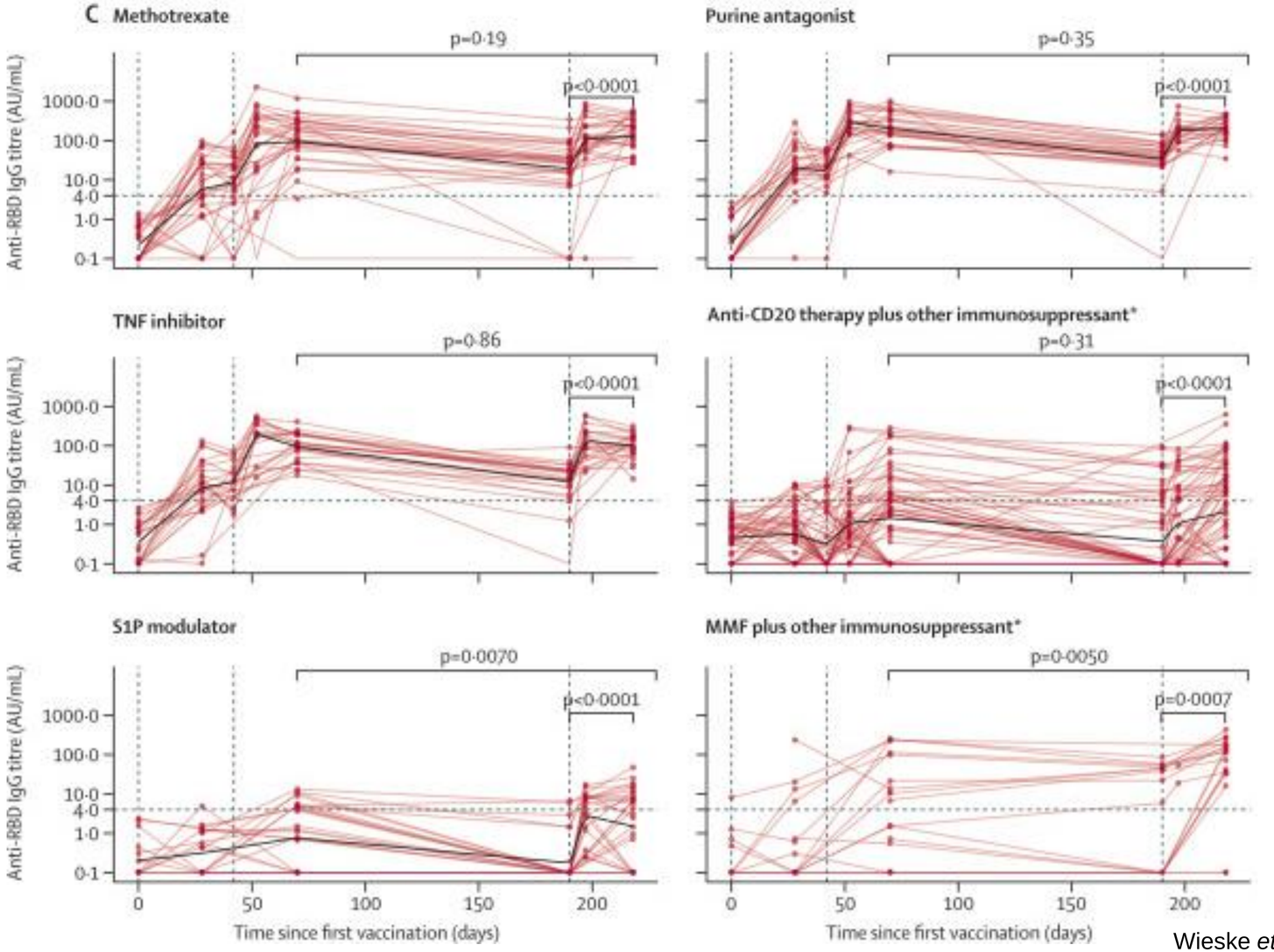
Beneficial effects of boosting

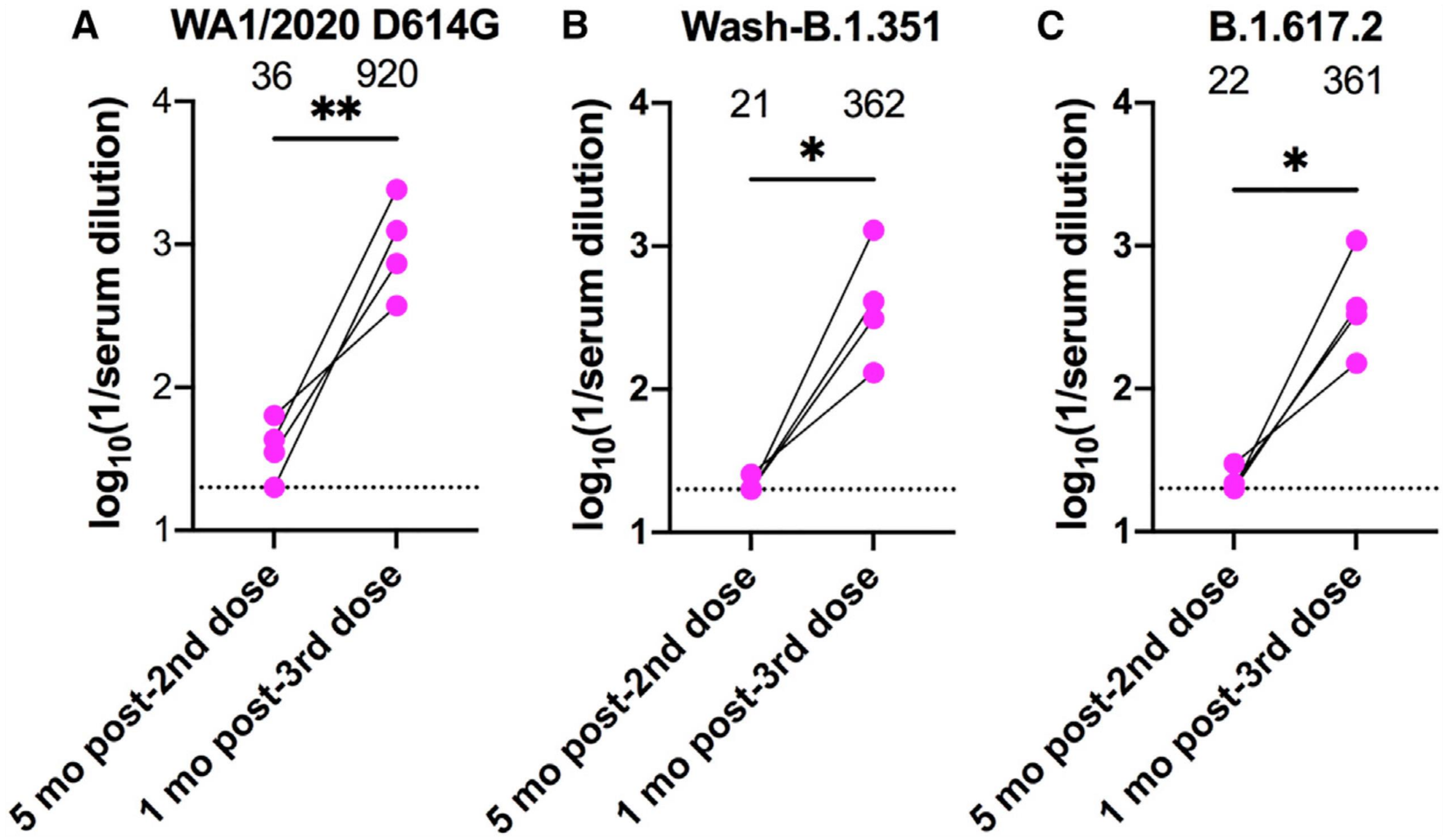
Vast majority of immunosuppressed improved Ab titers after 3rd dose



Wieske *et al, Lancet Rheumatol,* 2022, PMID:35317410

Beneficial effects of boosting

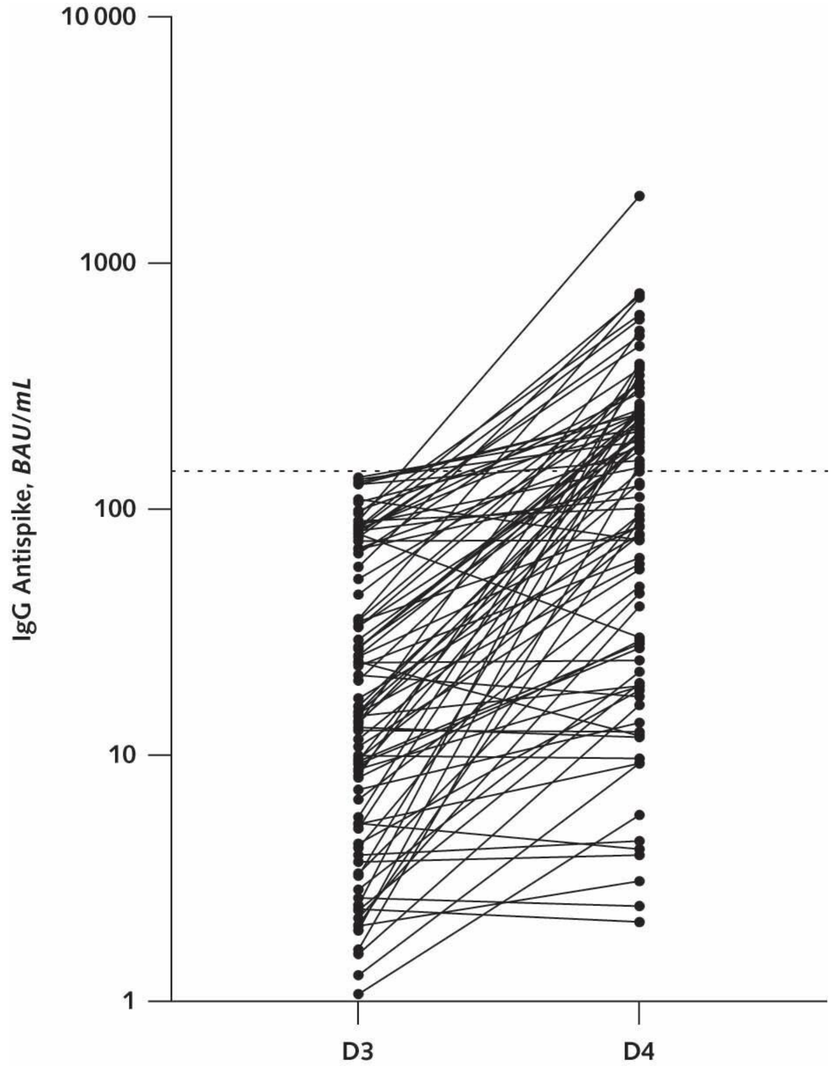
All TNFi users restored cross-variant neutralization after 3rd dose



Chen *et al, Med,* 2021, PMID: 34812429

Revisiting boosting: can it help everyone?

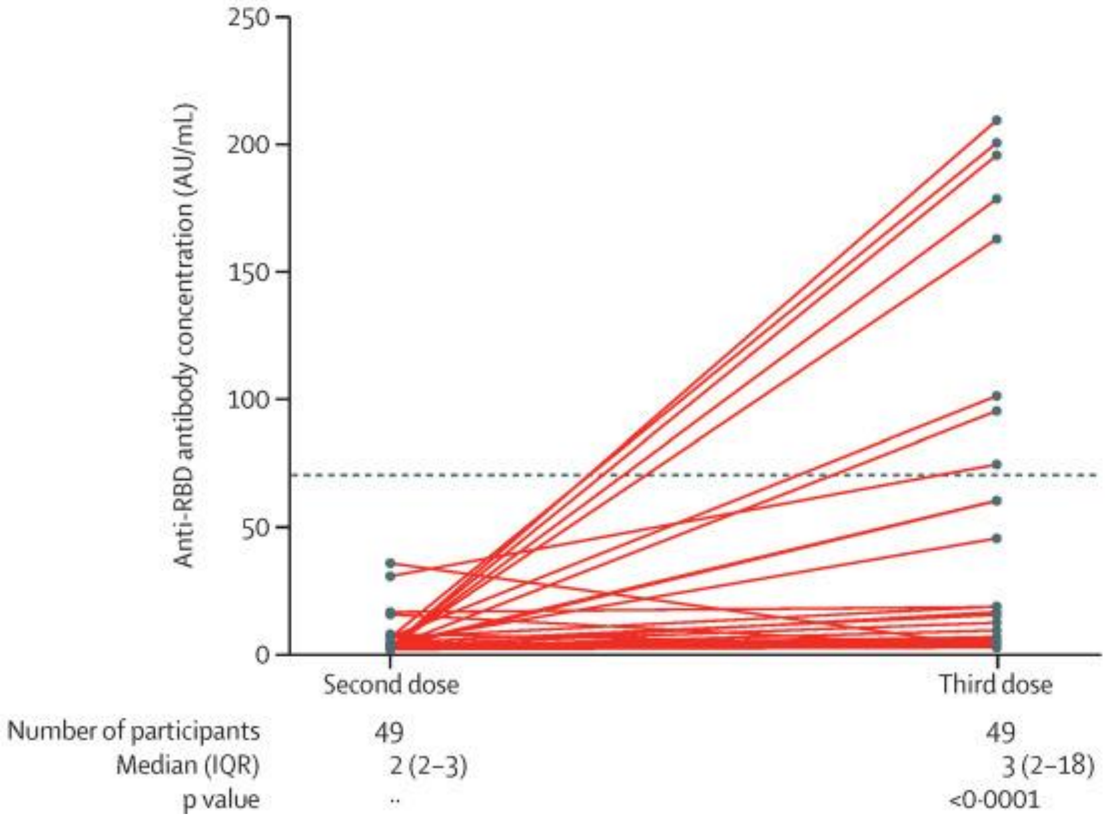
Patients with SOT continue to improve Ab titers with 4th dose

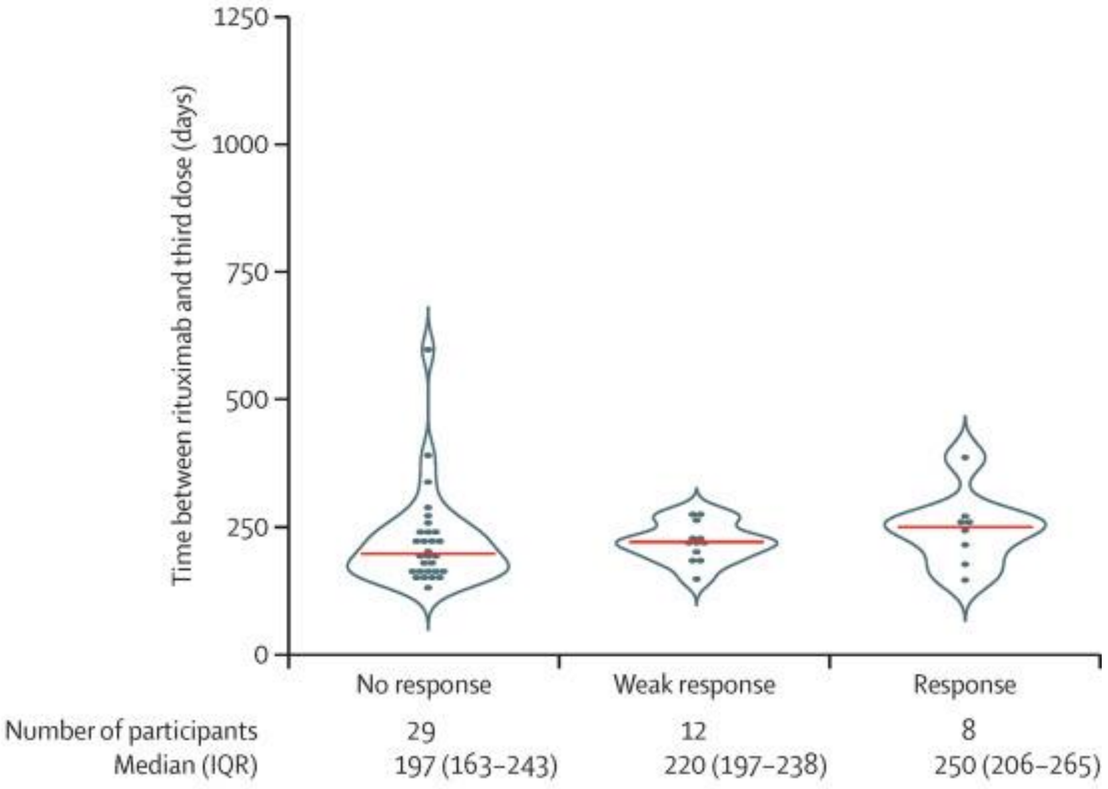


Caillard *et al, Ann Int Med,* 2022, PMID: 35007148
Alejo *et al*, *Transplantation*, 2021, PMID: 34428188
Kamar *et al, JAMA Netw Open*, 2021, PMID: *34817587*

Revisiting boosting: can it help everyone?

Majority on BCDT with poor responses still have poor responses post-booster





Jyssum *et al, Lancet Rheumatol,* 2022, PMID: 34977602

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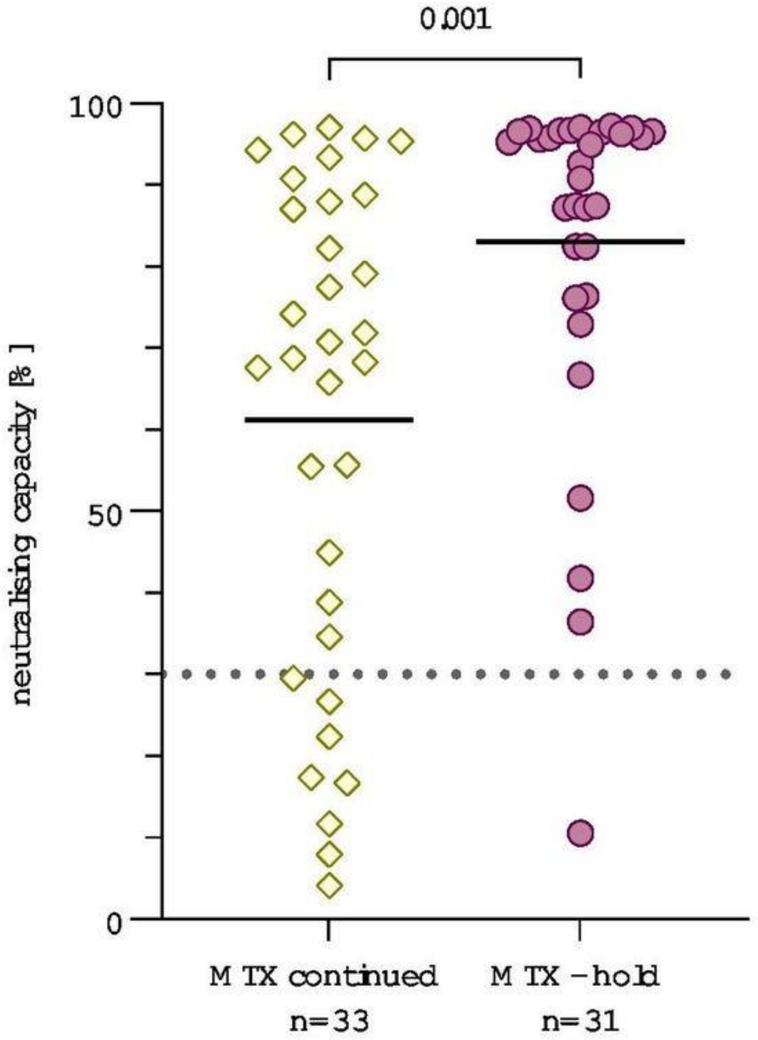
Holding meds: can it also help?

Neutralizing Ab titers to D614G improve with holding MTX for ≥10 days



De Silva *et al, Ann Rheum Dis,* 2022, PMID: 35288376

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Tixagevimab/cilgavimab (Evusheld)

Concerns about ability to neutralize Omicron subvariants: Is it useless?

May 31, 2022

Evusheld Appears Less Effective Against Omicron for Patients With Blood Cancer

Jonathan Goodman, MPhil

Tixagevimab-cilgavimab (Evusheld) appears less effective against the omicron variant of SARS-CoV-2 in patients with hematologic cancer, according to research published in *Cancer Cell*.

Researchers found that a single 150 mg dose of tixagevimab-cilgavimab demonstrated neutralizing activity against wild-type SARS-CoV-2 but not the omicron variant.

The current recommended dose, 300 mg, seemed to be more effective against omicron than the 150 mg dose, but results varied.

A single 150 mg dose of Evusheld demonstrated neutralizing activity against wild-type SARS-CoV-2 but not the omicron variant. *Source: Getty Images*

https://www.cancertherapyadvisor.com/home/cancer-topics/hematologic-cancers/covid19-omicron-blood-cancer-evusheld-appears-less-effective/
Accession date: 14 July 2022

Tixagevimab/cilgavimab (Evusheld)

Background

- Two mAbs (IgG1κ) with high affinity binding to distinct epitopes on spike protein
  - Kd tixagevimab = 2.76 pM
  - Kd cilgavimab = 13.0 pM
  - Kd combination = 13.7 pM
- Each Ab (300 mg, 1.5 mL) administered separately IM (gluteal ideally)
- Modifications to Fc domain nearly tripled IgG $t_{1/2}$

Table 4 Summary of PK Parameters and Properties of Tixagevimab and Cilgavimab Following a Single EVUSHELD Intramuscular Dose

PK Parameters	Tixagevimab	Cilgavimab
C_{max} (µg/mL)*	16.5 (35.6)	15.3 (38.5)
T_{max} (day)†	14.0 (3.1 – 30)	14.0 (3.1 – 60)
C_1 (µg/mL)‡	4.4 (92.2)	3.9 (94.4)
C_{150} (µg/mL)§	6.6 (25.6)	5.5 (35.2)
C_{210} (µg/mL)¶	4.0 (31.6)	3.9 (37.1)
AUC_{inf} (day•µg/mL)	2529 (30.2)	2133 (31.7)
Absorption		
Bioavailability#	68.5	65.8
Distribution		
Apparent Volume of Distribution (L)#	7.7 (1.97)	8.7 (2.73)
Elimination		
Half-life (days)#	87.9 (13.9)	82.9 (12.3)
Apparent Clearance (L/day)#	0.062 (0.019)	0.074 (0.028)
Metabolism	Catabolic pathways; Same manner as endogenous IgG	
Excretion	Not likely to undergo renal excretion	

* Geomean (geometric %CV)
† Median (range)
‡ Observed geomean (geometric %CV) concentration 1 day after dosing
§ Observed geomean (geometric %CV) concentration 150 days after dosing
¶ Observed geomean (geometric %CV) concentration 210 days after dosing
# Arithmetic mean (SD)

Tixagevimab/cilgavimab (Evusheld)

FDA EUA granted for use as PrEP 08 Dec 2021

- For use in individuals ≥ 12 yo weighing ≥ 40 kg
- Broad indications for use

  Who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to an individual infected with SARS-CoV-2 **and**
  - Who have moderate to severe immune compromise due to a medical condition or receipt of immunosuppressive medications or treatments **and** may not mount an adequate immune response to COVID-19 vaccination[1] **or**
  - For whom vaccination with any available COVID-19 vaccine, according to the approved or authorized schedule, is not recommended due to a history of severe adverse reaction (e.g., severe allergic reaction) to a COVID-19 vaccine(s) and/or COVID-19 vaccine component(s).

Tixagevimab/cilgavimab (Evusheld)

Wide range of medical conditions eligible, similar to vaccine rollout

Medical conditions or treatments that may result in moderate to severe immune compromise and an inadequate immune response to COVID-19 vaccination include but are not limited to[1]:

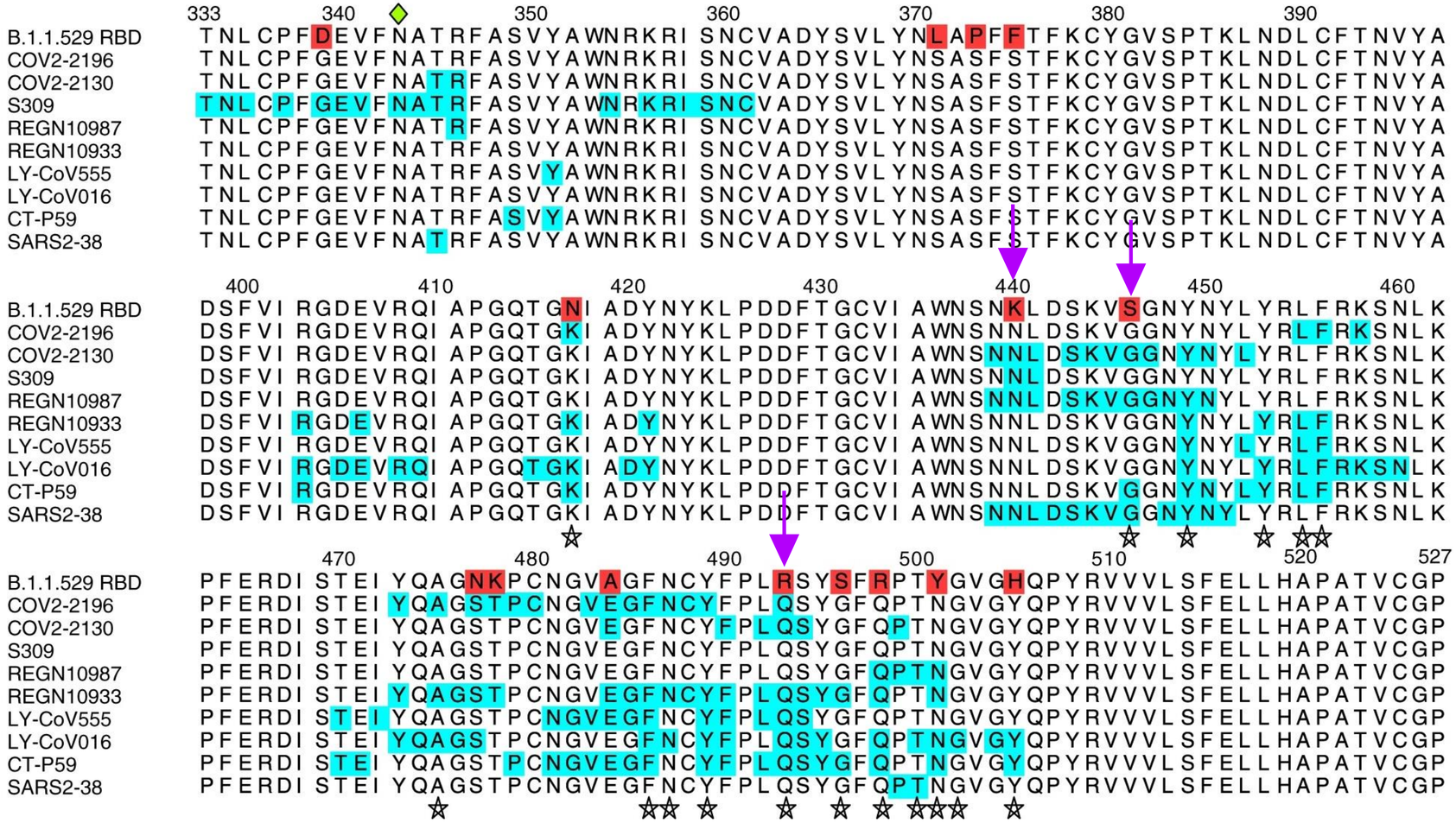
- Active treatment for solid tumor and hematologic malignancies
- Receipt of solid-organ transplant and taking immunosuppressive therapy
- Receipt of chimeric antigen receptor (CAR)-T-cell or hematopoietic stem cell transplant (within 2 years of transplantation or taking immunosuppression therapy)
- Moderate or severe primary immunodeficiency (e.g., DiGeorge syndrome, Wiskott-Aldrich syndrome)
- Advanced or untreated HIV infection (people with HIV and CD4 cell counts <200/mm^3, history of an AIDS-defining illness without immune reconstitution, or clinical manifestations of symptomatic HIV)
- Active treatment with high-dose corticosteroids (i.e., ≥20 mg prednisone or equivalent per day when administered for ≥2 weeks), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive, tumor-necrosis (TNF) blockers, and other biologic agents that are immunosuppressive or immunomodulatory (e.g., B-cell depleting agents)

- No utility of Ab testing

Tixagevimab/cilgavimab (Evusheld)

Generally, mAbs for SARS-CoV-2 have issues binding to Omicron RBD

COV2-2196: parent mAb of AZD8895 (tix)
COV2-2130: parent mAb of AZD1061 (cil)
S309: parent mAb of VIR-7831 (sotrovimab)



VanBlargan *et al, Nat Med,* 2022, PMID: 35047673

Tixagevimab/cilgavimab (Evusheld)

Generally, mAbs for SARS-CoV-2 have issues binding to Omicron RBD

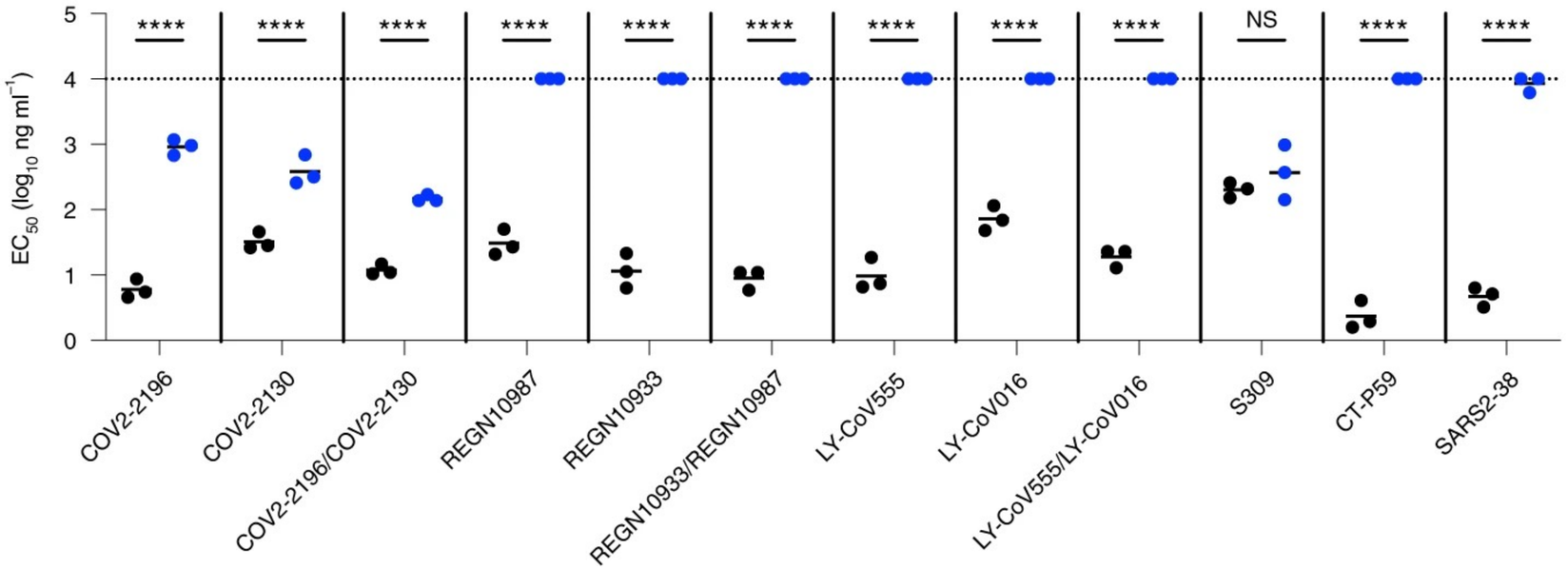
g

Vero-TMPRSS2 cells

mAb	SARS2-COV-2	
	WA1/2020 D614G	B.1.1.529
COV2-2196	6	913
COV2-2130	32	381
COV2-2196/COV2-2130	12	147
REGN10987	31	>10,000
REGN10933	11	>10,000
REGN10933/REGN10987	9	>10,000
LY-CoV555	10	>10,000
LY-CoV016	72	>10,000
LY-CoV555/LY-CoV016	19	>10,000
S309	202	373
CT-P59	2	>10,000
SARS2-38	5	8,520

147/12 = **12.5-fold reduction** in EC50 against Omicron for Evusheld

h



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S309: parent mAb of VIR-7831 (sotrovimab)

VanBlargan *et al, Nat Med,* 2022, PMID: 35047673

Cilgavimab unique in its binding of Spike

Binding site largely away from RBM of Spike

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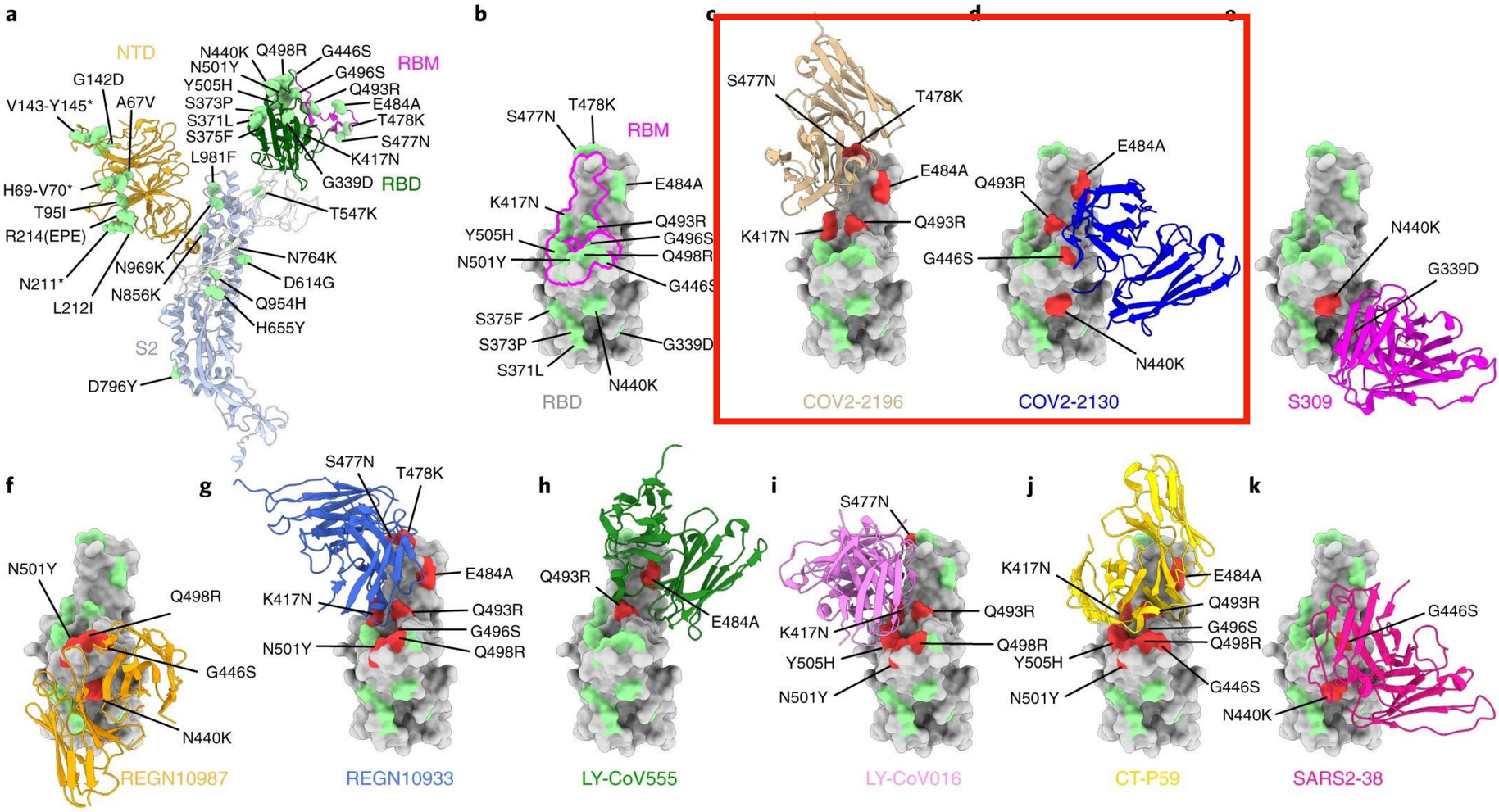

VanBlargan *et al, Nat Med,* 2022, PMID: 35047673

Tixagevimab/cilgavimab (Evusheld)

Omicron neutralization

- Is that bad? Is Evusheld DOA?
- Remember, IC50 is 147 ng/mL against BA.2
- At 7 months post-administration, serum Ab levels ~27x higher than IC50
- Thinking we should be OK?

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T_{max} (day)†	14.0 (3.1 – 30)	14.0 (3.1 – 60)
C_1 (µg/mL)‡	4.4 (92.2)	3.9 (94.4)
C_{150} (µg/mL)§	6.6 (25.6)	5.5 (35.2)
C_{210} (µg/mL)¶	4.0 (31.6)	3.9 (37.1)
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Absorption		
Bioavailability#	68.5	65.8
Distribution		
Apparent Volume of Distribution (L)#	7.7 (1.97)	8.7 (2.73)
Elimination		
Half-life (days)#	87.9 (13.9)	82.9 (12.3)
Apparent Clearance (L/day)#	0.062 (0.019)	0.074 (0.028)
Metabolism	Catabolic pathways; Same manner as endogenous IgG	
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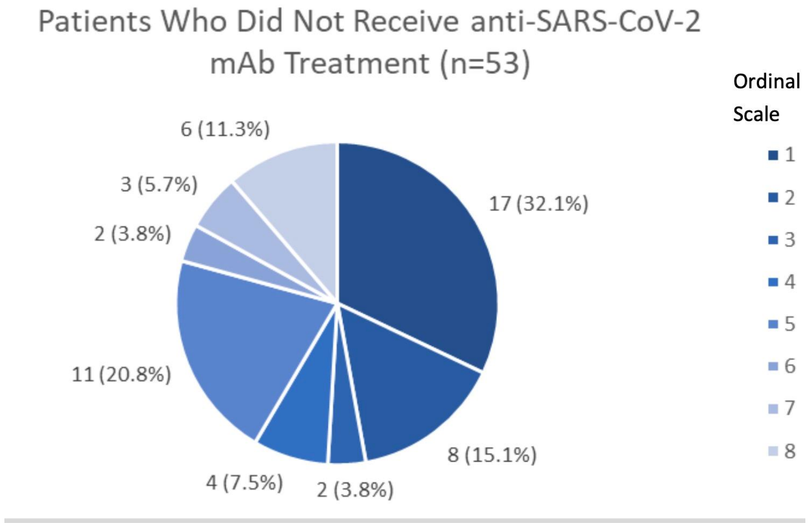
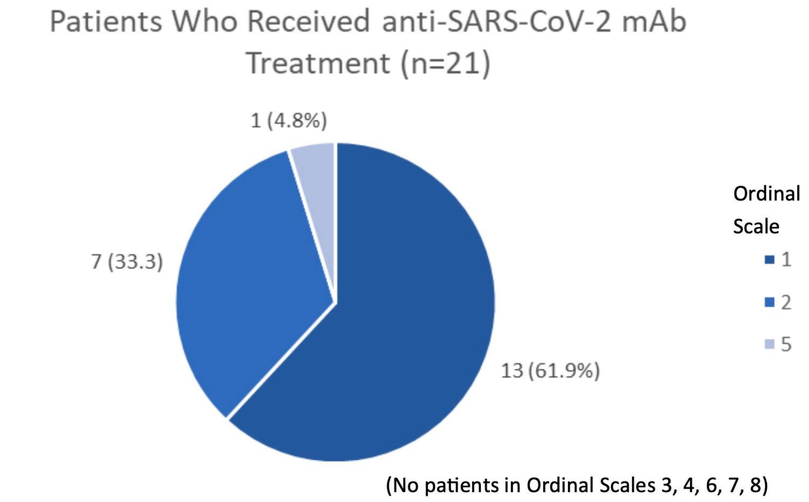
* Geomean (geometric %CV)
† Median (range)
‡ Observed geomean (geometric %CV) concentration 1 day after dosing
§ Observed geomean (geometric %CV) concentration 150 days after dosing
¶ Observed geomean (geometric %CV) concentration 210 days after dosing
# Arithmetic mean (SD)

Real-world tix/cil experience appears good

BCDT patients fully vaccinated with documented COVID-19





(No patients in Ordinal Scales 3, 4, 6, 7, 8)

Ordinal Scale Legend

1 Ambulatory (no limitation)

2 Ambulatory (with limitation)

3 Hospitalized (no O_2, no medical treatment)

4 Hospitalized (no O_2, but requiring ongoing medical treatment)

5 Hospitalized (any O_2)

6 Hospitalized (NIV or HFNC)

7 Hospitalized (IMV or ECMO)

8 Death

Calabrese *et al, Arthritis Rheumtol*, 2022, PMID: 35791921

Conclusions

- Most immunosuppressed patients with IMID will mount acute humoral responses
  - Greatest risk of poor responses:
    - BCDT >> MMF >> GCC > MTX/AZA/JAKi/TNFi > immunocompetent
  - T cells in BCDT patients present, but likely are dysfunctional and may not be protective
  - Intensive immunosuppressive therapies destroy GC responses
  - TNFi associates with poorer cross-variant neutralization in the long-term, which restores with boosting (clinical impact of impaired Fc effector functions?)

- How to mitigate, especially for the B cell depleted?
  - Keep vaccinating: solid organ transplant patients eventually make responses
  - Pre-exposure prophylaxis (PrEP): **Tixagevimab/cilgavimab (Evusheld)!!** Probably the single best option for many of our patients in the short-term
  - Drug holidays?

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Research Letter | Infectious Diseases

Comparison of SARS-CoV-2 Antibody Response After 2-Dose mRNA-1273 vs BNT162b2 Vaccines in Incrementally Immunosuppressed Patients

Jonathan Mitchell, MBBS; Caoilfhionn M. Connolly, MD, MSc; Teresa Po-Yu Chiang, MD, MPH; Jennifer L. Alejo, MD; William A. Werbel, MD; Dorry L. Segev, MD, PhD; Allan B. Massie, PhD, MHS

Table 2. Anti–Receptor Binding Domain Response to 2-Dose Messenger RNA SARS-CoV-2 Vaccination Stratified by Vaccine Platform

Antibody titer, U/mL[a]	BNT162b2, %	mRNA-1273, %	IRR (95% CI)	*P* value
Patients with RMDs not receiving immunosuppression (n = 220)[b]				
≥50	98.3	95.1	0.97 (0.92-1.02)	.20
≥100	95.8	95.1	0.99 (0.94-1.05)	.81
≥250	91.5	93.1	1.02 (0.94-1.10)	.67
Patients with RMDs receiving immunosuppression (n = 938)[b]				
≥50	75.4	83.1	1.10 (1.03-1.17)	.005
≥100	72.4	82.4	1.13 (1.06-1.21)	<.001
≥250	60.5	79.2	1.30 (1.20-1.42)	<.001
SOTRs not receiving mycophenolic acid or mycophenolate mofetil (n = 260)[c]				
≥50	59.1	78.9	1.38 (1.16-1.64)	<.001
≥100	54.6	77.3	1.47 (1.22-1.77)	<.001
≥250	44.7	66.4	1.56 (1.24-1.96)	<.001
SOTRs receiving mycophenolic acid or mycophenolate mofetil (n = 437)[c]				
≥50	12.8	21.8	1.69 (1.11-2.58)	.02
≥100	7.7	18.8	2.40 (1.42-4.07)	.008
≥250	4.3	11.4	2.62 (1.28-5.37)	.01