Online supplement

Syversen SW, Jyssum I, Tveter AT et al.

Immunogenicity and safety of a three-dose SARS-CoV-2 vaccination strategy in patients with immune-mediated inflammatory diseases on immunosuppressive therapy

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Supplemental appendix 1 Inclusion and exclusion criteria Nor-vaC

Inclusion Criteria	• An established clinical diagnosis of one of the following immune-mediated diseases: rheumatoid arthritis (RA), spondyloarthritis (SpA), psoriatic arthritis (PsA), ulcerative colitis (UC), and Crohn's disease (CD) • On treatment with relevant immunosuppressive and/or immunomodulating medication (see below) • Adult patients (≥ 18 years) • Patient intends to obtain vaccination against COVID-19 during the next six months
Exclusion Criterion	• Allergy or intolerance to elements of the COVID-19 vaccines

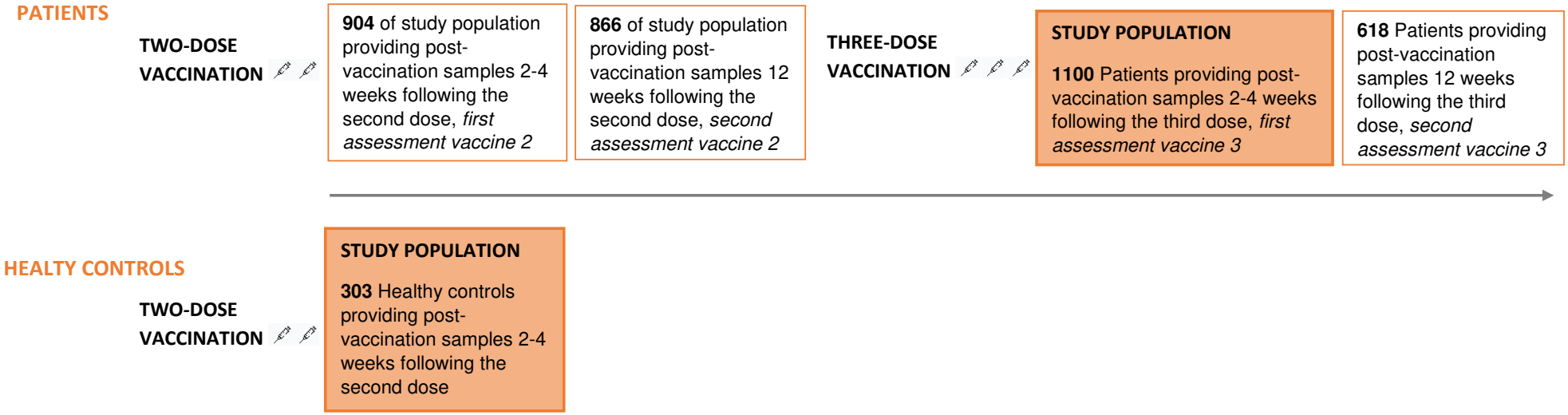
Relevant immunosuppressive medication:

Medication group	**Included medications**
Tumour necrosis factor inhibitor	Infliximab, etanercept, golimumab, adalimumab, certolizumab pegol
Janus kinases inhibitor	Tofacitinib, baricitinib, upadacitinib, filgotinib
Tumour necrosis factor inhibitor in combination	+ methotrexate, azathioprine, sulfasalazine or leflunomide
Methotrexate	
Azathioprine	
Tocilizumab	
Abatacept	
Sulfasalazine	
Vedolizumab	
Ustekinumab	
Secukinumab	
Leflunomide	
High dose prednisolone (≥15mg)	
6-mercaptopurine	

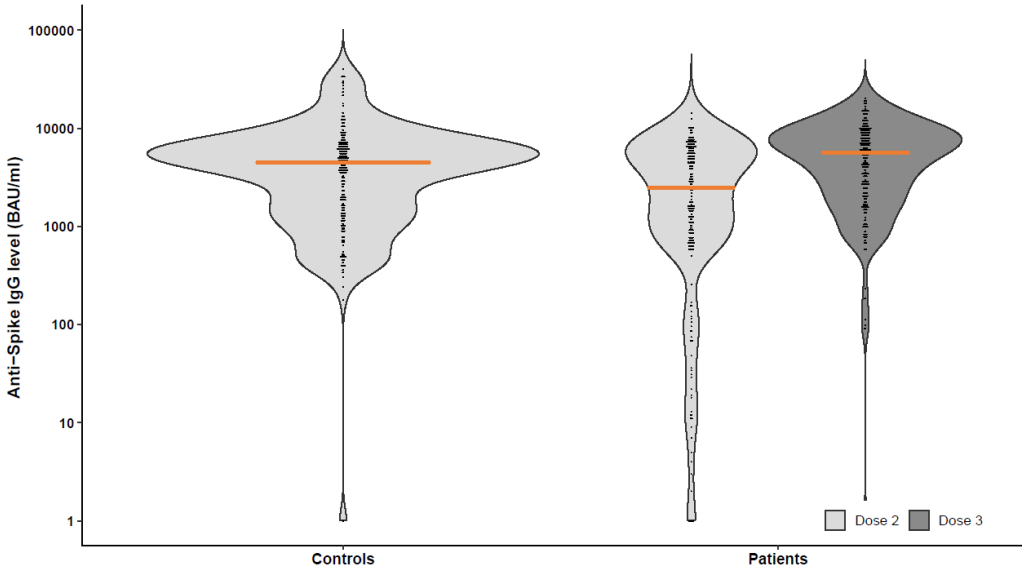
Supplemental appendix 2 Inclusion and exclusion criteria healthy controls

Inclusion criterion	• Health care worker employed at Diakonhjemmet Hospital, Akershus University Hospital or Oslo University Hospital • Intends to obtain vaccination against COVID-19 during the next six months
Exclusion criteria	• Having an immune mediated inflammatory disease • Using immunosuppressive therapy

Supplemental figure 1 Study disposition

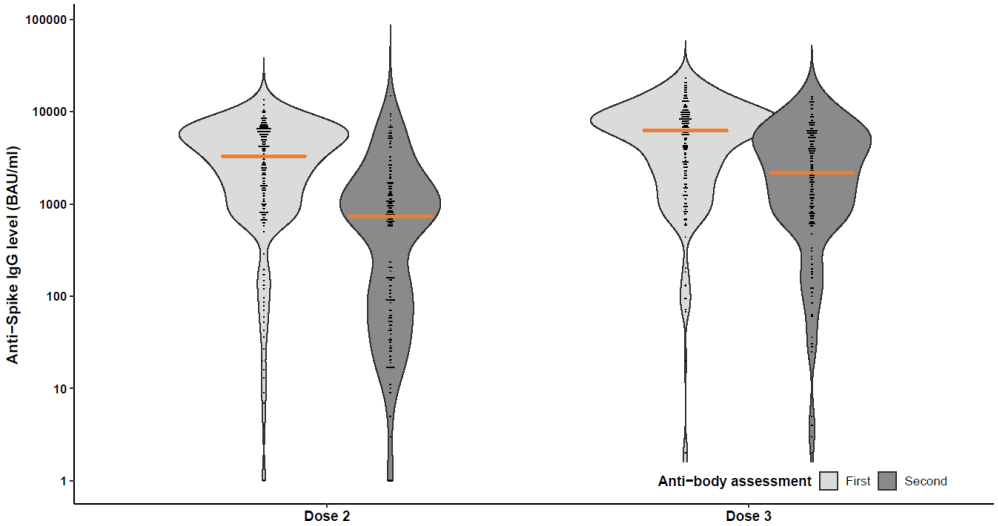


Supplemental figure 2 Anti-Spike antibody levels following three-dose vaccination in IMID patients vs two-dose vaccination in healthy controls (Robustness analysis of age and gender matched patents and controls)



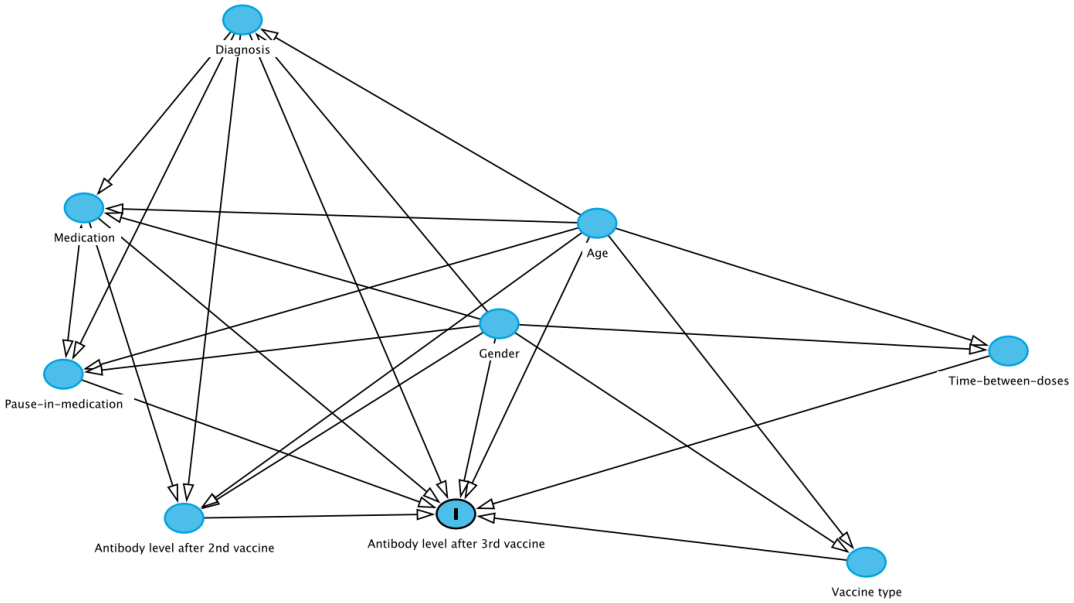
	Controls	Patients
No. observations	303	303
Dose 2 (median)	4495	2500
Dose 3 (median)	–	5607

Supplemental figure 3 Antibody level at first and second assessments after second and third vaccine dose in patients



First assessment 2-4 weeks after vaccination, second assessment 12 weeks after vaccination.

Supplemental figure 4 DAGitty model



Supplemental table 1 Baseline characteristics of the study population and participants not included due to not providing samples following the third (patients) /second (controls) dose

	Study patients (n=1100)	Study controls (n=303)	Patients not included (n=687)	Controls not included (n=91)
Age (years), median (IQR)	54.2 (42.6-64)	43 (33-55)	49.5 (38.7-59.5)	31.2 (26.6-46.3)
Female	602 (55%)	226 (75%)	367 (53%)	65 (71%)
Disease				
Rheumatoid arthritis	361 (33%)		266 (41%)	
Crohn's disease	217 (20%)		201 (31%)	
Psoriatic arthritis	184 (17%)		148 (23%)	
Spondyloarthritis	177 (16%)		21 (3%)	
Ulcerative colitis	154 (14%)		19 (3%)	
Medication				
Tumour necrosis factor inhibitor, monotherapy[a]	461 (42%)		282 (42%)	
Tumour necrosis factor inhibitor combination therapy[b]	254 (23%)		122 (18%)	
Methotrexate	220 (20%)		158 (23%)	
Vedolizumab	46 (4%)		3 (1%)	
Janus kinases inhibitor	33 (3%)		12 (1%)	
Ustekinumab, secukinumab, tocilizumab	60 (5%)		19 (3%)	
Abatacept	15 (1%)		3 (1%)	
Other[c]	11 (1%)		5 (1%)	
Vaccines				
BNT162b2	596 (54%)	163 (54%)	370 (54%)	38 (42%)
mRNA-1273	186 (17%)	70 (23%)	145 (21%)	23 (25%)
Combination of vaccines[d]	318 (29%)	70 (23%)	172 (25%)	30 (33%)

[a]Tumour necrosis factor inhibitors: Infliximab, etanercept, adalimumab, golimumab, certolizumab pegol.
[b]Combination therapy: Tumour necrosis factor inhibitor in combination with either methotrexate, sulfasalazine, leflunomide or azathioprine.
[c]Drugs with less than 10 patients included: sulfasalazine, leflunomide, azathioprine, risankizumab, prednisolone monotherapy
[d]Combination of the following vaccines: ChAdOx1, BNT162b2, mRNA-1273

Supplemental table 2 Decline in antibody levels following second and third vaccination

Characteristic	Beta (SE)	Exp (Beta) (95% CI)	P-value
(Intercept)	-0.001 (0.169)	0.999 (0.718,1.39)	0.995
Second dose, days between antibody assessments	-0.028 (0.002)	0.973 (0.968,0.977)	<0.001
Third dose, days between antibody assessments	-0.017 (0.003)	0.983 (0.978,0.988)	<0.001
Comparison			
Difference	0.01 (0.001)	1.01 (1.008,1.013)	<0.001

Results from GEE regression where the outcome is the difference between the two (log-transformed) antibody assessments following each vaccination. The explanatory variable in the regression is «number of days between antibody assessments», estimated with separate regression coefficients (beta) for the second and third vaccinations. Adjustments have been made for age, gender, diagnosis, medication and vaccine type.

Supplemental table 3 Factors associated with anti-Spike antibody levels (BAU/ml on log scale)

Characteristics	Beta (SE) (univariate)	P-value (univariate)	Total effect (SE)	P-value (Total effect)
Age in years	0 (0)	<0.001	0 (0)	<0.001
Male gender	-0.1 (0.1)	0.235	-0.1 (0.1)	0.235
Pause in medication	0 (0.1)	0.847	0 (0.1)	0.7
Anti-RBD level after 2nd vaccine dose	0.3 (0)	<0.001	0.3 (0)	<0.001
Time between 2nd and 3rd dose				
Less than 3 months	(reference)		(reference)	
Between 3-4 months	0.5 (0.1)	<0.001	0.6 (0.1)	<0.001
Between 4-5 months	0.5 (0.1)	<0.001	0.6 (0.1)	<0.001
More than 5 months	0.7 (0.1)	<0.001	0.8 (0.1)	<0.001
Diagnosis				
Rheumatoid arthritis	(reference)		(reference)	
Spondyloarthritis	-0.2 (0.1)	0.093	-0.3 (0.1)	0.009
Psoriatic arthritis	0.2 (0.1)	0.158	0.1 (0.1)	0.386
Crohn's disease	-0.2 (0.1)	0.157	-0.4 (0.1)	<0.001
Ulcerative colitis	-0.1 (0.1)	0.612	-0.3 (0.1)	0.025
Medication				
Tumour necrosis factor inhibitor, monotherapy [a]	(reference)		(reference)	
Tumour necrosis factor inhibitor combination therapy [b]	-0.2 (0.1)	0.057	-0.3 (0.1)	0.004
Methotrexate	0.5 (0.1)	<0.001	0.4 (0.1)	0.001
Vedolizumab	0.5 (0.2)	0.012	0.5 (0.2)	0.009
Janus kinases inhibitor	-0.8 (0.2)	<0.001	-0.9 (0.2)	<0.001
Ustekinumab, secukinumab, tocilizumab	0.4 (0.2)	0.011	0.4 (0.2)	0.015
Abatacept	-0.1 (0.3)	0.816	-0.3 (0.4)	0.384
Other[c]	0.2 (0.4)	0.672	0.2 (0.4)	0.682
Vaccine				
BNT162b2	(reference)		(reference)	
mRNA-1273	0.6 (0.1)	<0.001	0.6 (0.1)	<0.001
Combination of vaccines [d]	0.4 (0.1)	<0.001	0.4 (0.1)	<0.001

Univariate associations with antibody level after 3rd vaccination (BAU/ml), and estimated total effects from posited causal associations. Total effect estimates based on posited causal model (Supplemental figure 4). Total effect of D estimated by model adjusting for M and G, denoted D|M, G; similarly: M|A, G, D; P|A, D, G, M; V|A, G; T|A, G; A|none; G|none; L|A, D, G, M. Here D=Diagnosis, M=Medication; P=Pause; V=Vaccine; T=Time between dose 2 and 3; A=Age; G=Gender; L=Antibody level after dose 2.
Abbreviation: SE=Standard error
[a]Tumour necrosis factor inhibitors: infliximab, etanercept, adalimumab, golimumab, certolizumab.
[b]Combination therapy: Tumour necrosis factor inhibitor in combination with either methotrexate, sulfasalazine, leflunomide or azathioprine.
[c]Drugs with less than 10 patients included: sulfasalazine, leflunomide, azathioprine, risankizumab, prednisolone monotherapy
[d]Combination of the following vaccines: ChAdOx1, BNT162b2, mRNA-1273

Supplemental table 4 Adverse events

	Controls						Patients								
	1st dose (n=255)			2nd dose (n=252)			1st dose (n=966)			2nd dose (n=927)			3rd dose (n=981)		
	<2 days[a] n	≥2 days[a] n	Total n (%)	<2 days[a] n	≥2 days[a] n	Total n (%)	<2 days[a] n	≥2 days[a] n	Total n (%)	<2 days[a] n	≥2 days[a] n	Total n (%)	<2 days[a] n	≥2 days[a] n	Total n (%)
Any adverse events			186 (64.7%)			196 (67.5%)			459 (48.5%)			488 (52.6%)			464 (47.3%)
Fever	54	5	59 (23.1%)	64	9	73 (29.0%)	33	7	40 (4.1%)	94	15	109 (11.8%)	90	20	110 (11.2%)
Chills	65	6	71 (27.8%)	71	5	76 (30.2%)	49	12	61 (6.3%)	91	13	104 (11.2%)	100	18	118 (12.0%)
Discomfort	36	15	51 (20.0%)	57	16	73 (30.2%)	53	16	69 (7.1%)	89	32	121 (13.1%)	78	32	110 (11.2%)
Slackness	51	28	79 (31.0%)	78	26	104 (41.3%)	76	45	121 (12.5%)	133	57	190 (20.5%)	125	61	186 (19.0%)
Feeling of flu	48	7	55 (21.6%)	56	11	67 (26.6%)	37	15	52 (5.4%)	93	24	117 (12.6%)	89	31	120 (12.2%)
Tiredness	32	22	54 (21.2%)	42	25	67 (26.6%)	86	41	127 (13.1%)	107	50	157 (16.9%)	81	56	137 (12.9%)
Pain at injection site	47	46	93 (36.5%)	58	54	112 (44.4%)	286	83	369 (38.2%)	260	85	345 (37.2%)	231	81	312 (31.8%)
Swollen glands in axillary	3	7	10 (3.9%)	3	9	12 (4.8%)	4	2	6 (0.6%)	9	17	26 (2.8%)	19	17	36 (3.7%)
Headache	48	22	70 (27.5%)	50	22	72 (28.6%)	85	34	119 (12.3%)	126	40	166 (17.9%)	102	43	145 (14.8%)
Dizziness	7	11	18 (7.1%)	8	4	12 (4.8%)	16	10	26 (2.7%)	33	13	46 (5.0%)	21	18	39 (4.0%)
Abdominal discomfort	5	1	6 (2.4%)	6	3	9 (3.8%)	7	4	11 (1.1%)	9	8	17 (1.8%)	10	10	20 (2.0%)
Reduced appetite	5	5	10 (3.9%)	12	3	15 (6.0%)	11	4	15 (1.6%)	15	8	23 (2.5%)	14	7	21 (2.1%)
Nausea/vomiting	8	4	12 (4.7%)	14	4	18 (7.1%)	18	4	22 (2.3%)	23	6	29 (3.1%)	14	10	24 (2.4%)
Diarea	4	0	4 (1.6%)	3	1	4 (0.2%)	7	3	10 (1.0%)	7	7	14 (1.5%)	8	5	13 (1.3%)
Dyspnoea	3	5	8 (3.1%)	2	1	3 (0.1%)	5	6	11 (1.1%)	5	4	9 (1.0%)	3	14	17 (1.7%)
Cough	0	1	1 (0%)	2	1	3 (0.1%)	4	4	8 (0.8%)	4	5	9 (1.0%)	6	4	11 (1.1%)
Muscular pain	43	15	58 (22.7%)	53	13	66 (26.2%)	35	35	70 (7.2%)	76	43	119 (12.8%)	57	42	99 (10.1%)
Rash	1	2	3 (0.1%)	3	2	5 (0.2%)	4	5	9 (0.9%)	4	7	11 (1.1%)	2	7	9 (0.9%)
Sleep disorders	13	2	15 (5.9%)	14	1	15 (6.0%)	9	4	13 (1.3%)	22	7	29 (3.1%)	7	19	26 (2.7%)
Unrest	3	4	7 (2.7%)	2	6	8 (3.2%)	3	1	4 (0.4%)	3	5	9 (1.0%)	4	10	14 (1.4%)
Confusion	1	0	1 (0%)	1	0	1 (0%)	2	0	2 (0.2%)	3	3	6 (0.6%)	2	0	2 (0.2%)
Allergic reaction	0	0	0 (0%)	1	0	1 (0%)	1	0	1 (0.1%)	1	0	1 (0.1%)	0	0	0 (0%)
Anaphylaxis	0	0	0 (0%)	0	0	0 (0%)	0	0	0 (0%)	0	0	0 (0%)	0	0	0 (0%)
Bleeding/bruises			8 (3.1%)			5 (0.2%)			17 (1.8%)			26 (2.8%)			22 (2.2%)
Thrombosis			0 (0%)			0 (0%)			1 (0.1%)			0 (0%)			1 (0.1%)
Severe headache			0 (0%)			0 (0%)			19 (2.0%)			14 (1.6%)			27 (2.8%)
Disease flare			-			-			70 (7.2%)			50 (5.4%)			70 (7.1%)

[a]Duration of symptoms