Πρόληψη, πορεία και έκβαση λοίμωξης από SARS-CoV-2 σε ασθενείς με ρευματικά νοσήματα: Ελληνική και διεθνής εμπειρία

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Conflict of interest

- Last 5 years

Honoraria: UCB, Aenorasis, Novartis, Jannsen

Outline

- Prevention (Vaccines)
  - Safety
  - Immunogenicity
- Disease course & outcomes
  - Breakthrough infections
  - Symptomatology
  - Hospitalization/Death
- Quotes for treatment

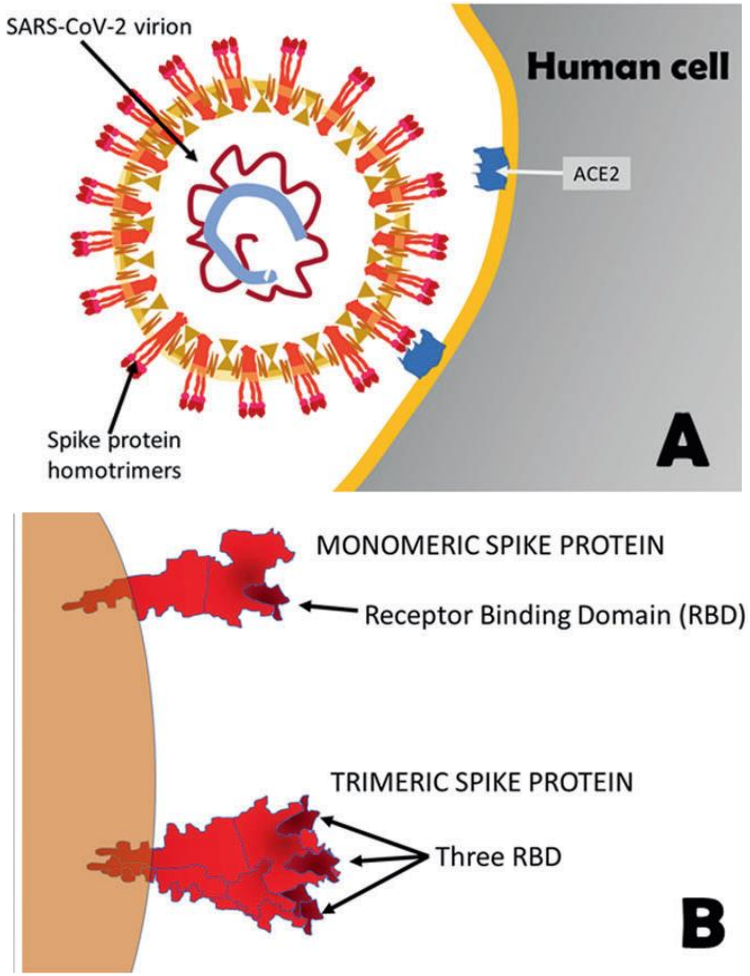
Covid-19 related studies

Problems with interpretation

- Small samples
  - Letters/correspondence
- Quickly outdated
- Many different vaccines
  - Focused on mRNA vaccines
- Study design
  - Surveys
  - Selection bias

Vaccines

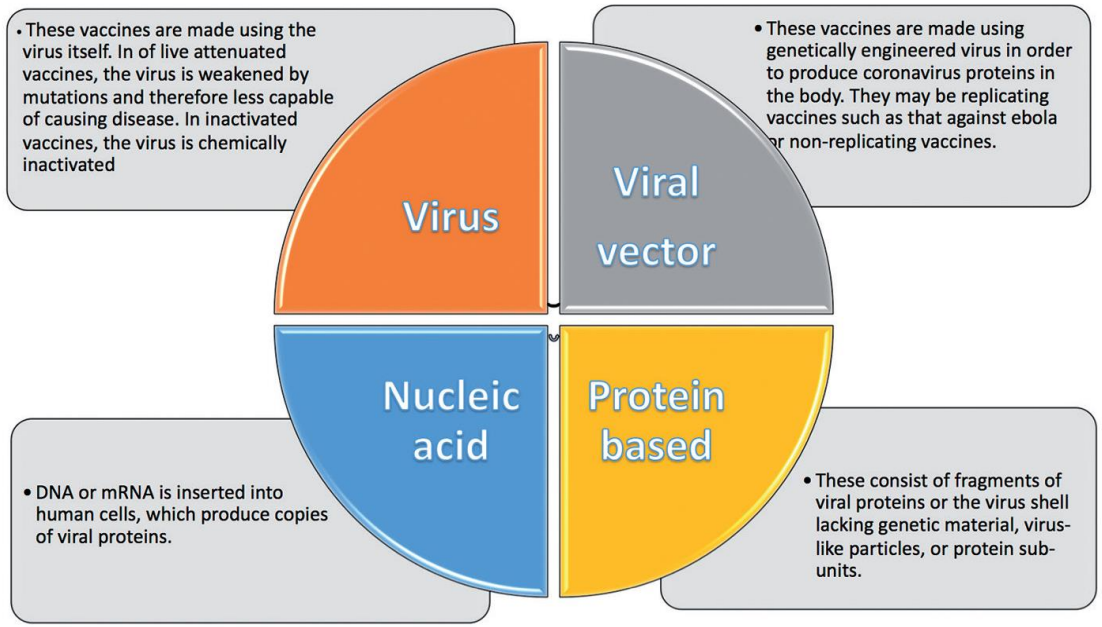
- S protein is the target (receptor binding domain)
  - Trimeric aggregates
  - Plays a major role in infection
    - receptor recognition, viral attachment, entry and fusion into host cells.
      - ✓ ACE2

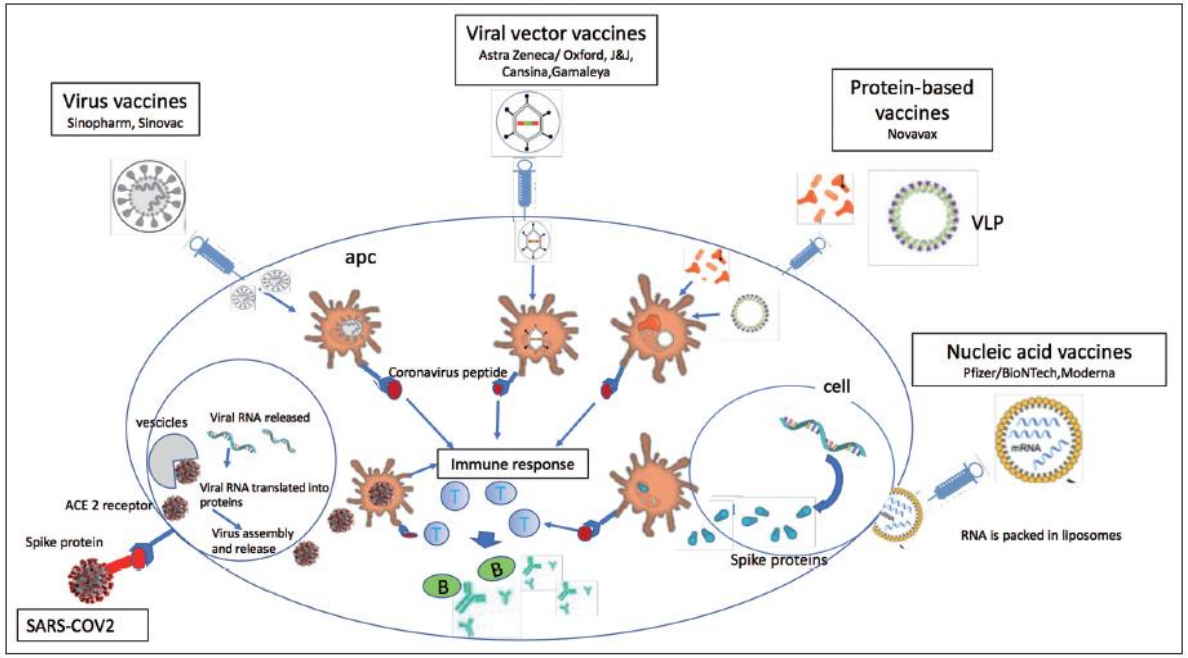


Forni et al Cell Death & Diff 2021

Vaccines

Types



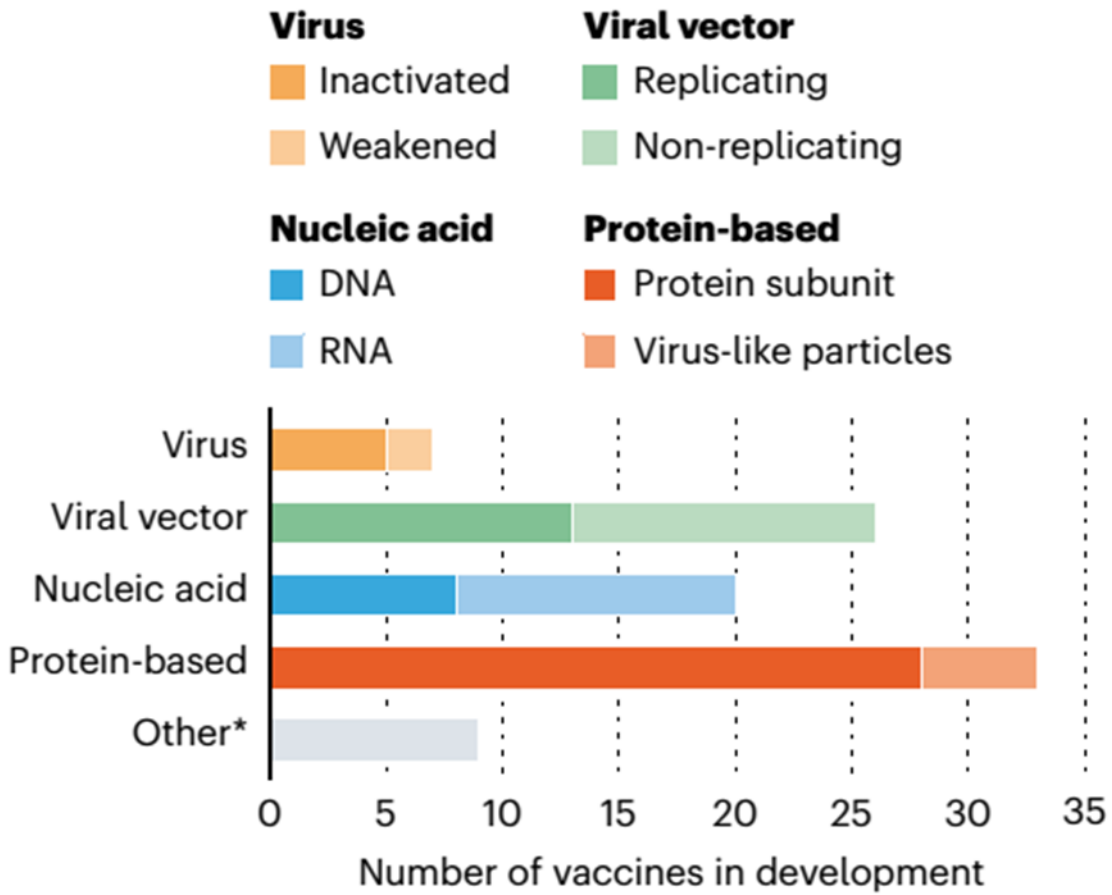


Benucci et al Clin Exp Rheum 2021

Vaccines

Types

Currently, >80 vaccines are included in the overall of 152 trials in 41 countries



GREECE

Last Updated 26 January 2022.

5 Vaccines Approved for Use in Greece

Protein Subunit

Novavax

Nuvaxovid

Approved in 32 countries

11 trials in 7 countries

Approval Source: ema.europa.eu

RNA

Moderna

Spikevax

Approved in 85 countries

45 trials in 19 countries

Approval Source: ema.europa.eu

RNA

Pfizer/BioNTech

Comirnaty

Approved in 136 countries

58 trials in 24 countries

Approval Source: ema.europa.eu

Non Replicating Viral Vector

Janssen (Johnson & Johnson)

Ad26.COV2.S

Approved in 106 countries

18 trials in 18 countries

Approval Source: ema.europa.eu

Non Replicating Viral Vector

Oxford/AstraZeneca

Vaxzevria

Approved in 137 countries

56 trials in 30 countries

Approval Source: ema.europa.eu

ARD patients

Vaccination uptake - I

- VAXICOV to explore the feelings of patients and health-care professionals regarding COVID-19 vaccination
  - Type: 57 web-based questions
  - Population: ARD patients and Healthy subject (control group)
  - 12-20 December 2020
- 1531 participants (84.3%)
- SLE (38.9%), SpA (13.9%), RA (12.6%)
- 56 countries

Felten et al Lancet Rheum 2021

Results

- Uncertainty: 32.2%
- Unwillingness to get vaccinated: 13.6%
- willing to get vaccinated: 54.2%
  - increased to 62.8% when recommended by a physician
  - higher
    - in men (71.2%) p=0.02
    - Higher age (p<0.0001)
    - vaccinated against influenza at least once in the last 3 years (p<0.0001)
    - received the pneumococcal vaccine in the last 5 years (p=0.0002)
    - Not with comorbidities and type of ARDs

Felten et al Lancet Rheum 2021

Results

- Why they wanted to get vaccinated ?
  - protect themselves (67.1%), their relatives (54.2%), and the general population (62.5%)
  - associated with the fear of being infected by SARS-CoV-2 ($p<0.0001$)
- Why not ?
  - **Scarcity of experience and background information regarding new COVID-19 vaccines**
  - **The use of a new technology (eg, mRNA vaccines)**
  - **Possible induction of a flare of their disease**
  - **Risk to develop a local reaction or side-effect**

Covid-19 Vaccines

Are they safe for ARD patients?

- Most clinical trials studying the vaccines against COVID-19 excluded immunosuppressed patients
  - However… phase 3 trial with BNT162b2 vaccine (Pfizer) included 118 ARD patients
    - without specific details on the type of rheumatic disease and/or treatment
- Few data
  - Side-effects
  - Disease flare

Furer et al RMD Open 2021

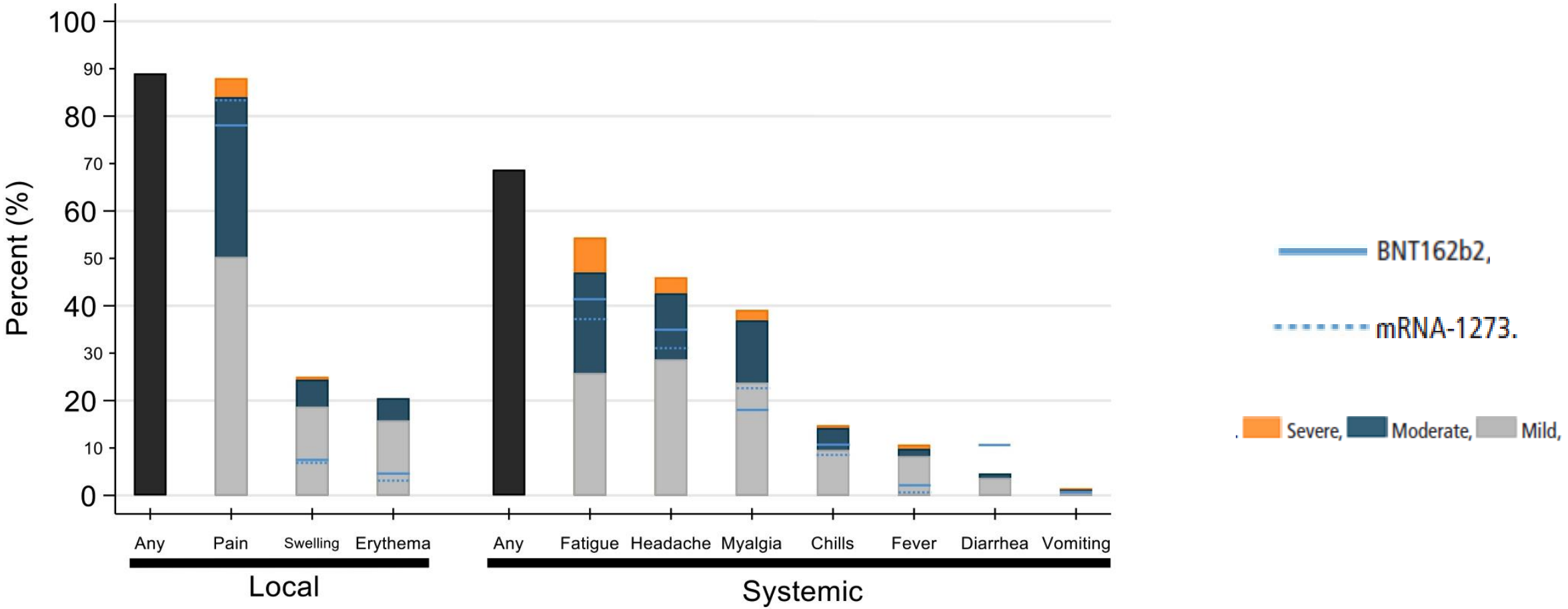
Vaccines - Safety side-effects (I)

- Date: 17 December 2020 - 11 February 2021
- Type: online questionnaire: any reactions experienced within the first week following the first vaccine dose
- 325 RMD pts
  - 51% received Pfizer/BioNTech
  - 49% received Moderna vaccine
  - Median (IQR) age was 43 (34–54) years; 96% were female
  - inflammatory arthritis (38%), SLE (28%) and connective tissue disease (19%)
  - Tx: non-biologic DMARDs (44%), bDMARDs (19%) and combination therapy (37%).

Conolly et al Ann Rheum Dis 2021

Safety

side-effects (I)



Conolly et al Ann Rheum Dis 2021

Vaccines - Safety

side-effects (II)

- 26 ARD patients and 42 healthy controls
  - Mostly health-care workers
- Vaccine: Pfizer
- side effects
  - assessed prior to and 7 days after both vaccinations
  - did not differ between groups
  - fatigue little higher in ARD pts

Table 2 Side effects after secondary immunisation in healthy controls and patients with CID as documented 7 days after the vaccination

	Healthy donors n=38/42 (%)		Patients n=26/26 (%)	
Symptoms	N	%	N	%
Local pain at injection side	25	65.8	17	65.4
Local reddening	2	5.6	2	7.7
Local swelling	4	11.1	4	15.4
Fatigue	16	43.2	14	53.8
Headache	13	35.1	10	38.5
Fever >38°C	5	13.5	0	0
Fever >40°C	0	0	0	0
Lymph node swelling	4	10.8	3	11.5
Chills	8	21.6	1	3.8
Arthralgia	6	16.2	4	15.4
Myalgia	12	31.6	11	42.3
Other side effects	7	18.4	5	19.2
Need for NSAIDs	10	26.3	9	34.6

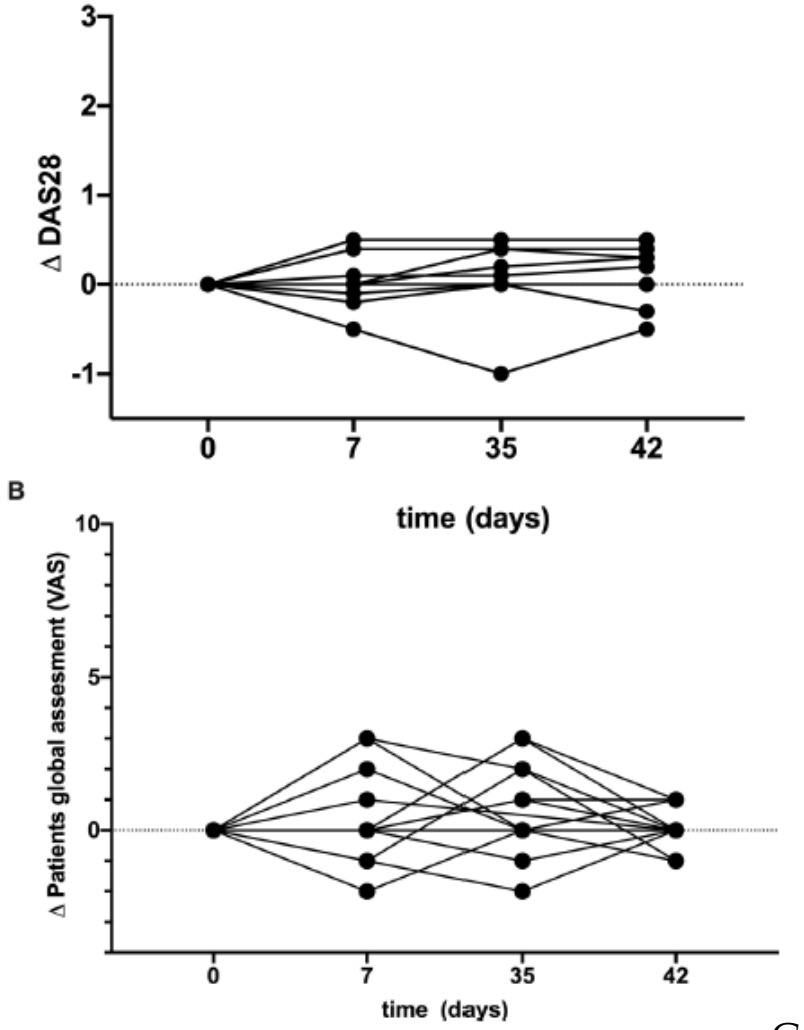
NSAIDs, non-steroidal anti-inflammatory drugs.

Geisen et al ARD 2021

Vaccines - Safety

Disease flares

- NO flares in inflammatory arthritis patients in the context of either vaccination time points.
- Delta Patient Global (PGA) for the last time point (7 days after secondary vaccination) was 0.076 (±0.4) compared with baseline.
- No ARD patient needed to adjust DMARD or glucocorticoid therapy

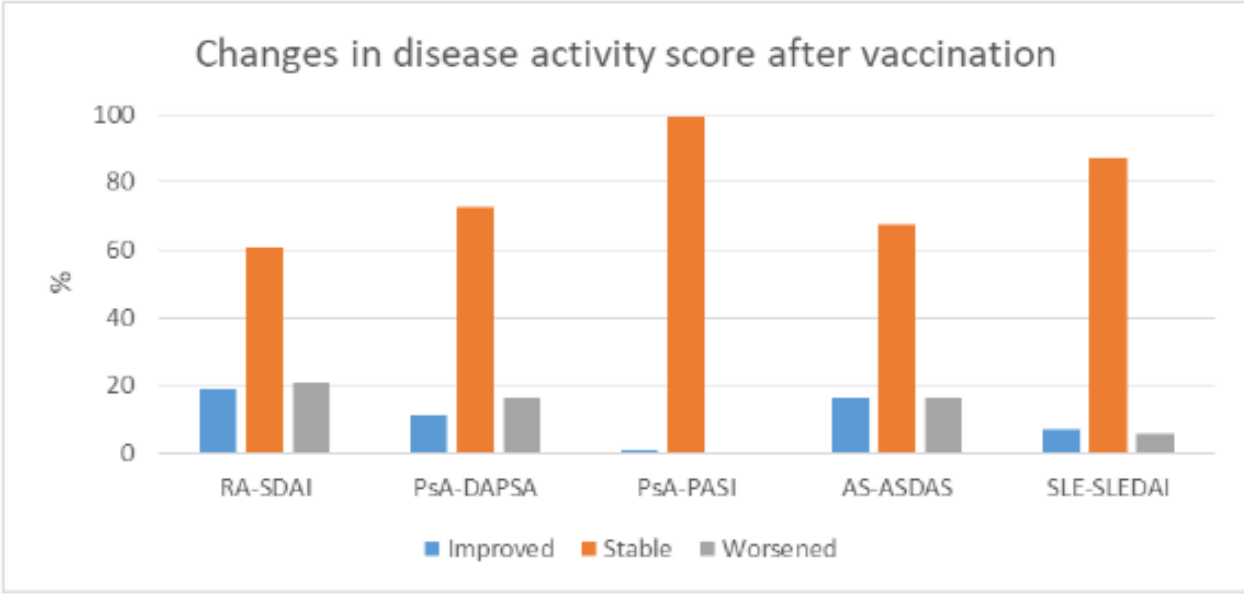


Geisen et al ARD 2021

Vaccines - Safety

Disease flares

- A multicentre observational study
  - BNT162b2 mRNA vaccine in adult patients with AIIRD (n=686)
  - Vs general population (n=121).
- Adverse events were similar in patients with AIIRD and controls
- No significant change in disease activity in a variety of ARDs



Furer et al ARD 2021

Vaccines – Safety

AEs and Disease flare

- Telephone interviews were conducted of SRD patients consecutively enrolled (15/06/2021–1/7/2021)
- Participants were asked about the type of AEs and disease flare after vaccination
- Reasons for vaccination hesitancy were recorded

Table 1 Demographic characteristics of the patients included in the study

Characteristics	$n=561$
Female Gender, *n* (%)	424 (75.6%)
Age, mean ± SD	54.4 ± 14.8
Smoking (current), *n* (%)	151 (26.9%)
Disease	
Inflammatory arthritis, *n* (%)	326 (58.1)
Connective tissue diseases, *n* (%)	154 (27.5)
Autoinflammatory, *n* (%)	22 (3.9)
Vasculitis, *n* (%)	59 (10.5)
Disease duration (years), mean ± SD	9.8 ± 8.1
College/university level of education, *n* (%)	207 (36.8)
Unemployment, *n* (%)	101 (18.0)
Treatment	
On steroids, *n* (%)	201 (35.8)
On cDMARDs, *n* (%)	362 (64.5)
On b/tsDMARDs, *n* (%)	313 (55.8)

Fragoulis et al Rheum Int 2021

Vaccines – safety

AEs and disease flare

Table 2 Vaccination characteristics of patients included in the study

COVID-19 vaccinated	*n* = 441
Vaccine	
Pfizer, *n* (%)	380 (86.2)
Moderna, *n* (%)	14 (3.2)
Astra-Zeneca, *n* (%)	44 (10.0)
Johnson & Johnson, *n* (%)	3 (0.7)
Adverse effects, rates	148/441
1st dose, *n* (%)	107 (24.3)
2nd dose, *n* (%)	108 (24.5)
Both doses, *n* (%)	67 (15.2)
Disease flare, rates	
1st dose, *n* (%)	1 (0.23)
2nd dose, *n* (%)	8 (1.81)

Type of vaccine received, rates of adverse effects and disease flare

Table 3 Adverse effects reported after COVID-19 vaccination in 441 patients with systemic rheumatic disease

	Astra-Zeneca (*n* = 45)	Pfizer (*n* = 380)	Moderna (*n* = 14)	Johnson & Johnson (*n* = 2)	Total doses (*n* = 880)
	N, 1st dose/2nd dose (% first dose/% second dose)				
Fatigue	4/1 (9.1/2.3)	38/36 (10.0/9.5)	0/3 (0/2.1)	1/NA (33.3/NA)	83 (9.4)
Local pain	1/0 (2.3/0)	33/32 (8.7/8.4)	2/2 (14.3/14.3)	1/NA (33.3/NA)	71 (8.1)
Fever	8/5 (18.2/11.4)	12/29 (3.2/7.6)	1/2 (7.1/14.3)	1/NA (33.3/NA)	58 (6.6)
Headache	1/0 (2.3/0)	16/19 (4.2/5.0)	1/0 (7.1/0)	0/NA (0/NA)	37 (4.2)
Dizziness	1/1 (2.3/2.3)	13/7 (3.4/1.8)	0/0 (0/0)	0/NA (0/NA)	22 (2.5)
Myalgias/arthralgias	1/0 (2.3/0)	5/11 (1.3/2.9)	1/0 (7.1/0)	1/NA (33.3/NA)	19 (2.2)
Rash	0/0 (0/0)	6/2 (1.6/0.5)	0/0 (0/0)	0/NA (0/NA)	8 (0.91)
Chills	1/1 (2.3/2.3)	0/3 (0/0.8)	0/1 (0/7.1)	0/NA (0/NA)	6 (0.68)
Numbness	0/0 (0/0)	2/2 (0.5/0.5)	0/0 (0/0)	0/NA (0/NA)	4 (0.45)
Panic attack	0/0 (0/0)	1/3 (0.3/0.8)	0/0 (0/0)	0/NA (0/NA)	4 (0.45)
ENT symptoms	0/0 (0/0)	1/2 (0.3/0.5)	0/0 (0/0)	0/NA (0/NA)	3 (0.34)
Arrhythmias/BP	0/0 (0/0)	1/2 (0.3/0.5)	0/0 (0/0)	0/NA (0/NA)	3 (0.34)
Local swelling	0/0 (0/0)	0/2 (0/0.5)	1/0 (7.1/0)	0/NA (0/NA)	3 (0.34)
Lymphadenitis	0/0 (0/0)	0/2 (0/0.5)	0/0 (0/0)	0/NA (0/NA)	2 (0.23)
Leukopaenia	0/0 (0/0)	1/1 (0.3/0.3)	0/0 (0/0)	0/NA (0/NA)	2 (0.23)
Cough	0/0 (0/0)	1/0 (0.3/0)	0/0 (0/0)	0/NA (0/NA)	1 (0.11)
Pericarditis	0/0 (0/0)	0/1 (0/0.3)	0/0 (0/0)	0/NA (0/NA)	1 (0.11)
Itching	0/0 (0/0)	0/1 (0/0.3)	0/0 (0/0)	0/NA (0/NA)	1 (0.11)
GI symptomatology	0/0 (0/0)	0/1 (0/0.3)	0/0 (0/0)	0/NA (0/NA)	1 (0.11)

Why not vaccination?

nocebo-prone behaviour (OR; 95% CI, 3.88; 1.76-8.55), negative vaccination behaviour (6.56; 3.21-13.42)

Fragoulis et al Rheum Int 2021

Vaccines – safety

EULAR COVAX registry

- 5121 participants from 30 countries
  - Inflammatory joint diseases (58%), connective tissue diseases (18%) and vasculitis (12%)
  - 54% cDMARDs, 42% bDMARDs, 35% immunosuppressants
- Pfizer (70%), AstraZeneca (17%), Moderna (8%)
- Flares: 4.4% of cases (similar results from Global Rheum alliance vaccine survey)
  - 0.6% severe
  - 1.5% resulting in medication changes.
- AEs were reported in 37% of cases
  - serious AEs in 0.5%

Machado et al ARD 2021
Sattui et ar RMD Open 2021

Vaccines safety – disease flare

EULAR SLR

- “Three studies found no postvaccination disease flare of the underlying RMD in 868 patients with RMD, while a report from the EULAR COVAX registry describes a disease flare in 73 out of 1375 (5%) patients, of whom 17 experienced a severe flare (mean±SD) 5±5 days postvaccination”

Kroon et al ARD 2021
Machado et al ARD 2021 (abs)

Outline

- Prevention (Vaccines)
  - Safety
  - Immunogenicity
- Disease course & outcomes
  - Breakthrough infections
  - Symptomatology
  - Hospitalization/Death
- Quotes for treatment

Immunogenicity

After second dose (1)

- When: 12 July 2020 and 16 March 2021
- One month after the second dose
- N=404
  - 49% received the Pfizer/BioNTech vaccine and 51% received Moderna
  - Inflammatory arthritis: 45%, SLE: 22%
- Method: semiquantitative Roche ELISA for anti-receptor-binding domain (RBD) of the SARS-CoV-2 spike protein

Ruddy et al ARD 2021

Immunogenicity

After second dose (1)

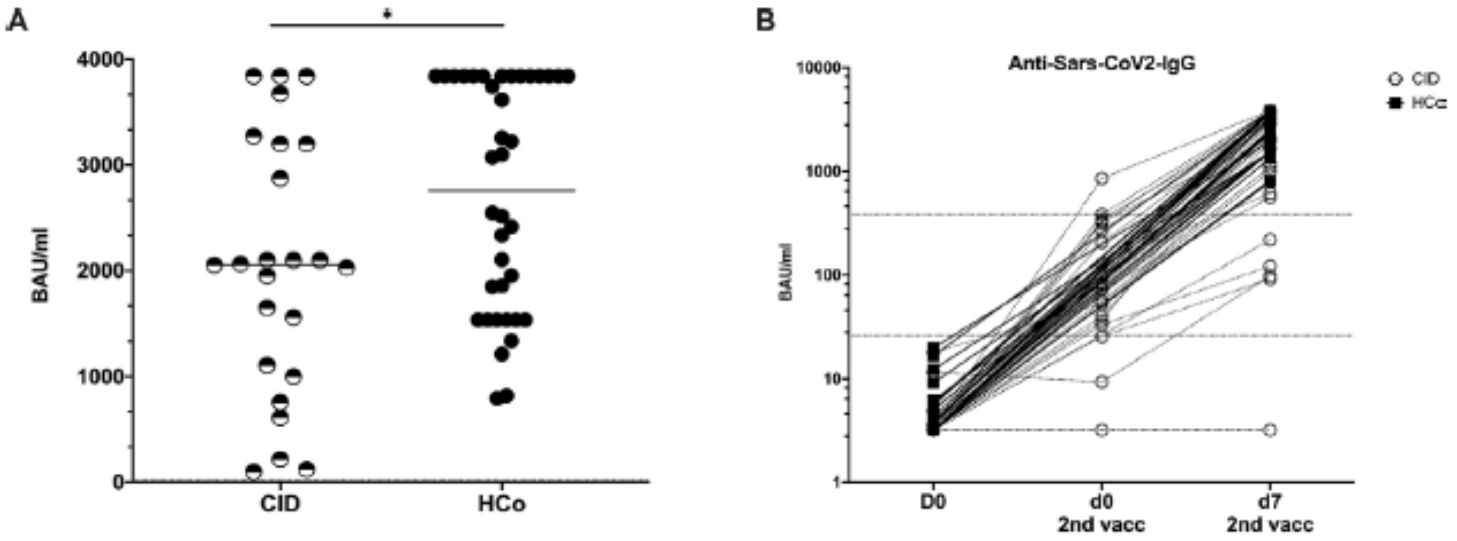
- Positive abs 378/404 (94%)
- Seroconversion
  - Following D1 (74%) increased to 94% (after D2)
- **MMF, RTX, Steroids** associated with negative response ($p<0.001$)
  - For MMF: Seroconversion was 73% Vs 27% after D1
  - For RTX: remained poor (33% seroconversion after D1, 26% seroconversion after D2).

Ruddy et al ARD 2021

Immunogenicity

After second dose (2)

- 42 healthy controls and 26 patients with ARDs
- Method: EUROIMMUN ELISA and neutralizing ab
  - Day 0
  - Day of D2
  - D2 + 7 days
- At D2+7, Patients
  - Lower mean anti-SARS-CoV-2-IgG titre Vs HCs (p=0.037)
  - But all (-1) above cut-off
- No significant difference between treatments arms
  - Not detailed



Geisen et al ARD 2021

Immunogenicity

After second dose (3)

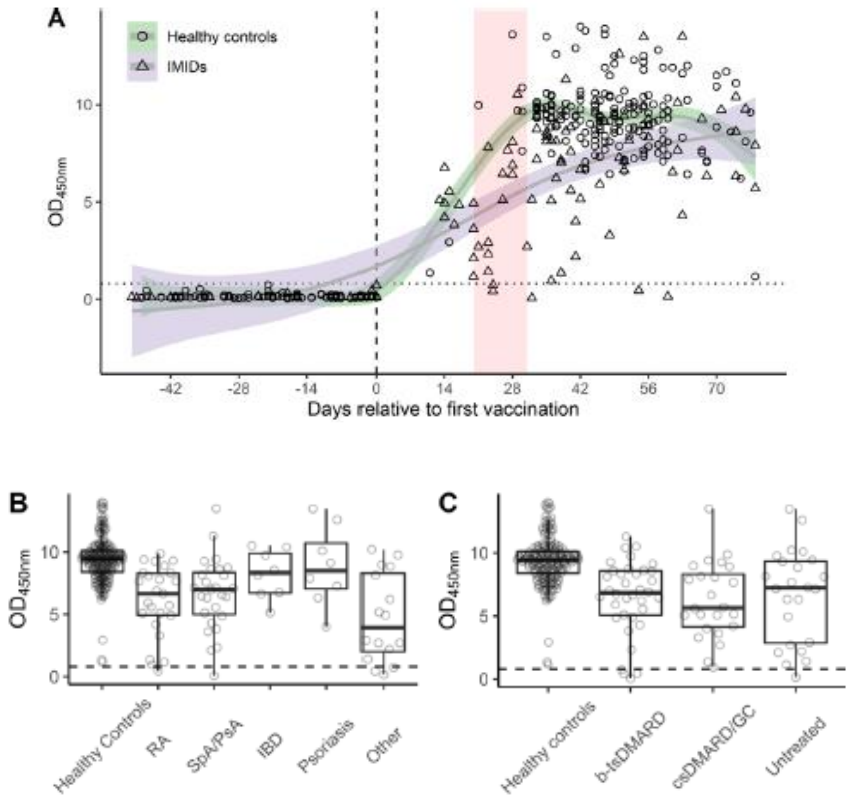
- 84 IMID patients & 182 controls
- Vaccine: Pfizer
- The vast majority (96%): two shots
- Method: EUROIMMUN ELISA and neutralizing ab
- IMID
  - SpA/ psoriatic arthritis: 32.1%
  - RA: 29.8%
  - Inflammatory bowel disease: 9.5%
  - Psoriasis: 9.5%
  - Systemic IMIDs (e.g SLE): 19.1%
- bDMARDs/tsDMARDs: 42.9%, cDMARDs: 23.9%, No Tx: 28.6%

Simon et al ARD 2021

Immunogenicity

After second dose (3)

- 5 (6%) IMID patients failed to develop a response (p=0.003)
- IMID patients
  - large OD difference shortly after the second vaccination
    - but this difference converged over time
  - No differences across
    - Diseases
    - Drugs (no RTX included)



Simon et al ARD 2021

Immunogenicity

After second dose (4) - MTX?

- Vaccine: BNT162b2
- IMID (n=51) (**mostly PsA/RA**) Vs healthy (n=26)
- Assessment: baseline and after second immunization
  - Humoral response (EUROIMMUN)
  - Cellular immune response (flow cytometry)
  - Validation cohort of controls (n=182) and patients with IMID (n=31)
- About 15% previous covid infection

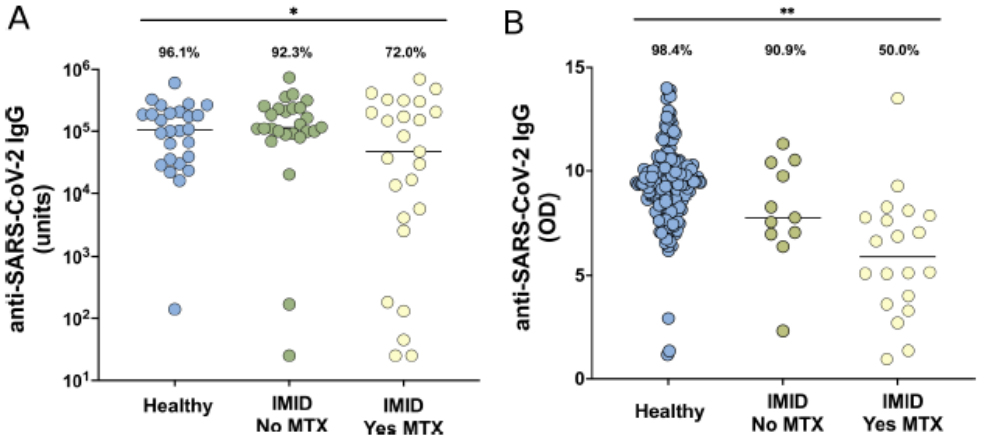
Characteristic	Healthy (n = 26)	IMID No MTX* (n = 26)	IMID Yes MTX* (n = 25)	p-value
Age- mean (range, SD)	49.2 [28-74, 11.9]	49.1 [29-79, 14.9]	63.2 [22-77, 11.9]	<0.001
Female- n (%)	16 (61.5)	18 (69.2)	18 (66.7)	
Race- n (%)				0.352
White	16 (61.5)	20 (76.9)	17 (63.0)	
Black	1 (3.8)	2 (7.7)	3 (11.1)	0.220
Asian	9 (34.6)	3 (11.5)	3 (11.1)	
Other	0 (0.0)	1 (3.8)	2 (7.4)	0.200
Hispanic ethnicity- n(%)	1 (3.8)	3 (11.5)	5 (18.5)	
Primary Immune Mediated Inflammatory Disease - n (%)				0.107
Psoriasis and/or Psoriatic Arthritis	--	15 (57.7)	9 (36.0)	
Rheumatoid Arthritis	--	10 (38.5)	12 (48.0)	
Other*	--	1 (3.8)	4 (16.0)	

Habermann et al ARD 2021

Immunogenicity

After second dose (4) – MTX ?

- IMID **not on** methotrexate
  - Similar rate of high antibody titers (24/26, 92.3%)
- IMID **on methotrexate**
  - lower rate of adequate humoral response (18/25, 72.0%) (p=0.02)
    - Validation cohort: similar results (91% Vs 50%)
    - Remained significant when patients with previous infection were excluded (p=0.045)
    - Differences remained when 55 years-old was used as a cut-off
- Cellular response
  - Activated CD8+ T cells (Ki67+ CD38+) and CD8+GZMB subset
    - **<u>were induced in healthy adults and participants with IMID not on methotrexate, but not induced in patients receiving methotrexate</u>**



Habermann et al ARD 2021

Immunogenicity

After second dose (5)

686 ARD patients and **121** controls
ARD were significantly older p<0.0001

- Seropositivity rate: 86% (ARD) Vs 100% in controls (p <0.0001)
  - Type of disease
    - RA: 82.1%
    - AAV and myositis: <40%
    - All others >90%

- Seropositivity per Treatment
  - Anti-cytokine:
    - >97% as monotherapy
    - 93% in combination with MTX
  - MTX: 92% monotherapy and 84% combinations
    - lesser magnitude than anti-CD20, MMF, and abatacept.
  - GC, MMF, Abatacept: lower rate of seropositivity (~60%)
  - Anti-CD20: 39%

Furer et al ARD 2021

Immunogenicity

After third dose (booster)

- 18 patients received booster dose
- Anti-spike antibodies
  - Negative in 10 (<0.8 U/mL)
  - Low-positive (0.8–500 U/mL) in 6
- 30 days after booster re-tested Abs
  - 89% responded

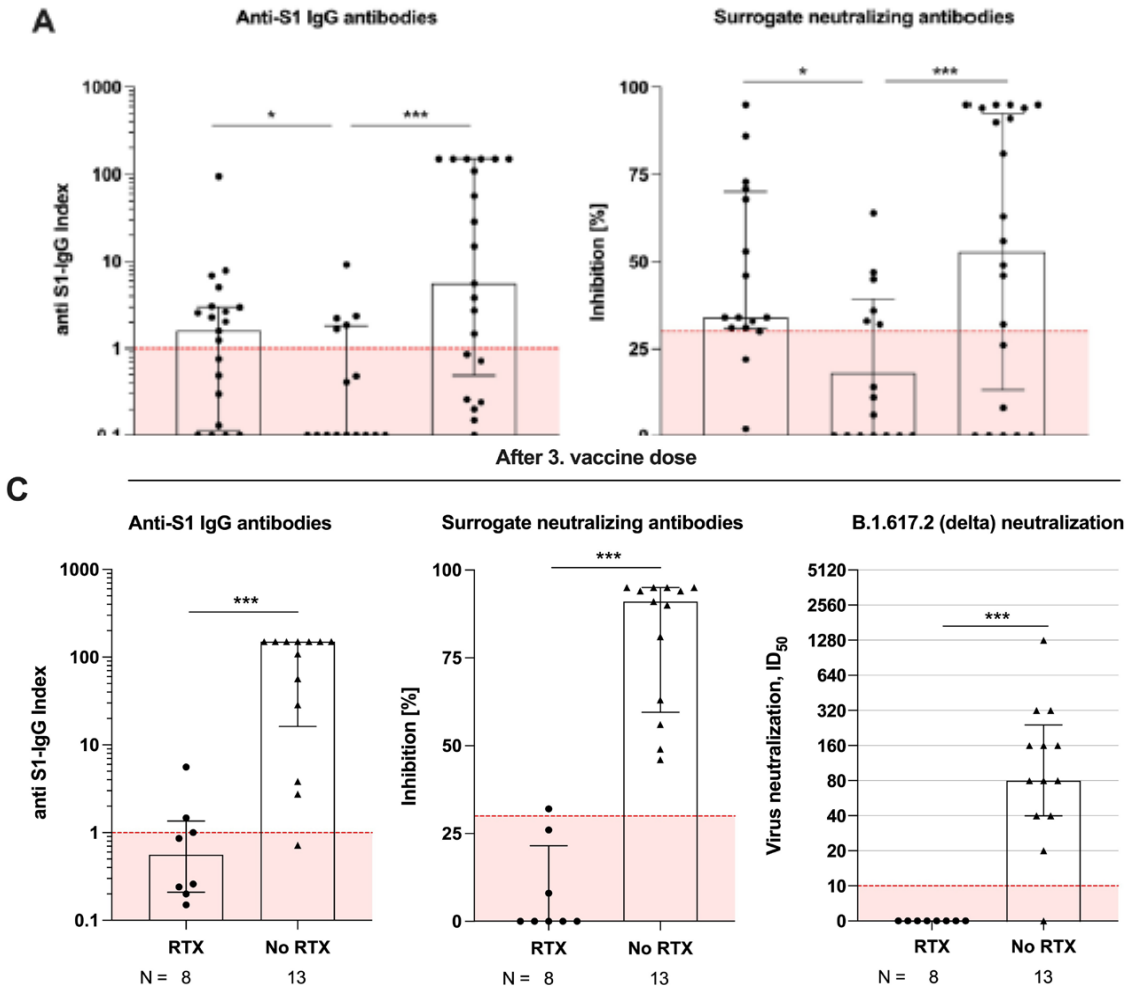
Age	Sex	Diagnosis	Immunosuppressive therapy	Initial vaccine series	Meds held during initial vaccine	Pre-booster antibody	Booster vaccine type	Days from initial to booster vaccine	Post-booster antibody	Therapy held peri-booster*
39	F	Multiple sclerosis	Ocrelizumab	Pfizer	Yes	<0.40	J&J	60	<0.40	No
56	F	Mucous membrane pemphigoid	Mycophenolate	Pfizer	No	<0.40	J&J	47	<0.40	No
43	F	Inflammatory bowel disease†	Mycophenolate Tacrolimus	Pfizer	No	<0.40	Moderna	72	8.9	No
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	Sarcoidoisis	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
64	F	Autoimmune hepatitis	Azathioprine Tacrolimus	Moderna	Yes	260	Moderna	83	>2500	Yes
44	M	Inflammatory bowel disease†	Golimumab Methotrexate	Pfizer	NA‡	359.8	Pfizer	68	>2500	Yes
75	F	Autoimmune hepatitis	Mycophenolate	Moderna	No	825.8	Moderna	96	>2500	No
57	M	Inflammatory arthritis¶	Secukinumab	Pfizer	Yes	2418	Moderna	54	>2500	Yes

Connolly et al ARD 2021

Immunogenicity

After third dose (booster)

- 21 patients with AAV
- The third vaccine dose was administered a median (IQR) of 103 (72–126) days after second vaccination
- Effective for some patients
- ….but not for those treated with RTX

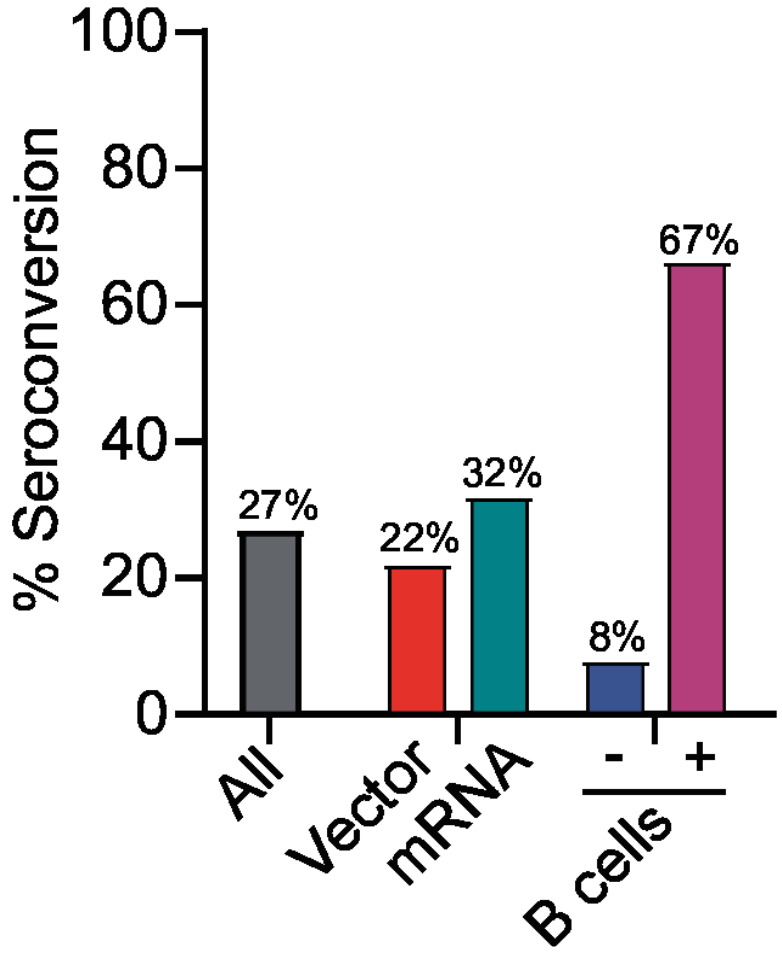


Speer et al ARD 2022

Immunogenicity

After third dose (booster)

- RCT
- Efficacy & safety of booster vaccination
  - Vector Vs mRNA vaccine in non-seroconverted patients
- 60 RTX patients (non-seroconverted patients)
- Receive a third dose, mRNA or the vector vaccine
- Overall, 27% seroconverted at week 4
  - More pronounced in those who had B cell responses

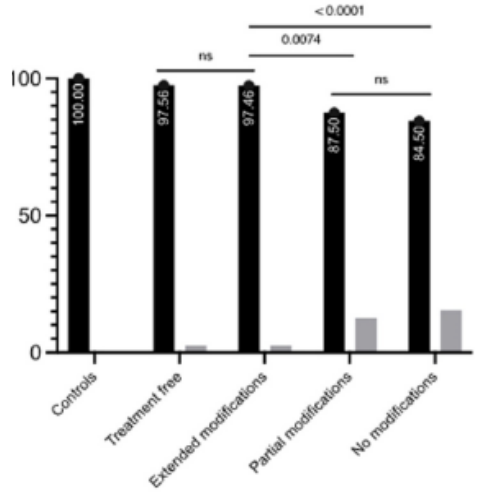


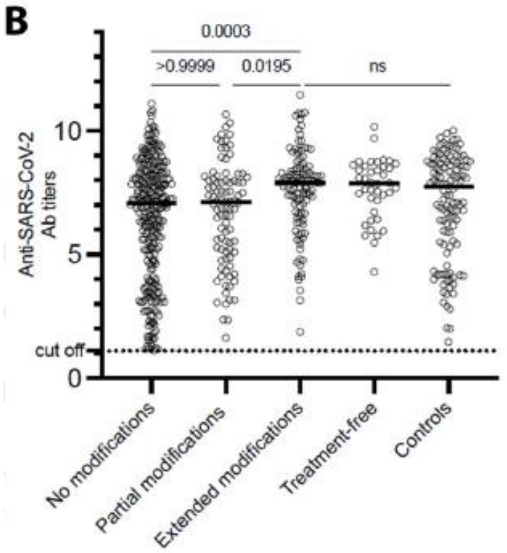
Bonelli et al ARD 2022

Vaccinations

Treatment modifications (Rituximab, MMF)

- 605 SAARD patients and 116 controls
- anti-SARS-CoV-2 titers, side-effects, and disease activity
- treatment modification strategies
  - None
  - Partial [MTX, MMF, JAKi, abatacept and RTX] (ACR)
  - Extended modifications
- Extended treatment modifications
  - responded to vaccines similarly to controls as well as SAARD patients without immunosuppressive therapy
  - developed higher anti-SARS-CoV-2 antibody levels compared to those without or with partial modifications
- **<u>In contrast,</u>** patients with partial or without therapeutic modifications responded in 87.50% and 84.50%, respectively



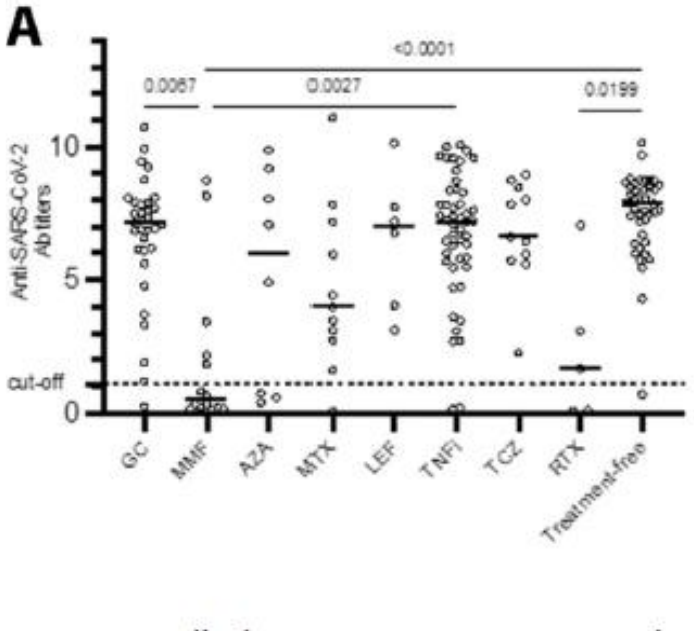


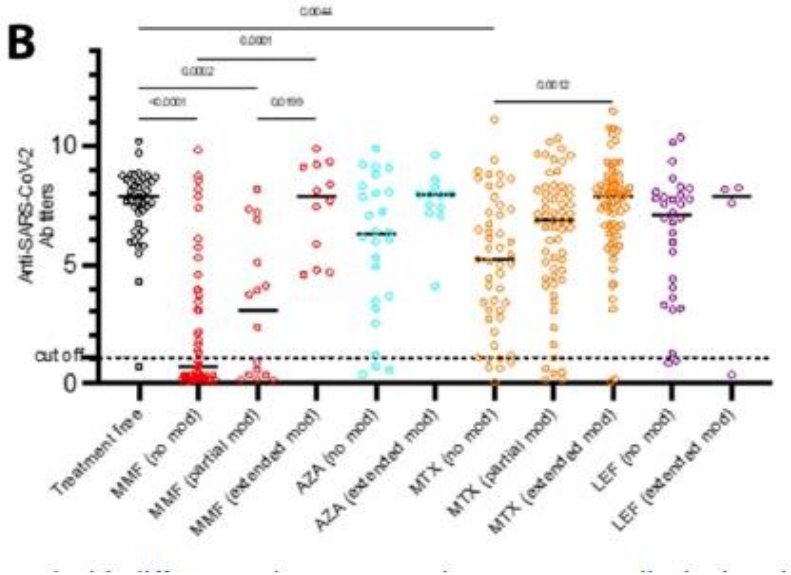
Tzioufas et al J Autoimm 2021

Vaccinations

Treatment modifications (Rituximab, MMF)

- Mycophenolate mofetil (MMF), rituximab (RTX) and methotrexate (MTX) negatively affected anti-SARS-CoV-2 humoral responses
- 10.5% of vaccinated patients, mild clinical deterioration was noted
  - No differences in deterioration among the distinct treatment modification





Tzioufas et et al J Autoimm 2021

Vaccinations

Treatment modifications (Rituximab)

- 11 pts treated with RTX
  - 1st dose of the vaccine in mean ± SD 20.4 ± 13.4 weeks after the last RTX
  - only 2 of 11 (18.2%) patients had antibody levels over the cut-off value of 50 AU/mL

Evangelatos et al Arthr & Rheum 2021

Rituximab

any predictors for response?

- 108 AIIRD-RTX patients and 122 immunocompetent controls immunized with BNT162b2 mRNA
- anti-SARS-CoV-2 @2 to 6 weeks after the second vaccine dose
- ⇩ immunogenic response
  - AAV (vs RA)
  - Myositis (Vs RA)
  - higer number of RTX courses
  - higher cumulative RTX dose
  - lower IgG level prior to last RTX course
  - short interval between RTX tr

BNT162b2 mRNA vaccination (n=104)

Predictors	OR	95% CI	p value
RA	Ref	Ref	Ref
AIIRD diagnosis			
SLE	4.225	0.543-32.89	0.169
ANCA-associated vasculitis	0.209	0.046-0.96	0.044
Other systemic vasculitis	0.478	0.044-5.244	0.546
IIM	0.189	0.036-0.987	0.048
Rituximab-relevant details			
Serum IgG level (50 mg/dL increments, prior to last RTX course)	1.104	1.019-1.196	0.016
Total number of RTX courses	0.874	0.75-1.018	0.084
Time interval between last RTX course and BNT162b2 vaccine (weeks)	1.048	1.018-1.079	0.002

Furer et et al PrePrint

EULAR guidance

EULAR RECOMMENDATIONS FOR THE MANAGEMENT OF RHEUMATIC AND MUSCULOSKELETAL DISEASES IN THE CONTEXT OF SARS-CoV-2:
The July 2021 update

8.	In patients with RMD not using immunomodulatory or immunosuppressive treatment, SARS-CoV-2 vaccination should precede a treatment start with such therapy if clinically feasible.	9.6 (1.1)	93
9.	In patients with RMD using rituximab or another B-cell depleting therapy, SARS-CoV-2 vaccination should be scheduled in a way to optimise vaccine immunogenicity.	9.6 (1.1)	96

EULAR guidance
Landewe et al 2020

ACR guidance

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COVID-19 Vaccine Clinical Guidance Summary for Patients with Rheumatic and Musculoskeletal Diseases

Version 4
Revised December 15, 2021

Developed by the ACR COVID-19 Vaccine Clinical Guidance Task Force

Abatacept SQ	**Hold for one to two weeks (as disease activity allows) after each COVID vaccine dose**	**Moderate**
TNFi, IL-6R, IL-1R, IL-17, IL12/23, IL-23, and other cytokine inhibitors†	**The Task Force failed to reach consensus on whether or not to temporarily interrupt these following each COVID vaccine dose, including both primary vaccination and supplemental (booster) dosing**	**Moderate**
Cyclophosphamide IV	**Time CYC administration so that it will occur approximately 1 week after each vaccine dose, when feasible**	**Moderate**
Rituximab or other anti-CD20 B-cell depleting agents	**Discuss the optimal timing of dosing and vaccination with the rheumatology provider before proceeding‡**	**Moderate**
All other conventional and targeted immunomodulatory or immunosuppressive medications (e.g., JAKi, MMF) except those listed above§	**Hold for one to two weeks (as disease activity allows) after each COVID vaccine dose**	**Moderate**

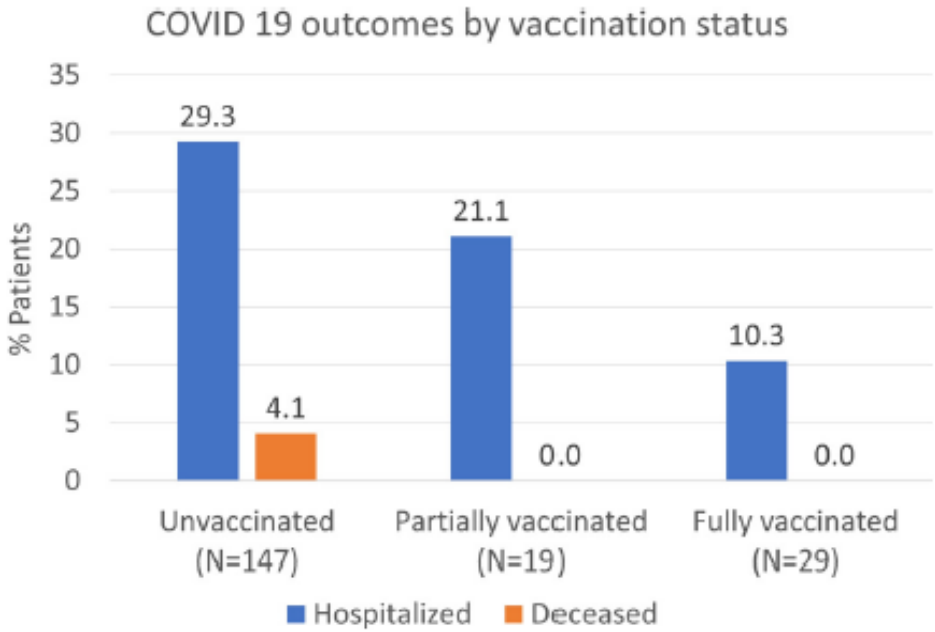
Outline

- Prevention (Vaccines)
  - Safety
  - Immunogenicity
- Disease course & outcomes
  - Breakthrough infections
  - Symptomatology
  - Hospitalization/Death
- Quotes for treatment

Breakthrough infections

Better outcomes for vaccinated…

- March 2020 - August 2021
- 195 patients with SRD with COVID-19 were included
- 147 unvaccinated and 48 vaccinated with at least one dose of a SARS-CoV- 2 vaccine (Pfizer n=38 or AstraZeneca n=10).
- Among vaccinated patients, 29 developed breakthrough COVID-19 >14 days after the second vaccine dose (fully vaccinated), while 19 between the first and <14 days after the second vaccine dose (partially vaccinated).
- No differences in demographics, SRD type, treatment or comorbidities between unvaccinated and vaccinated patients

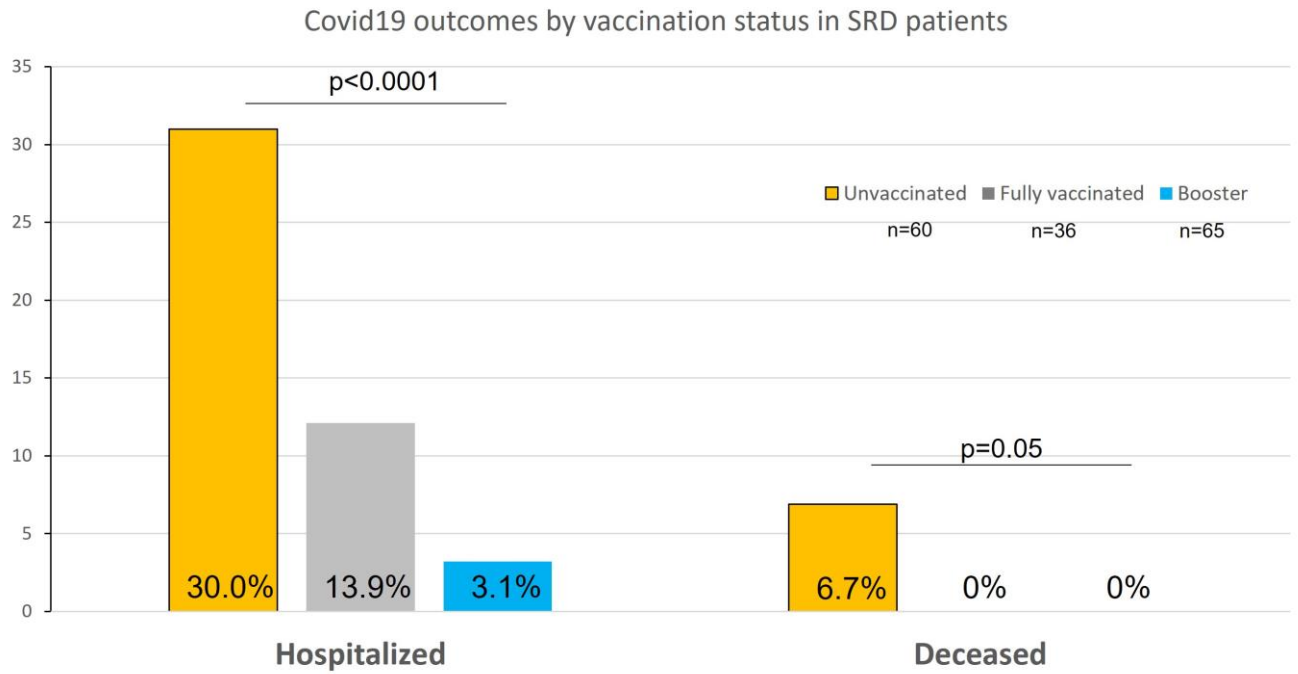


Papagoras et al ARD 2021

Breakthrough infections

Better outcomes for booster vaccinated

- 154 SRD patients March 2020 till - January 2022.
- 60 were unvaccinated, while 36 and 65 were fully-vaccinated and booster-vaccinated
- Also, data from 80 booster-vaccinated individuals without SRD who had breakthrough infection were recorded. Seventy-seven were vaccinated with mRNA vaccines
- Similar characteristics (lung disease more common in SRD (especially in booster-vaccinated)
- Booster offered protection from severe outcomes
- Comparable outcomes between SRD and healthy booster



Fragoulis et al Under Review

Outline

- Prevention (Vaccines)
  - Safety
  - Immunogenicity
- Disease course & outcomes
  - Symptomatology
  - Breakthrough infections
  - Hospitalization/Death

Covid-19 course

- 77 consecutive patients with underlying AARD infected by SARS-CoV-2
  - Most patients (68.8%) had a mild COVID-19 course
    - prior treatment with corticosteroids, mycophenolate mofetil or rituximab was more common in patients who developed a more serious disease course
  - The predominant clinical manifestations were fatigue (58.4%), low grade fever (45.4%) and upper respiratory tract symptoms (68.8%)
  - 23.3% required hospitalization and the mortality rate was 1.3%

Bakasis et et al J Autoimm 2021

Outcomes

Increased hospitalization risk??

- Three **nationwide** studies (Sweden, Denmark and Iceland), **reporting ⇧ hospitalization risk**
- Two meta-analyses report different results on this matter
- Several differences between countries
  - Local guidelines
  - Intensity of pandemic wave
  - Saturation level of health care system,
  - Access to healthcare facilities and other confounders

Condition	Outcome	N events (risk, %) in the IJD cohort	N events (risk, %) in the general population	Crude excess risk per 100 patients*	HR model 1†	HR model 2‡
All						
	Hospitalisation, all causes	8971 (8.1%)	24 273 (5.0%)	3.1	1.65 (1.61 to 1.69)	1.18 (1.15 to 1.21)
	Hospitalisation, COVID-19	581 (0.5%)	1443 (0.3%)	0.2	1.77 (1.61 to 1.95)	1.32 (1.19 to 1.46)
	Admission to ICU, COVID-19	45 (0.04%)	162 (0.03%)	0.01	1.22 (0.88 to 1.70)	1.17 (0.82 to 1.66)
	Death, all causes	1310 (1.2%)	3036 (0.6%)	0.6	1.90 (1.78 to 2.02)	1.13 (1.05 to 1.21)
	Death, COVID-19	161 (0.10%)	338 (0.07%)	0.03	2.09 (1.73 to 2.52)	1.18 (0.97 to 1.44)

TABLE 2 Numbers, incidence rates and hazard ratios for hospitalization with COVID-19 infection among patients with inflammatory rheumatic disease and the general population

	All inflammatory rheumatic diseases	RA	Spondyloarthritis	Connective tissue disease	Vasculitis	General population
n hospitalised with COVID-19	69	47	7	7	8	2536
Person years of observation	25 919	13 119	8006	2982	1812	2 032 099
Incidence rates per 1000 person years (age and sex standardized)	1.73 (1.34–2.23)	1.97 (1.38–2.81)	0.76 (0.36–1.63)	2.30 (0.86–6.17)	1.99 (0.98–4.05)	1.26 (1.21–1.31)
Median (interquartile range)/mean duration of hospitalization in days	3.1 (1.2–7.9)/6.1	2.8 (1.1–7.9)/6.5	2.4 (1.1–4.5)/3.1	5.5 (3.4–7.4)/6.7	4.5 (1.7–8,8)/5.7	2.8 (0.8–6.8)/5.1
HR adjusted for sex with age as underlying time scale	1.60 (1.26–2.03)	1.84 (1.38–2.46)	0.75 (0.36–1.57)	1.63 (0.78–3.43)	2.03 (1.02–4.08)	1 (Ref.)
HR adjusted for sex and comorbidities[a] with age as underlying time scale	1.46 (1.15–1.86)	1.72 (1.29–2.30)	0.67 (0.32–1.41)	1.38 (0.66–2.91)	1.82 (0.91–3.64)	1 (Ref.)

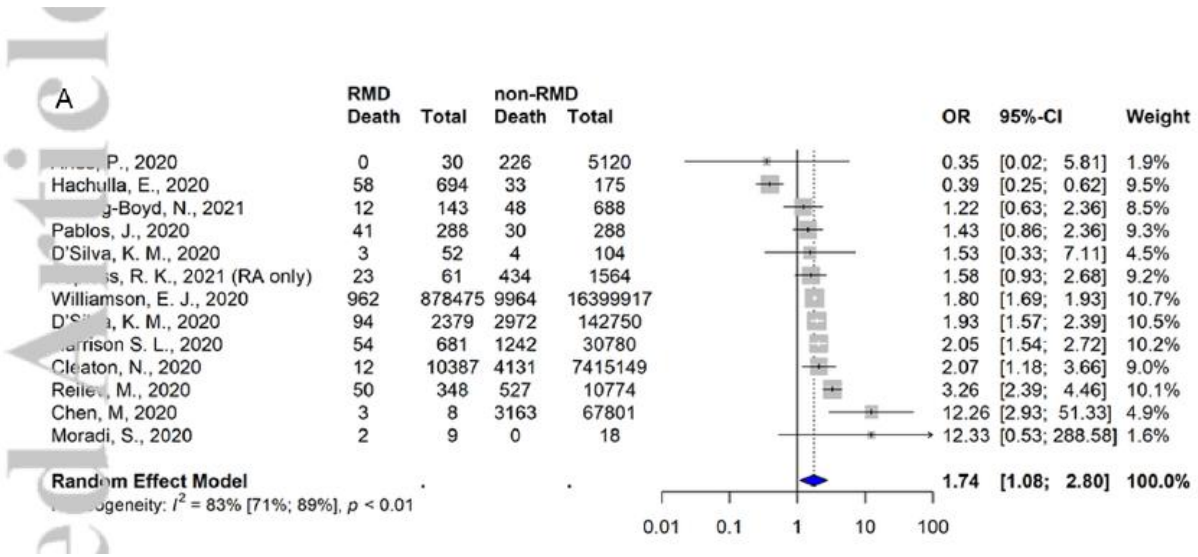
HR: hazard ratio. [a]Comorbidities included lung disease, cardiovascular disease, diabetes mellitus and cancer.

Bower et al ARD 2021
Cordtz et al Rheuamtology 2021
Bjornnson et al ARD 2021

Outcomes

Increased mortality risk??

- SLR to inform EULAR recommendations
  - Most studies: unclear/high risk of bias
  - Generally, do not have higher mortality risk
- Two meta-analysis show contradictory results
  - 14 databases from January 1st, 2019 to February 13th, 2021.
  - 100 studies met criteria for inclusion in the systematic review and 54/100 had a low risk-of-bias
  - odds of mortality was increased (OR 1.74 (95%CI 1.08, 2.80)).



Kroon et al ARD 2021
Conway et al Arth & Rheum 2021

Mortality rate

Nationwide study (Sweden)

- Nationwide study assessing mortality risk for patients with IA for 6 months
- Death rates were increased
  - but risk was mitigated when adjusting for comorbidities and socioeconomic factors.

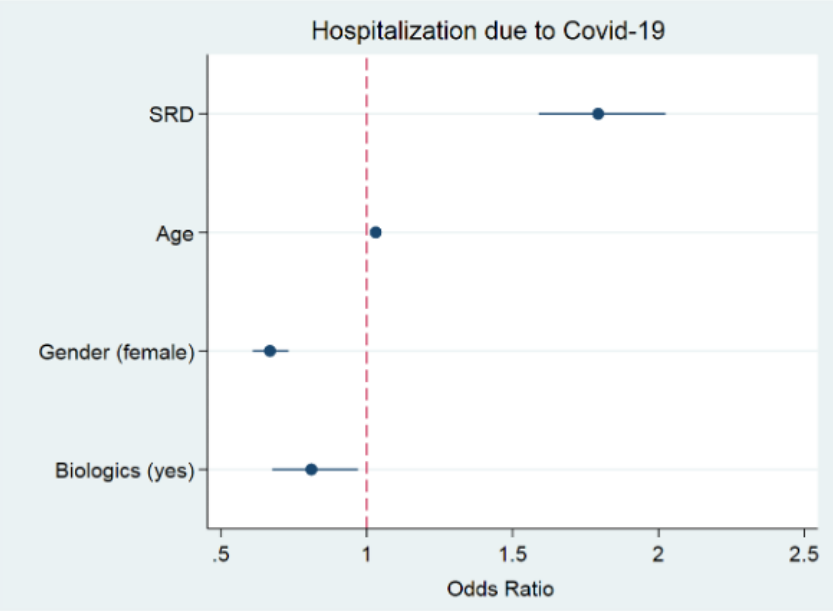
Condition	Year	N deaths in the inflammatory joint disease cohort‡	HR model 1*	HR model 2†
RA				
	2015	813	2.10 (1.93 to 2.28)	1.21 (1.11 to 1.32)
	2016	756	1.93 (1.77 to 2.10)	1.07 (0.98 to 1.17)
	2017	821	2.00 (1.84 to 2.18)	1.19 (1.09 to 1.29)
	2018	833	1.94 (1.78 to 2.10)	1.13 (1.04 to 1.23)
	2019	817	2.04 (1.88 to 2.22)	1.23 (1.13 to 1.34)
	2020	925	1.99 (1.84 to 2.16)	1.18 (1.09 to 1.28)
Other IJD				
	2015	264	1.61 (1.40 to 1.85)	0.94 (0.82 to 1.09)
	2016	239	1.41 (1.22 to 1.63)	0.83 (0.71 to 0.96)
	2017	267	1.53 (1.34 to 1.76)	0.96 (0.84 to 1.11)
	2018	294	1.52 (1.33 to 1.73)	0.94 (0.82 to 1.08)
	2019	280	1.50 (1.31 to 1.71)	0.96 (0.83 to 1.10)
	2020	322	1.52 (1.34 to 1.73)	0.96 (0.84 to 1.09)

Bower et al ARD 2021

Nationwide study (Greece)

⇧ hospitalization risk

- All adult patients with (RA), (AS), (PsA), (SLE) and (SSc)
- Electronic prescription database and matched (1:5) on age, gender, and region of domicile to random referents from the general population.
  - Crosslinking with the national Covid-19 registry
    - recorded confirmed infections and Covid-19-associated hospitalizations and deaths between 1-March-2020 and 28-Feb-2021
- 74,970 patients with SRD
  - 40014 RA patients (79% female)
  - 9566 AS patients (43% female)
  - 13405 PsA patients (55% female)
  - 9960 SLE patients (90% female)
  - 2025 SSc patients (88% female)



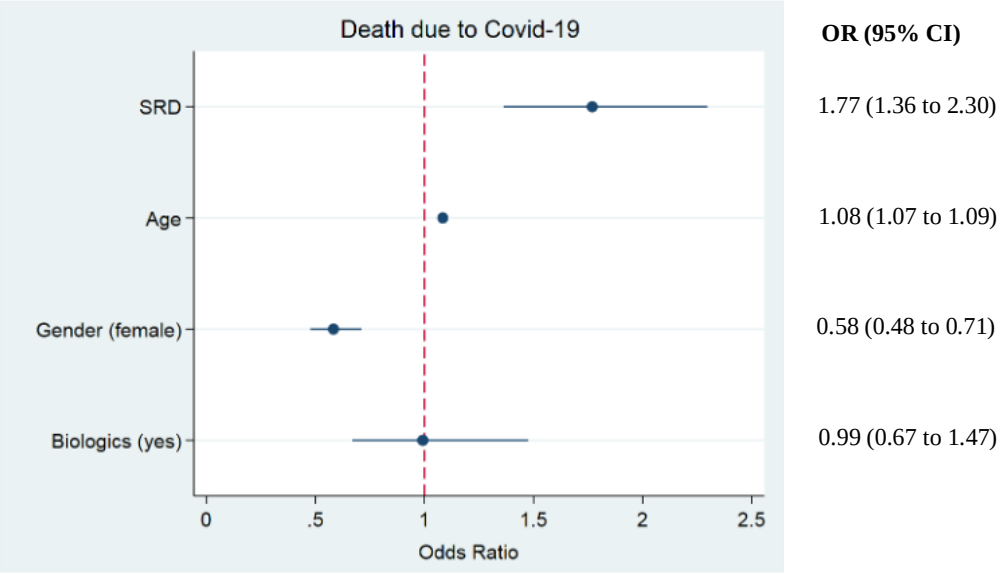
79% higher risk to get hospitalized (OR 1.79, 95% CI: 1.59 to 2.02)

Bournia et al Under Review

Nationwide study (Greece)

⇧ Mortality risk

- All adult patients with (RA), (AS), (PsA), (SLE) and (SSc),
- Electronic prescription database and matched (1:5) on age, gender, and region of domicile to random referents from the general population.
  - Crosslinking with the national Covid-19 registry
    - recorded confirmed infections and Covid-19-associated hospitalizations and deaths between 1-March-2020 and 28-Feb-2021.
- SSc OR: 6.90, 95% CI: 1.41 to 33.72 for death)
- SLE OR: 4.05 95% CI: 0.96 to 17.12 for death),
- RA OR: 3.65, 95% CI: 1.06 to 12.54 for death),
- PsA/SpA patients had comparable risk for death



SRD patients increased mortality risk (OR 1.77, 95% CI: 1.36 to 2.30)

Bournia et al Under Review

Risk factors

- Hospitalization
- Age
- Male gender
- Comorbidities
- Disease activity
- Glucocorticoids >10mg pred ???
- No-use of TNFi??

Kroon et al ARD 2021
Habermann et al Arthritis & Rheum 2020
Gianfrancesco et al, ARD 2020

- Death
- Age
- Male gender
- BMI
- Concurring comorbidities (e.g dyslipidemia, cardiovascular and lung disease) (santos20)
- High disease activity
- Rituximab
- Glucocorticoids >10mg pred ???
- No association with other medications

Kroon et al ARD 2021
Santos et al Clin Rheum 2020

EULAR guidance

EULAR RECOMMENDATIONS FOR THE MANAGEMENT OF RHEUMATIC AND MUSCULOSKELETAL DISEASES IN THE CONTEXT OF SARS-CoV-2:
The July 2021 update

5.	If a patient with RMD receiving RTX treatment contracts SARS-CoV-2, postponing the next cycle of RTX should be considered.	9.7 (0.6)	100
4.	If a patient with RMD receiving long-term glucocorticoid treatment develops suspected or confirmed COVID-19, this treatment should be continued.	9.3 (0.9)	96

Previous statement….

9.	If patients with RMD experience mild* symptoms of COVID-19, potential treatment changes in DMARDs should be discussed on a case-by-case basis.	8.9±1.4	84

EULAR guidance
Landewe et al 2020

Outline

- Prevention (Vaccines)
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EULAR recommendations management

Hydroxychloroquine should be avoided for treating any stage of SARS-CoV-2 infection since it does not provide any additional benefit to the standard of care, and could worsen the prognosis in more severe patients particularly if coprescribed with azithromycin (LoE 2).	9.92 (0.3) 100
In patients with COVID-19 requiring supplemental oxygen, non-invasive or mechanical ventilation, systemic glucocorticoids should be used since they can decrease mortality; most evidence concerns the use of dexamethasone (LoE 2/3).	9.75 (0.4) 100
In patients with COVID-19 requiring supplemental oxygen, non-invasive or mechanical ventilation combination of glucocorticoids and tocilizumab should be considered since it reduces disease progression and mortality (LoE 2). More data are needed to fully appreciate the effect of other IL-6R inhibitors (LoE 2/3).	9.17 (1.7) 87.5
In patients with COVID-19 requiring oxygen therapy, non-invasive ventilation or high-flow oxygen, the combination of glucocorticoids and baricitinib or tofacitinib could be considered since it might decrease disease progression and mortality (LoE 2).	8.92 (1.4) 87.5

Alunno et al ARD 2021

Treatment

The role of baricitinib

- 2-center, observational, retrospective cohort study of patients with severe COVID-19
- Outcomes and serious events
  - SOC Vs Baricitinib combination
- 369 patients with sCOVID-19
  - SOC: 47.7% and combination in 52.3%
- Patients treated with the combination reached the **composite outcome (intensive care unit [ICU] admission or death)** less frequently compared with SOC (22.3% vs 36.9%, *P* = .002).
- **Mortality rate** was lower with the combination in the total cohort (14.7% vs 26.6%, *P* = .005),
- **No difference in serious events** was noted between treatment groups

Table 3. Multivariate Logistic Regression Analysis of Factors Associated With Composite Outcome (ICU Admission or Death)

	Multivariate	
Variable	OR (95% CI)	P[a]
Male sex	1.55 (0.76–3.17)	.23
Age (per 10 years)	1.82 (1.36–2.44)	**<.001**
CRP (per 100 mg/L)	1.22 (0.83–1.79)	.32
PaO_2/FiO_2 ratio (per 10 units)	0.60 (0.52–0.68)	**<.001**
CVD/heart failure	1.99 (0.77–5.15)	.16
HFNC	0.34 (0.16–0.74)	**.006**
Remdesivir	0.68 (0.32–1.44)	.31
Baricitinib	0.52 (0.26–1.03)	.06
Baricitinib (IPWR)[b]	0.93 (0.87–0.99)	**.03**

Tziolos et al Op F Inf Dis 2021

Take home messages

- Vaccinations: most important
  - Generally safe (compared to general population)
  - Disease flare: rare
  - Booster Vaccines are needed
  - Treatment discontinuation (RTX, MMF, others?)
  - Encourage patients to vaccinate (benefit outweigh risk)
- Course
  - Possibly at higher risk for worse outcomes