

# THE LANCET

## Rheumatology

### Supplementary appendix

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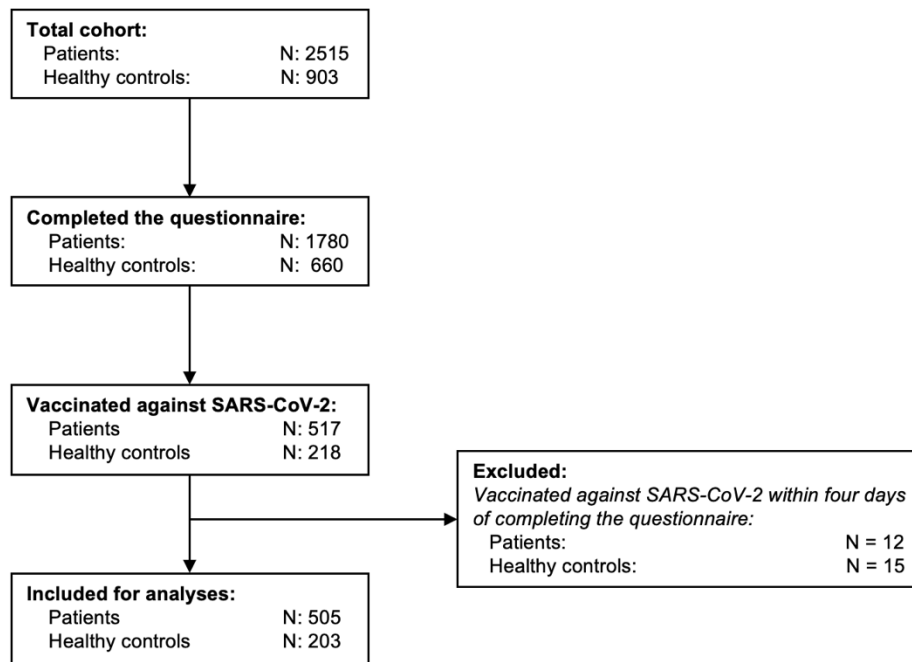
# Adverse events after first COVID-19 vaccination in patients with autoimmune diseases

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**Figure S1.** Flow-chart.

**Table S1. Characteristics of patients with autoimmune diseases compared to healthy controls who have been vaccinated against COVID-19.**

Patient characteristics	All patients (n=505)	Rheumatoid arthritis (n=204)	Multiple sclerosis (n=81)	Healthy controls (n=203)
Mean age – yr	64 ± 11	67 ± 8	54 ± 13	64 ± 11
Female sex – no. (%)	329 (65)	149 (73)	55 (68)	133 (66)
Male sex – no. (%)	176 (35)	55 (27)	26 (32)	70 (34)
White race* – no. (%)	381/422 (90)	181/204 (89)	N.A.	183/197 (93)
Mean BMI	26 ± 5	26 ± 5	25 ± 4	25 ± 4
Coexisting conditions – no. (%)				
Chronic pulmonary disease	56 (11)	26 (13)	1 (1)	15 (7)
Cardiovascular disease	67 (13)	24 (12)	4 (5)	21 (10)
Diabetes	27 (5)	10 (5)	3 (4)	8 (4)
Obesity	91 (18)	39 (19)	7 (9)	14 (7)
<b>Autoimmune disease type<sup>1</sup> – no. (%)</b>				
Rheumatoid arthritis	204 (40)	204 (100)	0 (0)	N.A.
Psoriatic arthritis	49 (10)	11 (5)	0 (0)	N.A.
Ankylosing spondylitis	39 (8)	3 (1)	0 (0)	N.A.
Axial or peripheral spondyloarthritis	8 (2)	0 (0)	0 (0)	N.A.
Juvenile idiopathic arthritis	5 (1)	1 (0.5)	0 (0)	N.A.
Systemic lupus erythematoses	25 (5)	2 (1)	0 (0)	N.A.
Vasculitis	10 (2)	2 (1)	0 (0)	N.A.
Polymyalgia rheumatica	17 (3)	3 (1)	0 (0)	N.A.
Sjogren's disease	28 (6)	10 (5)	0 (0)	N.A.
Other rheumatic diseases <sup>2</sup>	86 (17)	2 (1)	0 (0)	N.A.
Multiple sclerosis	81 (16)	0 (0)	81 (100)	N.A.
<b>Immunosuppressive medication<sup>1</sup> – no. (%)</b>				
No immunosuppressive medication	157 (31)	15 (7)	22 (27)	N.A.
csDMARDs	236 (47)	171 (84)	N.A.	N.A.
<i>Methotrexate</i>	169 (33)	138 (68)	N.A.	N.A.
<i>Other</i> <sup>3</sup>	67 (13)	33 (16)	N.A.	N.A.
Biologicals	147 (29)	68 (33)	28 (35)	N.A.
<i>TNF inhibitor</i>	93 (18)	49 (24)	0 (0)	N.A.
<i>IL-6 inhibitor</i>	1 (0.2)	1 (0.5)	0 (0)	N.A.
<i>Anti-CD20 therapy</i>	35 (7)	11 (5)	22 (27)	N.A.
<i>Other</i>	18 (4)	7 (3)	6 (7)	N.A.
Immunomodulatory MS therapies				
<i>Interferon-β</i>	6 (1)	N.A.	6 (7)	N.A.
<i>Other</i>	24 (5)	N.A.	24 (30)	N.A.
Oral glucocorticoids	77 (15)	41 (20)	1 (1)	0 (0)
<b>COVID-19 vaccination</b>				
Vaccine type – no. (%)				
<i>ChAdOx1 nCoV-19 (AstraZeneca)</i>	231 (46)	97 (48)	48 (59)	104 (51)
<i>BNT162b2 (Pfizer/BioNtech)</i>	209 (41)	92 (45)	16 (20)	90 (44)
<i>CX-024414 (Moderna)</i>	65 (13)	15 (7)	17 (21)	9 (4)
Vaccinated twice – no. (%)	73 (14)	19 (9)	12 (15)	32 (16)
Severity of adverse events – no. (%)				
Mild	258 (51)	107 (52)	53 (65)	106 (52)
Moderate	105 (21)	37 (18)	28 (35)	38 (19)
Severe	6 (1)	1 (0.5)	2 (2)	0 (0)

Table 1. Values are displayed as mean ± standard deviation (SD) or frequencies with corresponding percentages (%). csDMARDs = conventional disease modifying anti-rheumatic drugs, TNF = anti-tumor necrosis factor, IL = interleukin. <sup>1</sup>One person can be diagnosed with more than one autoimmune disease type and receive more than one immunosuppressive drug. <sup>2</sup>Other rheumatic diseases included mixed connective tissue disease, sarcoidosis, systemic sclerosis and myositis. <sup>3</sup>Other csDMARDs included hydroxychloroquine, sulfasalazine, leflunomide and azathioprine. \*Ethnicity was unknown in patients with multiple sclerosis, and there were some missing values in patients with rheumatic diseases and healthy controls. The provided proportions are based on the population in which ethnicity was known (valid percentages).

**Table S2. Adverse events following the first COVID-19 vaccination in patients with autoimmune diseases compared to healthy controls.**

All vaccines	Patients with autoimmune diseases (n = 505)			Healthy controls (n = 203)		
	No. events (%)	No. moderate or severe events (%)	Median duration, days (IQR)	No. events (%)	No. moderate or severe events (%)	Median duration, days (IQR)
Allergic reaction	4 (1)	2 (0.4)	3 (2-8)	0 (0)	0 (0)	N.A.
Injection site erythema	22 (4)	4 (1)	4 (3-7)	5 (2)	0 (0)	2 (2-6)
Swollen injection site	33 (7)	7 (1)	4 (2-7)	5 (2)	0 (0)	7 (4-8)
Painful injection site	196 (39)	34 (7)	3 (2-4)	82 (40)	5 (2)	3 (2-4)
Fever	56 (11)	29 (6)	1 (1-2)	21 (10)	17 (8)	1 (1-2)
Chills and shiver	72 (14)	28 (6)	1 (1-2)	33 (16)	15 (7)	1 (1-1)
Myalgia	20 (4)	11 (2)	3 (2-5)	6 (3)	1 (0.5)	2 (1-4)
Fatigue	139 (28)	76 (15)	3 (2-5)	51 (25)	23 (11)	2 (1-3)
Headache	124 (25)	47 (9)	2 (1-3)	45 (22)	18 (9)	2 (1-2)
Other	72 (14)	30 (6)	2 (2-5)	25 (12)	12 (6)	2 (1-7)
Increased disease activity <sup>1</sup>	26 (5)	N.A.	N.A.	N.A.	N.A.	N.A.
Joint complaints <sup>2</sup>	49 (10)	N.A.	N.A.	3 (1)	N.A.	N.A.
ChAdOx1 nCoV-19 <i>AstraZeneca</i>	Patients with autoimmune diseases (n = 231)			Healthy controls (n = 104)		
	No. events (%)	No. moderate or severe events (%)	Median duration, days (IQR)	No. events (%)	No. moderate or severe events (%)	Median duration, days (IQR)
Allergic reaction	4 (2)	2 (1)	3 (2-8)	0 (0)	0 (0)	N.A.
Injection site erythema	9 (4)	2 (1)	5 (4-7)	1 (1)	0 (0)	5 (N.A.)
Swollen injection site	17 (7)	4 (2)	5 (4-7)	4 (4)	0 (0)	6 (3-8)
Painful injection site	89 (39)	15 (6)	4 (2-6)	47 (45)	2 (2)	3 (2-5)
Fever	39 (17)	21 (9)	1 (1-2)	21 (20)	17 (16)	1 (1-2)
Chills and shiver	52 (23)	20 (9)	1 (1-2)	29 (28)	15 (14)	1 (1-1)
Myalgia	11 (5)	4 (2)	3 (2-5)	6 (6)	1 (1)	2 (1-4)
Fatigue	83 (36)	46 (20)	3 (2-6)	38 (37)	18 (17)	2 (1-3)
Headache	81 (35)	33 (14)	2 (1-3)	39 (38)	15 (14)	2 (1-2)
Other	34 (15)	18 (8)	2 (1-10)	17 (16)	9 (9)	2 (1-7)
Increased disease activity <sup>1</sup>	14 (6)	N.A.	N.A.	N.A.	N.A.	N.A.
Joint complaints <sup>2</sup>	31 (13)	N.A.	N.A.	2 (2)	N.A.	N.A.
BNT162b2 <i>(Pfizer/BioNTech)</i>	Patients with autoimmune diseases (n = 209)			Healthy controls (n = 90)		
	No. events (%)	No. moderate or severe events (%)	Median duration, days (IQR)	No. events (%)	No. moderate or severe events (%)	Median duration, days (IQR)
Allergic reaction	0 (0)	0 (0)	N.A.	0 (0)	0 (0)	N.A.
Injection site erythema	5 (2)	2 (1)	3 (2-10)	4 (4)	0 (0)	2 (1-6)
Swollen injection site	9 (4)	2 (1)	2 (2-4)	1 (1)	0 (0)	7 (N.A.)
Painful injection site	63 (30)	7 (3)	2 (2-3)	28 (31)	0 (0)	2 (2-3)
Fever	8 (4)	4 (2)	1 (1-2)	0 (0)	0 (0)	N.A.
Chills and shiver	7 (3)	5 (2)	2 (1-3)	2 (2)	0 (0)	1 (1-1)
Myalgia	6 (3)	5 (2)	4 (1-6)	0 (0)	0 (0)	N.A.
Fatigue	27 (13)	10 (5)	3 (2-6)	13 (14)	5 (6)	3 (2-6)
Headache	25 (12)	7 (3)	2 (2-5)	6 (7)	3 (3)	2 (1-2)
Other	22 (11)	8 (4)	3 (2-5)	6 (7)	1 (1)	2 (N.A.)
Increased disease activity <sup>1</sup>	9 (4)	N.A.	N.A.	N.A.	N.A.	N.A.
Joint complaints <sup>2</sup>	13 (6)	N.A.	N.A.	1 (1)	N.A.	N.A.
CX-024414 <i>(Moderna)</i>	Patients with autoimmune diseases (n = 65)			Healthy controls (n = 9)		
	No. events (%)	No. moderate or severe events (%)	Median duration, days (IQR)	No. events (%)	No. moderate or severe events (%)	Median duration, days (IQR)
Allergic reaction	0 (0)	0 (0)	N.A.	0 (0)	0 (0)	N.A.
Injection site erythema	8 (12)	2 (3)	3 (2-9)	0 (0)	0 (0)	N.A.
Swollen injection site	7 (11)	1 (2)	3 (2-10)	0 (0)	0 (0)	N.A.
Painful injection site	44 (68)	12 (18)	3 (2-3)	7 (78)	3 (33)	2 (2-2)
Fever	9 (14)	4 (6)	2 (1-3)	0 (0)	0 (0)	N.A.
Chills and shiver	13 (20)	3 (5)	1 (1-4)	2 (22)	0 (0)	1 (N.A.)
Myalgia	3 (5)	2 (3)	2 (N.A.)	0 (0)	0 (0)	N.A.
Fatigue	29 (45)	20 (31)	3 (2-5)	0 (0)	0 (0)	N.A.
Headache	18 (28)	7 (11)	2 (1-3)	0 (0)	0 (0)	N.A.
Other	16 (25)	4 (6)	3 (2-4)	2 (22)	2 (22)	4 (N.A.)
Increased disease activity <sup>1</sup>	3 (5)	N.A.	N.A.	N.A.	N.A.	N.A.
Joint complaints <sup>2</sup>	5 (8)	N.A.	N.A.	0 (0)	N.A.	N.A.

Values are displayed as frequencies with corresponding percentages (%) or median with corresponding interquartile range (IQR). <sup>1</sup>Self-reported increase of disease activity up to two months following SARS-CoV-2 vaccination, the duration and severity of diseases flares were not assessed. <sup>2</sup> (Increase of) joint complaints up to two months following SARS-CoV-2 vaccination, these questions were only applied to patients with rheumatic diseases and healthy controls.

**Table S3. Adverse events following the first COVID-19 vaccination in female participants compared to male participants.**

All vaccines	Female participants (n = 462)			Male participants (n = 245)		
	No. events (%)	No. moderate or severe events (%)	Median duration, days (IQR)	No. events (%)	No. moderate or severe events (%)	Median duration, days (IQR)
Allergic reaction	3 (0.6)	1 (0.2)	3 (N.A.)	1 (0.4)	1 (0.4)	3 (N.A.)
Injection site erythema	24 (5)	4 (0.9)	4 (2-7)	3 (1)	0 (0)	4 (N.A.)
Swollen injection site	30 (7)	7 (2)	5 (2-7)	8 (3)	0 (0)	4 (3-7)
Painful injection site	200 (43)	33 (7)	3 (2-4)	78 (32)	6 (2)	3 (2-4)
Fever	58 (13)	36 (8)	1 (1-2)	19 (8)	10 (4)	1 (1-3)
Chills and shiver	79 (17)	33 (7)	1 (1-2)	26 (11)	10 (4)	1 (1-2)
Myalgia	19 (4)	10 (2)	2 (2-5)	7 (3)	2 (0.8)	3 (1-7)
Fatigue	139 (30)	78 (17)	3 (2-5)	51 (21)	21 (9)	2 (1-5)
Headache	131 (28)	57 (12)	2 (1-3)	38 (16)	8 (3)	2 (1-3)
Other	75 (16)	37 (8)	2 (1-7)	22 (9)	5 (2)	2 (1-4)
Increased disease activity <sup>1</sup>	17 (4)	N.A.	N.A.	9 (4)	N.A.	N.A.
Joint complaints <sup>2</sup>	36 (8)	N.A.	N.A.	16 (7)	N.A.	N.A.
<b>ChAdOx1 nCoV-19</b>	<b>Female participants (n = 217)</b>			<b>Male participants (n = 118)</b>		
<i>AstraZeneca</i>	No. events (%)	No. moderate or severe events (%)	Median duration, days (IQR)	No. events (%)	No. moderate or severe events (%)	Median duration, days (IQR)
Allergic reaction	1 (0.8)	1 (0.5)	3 (N.A.)	1 (0.8)	1 (0.8)	3 (N.A.)
Injection site erythema	8 (4)	2 (0.9)	6 (4-7)	2 (2)	0 (0)	4 (N.A.)
Swollen injection site	15 (7)	4 (2)	5 (4-7)	6 (5)	0 (0)	4 (4-6)
Painful injection site	101 (47)	15 (7)	4 (2-6)	35 (30)	2 (2)	3 (2-5)
Fever	45 (21)	31 (14)	1 (1-2)	15 (13)	7 (6)	1 (1-3)
Chills and shiver	62 (29)	28 (13)	1 (1-2)	19 (16)	7 (6)	1 (1-2)
Myalgia	11 (5)	4 (2)	2 (1-3)	6 (5)	1 (0.8)	3 (2-7)
Fatigue	86 (40)	48 (22)	2 (2-5)	35 (30)	16 (14)	2 (1-5)
Headache	91 (42)	42 (19)	2 (1-3)	29 (25)	6 (5)	2 (1-3)
Other	39 (18)	23 (11)	2 (1-8)	12 (10)	4 (3)	2 (1-8)
Increased disease activity <sup>1</sup>	8 (4)	N.A.	N.A.	6 (5)	N.A.	N.A.
Joint complaints <sup>2</sup>	24 (11)	N.A.	N.A.	9 (8)	N.A.	N.A.
<b>BNT162b2</b>	<b>Female participants (n = 195)</b>			<b>Male participants (n = 103)</b>		
<i>(Pfizer/BioNTech)</i>	No. events (%)	No. moderate or severe events (%)	Median duration, days (IQR)	No. events (%)	No. moderate or severe events (%)	Median duration, days (IQR)
Allergic reaction	0 (0)	0 (0)	N.A.	0 (0)	0 (0)	N.A.
Injection site erythema	9 (5)	0 (0)	3 (2-7)	0 (0)	0 (0)	N.A.
Swollen injection site	10 (5)	2 (1)	2 (2-6)	0 (0)	0 (0)	N.A.
Painful injection site	64 (33)	5 (3)	2 (2-3)	27 (26)	2 (2)	2 (2-3)
Fever	6 (3)	2 (1)	1 (1-3)	2 (2)	2 (2)	2 (N.A.)
Chills and shiver	6 (3)	3 (2)	2 (1-3)	3 (3)	2 (2)	1 (N.A.)
Myalgia	5 (3)	4 (2)	5 (2-7)	1 (1)	1 (1)	1 (N.A.)
Fatigue	30 (15)	12 (6)	3 (2-6)	10 (10)	3 (3)	3 (2-4)
Headache	24 (12)	8 (4)	2 (2-5)	7 (7)	2 (2)	1 (1-4)
Other	20 (10)	8 (4)	3 (2-7)	8 (8)	1 (1)	2 (1-3)
Increased disease activity <sup>1</sup>	7 (4)	N.A.	N.A.	2 (2)	N.A.	N.A.
Joint complaints <sup>2</sup>	9 (5)	N.A.	N.A.	5 (5)	N.A.	N.A.
<b>CX-024414</b>	<b>Female participants (n = 50)</b>			<b>Male participants (n = 24)</b>		
<i>(Moderna)</i>	No. events (%)	No. moderate or severe events (%)	Median duration, days (IQR)	No. events (%)	No. moderate or severe events (%)	Median duration, days (IQR)
Allergic reaction	0 (0)	0 (0)	N.A.	0 (0)	0 (0)	N.A.
Injection site erythema	7 (14)	2 (4)	3 (2-10)	1 (4)	0 (0)	3 (N.A.)
Swollen injection site	5 (10)	1 (2)	3 (2-9)	2 (8)	0 (0)	6 (N.A.)
Painful injection site	35 (70)	13 (26)	3 (2-3)	16 (67)	2 (8)	3 (2-4)
Fever	7 (14)	3 (6)	2 (1-2)	2 (8)	1 (4)	2 (N.A.)
Chills and shiver	11 (22)	2 (4)	1 (1-1)	4 (17)	1 (4)	3 (1-4)
Myalgia	3 (6)	2 (4)	2 (N.A.)	0 (0)	0 (0)	N.A.
Fatigue	23 (46)	18 (36)	3 (2-5)	6 (25)	2 (8)	3 (1-6)
Headache	16 (32)	7 (14)	2 (1-2)	2 (8)	0 (0)	3 (N.A.)
Other	16 (32)	6 (12)	3 (1-5)	2 (8)	0 (0)	4 (N.A.)
Increased disease activity <sup>1</sup>	2 (4)	N.A.	N.A.	1 (4)	N.A.	N.A.
Joint complaints <sup>2</sup>	3 (6)	N.A.	N.A.	2 (8)	N.A.	N.A.

Values are displayed as frequencies with corresponding percentages (%) or median with corresponding interquartile range (IQR). <sup>1</sup>Self-reported increase of disease activity up to two months following SARS-CoV-2 vaccination, the duration and severity of diseases flares were not assessed. <sup>2</sup> (Increase of) joint complaints up to two months following SARS-CoV-2 vaccination, these questions were only applied to patients with rheumatic diseases and healthy controls.

**Table S4. The risk of adverse events following the first COVID-19 vaccination in patients with autoimmune diseases compared to healthy controls.**

	Any adverse event			Systemic adverse event			Moderate/severe adverse event		
First vaccination									
All patients	1.1	(0.7 – 1.6)	P = 0.73	1.1	(0.8 – 1.6)	P = 0.60	1.1	(0.8 – 1.8)	P = 0.48
RA patients	0.9	(0.6 – 1.4)	P = 0.54	1.0	(0.6 – 1.6)	P = 0.94	1.0	(0.6 – 1.7)	P = 0.96
MS patients	1.2	(0.6 – 2.4)	P = 0.55	1.5	(0.8 – 2.9)	P = 0.18	1.4	(0.7 – 2.8)	P = 0.32

Values are displayed as odds ratios with corresponding 95% confidence intervals and P-values. Odds ratios are adjusted for age, sex and vaccine type. RA = rheumatoid arthritis, MS = multiple sclerosis.

**Table S5. The risk of adverse events following the first COVID-19 vaccination in predefined subgroups.**

	Any adverse event			Systemic adverse event			Moderate/severe adverse event		
Vaccine type <sup>1</sup>									
BNT162b2 (Pfizer/BioNtech)	0.3	(0.2 – 0.5)	P < 0.001	0.1	(0.1 – 0.2)	P < 0.001	0.2	(0.1 – 0.3)	P < 0.001
CX-024414 (Moderna)	2.0	(0.9 – 4.8)	P = 0.11	0.5	(0.3 – 1.0)	P = 0.04	0.6	(0.3 – 1.2)	P = 0.14
Sex <sup>2</sup>									
Female participants	1.9	(1.3 – 2.7)	P < 0.001	1.7	(1.2 – 2.5)	P = 0.004	2.2	(1.4 – 3.5)	P < 0.001
Age <sup>3</sup>									
Participants ≤ 55 years	2.4	(1.3 – 4.4)	P = 0.01	1.8	(1.1 – 2.5)	P = 0.03	3.5	(2.0 – 6.0)	P < 0.001

Values are displayed as odds ratios with corresponding 95% confidence intervals and P-values. <sup>1</sup>Odds ratios are compared to all participants who received ChAdOx1 nCoV-19 (AstraZeneca) and adjusted for age, sex and presence of autoimmune diseases. <sup>2</sup>Odds ratios are compared to all male participants and adjusted for age, presence of autoimmune diseases and vaccine type. <sup>3</sup>Odds ratios are compared to all participants older than 55 years and adjusted for sex, presence of autoimmune diseases and vaccine type.

**Table S6. Psychological wellbeing of patients with autoimmune diseases compared to healthy controls 14 days or longer after COVID-19 vaccination.**

	All patients (n=289)	RA patients (n=111)	MS patients (n=49)	Healthy controls (n=120)
<b>Perceived sense of security – no. (%)</b>				
Safer	217 (75)	81 (72)	36 (74)	91 (76)
No change	72 (24)	31 (28)	13 (27)	29 (24)
Less safe	0 (0)	0 (0)	0 (0)	0 (0)
<b>Perceived quality of life* – no. (%)</b>				
Improved	58/288 (20)	21 (19)	8 (16)	17 (14)
No change	227/288 (79)	89 (80)	41 (84)	103 (86)
Reduced	3/288 (1)	1 (1)	0 (0)	0 (0)

Values are displayed as frequencies with corresponding percentages (%). RA = rheumatoid arthritis, MS = multiple sclerosis. \*Information on perceived quality of life was missing for one patient.