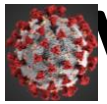
C  VID-19 Vaccination and Patients with Rheumatic Diseases

Michigan Rheumatology Society
Annual CME Meeting
Jiha Lee, MD MHS
Oct 2, 2021

Disclosure

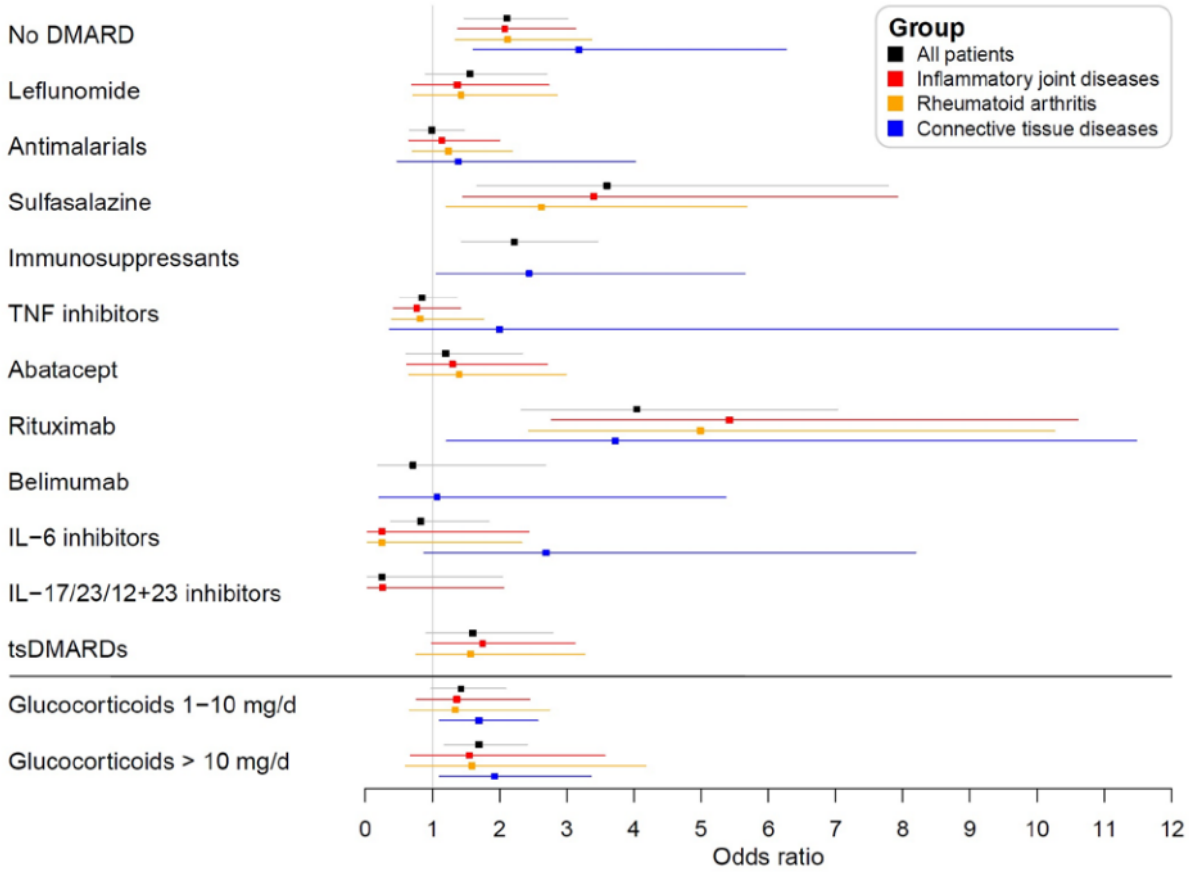
- None

SARS-CoV-2 infection in RMD patients

- Risk of severe COVID-19 infection higher in RMD patients
  - Older age, comorbidities

    (as in general population)

  - Immunosuppressive medications
    - SSZ, BCDT, PDN, JAKi, TNFi



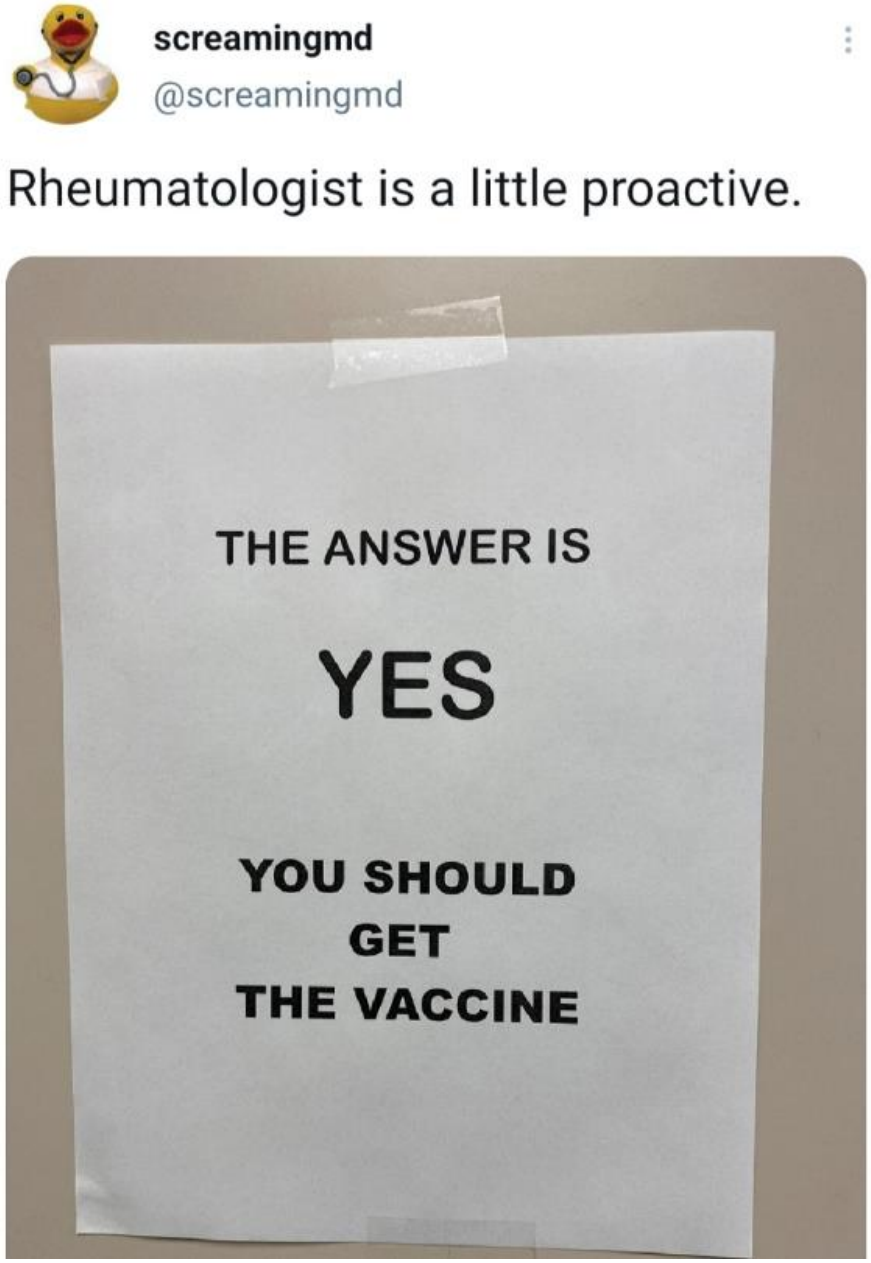
Pablos JL, et al. Ann Rheum Dis 2020
Strangfeld A, et al. Ann Rheum Dis 2021
Choi *et al*, *New Engl J Med,* 2020
Clark *et al, Cell*, 2021

Outline

- Review available vaccines
  - Define how immunogenicity is measured

- Efficacy of SARS-CoV-2 vaccination in RMD patients
  - Impact of immunosuppressive medications
  - Breakthrough infections
  - Additional dose of mRNA vaccination
  - Booster dose of mRNA vaccination

- Safety of vaccination in RMD patients
  - RMD flare after vaccination



Currently Available COVID-19 Vaccines in the US

	Pfizer (Comirnaty)	Moderna	J&J/Janssen
FDA Approval	12/11/20 (EUA) → 8/23/21 (Full)	12/18/2020 (EUA)	2/27/2021 (EUA)
Vaccine Type	mRNA	mRNA	Adenoviral vector
Recommended for	≥16 years of age Expanded to 12-15yo (May 2021)	≥18 years of age	≥18 years of age
Number of doses **(for primary series)**	2 doses 21 days apart	2 doses 28 days apart	Single dose (Phase III two doses, pending)
Additional dose for immunocompromised	28 days after D2	28 days after D2	-
Side effects	Rare anaphylaxis	Rare anaphylaxis	Milder?
Vaccine Effectiveness (VE) in clinical trials	95% 89% w/comorbidities	94% (but..86% in ≥65yo) >90% w/comorbidities	72% overall efficacy 86% severe disease
Major adverse events	Myocarditis/Pericarditis	Myocarditis/Pericarditis	Thrombosis with thrombocytopenia (TTS) JJ: 0.87 cases per million doses Pfizer: 0 per 97.9M Moderna: 3 per 84.7M

Adapted from CDC, FDA, Pfizer, Moderna, JJ, NEJM

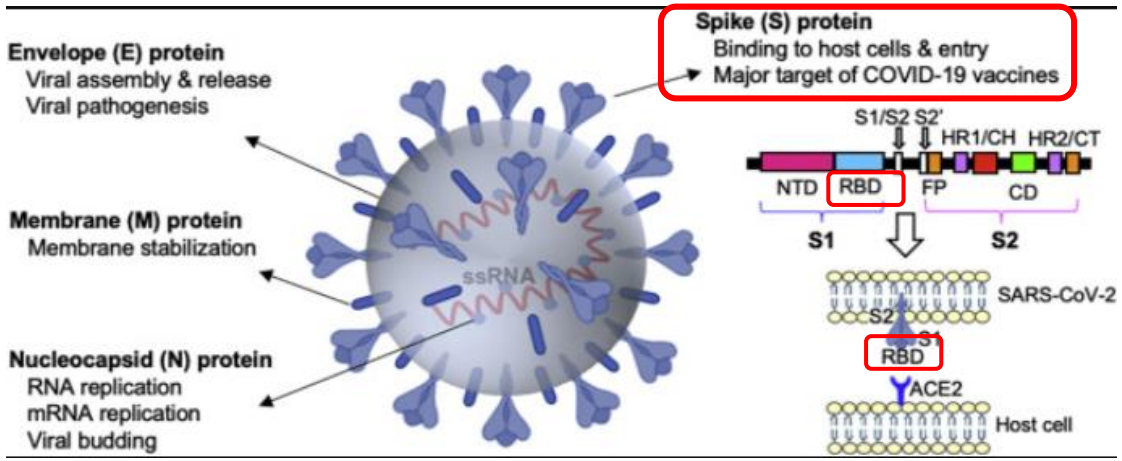
COVID-19 Vaccine Efficacy against Variants of Concern in US

	Original	Alpha (B.1.1.7)	Beta (B.1.351)	Gamma (P.1)	Delta (B.1.617.2)
First reported	2019 in China	Sep 2020 in UK	Oct 2020 in S. Africa	Dec 2020 in Brazil	Oct 2020 in India
Transmission	-	~50% increased	~50% increased	~40% increased	Increased
Severity	-	Higher fatality	No increase	No increase	Increased
Vaccine Efficacy					
Pfizer	95%	>87% efficacy	75% with reduced antibody neutralizing activities	More data needed	70-75% with reduced antibody neutralizing activities
Moderna	94%	Same efficacy	Reduced antibody neutralizing activities	More data needed	Reduced antibody neutralizing activities
J&J	72%	Same efficacy	64% in S. Africa trials	61% in Brazil trials	More data needed

CDC, NEJM

Terms used to assess response following vaccination

- Immunogenicity: the assessment of the several components of the immune response following vaccination
  - Antibody titers (levels): the levels of antibodies that bind to any part of the Spike protein (S antibodies, anti-S antibodies)
    - Seropositivity: the percent of people who have a positive antibody test (do not equal protection)
  - Neutralization titers (levels): the levels of antibodies that bind to specific parts of the Spike protein that prevent infection of cells by SARS-CoV-2 in a culture dish (*in vitro)* (antibodies usually bind to the RBD)



- Vaccine Effectiveness (VE):

$$VE = \frac{ARU - ARV}{ARU} \times 100\%,$$

with

- VE = Vaccine efficacy,
- ARU = Attack rate of unvaccinated people,
- ARV = Attack rate of vaccinated people.

An alternative, equivalent formulation of vaccine efficacy

$$VE = (1 - RR) \times 100\%,$$

J Clin Micro, CDC

SARS-CoV-2 Antibody Assay

At MM: Siemens Assay

SARS-CoV-2 Total Antibody, Spike (RBD) Qualitative	COVT / COVOH
SARS-CoV-2, Total Antibodies, Nucleocapsid, Qualitative	COVTN

Component	4 d ago
SARS-CoV-2 Total Antibody, Nucleocapsid, Qualitative	Negative
Comment: Antibodies to SARS-CoV-2 not detected. Negative results can occur in patients never infected by SARS-CoV-2, in serum samples collected too soon after infection, or in immunosupressed patients. Follow-up testing with a molecular test is recommended in symptomatic patients. This test should not be used to exclude active/recent COVID-19. Serologic test results should be used in conjunction with clinical findings, and should not form the sole basis for a diagnosis or treatment decision. The performance characteristics of this test were determined by the Michigan Medicine Department of Pathology Clinical Core Laboratory. This test has received Emergency USE authorization (EUA) from the FDA for clinical use. Methods : SARS-CoV-2 Total Antibodies	
SARS-CoV-2 Total Antibody, Spike (RBD), Qualitative	**PositiveAbnormal**
Comment: SARS-CoV-2 antibodies detected, suggestive of recent or prior infection with SARS-CoV-2 or history of COVID-19 vaccination. Serologic results should not be used as the sole basis to diagnose recent SARS-CoV-2 infection, to inform infection status, or determine potential protective immunity. The performance characteristics of this test were determined by the Michigan Medicine Department of Pathology Core Laboratory. This test has received Emergency USE authorization (EUA) from the FDA for clinical use. Serologic test results should be used in conjunction with clinical findings, and should not form the sole basis for a diagnosis or treatment decision. Symptomatic patients suspected of having acute COVID-19 disease should be tested using a molecular assay for SARS-CoV-2 RNA. Methods : SARS-CoV-2 Total Antibodies Chemiluminescent immunoassay	
Device:	Siemens Centaur XPT

J Clin Micro, ACR

SARS-CoV-2 Antibody Assay

At MM: Siemens Assay

SARS-CoV-2 Total Antibody, Spike (RBD) Qualitative	COVT / COVOH
SARS-CoV-2, Total Antibodies, Nucleocapsid, Qualitative	COVTN

Component	4 d ago
SARS-CoV-2 Total Antibody, Nucleocapsid, Qualitative	Negative
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Device:	Siemens Centaur XPT

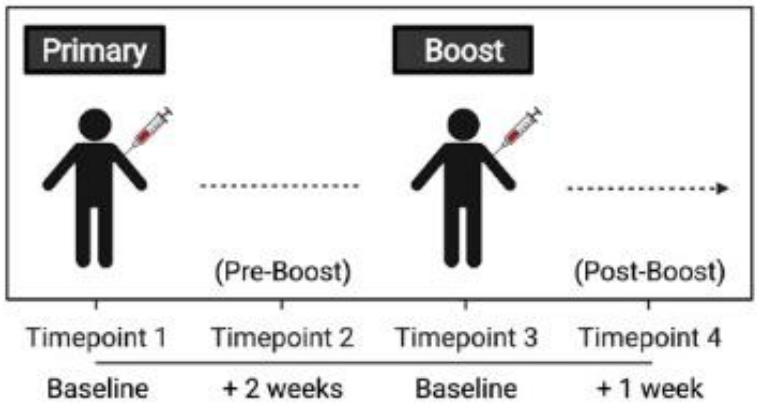
LabCorp/Quest/ARUP labs	Previous Infection	Vaccinated
SARS-CoV-2 IgG Nucleocapsid	+	-
SARS-CoV-2 IgG Spike protein	+	+

ACR Recommendations

Healthcare providers should not routinely order any lab testing (e.g., antibody tests for IgM and/or IgG to spike or nucleocapsid proteins) to assess immunity to COVID-19 post-vaccination, nor to assess the need for vaccination in a yet-unvaccinated person.[§]	Strong

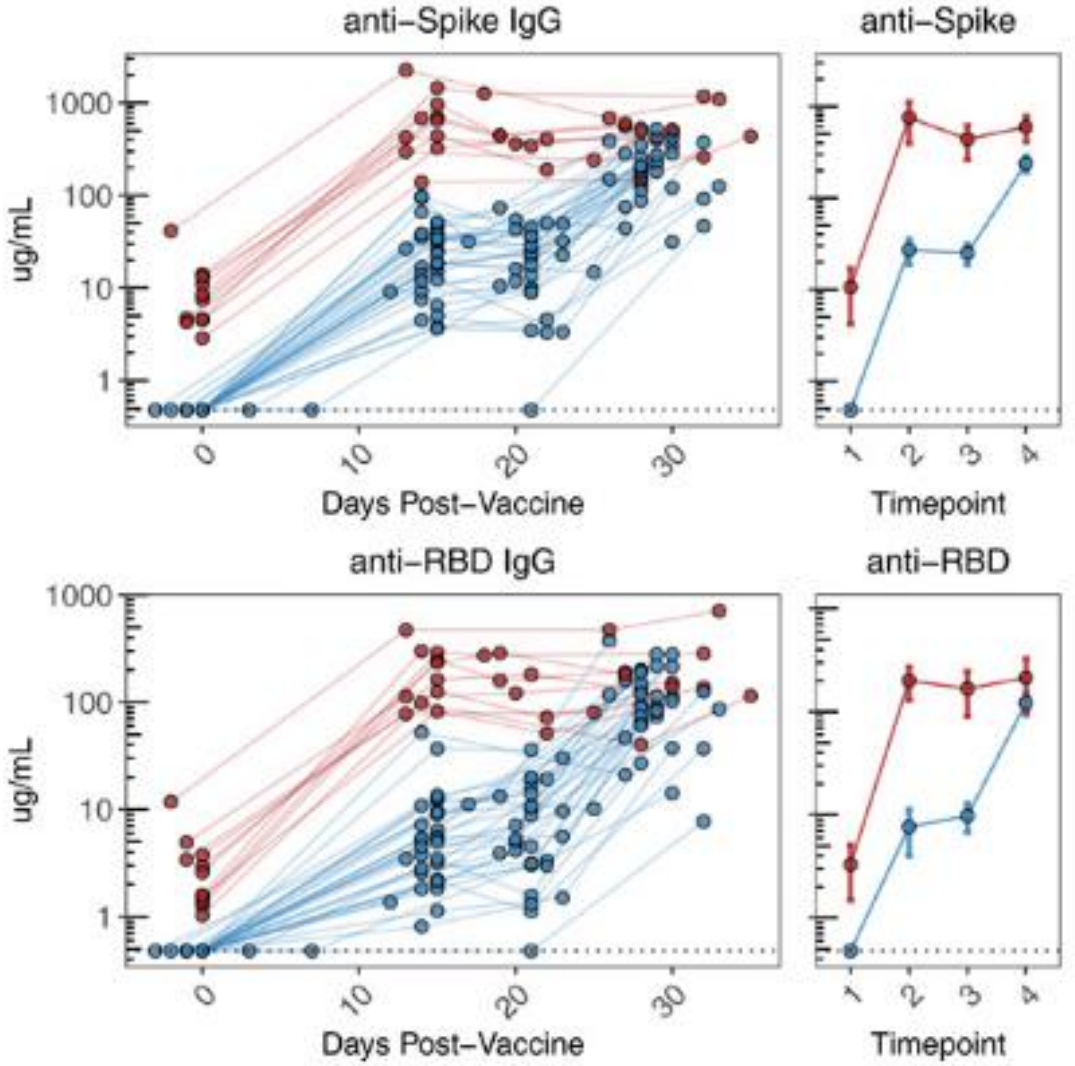
J Clin Micro, ACR

SARS-CoV-2 Vaccination: Natural vs Acquired Immunity



	SARS-CoV-2 Naive	SARS-CoV-2 Recovered
N	33	11
Age	37.3 [23-67]	34.7 [23-58]
Sex	15 M (46%) / 18 F (54%)	7 M (64%) / 4 F (36%)

Note
mRNA vaccine: Pfizer or Moderna
COVID-recovered: 65 to 275 days prior to vaccination



R. R. Goel et al., Sci. Immunol.

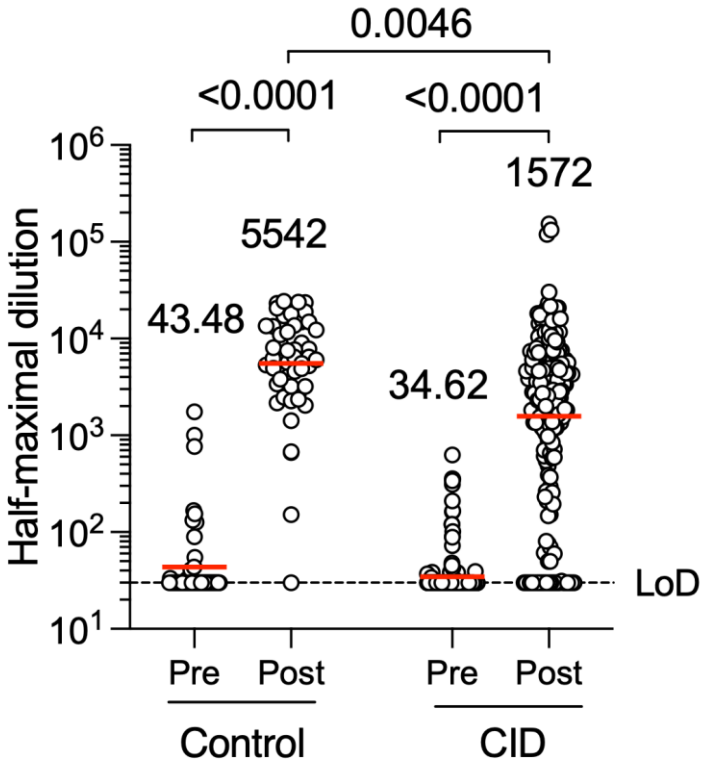
COVID-19 Vaccination and RMD patients

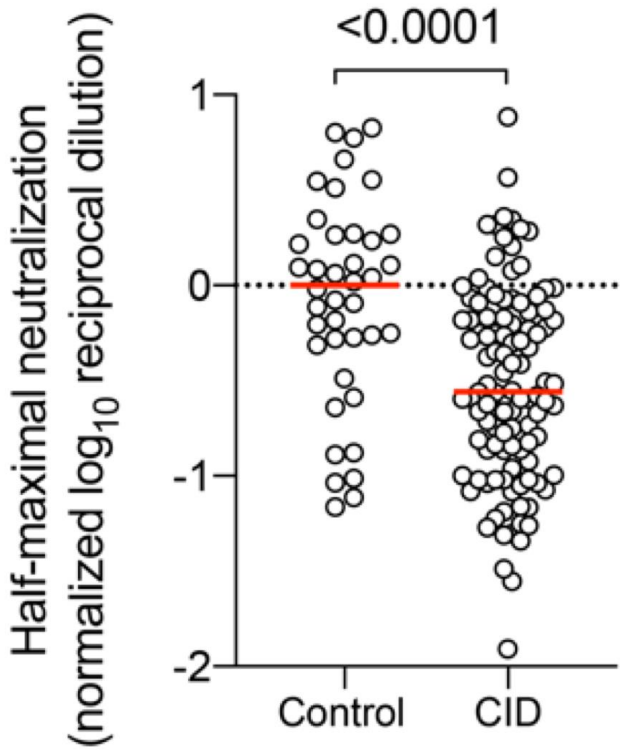
- Review available vaccines
  - How Immunogenicity is measured

- **Efficacy of vaccination in RMD patients**
  - **Effect of immunosuppressive medications on immunogenicity**
  - **Breakthrough infections**
  - **Additional dose of mRNA vaccination**
  - **ACR recommendations on timing of vaccination and medication use**
  - **Booster dose of mRNA vaccination**

- Safety of vaccination in RMD patients
  - Adverse events after vaccination
  - RMD flare after vaccination

SARS-CoV-2 Vaccine: Overall Immunogenicity

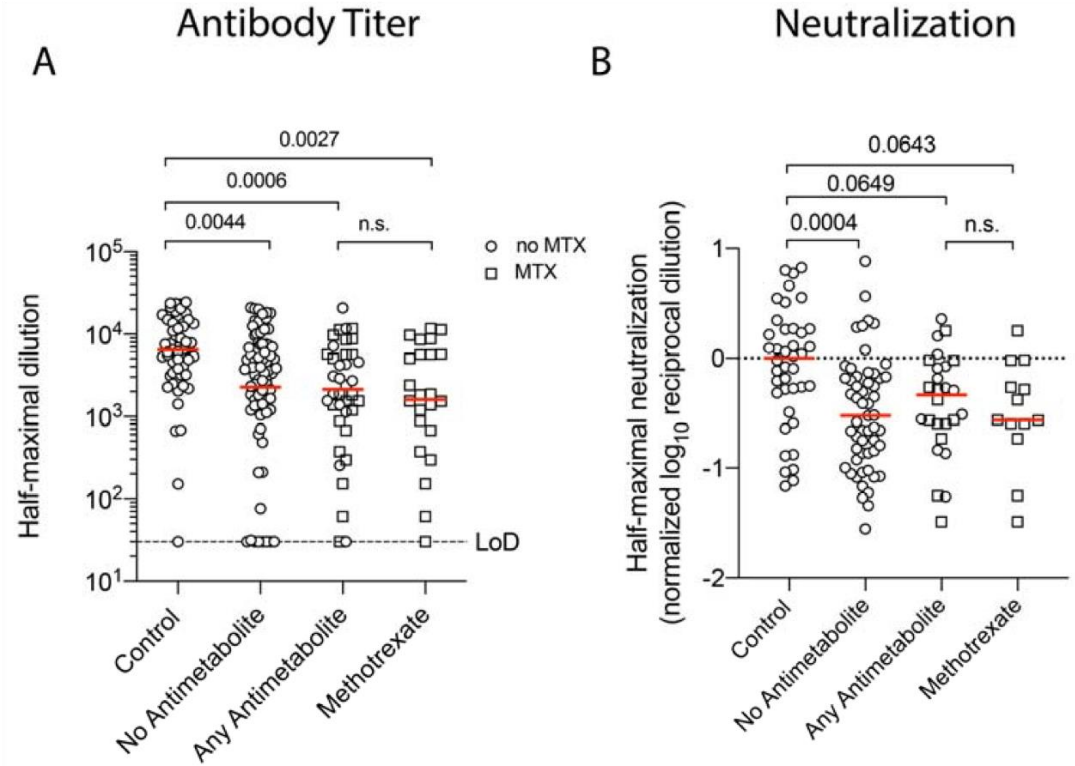


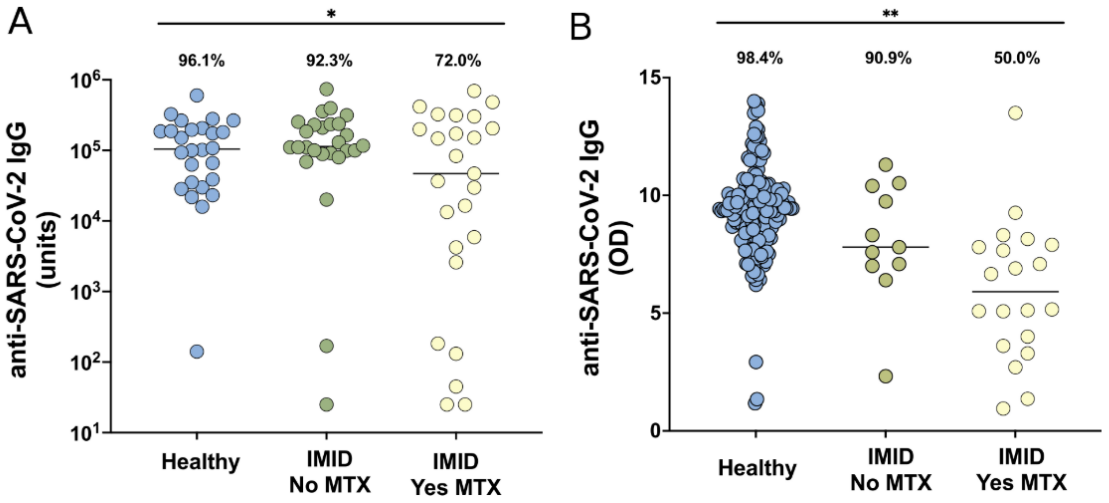


- Most immunosuppressed patients **WILL** become seropositive
  - Seroconversion rate improve with two doses of mRNA vaccination: 74% (after D1) → 94% (after D2)
- But antibody titers generally are less compared to the immunocompetent

Ruddy et al. Ann Rheum Dis
Deepak et al. Ann Intern Med, 2021

SARS-CoV-2 Vaccine: Antimetabolite and Immunogenicity

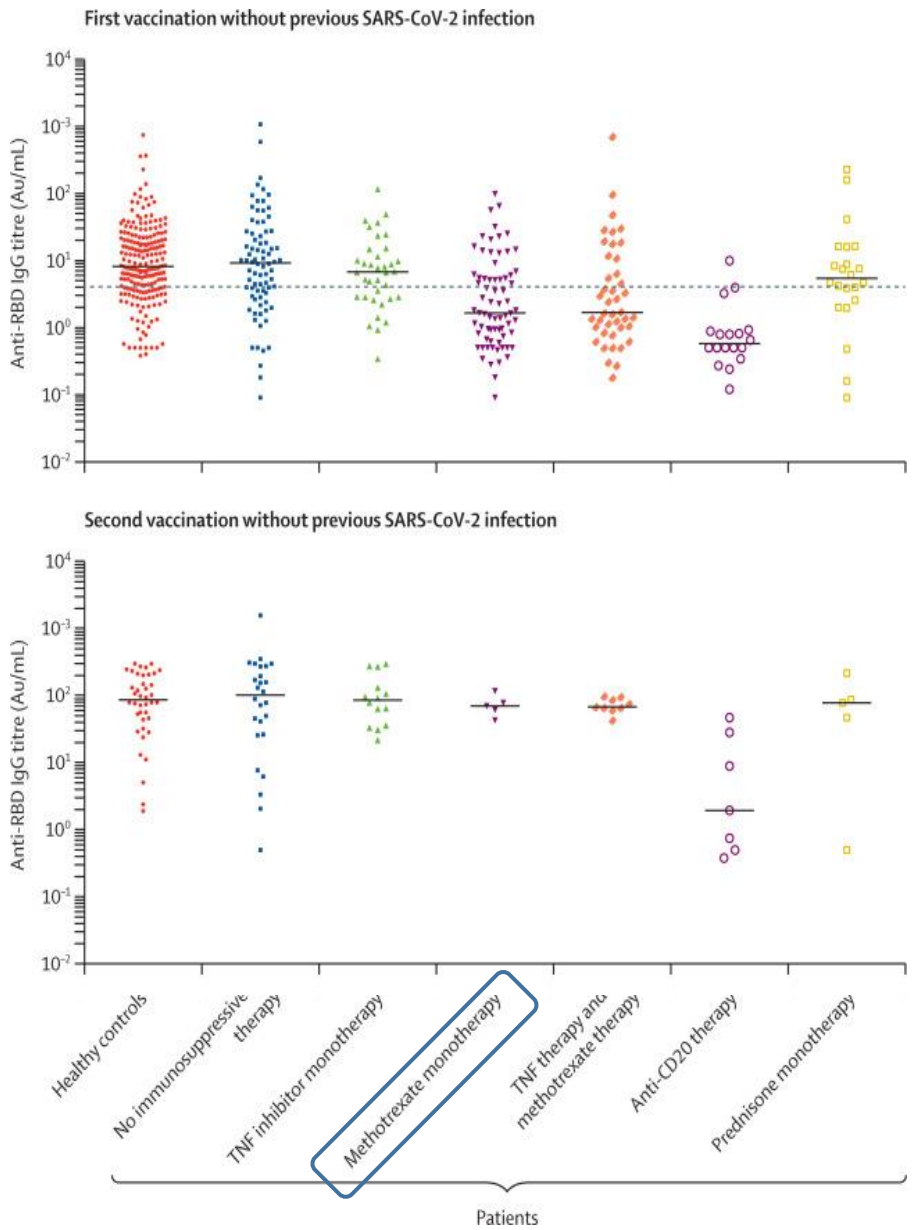


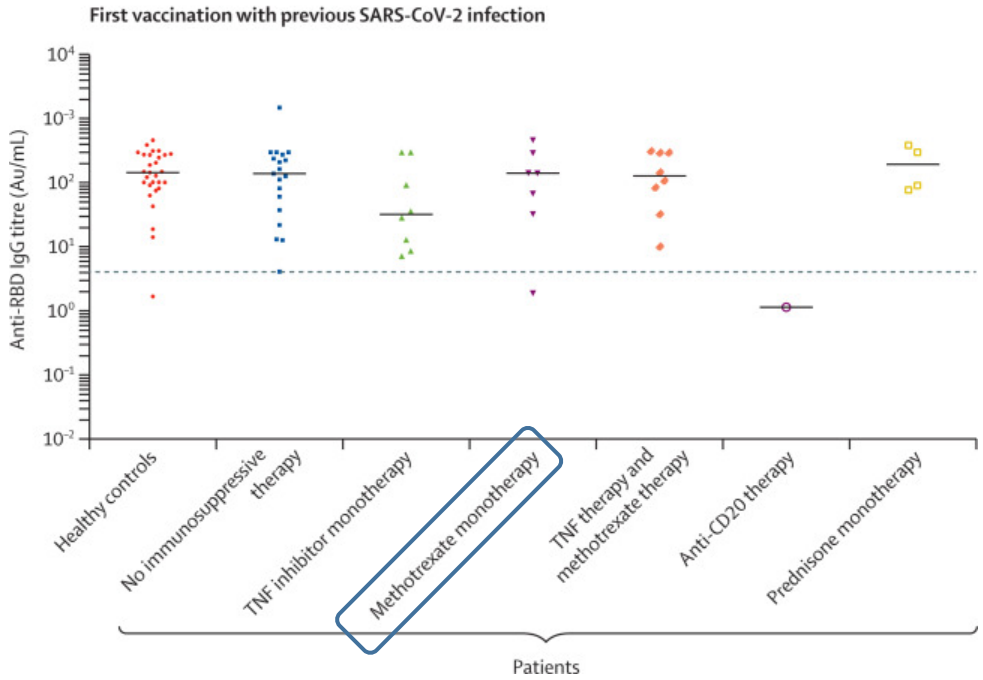


- MTX seropositivity: 47-87%
- MTX titers reduction:
  - 1.5- (Erlangen) to 2.2- (SAGA) to 3.25-fold (COVaRiPAD)

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

SARS-CoV-2 Vaccine: Antimetabolite and Immunogenicity

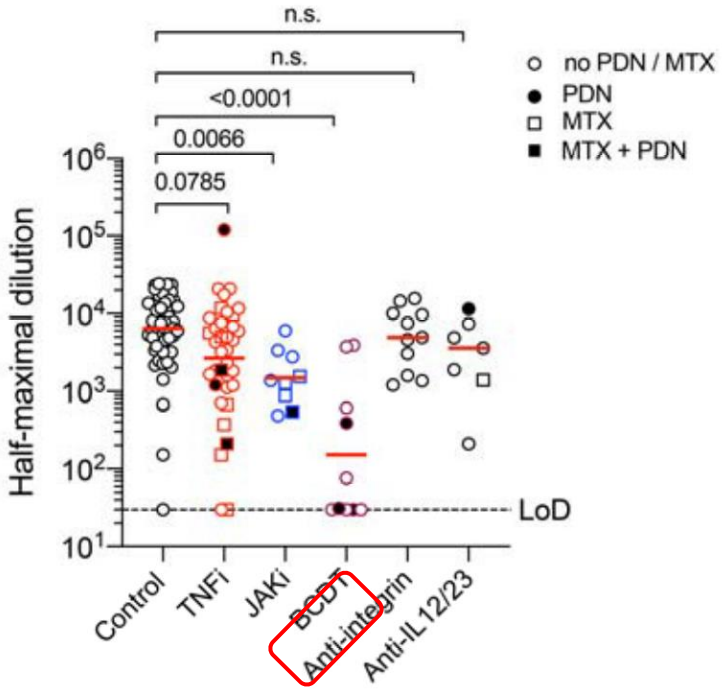


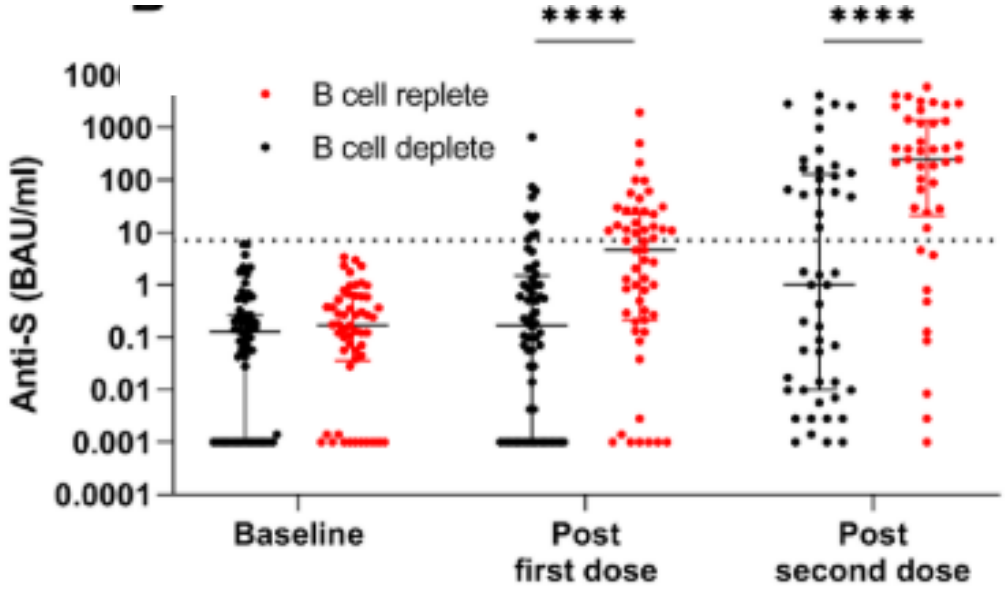


- MTX uniquely demonstrates the need for at least two exposures to antigen

Boekel *et al*, *Lancet Rheumatol*, 2021

SARS-CoV-2 Vaccine: MMF/BCDT and Immunogenicity

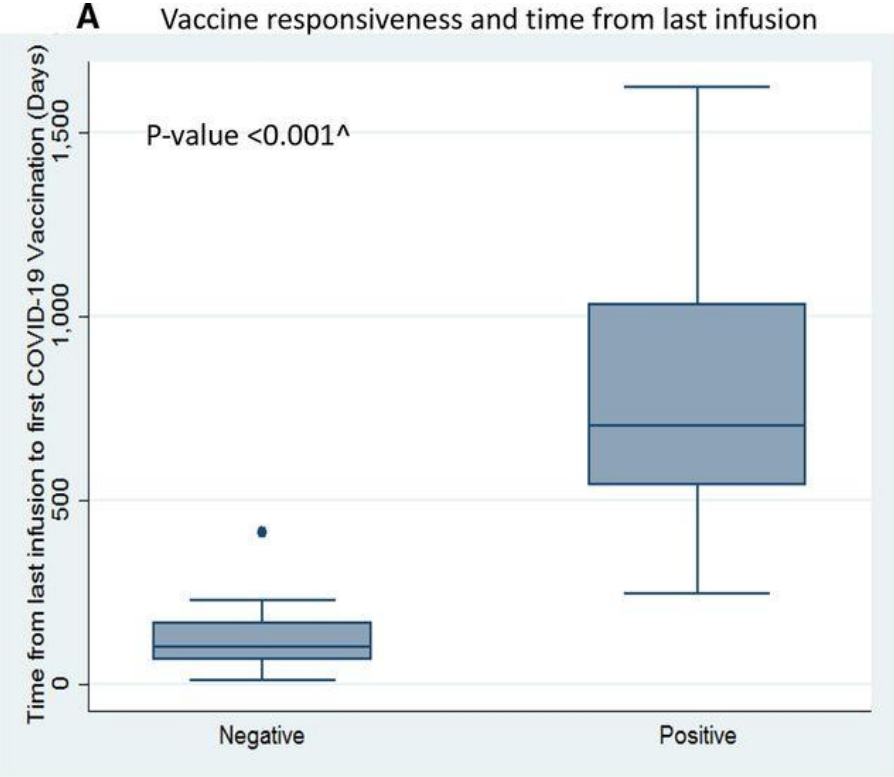


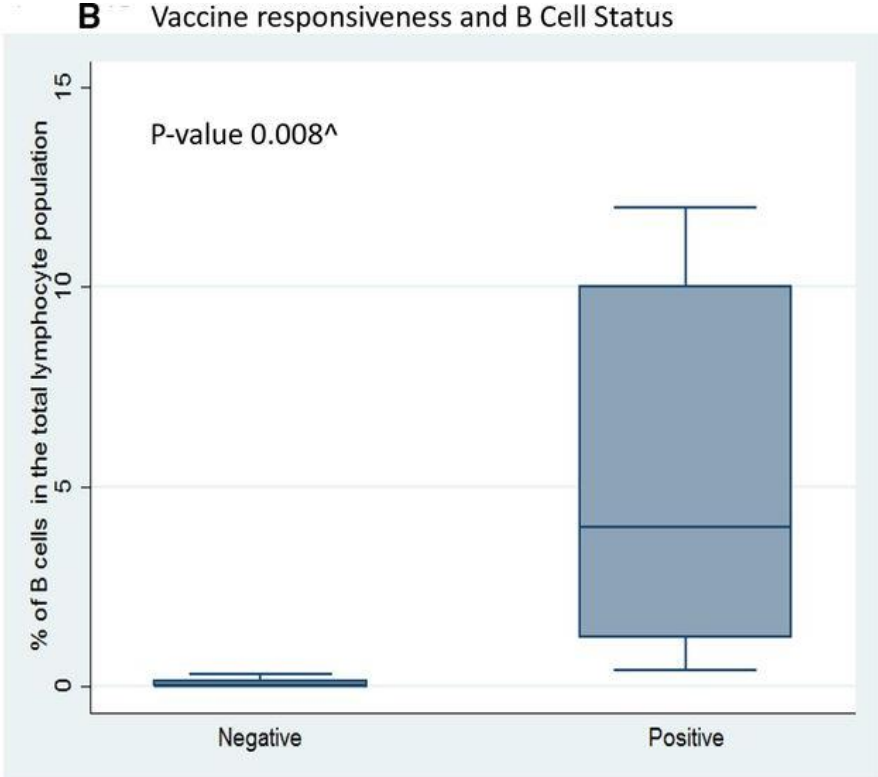


- Seropositivity with BCDT: 26-68%
- Seroconversion improve after two-doses
  - MMF: 27% → 73%
  - BCDT: 26% → 33%
- Antibody titers reduced 7 to >600 fold

Ruddy et al. Ann Rheum Dis
Deepak et al. Ann Intern Med, 2021
Mrak *et al, Ann Rheum Dis*, 2021
Braun-Moscovici *et al*, *Ann Rheum Dis*, 2021
Bonelli *et al*, *Ann Rheum Dis*, 2021
Prendecki *et al, Ann Rheum Dis*, 2021

SARS-CoV-2 Vaccine: BCDT and Immunogenicity





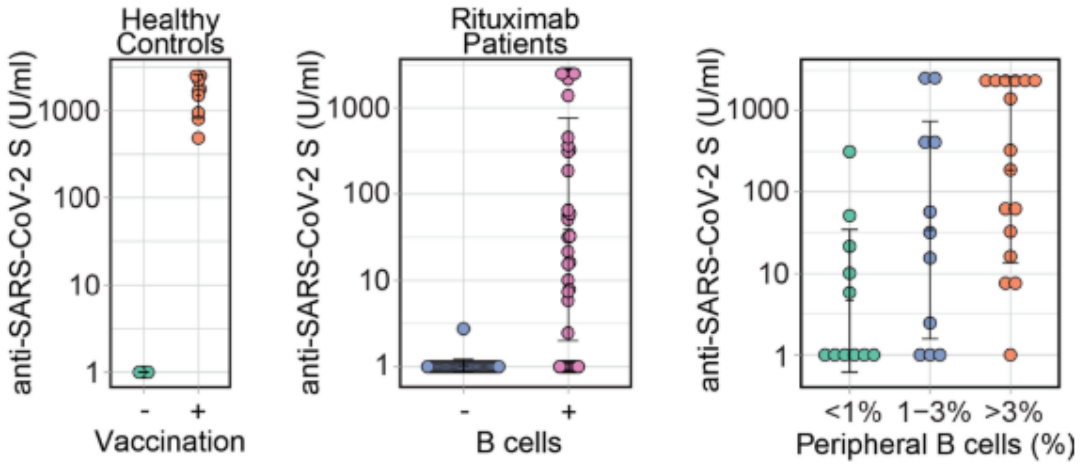
- Time from last RTX use: median (IQR)
  - Negative response: 98 (64-164) days
  - Positive response: 704.5 (540-1035) days

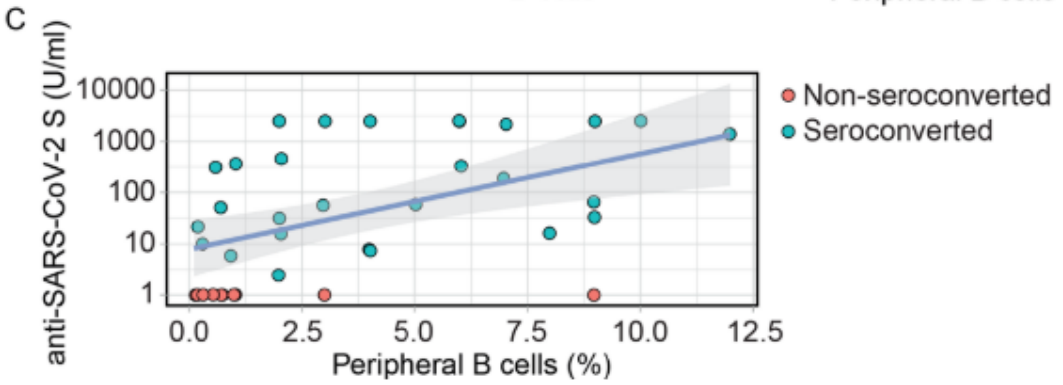
- % of B cells: median (IQR)
  - Negative response: 0 (0-0.15)
  - Positive response: 4 (1.2-10)

Spiera, Ann Rheum Dis

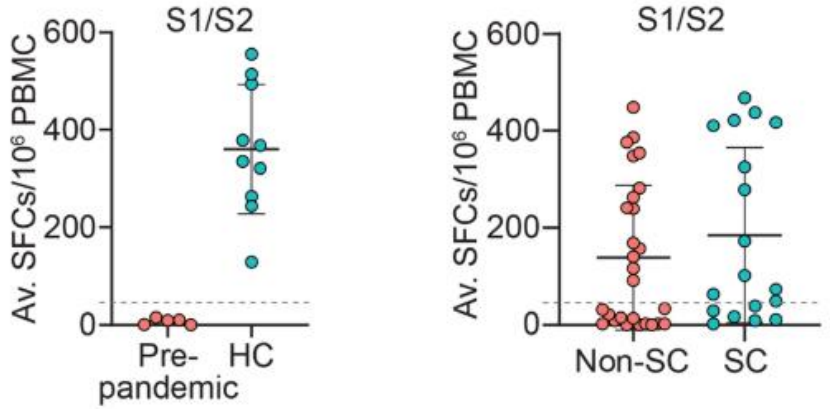
SARS-CoV-2 Vaccine: BCDT and Immunogenicity

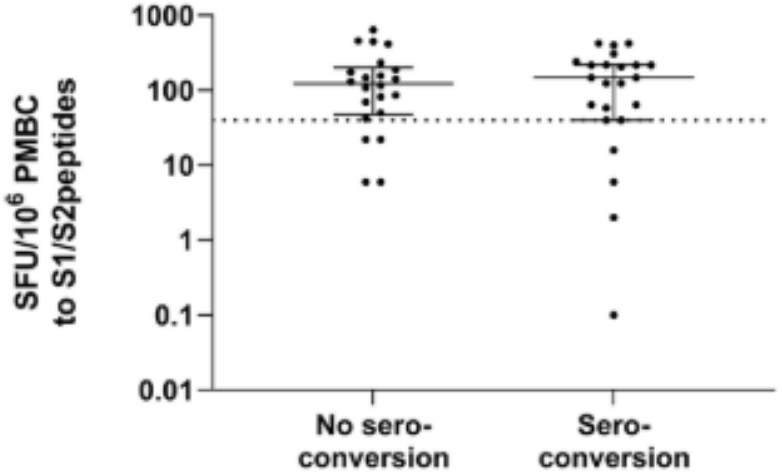
Humoral Response





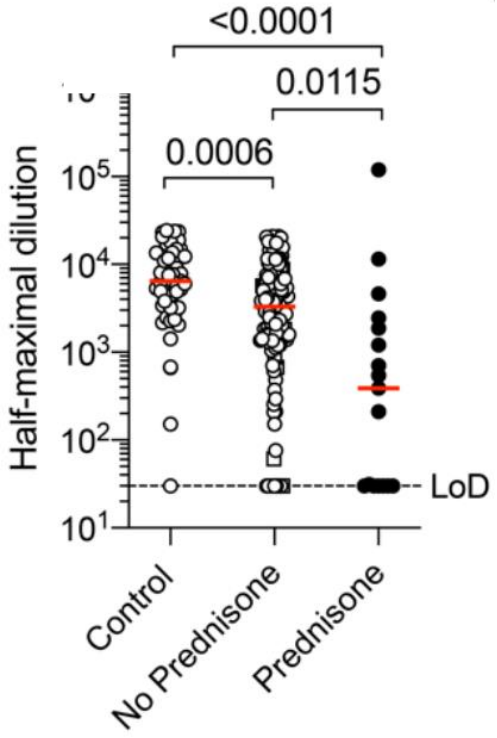
T-cell Response

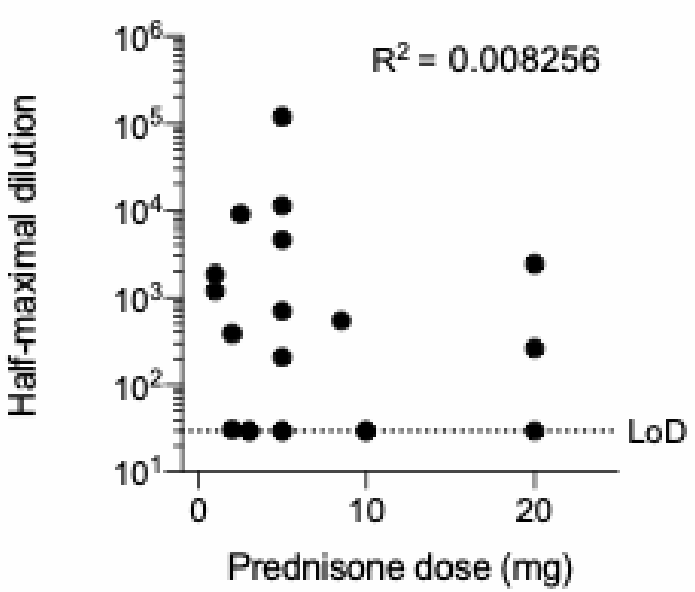


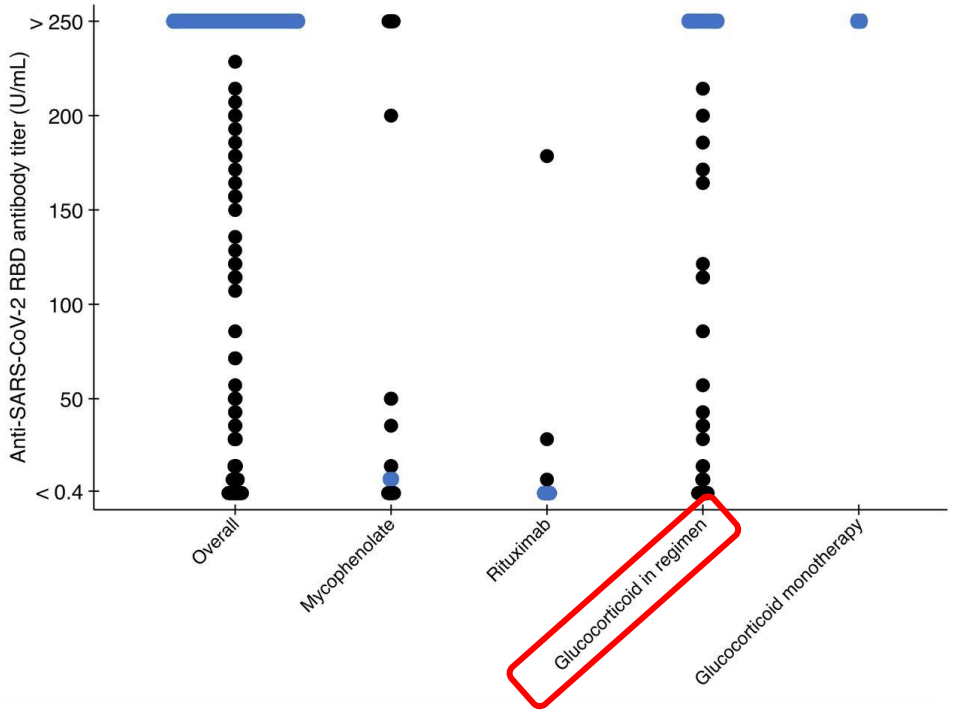


Mrak et al. Ann Rheum Dis 2021
Prendecki *et al, Ann Rheum Dis*, 2021

SARS-CoV-2 Vaccine: GCs and immunogenicity



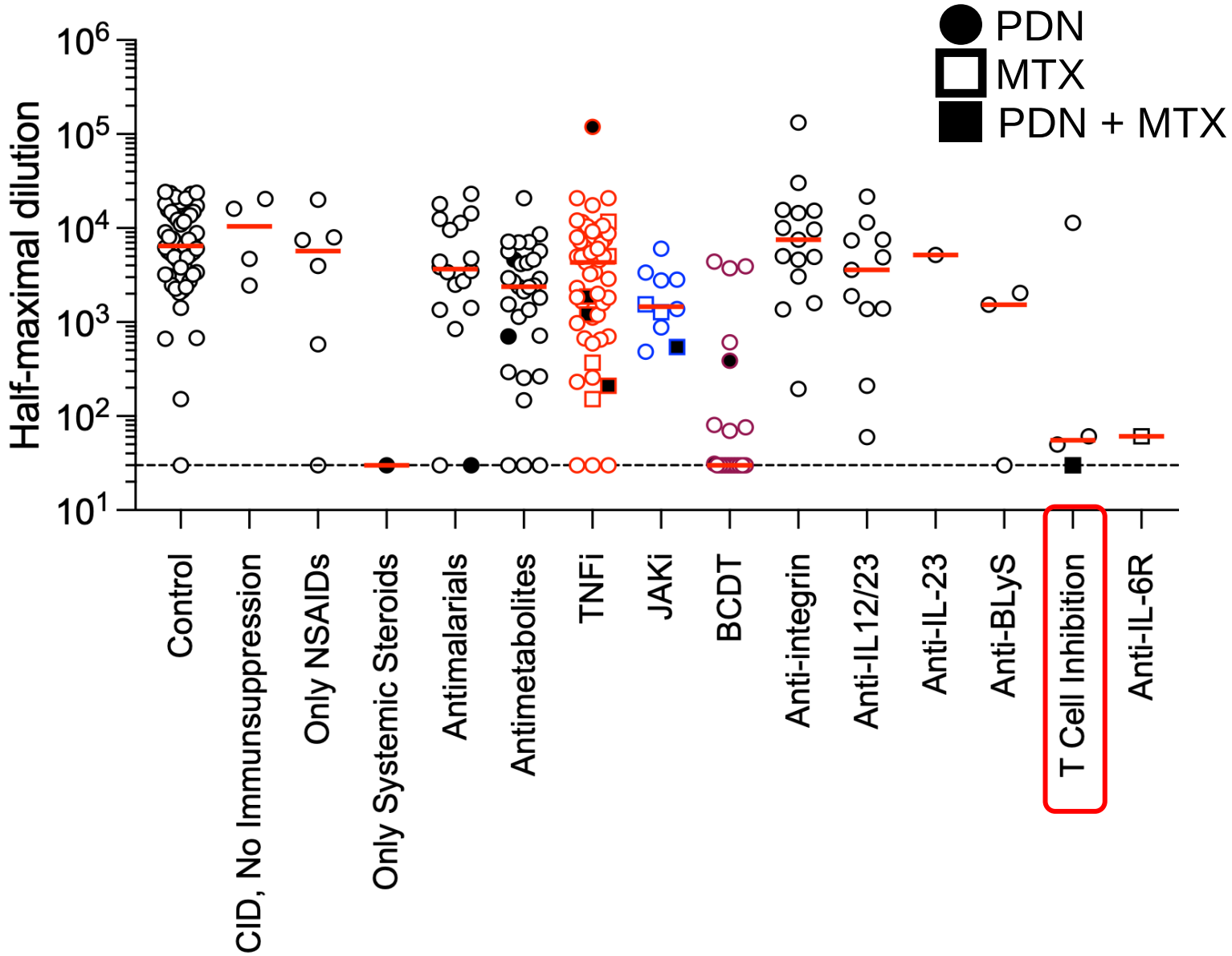




- Prednisone can lower antibody response, even at los doses (<5mg/kg)
- Prednisone effect confounded by concomitant medication use

Deepak et al. Ann Intern Med, 2021
Boekel *et al*, *Lancet Rheumatol*, 2021
Ruddy *et al.*, *Ann Rheum Dis*, 2021

SARS-CoV-2 Vaccine: Other immunosuppressives



Deepak et al. Ann Intern Med, 2021

Immune response to vaccination and Abatacept

Abatacept and reduced immune response to pandemic 2009 influenza A/H1N1 vaccination in patients with rheumatoid arthritis†

Ana C. Ribeiro, Ieda M. Laurindo, Lissiane K. Guedes, Carla G. Saad, Julio C. Moraes, Clóvis A. Silva, Eloisa Bonfa

First published: 04 September 2012 | https://doi.org/10.1002/acr.21838 | Citations: 60

† ClinicalTrials.gov identifier: NCT01151644.

Antibody response to pneumococcal and influenza vaccination in patients with rheumatoid arthritis receiving abatacept

Rieke Alten, Clifton O. Bingham III, Stanley B. Cohen, Jeffrey R. Curtis, Sheila Kelly, Dennis Wong & Mark C. Genovese

BMC Musculoskeletal Disorders **17**, Article number: 231 (2016) | Cite this article

Effect of abatacept on the immunogenicity of 23-valent pneumococcal polysaccharide vaccination (PPSV23) in rheumatoid arthritis patients

Kiyoshi Migita, Yukihiro Akeda, [...] Kazunori Oishi

Arthritis Research & Therapy **17**, Article number: 357 (2015) | Cite this article

Clinical Trial > J Rheumatol. 2007 Feb;34(2):272-9.

Immune responses following administration of influenza and pneumococcal vaccines to patients with rheumatoid arthritis receiving adalimumab

Jeffrey L Kaine [1], Alan J Kivitz, Charles Birbara, Allison Y Luo

Rituximab and abatacept but not tocilizumab impair antibody response to pneumococcal conjugate vaccine in patients with rheumatoid arthritis

Meliha Crnkic Kapetanovic, Tore Saxne, Göran Jönsson, Lennart Truedsson & Pierre Geborek

Arthritis Research & Therapy **15**, Article number: R171 (2013) | Cite this article

*Results variable, but Abatacept may reduce humoral response to polysaccharide and conjugate vaccines

ACR Clinical Guidance: Primary series of COVID-19 vaccination and med use

Immunomodulatory Therapy	Timing Considerations for vaccination	Level of Consensus
HCQ, IVIG, GCs (prednisone-equivalent <20mg/day)	none	Strong-moderate
SSZ, LEF, AZA, CYC PO, TNFi, IL-6R, IL-1, IL-17, IL12/23, Belimumab, High-dose GCs (prednisone-equivalent ≥20mg/day)*	none	Moderate
Mycophenolate, oral calcineurin inhibitors	Hold 1 week post each vaccine dose	Moderate
Methotrexate	Hold 1 week post each mRNA vaccine dose Hold for 2 weeks post single-dose vaccine	Moderate
JAK inhibitors	Hold one week post each vaccine dose	Moderate
Abatacept SQ	Hold one week pre- and post- 1st dose only	Moderate
Abatacept IV	1st vaccine 4 weeks after infusion & postpone subsequent infusion by one week (i.e. 5 week gap)	Moderate
Cyclophosphamide IV	Try time CYC for one week after each vaccine dose	Moderate
Rituximab	Initiate vaccine 4 weeks prior to next scheduled infusion, and delay subsequent infusion by 2-4 weeks after 2nd vaccine dose	Moderate
Acetaminophen, NSAIDs	Hold 24hrs prior to vaccination (no restriction post)	Moderate

Adapted from ACR, updated Aug 19, 2021

Prevalence of drug-induced immunosuppression in US

Characteristic	No. (%) (N = 89 925)
Age, y	
18-35	10 350 (11.5)
36-45	14 478 (16.1)
46-55	27 516 (30.6)
56-64	37 581 (41.8)
Men	34 882 (38.8)
Women	55 043 (61.2)
Elixhauser comorbidity index score, median (interquartile range)[a]	2 (1-4)

Immunosuppressive (IS) use

1. One dose or more of antineoplastic IS
2. ≥30 days of oral GCs
3. 90 days of any other PO or SC IS
4. 2 doses of IV non-steroidal IS

Results

- **2.8%** met criteria for drug-induced immunosuppression

Table 2. Most Commonly Prescribed Immunosuppressive Medications and Medical Diagnoses Among Patients Experiencing Drug-Induced Immunosuppression, 2018-2019

Medications and diagnoses	No. (%) (N = 89 925)[a]
Drug class	
1. Oral corticosteroids[b]	60 860 (67.7)
2. Methotrexate	22 013 (24.5)
3. Nonbiological DMARDs and transplant antirejection medications	23 315 (25.9)
4. TNF inhibitors	20 434 (22.7)
5. Other biological product medications[c]	12 276 (13.7)
6. Antineoplastic medications	16 191 (18.0)
Most common immunosuppression-associated diagnoses	
1. Malignant neoplasm	66 385 (73.8)
2. Immune-mediated conditions	61 822 (68.8)
3. Inflammatory skin conditions	34 895 (38.8)
4. Asthma or COPD	24 205 (26.9)
5. Organ transplant[d]	7105 (7.9)
Most common primary diagnoses	
1. Neoplasm-related encounters	46 624 (51.8)
2. Exposure, encounters, screening, or contact with infectious disease	45 489 (50.6)
3. Musculoskeletal pain, not low back pain	43 457 (48.3)
4. Respiratory signs and symptoms	33 019 (36.7)
5. Abdominal pain and other digestive/abdomen signs and symptoms	31 509 (35.0)

Wallace. JAMA Netw Open. 2021

Breakthrough COVID-19 infection after vaccination: US

Rheumatic disease treatment use prior to first vaccine dose†	n, %
Rituximab	5, 31
Glucocorticoids	5, 31
Mycophenolate mofetil or mycophenolic acid	4, 25
Methotrexate	3, 19
Tacrolimus	2, 13
Adalimumab	1, 6
Azathioprine	1, 6
Belimumab	1, 6
Hydroxychloroquine	1, 6
Intravenous immunoglobulin	1, 6
Sulfasalazine	1, 6
Tocilizumab	1, 6
Ustekinumab	1, 6
None	1, 6

- 16/340 breakthrough cases (**4.7%**)
  - Between Jan-July 2021
  - Days from last vaccine dose 54.0 (29.8–79.0)
  - Six hospitalized (38%)
    - 2 RTX Monotherapy
    - RTX + Pred 20mg/day
    - RTX + AZA
    - MFF + Tac + Pred 5mg/day
    - MMF + BLM
  - Two deaths (13%)
    - Both RTX + ILD

Cook et al. Annals Rheum Dis 2021

Breakthrough COVID-19 infection after vaccination: Europe

COVID-19 vaccine type: N of reinfections/total N of vaccine in registries (% of reinfection per vaccine)	
Pfizer-BioNTech	30/3038 (1)
Moderna	1/375 (<1)
AstraZeneca/Oxford	4/730 (1)
Janssen/Johnson & Johnson	0/40 (0)
Sputnik V	0/4 (0)
CoronaVac/Sinovac	3/49 (6)
Other	0/2 (0)
Unknown	0/120 (0)
COVID-19 outcome	
Deceased due to COVID-19	3 (8)
Vital status not known at this time	1 (3)
Full recovery	28 (74)
Resolved, with sequelae	3 (8)
Missing	3 (8)
Number of days from COVID-19 vaccine to infection, median (IQR)	
COVID-19 registry, most recent dose	23 (17–30)
COVAX registry, first dose	26.5 (20–52)
COVAX registry, second dose	24 (13–55)
COVAX registry, third dose	26.5 (23–30)

- **<1%** of EULAR and COVAX registry
  - RA 45%, axSpA 24%, SSc 8%, SLE 8%
  - Remission 47%, low disease activity 34%
  - GC 32%, MTX 26%, anti-TNF 26%
  - 8% died (>70years of age, not fully vaccinated, on MMF or RTX)
- Conclusion
  - Overall rates of breakthrough infection are low, and associated with high-risk immunosuppressive therapy

Lawson-Tovey et al. Annals Rheum Dis 2021

Improving vaccine effectiveness in RMD patients

CDC Definition:

- **Additional dose**: administration of an additional vaccine dose when the initial immune response following a primary vaccine series is likely to be **insufficient**
  - Third dose of mRNA vaccination authorized, August 2021 for immunocompromised
  - ACIP voted unanimously on Aug 13th 2021, for additional dose in immunocompromised patients
  - Does NOT apply to JJ vaccine

- **Booster dose:** a dose of vaccine administered when the initial sufficient immune response to a primary vaccine series is likely to have **waned over time**. The need for and timing of a COVID-19 booster dose have not been established
  - Dependent on durability of vaccine response, and vaccine efficacy against variants
  - FDA/CDC approved booster dose for certain groups (65+, high-risk, occupational exposure etc.)
  - Moderna submitted request for approval of booster dose for 18+

Additional dose of mRNA SARS-CoV-2 vaccination

- Eligibility
  - Received two doses of *mRNA vaccination as primary series*, at least 28 days ago
  - All RMD patients, except those on HCQ monotherapy
    - CDC recommendation includes pregnant, lactating individuals
  - Clinical considerations:
    - Antibody testing prior to additional dose NOT needed
    - Okay to give after recent COVID-19 infection
    - Delay if patient received monoclinal Ab or convalescent serum <90 days ago
    - Do NOT given if patient had anaphylaxis or myocarditis/pericarditis with prior dose
    - NOT eligible if received JJ vaccination as primary series
- Scheduling
  - Patient attest to “immunocompromised status” (honor system)
  - Local pharmacy and health department
  - Vaccine.gov or call 1-800-232-0233
- Planning
  - Encourage unvaccinated RMD patients to receive either Pfizer or Moderna mRNA vaccine as their primary series to become eligible for additional dose (ACR recommendation)

CDC, ACR

BMJ Journals
Annals of the Rheumatic Diseases

Booster-dose SARS-CoV-2 vaccination in patients with autoimmune disease: a case series FREE

Caoilfhionn M Connolly [1], Mayan Teles [2], Sarah Frey [2], Brian J Boyarsky [2], Jennifer L Alejo [2], William A Werbel [3], Jemima Albayda [1], Lisa Christopher-Stine [1], Jacqueline Garonzik-Wang [2], Dorry L Segev [2, 4], Julie J Paik [1]

Table 1 Vaccines administered, autoimmune diagnoses, immunosuppression and peri-vaccination management with longitudinal anti-spike antibody responses

Age	Sex	Diagnosis	Immunosuppressive therapy	Initial vaccine series	Meds held during initial vaccine	Pre-booster antibody	Booster vaccine type	Days from initial to booster vaccine	Post-booster antibody	Therapy held peri-booster*
54	F	Myositis	Mycophenolate	Moderna	Yes	<0.40	J&J	98	205	Yes
53	F	Myositis	Methotrexate Hydroxychloroquine Prednisone	Moderna	Yes	<0.40	J&J	86	1111	Yes
56	M	Sarcoidosis	Infliximab Mycophenolate Prednisone	Pfizer	NA‡	<0.40	Moderna	86	1276	Yes
44	F	SLE§	Belimumab Hydroxychloroquine Leflunomide Prednisone	J&J	No	<0.40	Moderna	91	2013	Yes
54	F	Sjogren's syndrome	Azathioprine	J&J	NA‡	<0.40	Pfizer	36	>2500	Yes
75	M	Myositis	Mycophenolate	Pfizer	No	<0.40	Moderna	56	>2500	Yes
66	F	Inflammatory arthritis¶	Abatacept	J&J	No	<0.40	Pfizer	94	>2500	Yes
38	F	Myositis	Azathioprine Prednisone Tacrolimus	Moderna	No	2.7	Moderna	95	>2500	No
59	F	Myositis/scleroderma overlap	Hydroxychloroquine Mycophenolate Prednisone	Moderna	No	8.8	J&J	54	>2500	Yes
53	M	Myositis/inflammatory arthritis overlap	Hydroxychloroquine Mycophenolate	J&J	No	18.6	Pfizer	NA‡	>2500	Yes
72	F	Inflammatory arthritis¶	Methotrexate	Pfizer	No	222.7	J&J	95	>2500	Yes
57	M	Inflammatory arthritis¶	Secukinumab	Pfizer	Yes	2418	Moderna	54	>2500	Yes

Connolly et al, Annals of Rheum Dz 2021

ACR Clinical Guidance: Additional dose of COVID-19 vaccination and med use

Immunomodulatory Therapy	Timing Considerations for vaccination	Level of Consensus
All immunomodulatory or immunosuppressive therapies (except GCs, IL-17, IL12/23, Il-23, IL-1R, IL-6R)	Hold for 1-2 weeks after additional dose of mRNA vaccination	Moderate
Rituximab	Discuss optimal timing with rheumatologist	Strong

- Unlike with primary vaccination series, ACR recommends to hold many DMARDs including SSZ, LEF, AZA, Benlysta, and anti-TNFs after additional dose

- For RTX, some providers may measure CD19 B cells to assess timing or provide additional dose 2- weeks before next scheduled RTX dose (but no threshold provided)

Adapted from ACR, updated Aug 19, 2021

Review

Impact of disease-modifying antirheumatic drugs on vaccine immunogenicity in patients with inflammatory rheumatic and musculoskeletal diseases

Marcia A Friedman [1], Jeffrey R Curtis [2], Kevin L Winthrop [1,3]

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]	↓[50 51]	OK (ZVL)[52]		OK[117 132 133]	↓[121]	↓[82 84 85]
TNF inhibitors	OK[14 16 20 27 28]	OK[14 56]	OK (ZVL)[64]	↓[103–105]	OK[117 132]	OK[121 124]*	OK[84 85 88]
Rituximab	↓↓[14–17 19–21 24 134]	↓↓[14 18 45–47]				↓[18 121]	↓↓[81–84]
Abatacept	↓[24 26]	↓[45 46]				OK (SQ)[122] ↓(IV)[123]	↓[84]
JAK inhibitor	OK[30]	↓[30]				OK (tofacitinib)[120] ↓(baricitinib)[53]	↓[82 84]
IL-6R inhibitor	OK[31]	OK[31]				OK[125]	OK[84]
IL-12/IL-23 inhibitor	OK[32]	OK[54]		↓[105]		OK[54]	OK[82]
IL-17 inhibitor	OK[33–35]	OK[55]				OK[55]	OK[84]

SARS-CoV-2 Vaccine: cross-variant neutralization

	# (%) 3 months after 2nd vaccination below NT_{50} of 1/50				# (%) 5[a] or 6[b] months after 2nd vaccination 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)
CID patients	74	16 (19)	29 (34)	30 (35)	39	13 (28)	22 (51)	25 (54)
Antimetabolites	12	2 (17)	5 (42)	4 (33)	5	2 (40)	2 (40)	2 (40)
Anti-TNF-α	11	3 (27)	7 (64)	7 (64)	3	2 (67)	2 (67)	3 (100)
Antimalarials	10	0 (0)	1 (10)	3 (30)	7	1 (14)	4 (57)	3 (43)
Anti-integrin	10	0 (0)	1 (10)	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)

Chen *et al,* medRxiv 2021

Booster dose of mRNA SARS-CoV-2 vaccination


The New York Times

The Coronavirus Pandemic › | LIVE Covid-19 Updates | Coronavirus Map and Cases | Your Booster Shot Questions, Answered | Vaccine Mandate

C.D.C. Chief Overrules Agency Panel and Recommends Pfizer-BioNTech Boosters for Workers at Risk

In a highly unusual decision, the C.D.C. director, Rochelle Walensky, reversed a move by agency advisers and endorsed additional doses of the Pfizer-BioNTech vaccine for health care workers, teachers and other workers at risk.

- CDC recommends that the following groups **should** receive a booster shot of Pfizer-BioNTech's COVID-19 Vaccine at least 6 months after completing their Pfizer-BioNTech primary series (i.e., the first 2 doses of a COVID-19 vaccine):
  - people aged 65 years and older
  - residents aged 18 years and older in long-term care settings
  - people aged 50–64 years with underlying medical conditions
- CDC also recommends that the following groups **may** receive a booster shot of Pfizer-BioNTech's COVID-19 Vaccine at least 6 months after completing their Pfizer-BioNTech primary series, based on their individual benefits and risks:
  - people aged 18–49 years with underlying medical conditions
  - people aged 18–64 years at increased risk for COVID-19 exposure and transmission because of occupational or institutional setting
- These recommendations only apply to people who previously received a Pfizer-BioNTech primary series (i.e., the first 2 doses of a COVID-19 vaccine).

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Protection of BNT162b2 Vaccine Booster against Covid-19 in Israel

Yinon M. Bar-On, M.Sc., Yair Goldberg, Ph.D., Micha Mandel, Ph.D., Omri Bodenheimer, M.Sc., Laurence Freedman, Ph.D., Nir Kalkstein, B.Sc., Barak Mizrahi, M.Sc., Sharon Alroy-Preis, M.D., Nachman Ash, M.D., Ron Milo, Ph.D., and Amit Huppert, Ph.D.

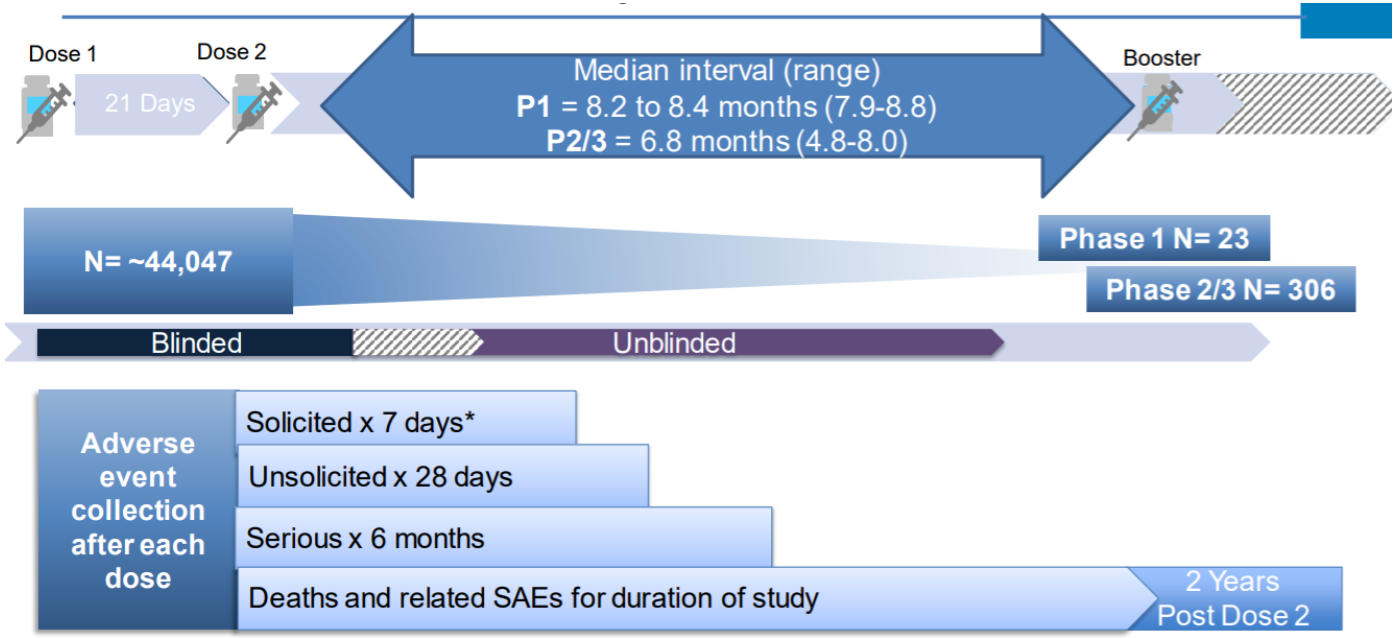
Limitations

- Include only ≥60 yo
- Broader definition of severe illness compared to US

Table 2. Primary Outcomes of Confirmed Infection and Severe Illness.*

Outcome	Nonbooster Group	Booster Group	Adjusted Rate Ratio (95% CI)†
Confirmed infection			11.3 (10.4 to 12.3)
No. of cases	4439	934	
No. of person-days at risk	5,193,825	10,603,410	
Severe illness			19.5 (12.9 to 29.5)
No. of cases	294	29	
No. of person-days at risk	4,574,439	6,265,361	

Pfizer 1/2/3 Booster Trial

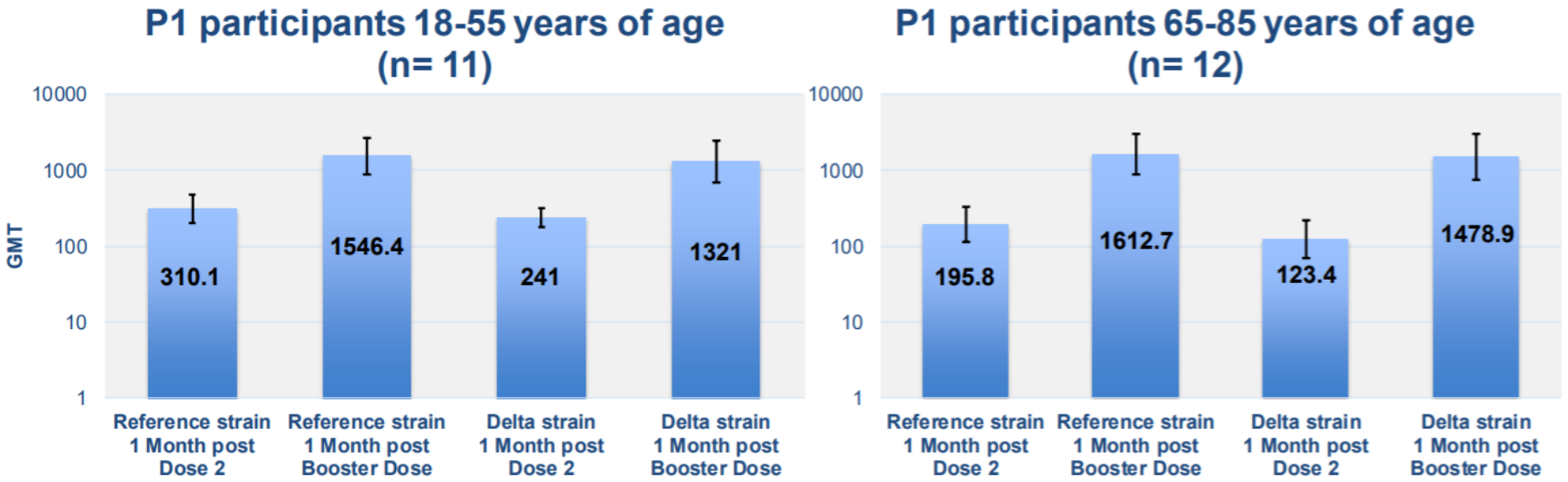


Phase 1 N=23

18-55 (n=11), 65-85 (n=12)

Phase 2/3 N=306

18-55yo only



https://www.fda.gov/media/152161/download

Efficacy of mRNA vaccines against severe disease in settings where Delta variant is circulating, Sept 2021

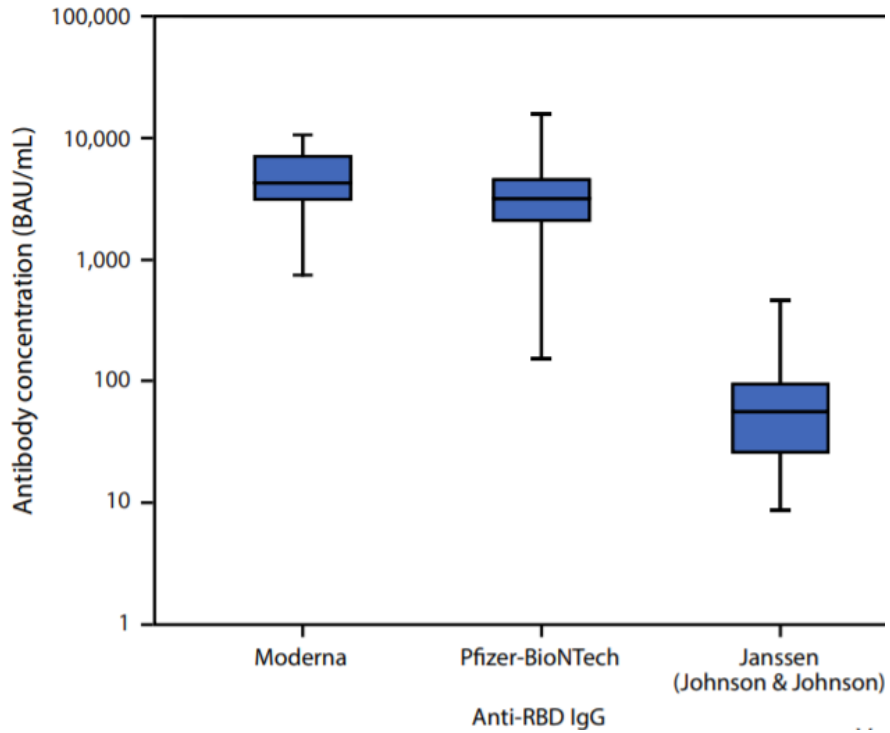
Study Location (reference)	Vaccine	Effectiveness vs. severe disease or hospitalization	Lower limit of 95% CI	Upper limit of 95% CI
USA, Southern California KPSC (1)	BNT162b2 or mRNA-1273	93	84	96
USA, Minnesota (2)	BNT162b2	75	24	94
	mRNA-1273	81	33	96
USA, New York (3)	BNT162b2; mRNA-1273; Ad26.COV2.S	94.4	92.7	95.7
USA 13 jurisdictions (5)	BNT162b2; mRNA-1273; Ad26.COV2.S	90.4	87.7	92.5
USA, 7 locations VISION network (7)	BNT162b2	87	85	90
	mRNA-1273	91	83	93
USA, 9 States VISION network (8)	BNT162b2	80	73	85
	mRNA-1273	95	92	97
USA, 5 VA Medical Centers (9)	mRNA-1273	89	80	94
USA (14)	mRNA-1273	96	91	98
Israel, (4)	BNT162b2	88	94	91
Qatar (10)	BNT162b2	89.7	61	98.1
Qatar (11)	mRNA-1273	100	41.2	100
Singapore (12)	BNT162b2 or mRNA-1273	93	66	98
UK (13)	BNT162b2	96	86	99

Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Early Release / Vol. 70
September 17, 2021

Comparative Effectiveness of Moderna, Pfizer-BioNTech, and Janssen (Johnson & Johnson) Vaccines in Preventing COVID-19 Hospitalizations Among Adults Without Immunocompromising Conditions — United States, March–August 2021

Characteristic†	No./Total no. (%)				
		Vaccine (fully vaccinated participants)§			
	All participants (N = 3,689)	Moderna (n = 476)	Pfizer-BioNTech (n = 738)	Janssen (Johnson & Johnson) (n = 113)	Unvaccinated participants (n = 2,362)
COVID-19 case	**682/3,689 (45.6)**	**54/476 (11.3)**	**128/738 (17.3)**	**37/113 (32.7)**	**1,463/2,362 (61.9)**
Median age (IQR, yrs)	58 (44–69)	66 (56–75)	68 (57–77)	61 (48–67)	53 (40–64)

Vaccine/ Observation period	VE against COVID hospitalization, % (95% CI)		
	Moderna	Pfizer	JJ
Full period	93 (91-95)	88 (85-91)	71 (56-81)
14-120 days	93 (90-95)	91 (88-93)	68 (48-80)
>120 days	92 (87-96)	77 (67-84)	n/a



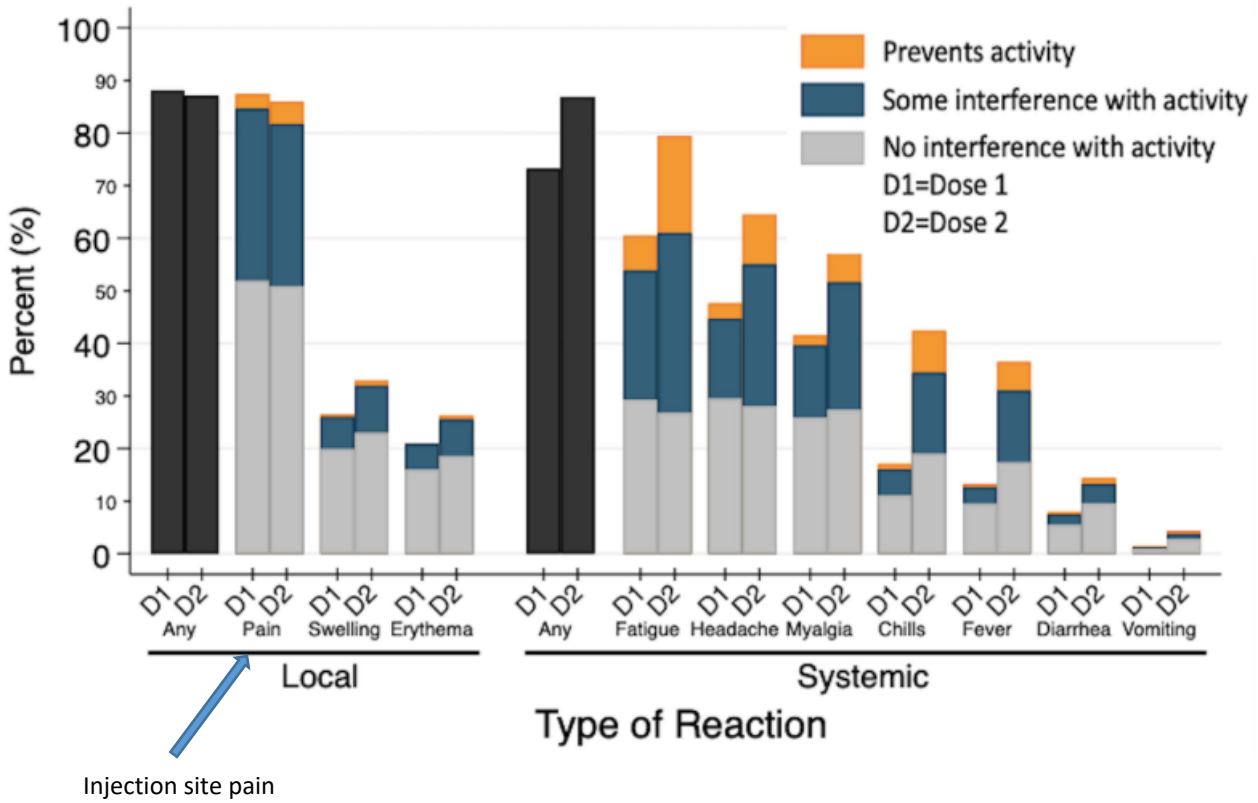
COVID-19 Vaccination and RMD patients

- Review available vaccines
  - How Immunogenicity is measured

- Efficacy of vaccination in RMD patients
  - Effect of immunosuppressive medications on vaccine response
    - ACR recommendations on timing of vaccination and medication use
  - Additional dose of mRNA vaccination
  - Breakthrough infections

- **Safety of vaccination in RMD patients**
  - **Adverse events after vaccination**
  - **RMD flare after vaccination**

RMD Disease Flare after vaccination



- 11% self-reported a disease flare requiring treatment
- No hospitalization; no severe disease.
- Lasted about 10 days; treated with steroids
- No difference with type of mRNA vaccine
- Factors associated with a flare requiring treatment:
  - - Prior COVID-19 infection
  - - Flare within 6 months prior to D1
  - Use of combination immunomodulatory therapy

Connolly et al. A&R 2021

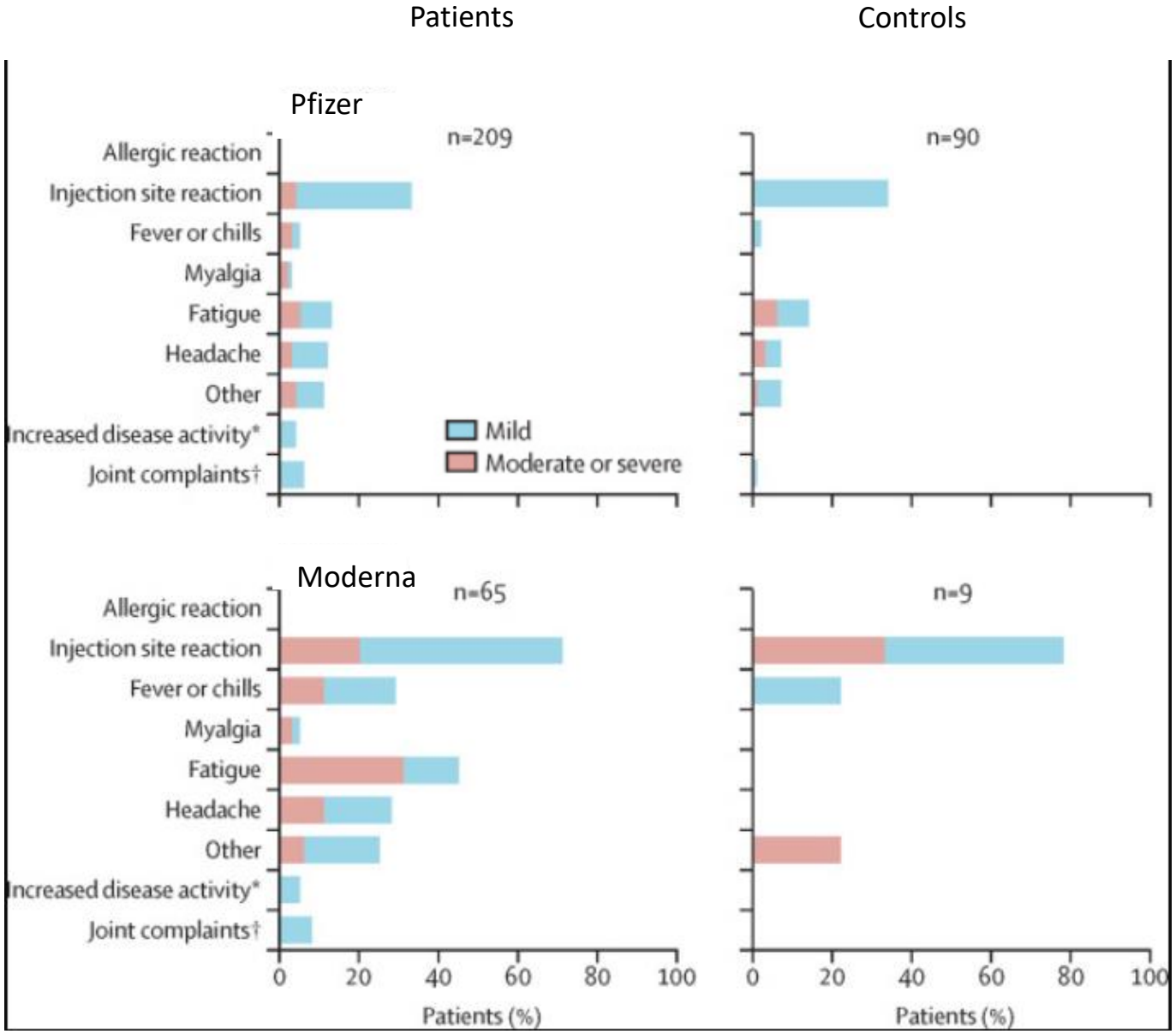
THE LANCET
Rheumatology

Adverse events after first COVID-19 vaccination in patients with autoimmune diseases

Laura Boekel • Laura Y Kummer • Koos P J van Dam • Femke Hooijberg • Zoé van Kempen • Erik H Vogelzang • et al. Show all authors

Published: June 18, 2021 • DOI: https://doi.org/10.1016/S2665-9913(21)00181-8 • Check for updates

- 505 patients with autoimmune disease
  - 40% with RA
- Survey to assess
  - Adverse events within 7 days of D1
  - RMD flare in the first 2 months after D1
- Results
  - Severe adverse events were rare (1%)
  - No serious events occurred
  - Most common AE
    - Injection site reaction 40%



More data on RMD flare after COVID-19 vaccination

- EULAR COVAX
  - 5%: flare
  - 1.2%: severe flare

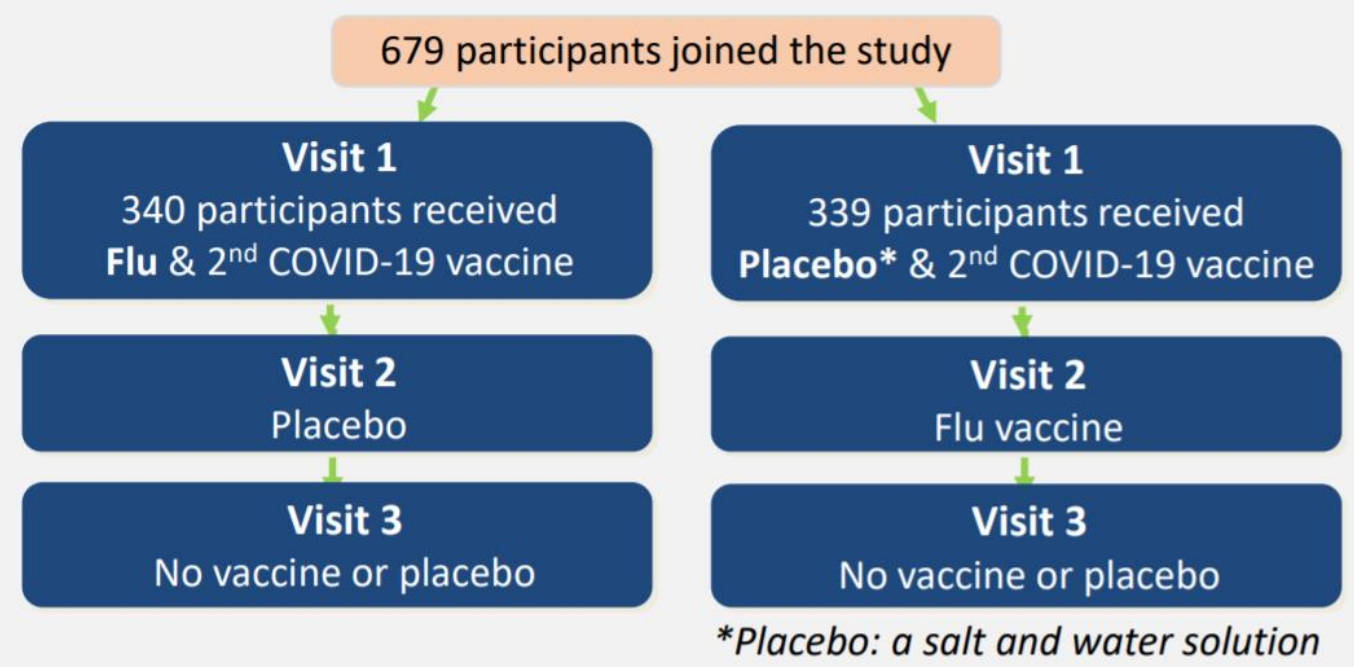
- GRA Vax Survey
  - 13.4%: flare lasting at least 2 days
  - 4.6%: flare requiring a new or increased dose of medication

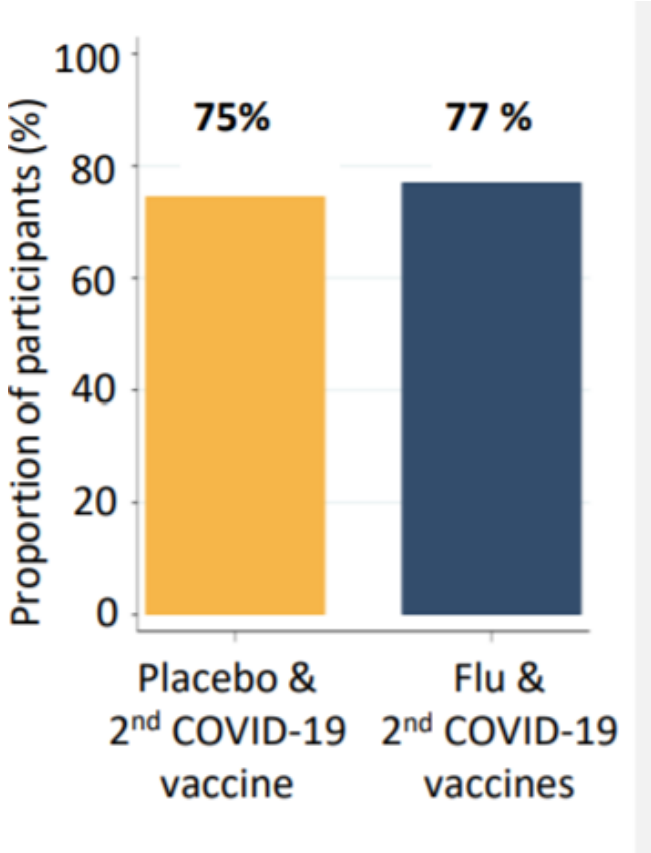
- VACOLUP survey (SLE): 3% flare

- Prospective cohorts (Germany, Israel)
  - Disease activity remained stable after COVID-19 vaccination

ACR Townhall, EULAR convergence, Furer et al. Geisen et al.

ConFluCOV Study (UK):
Combining Influenza and COVID-19 Vaccination





- Giving the flu and COVID-19 vaccines together did not affect the immune responses to either vaccine

Unanswered Questions/Future Directions

- Correlation between levels/titers of Ab and degree of protection?
- Durability of vaccine induced antibody?
- Influence of additional dose (US: NIH ACV01 trial)?
- Vaccine effectiveness against Delta or other emerging variants?
- Role of T-cell in mediating vaccine response?
- Booster vs Mix-match?

Take home points

- Most RMD patients WILL become seropositive, especially after vaccination
- Even those with natural immunity after COVID infection have improved Ab levels after vaccination
- COVID-19 vaccine response may be lower with immunomodulatory therapy, especially BCDT
  - Consider holding MTX, MMF, JAKi, ABA, CYC, RTX before/after COVID-19 vaccination to improve response
- Immunocompromised patients who received mRNA vaccination as their primary series should receive a 3rd additional dose of the same vaccine
  - Does NOT apply to those who received JJ vaccine

Thank you!