

Clinical science

# Safety and tolerance of vaccines against SARS-CoV-2 infection in systemic lupus erythematosus: results from the COVAD study

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Received: 16 September 2022. Accepted: 10 November 2022

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## Abstract

**Objective:** To determine COVID-19 vaccine-related adverse events (AEs) in the seven-day post-vaccination period in patients with SLE vs autoimmune rheumatic diseases (AIRDs), non-rheumatic autoimmune diseases (nrAIDs), and healthy controls (HC).

**Methods:** Data were captured through the COVID-19 Vaccination in Autoimmune Diseases (COVAD) questionnaire (March–December 2021). Multivariable regression models accounted for age, gender, ethnicity, vaccine type and background treatment.

**Results:** Among 9462 complete respondents, 583 (6.2%) were SLE patients (mean age: 40.1 years; 94.5% females; 40.5% Asian; 42.9% Pfizer-recipients). Minor AEs were reported by 83.0% of SLE patients, major by 2.6%, hospitalization by 0.2%. AE and hospitalization frequencies were similar between patients with active and inactive SLE. Rashes were more frequent in SLE patients vs HC (OR; 95% CI: 1.2; 1.0, 1.5), chills less frequent in SLE vs AIRDs (0.6; 0.4, 0.8) and nrAIDs (0.5; 0.3, 0.8), and fatigue less frequent in SLE vs nrAIDs (0.6; 0.4, 0.9). Pfizer-recipients reported higher overall AE (2.2; 1.1, 4.2) and injection site pain (2.9; 1.6, 5.0) frequencies than recipients of other vaccines, Oxford/AstraZeneca-recipients more body ache, fever, chills (OR: 2.5, 3.0), Moderna-recipients more body ache, fever, chills, rashes (OR: 2.6, 4.3). Hospitalization frequencies were similar across vaccine types. AE frequencies were similar across treatment groups, although chills were less frequent in antimalarial users vs non-users (0.5; 0.3, 0.9).

**Conclusion:** While COVID-19 vaccination-related AEs were reported by four-fifths of SLE patients, those were mostly minor and comparable to AEs reported by healthy individuals, providing reassurance regarding COVID-19 vaccination safety in SLE.

**Keywords:** COVID-19, vaccine, adverse events, systemic lupus erythematosus, rheumatology

### Rheumatology key messages

- While four-fifths of SLE patients reported COVID-19 vaccination-related adverse events (AEs), the majority were minor.
- Frequencies of major AEs (2.6%) and hospitalizations (0.2%) were similar to those in healthy individuals.
- Active SLE yielded increased post-vaccine fever, fatigue and tachycardia frequencies. Background therapies had no influence.

## Introduction

Vaccination against SARS-CoV-2 infection (COVID-19) has at large been proven efficacious and safe for the healthy population [1]. However, data concerning populations considered vulnerable due to background diseases or ongoing immunosuppressant therapy, such as patients with SLE, are limited. Increasing knowledge and experience on the management of COVID-19 has been pivotal in addressing the controversies surrounding the use of or discontinuation of immunosuppression prior to COVID-19 vaccination [2–6]. Current recommendations encourage COVID-19 vaccination prior to B-cell depleting therapy and withholding immunosuppression post-vaccination in some circumstances, depending on agent and dose [7]. Furthermore, hesitancy for vaccination remains a concern, especially among patients with autoimmune rheumatic diseases (AIRDs) [8, 9]. Interestingly, toll-like receptor agonists used as COVID-19 vaccine adjuvants have the potential to induce SLE flares via upregulation of the type I interferon pathway [10].

We recently reported vaccine safety data from patients with idiopathic inflammatory myopathies (IIMs) from the global COVID-19 Vaccination in Autoimmune Diseases (COVAD) study initiative, which demonstrated self-reported safety and tolerance for COVID-19 vaccination, yet a higher frequency of skin rashes post-vaccination among dermatomyositis patients, especially those with active disease during vaccination [11]. Similarly, we recently reported data on COVID-19 vaccine safety in patients with RA from the same survey, wherein most of the adverse events were minor and comparable to those reported by healthy individuals. In that work, patients on methotrexate and antimalarial agents were reported to have experienced fewer minor adverse events

post-vaccination compared with RA patients on other drugs [12]. The international vaccination against COVID in systemic lupus (VACOLUP) study that comprised 696 patients with SLE showed an adequate safety and tolerability profile for COVID-19 vaccination, with a minimal risk for disease flares, including following mRNA vaccines [13]. However, assessment of relative risks was not possible in that study due to the absence of a control group [13].

There is a dearth of data in terms of the impact of disease activity or use of immunosuppressant or immunomodulatory therapies on vaccine-specific adverse events (AEs) in patients with SLE. Moreover, the paucity of data on COVID-19 vaccine safety in SLE from diverse populations makes impossible their generalizability to the global population. The present study from the COVAD initiative addresses the COVID-19 vaccine safety and tolerance in the short term, that is, within seven days post-vaccination among patients with SLE compared with patients with other AIRDs, non-rheumatic autoimmune diseases (nrAIRDs), or healthy controls (HC), through a multicentre patient-reported electronic survey.

## Methods

### Study design and data collection

We conducted an international, online, cross-sectional, multicentre survey-based study, as a part of the COVAD initiative [14]. A comprehensive patient self-reporting electronic survey was developed, consisting of questions related to COVID-19 and AIRDs. This questionnaire included demographic details, AIRD-specific diagnosis, treatment details, current symptom status, COVID-19 infection history including symptoms, duration and complications (hospitalization and requirement of

oxygen therapy), COVID-19 vaccination details, short-term (seven days) post-vaccination AEs (based on the Centre for Disease Control and Prevention criteria) and patient-reported outcome measures as per the Patient Reported Outcomes Measurement Information System (PROMIS) tool [15]. After vetting by international experts, pilot testing, revisions, validation and translation into 18 languages, the survey was hosted on an online platform (<http://surveyMonkey.com>) and was circulated by the international COVAD study group (106 physicians) across 94 countries (Supplementary Table S1, available at *Rheumatology* online), as well as through numerous social media platforms and online patient support groups. Convenience sampling was used and all participants over the age of 18 years were included. Duplicate responses were removed manually. Methods have been detailed at length in the published COVAD study protocol [14].

Informed consent of the participants was obtained electronically through an initial question in the online survey, prior to the main study questionnaire. No incentives were offered for survey completion. Central approval was obtained from the Sanjay Gandhi Postgraduate Institute of Medical Sciences (SGPGIMS) ethics committee as per local guidelines [Institutional Ethics Committee of Sanjay Gandhi Postgraduate Institute of Medical Sciences, Raebareilly Road, Lucknow, 226014 (IEC Code: 2021–143-IP-EXP-39)] and the Checklist for Reporting results of the Internet E-Surveys (CHERRIES) was adhered to when reporting results [16, 17].

**Data extraction**

Data were retrieved at the time of survey closure on 30 December 2021. Subjects who had not received at least one dose of any COVID-19 vaccine at the time of the survey completion and subjects who had not completed the survey in full were excluded from the analysis (Fig. 1). Respondents who had received at least one dose of any COVID-19 vaccine and

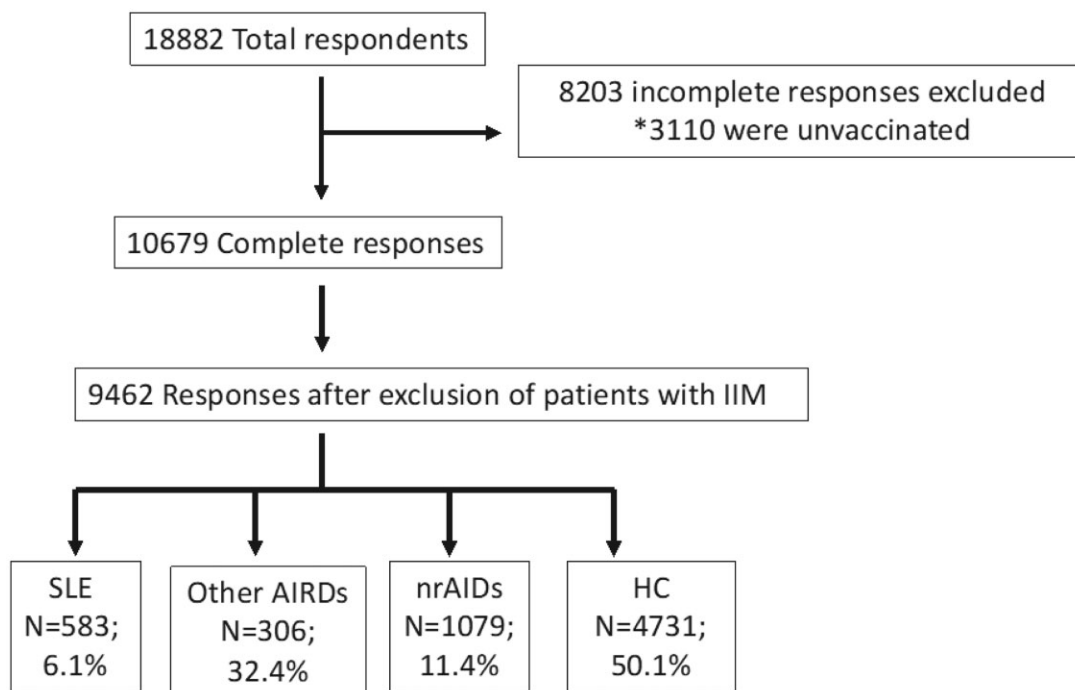
had completed the survey in full formed the study population that was deemed eligible for analysis. Multiple relevant variables were extracted from the survey responses, including AEs during the seven-day post-vaccination period.

**Active and inactive disease**

Active and inactive disease state four weeks prior to vaccination was assessed by the patient’s response to the question ‘What was the status of your autoimmune disease in the four weeks (prior to) before the first dose of COVID-19 vaccine?’. Responses of active and worsening/static/improving disease were grouped together to designate ‘active disease’. Patients who indicated ‘inactive’ as response formed the inactive disease group. Those who responded ‘I don’t know’ or ‘Other’ were assessed for activity at an individual basis based on answers to the following questions: (i) What were your symptoms four weeks prior to vaccination? (ii) If you have any swelling of your joints, how many joints are swollen? (iii) Did you require an increase in the dose of any of these [referring to previous answers] immunosuppressant medications (IS), or start a new immunosuppressant medicine within the six months prior to the first COVID-19 vaccine?

**Adverse events post vaccination**

Seven-day AEs were categorized into injection site pain or reaction, minor AEs, major AEs, and hospitalizations. Minor AEs included myalgia, body aches, fever, chills, nausea and vomiting, headache, rashes, fatigue, diarrhoea, abdominal pain, high pulse rate or palpitations, rise in blood pressure, fainting, difficulty in breathing, dizziness, and chest pain. Major AEs consisted of serious reactions to vaccination, requiring urgent medical attention, including anaphylaxis, a marked difficulty in breathing, throat closure (choking) and severe rashes. AEs not listed above were reported as ‘others’ in an open-ended question.



**Figure 1.** Flow diagram of patients included in the study. \*An electronic protocol terminated the survey automatically if respondents indicated not having received any COVID-19 vaccine. AIRDs: autoimmune rheumatic diseases (excluding SLE and IIM); HC: healthy controls; IIM: idiopathic inflammatory myositis; nrAIDs: non-rheumatic autoimmune diseases; SLE: systemic lupus erythematosus

## Statistical analysis

As the survey was originally designed for patients with IIMs and distributed to IIM patient groups, patients with IIM formed a disproportionately large subgroup and were therefore excluded from the other AIRDs group prior to analysis to avoid selection bias. Patients with SLE were excluded from the other AIRDs group. Comparisons were performed for vaccination-related AEs in patients with active *vs* inactive SLE. Also, comparisons between patients with SLE and patients with other AIRDs (IIM and SLE patients excluded) were conducted, as well as between patients with SLE and patients with nrAIRDs, and between patients with SLE and HC. Patients with SLE and autoimmune disease comorbidities were compared with those without autoimmune disease comorbidities. Autoimmune disease comorbidities included other AIRDs and nrAIRDs reported by SLE patients. Chi-squared ( $\chi^2$ ) and Mann–Whitney *U* tests were used for comparisons between groups for categorical and continuous variables, respectively. The variables that differed across SLE, other AIRDs, nrAIRDs and HC in univariable analysis were included in multivariable binary logistic regression analysis (BLR) with adjustment for baseline factors defined *a priori*, that is, age, gender, ethnicity, country group defined by human development index (HDI), as well as factors with  $P < 0.200$  in the univariable analyses. Stepwise forward regression methodology was used to build the regression models starting with age, gender, ethnicity and country group by HDI first, followed by addition of other covariates. The results for continuous variables were expressed as median (IQR) in view of the non-normal distribution of the data (by Kolmogorov–Smirnov test and Shapiro–Wilk test). In multivariable models,  $P < 0.05$  was considered statistically significant. Statistical analysis was performed using the IBM SPSS version 26 (IBM, Armonk, NY, USA).

## Results

### Characteristics of study participants

Of 10 679 survey participants with complete responses, 1227 patients with IIM (11.4%) were excluded (Fig. 1; Table 1). Of 9462 respondents forming the population under study, 583 were patients with SLE (6.2%), 3069 patients with other AIRDs (32.4%), 1079 patients with nrAIRDs (11.4%) and 4731 were HC (50.0%). Within the total study population, 7028 (74.3%) respondents were females, the respondents' mean age was  $42.2 \pm 14.8$  years, and the most frequently reported ethnicity was Caucasian (49.3%). The three most represented countries were Turkey (16.1%), India (15.3%) and Mexico (13.3%; Supplementary Table S1, available at *Rheumatology* online). Seventy-two per cent had taken at least two doses of COVID-19 vaccine and all had received at least one vaccine dose. Table 1 shows the type and proportion of patients with other AIRDs. The most common vaccine received was Pfizer-BioNTech (BNT162b2) in 39.3%. The most common immunosuppressants or immunomodulatory agents used by the SLE patients at the time of survey completion were antimalarial agents (62.6%), followed by glucocorticoids (55.6%) and azathioprine (14.4%; Table 1). Other population characteristics are shown in Table 1.

### Population characteristics of SLE patients

Among the SLE patients, the mean age was  $40.1 \pm 12.0$  years, and the majority (94.5%) were females. The most frequent

ancestry was Asian (40.5%), followed by Caucasian (37.9%). Seventy-one per cent had taken two doses of COVID-19 vaccine. Pfizer-BioNTech (BNT162b2) (42.9%) and Oxford/AstraZeneca (ChAdOx1 nCoV-19) (11.7%) were the most common vaccines received. The most common co-existing other AIDs within SLE patients was thyroid disorder ( $n = 46$ ; 7.8%), type 1 diabetes ( $n = 5$ ; 0.8%) and haemolytic anaemia ( $n = 8$ ; 1.3%).

Patients with SLE were older than HC (median: 39 *vs* 34 years;  $P < 0.001$ ), but younger than those with other AIRDs (median: 39 *vs* 49 years;  $P < 0.001$ ) and nrAIRDs (median: 39 *vs* 42 years;  $P < 0.001$ ) and had a higher female representation compared with all other groups ( $P < 0.001$  for all comparisons; Table 1). Furthermore, differences were noted regarding ethnicity and the proportion of vaccines received by SLE patients (Table 1). Patients with SLE were more frequently on glucocorticoids compared with other AIRDs (OR: 3.8; 95% CI: 3.1, 4.5;  $P < 0.001$ ) as well as compared with nrAIRDs (OR: 9.9; 95% CI: 7.7, 12.8;  $P < 0.001$ ). Also, they were more frequently on mycophenolate mofetil, azathioprine and antimalarial agents compared with patients with other AIRDs (Table 1).

### Adverse events in SLE and comparisons with other subgroups

Overall, AEs within seven days following vaccination were reported by 484 (83.0%) of the SLE patients; all these patients reported minor AEs (Supplementary Table S2, available at *Rheumatology* online). Major AEs were reported by 15 patients (2.6%) and hospitalization by one (0.2%). Injection site pain was reported by 415 (71.2%) patients with SLE.

Among the minor AEs, the most frequently reported was fatigue ( $n = 162$ ; 27.8%), followed by headache ( $n = 147$ ; 25.2%) and body ache ( $n = 120$ ; 20.6%; Supplementary Table S2, available at *Rheumatology* online). Specific major AEs reported included anaphylaxis ( $n = 3$ ; 0.5%), throat closure ( $n = 1$ ; 0.2%), severe rashes ( $n = 2$ ; 0.3%) and others ( $n = 11$ ; 1.9%). Among 11 SLE patients with self-reported coexisting antiphospholipid syndrome (APS), none reported thrombosis (stroke, deep vein thrombosis or myocardial infarction) in the seven-day period post-vaccination, and none reported chest pain, fainting, dizziness or difficulty in breathing. Only minor AEs ( $n = 7$ ; 63.3%) were reported, mainly fatigue ( $n = 6$ ; 54.5%) and headache ( $n = 3$ ; 27.2%).

Within the SLE study population, 328 patients (56.3%) had active disease prior to vaccination. The reported post-vaccination AEs were similar between those with active and inactive disease except for higher fever (OR: 1.6; 95% CI: 1.1, 2.5;  $P = 0.026$ ), fatigue (OR: 1.5; 95% CI: 1.1, 2.3;  $P = 0.025$ ) and tachycardia (OR: 8.0; 95% CI: 1.8, 35.0;  $P = 0.006$ ) in patients with active SLE (Table 2). Hospitalization frequencies were similar between the two groups (Table 2). A greater percentage of patients with self-reported active SLE were on glucocorticoids (64.9% *vs* 43.9%;  $P < 0.001$ ) compared with inactive SLE patients; the differences in AEs between patients with active and patients with inactive SLE persisted upon adjustments for glucocorticoid dose and intake of other immunosuppressive or immunomodulatory agents, yielding an OR of 1.9 for fever (95% CI: 1.1, 3.2;  $P = 0.012$ ), an OR of 1.7 for fatigue (95% CI: 1.1, 2.7;  $P = 0.007$ ) and an OR of 8.7 for tachycardia (95% CI: 1.8, 41.4;  $P = 0.006$ ).



**Table 1.** Baseline characteristics of survey respondents

Variable	Total (n = 9462)	SLE (n = 583)	HC (n = 4731)	Other AIRDs (n = 3069)	Other nrAIDs (n = 1079)
Median age in years (IQR)	41 (29–53)	39 (32–49)	34 (26–47)	49 (39–60)	42 (32–53)
Gender (Male: Female)	2378:7028 (1:2.9)	31:551 (1:17)	1659:3043 (1:1.8)	545:2508 (1:4.6)	143: 926 (1:6.5)
No. of vaccine doses, n (%)					
1	2617 (27.7)	209 (35.8)	1201 (25.3)	858 (27.9)	349 (32.3)
2	6845 (72.3)	374 (64.2)	3530 (74.7)	2211 (72.1)	730 (67.6)
Ethnicity, n (%)					
Caucasian	4668 (49.3)	221 (37.9)	1984 (41.9)	1823 (59.4)	640 (59.3)
African-American/African heritage	66 (0.7)	7 (1.2)	33 (0.7)	21 (0.7)	5 (0.5)
Asian	2516 (26.6)	236 (40.5)	1315 (27.7)	750 (24.4)	215 (19.9)
Hispanic	1173 (12.4)	73 (12.5)	764 (16.1)	206 (6.7)	130 (12.0)
Native American/Indigenous/Pacific Islandic	46 (0.5)	7 (1.2)	24 (0.5)	11 (0.4)	4 (0.4)
Do not wish to disclose	559 (5.9)	20 (3.4)	345 (7.3)	152 (4.9)	42 (3.8)
Other	434 (4.6)	19 (3.3)	266 (5.6)	106 (3.5)	43 (3.9)
Vaccine taken, n (%)					
Pfizer-BioNTech (BNT162b2)	3723 (39.3)	250 (42.9)	1623 (34.3)	1376 (44.8)	474 (43.9)
Oxford/Astra Zeneca (ChAdOx1 nCoV-19)	1292 (13.7)	68 (11.7)	466 (9.8)	612 (19.9)	146 (13.5)
Johnson & Johnson (J&J) (JNJ-78436735)	89 (0.9)	16 (2.7)	37 (0.8)	18 (0.6)	18 (1.7)
Moderna (mRNA-1273)	599 (6.3)	59 (10.1)	160 (3.4)	261 (8.5)	119 (11.0)
Novavax (NVX-CoV2373)	10 (0.1)	—	2 (0.0)	5 (0.2)	3 (0.3)
Covishield (ChAdOx1 nCoV-19)	1149 (12.1)	46 (7.8)	677 (14.3)	323 (10.6)	103 (9.6)
Covaxin (BBV152)	222 (2.4)	10 (1.7)	120 (2.6)	75 (2.4)	17 (1.6)
Sputnik (Gam-COVID-Vac)	188 (2.0)	7 (1.2)	131 (2.8)	29 (0.9)	21 (1.9)
Sinopharm (BBIBP-CorV)	1564 (16.6)	33 (5.7)	1244 (26.3)	163 (5.3)	124 (11.5)
Others <sup>a</sup>	570 (6.0)	93 (16.0)	238 (5.0)	189 (6.2)	50 (4.6)
I am not sure	56 (0.6)	1 (0.2)	33 (0.7)	18 (0.6)	4 (0.4)
Diagnosis, n (%)					
No autoimmune disease	4731 (44.0)	—	4731 (44.0)	—	—
Rheumatoid arthritis	1347(14.2)	—	—	1347 (31)	—
SLE	583 (5.5)	583 (6.1)	—	—	—
Systemic sclerosis	407 (3.8)	—	—	407 (9.4)	—
Ankylosing spondylitis or psoriatic arthritis	372 (3.5)	3 (0.5)	—	372 (8.6)	—
Sjögren's syndrome	218 (2)	—	—	218 (5.0)	—
Mixed connective tissue disorder (MCTD)	142 (1.3)	—	—	142 (3.3)	—
Vasculitis	114 (1.0)	—	—	114 (2.6)	—
Crohn's disease or ulcerative colitis (IBD)	175 (1.6)	3 (0.5)	—	—	175 (16)
Thyroid (hypothyroid or hyperthyroid)	498 (4.7)	46 (7.8)	—	—	498 (46)
Type 1 Diabetes	63 (0.6)	5 (0.8)	—	—	63 (5.8)
Multiple sclerosis	31 (0.3)	—	—	—	31 (3.0)
Myasthenia gravis	30 (0.3)	3 (0.5)	—	—	30 (2.8)
Pernicious anaemia	10 (0.1)	1 (0.1)	—	—	10 (0.9)
Haemolytic anaemia/idiopathic thrombocytopenic purpura (ITP)	18 (0.2)	8 (1.3)	—	—	18 (1.7)
Polymyalgia rheumatica	18 (0.2)	1 (0.1)	—	18 (0.4)	—
Others	705 (6.8)	38 (6.5)	—	451 (10.5)	254 (23.5)
Treatment, n (%)					
Methotrexate	989/4731 (21.0)	44 (7.5)	—	913 (29.7)	32 (2.9)
Mycophenolate mofetil	328 (7.0)	125 (21.4)	—	182 (5.9)	20 (1.8)
Rituximab	67 (1.4)	7 (1.2)	—	56 (1.8)	4 (0.4)
Azathioprine	261 (5.6)	84 (14.4)	—	120 (3.9)	57 (5.3)
Hydroxychloroquine	1007 (21.2)	365 (62.6)	—	616 (20.0)	730 (67.6)
Sulfasalazine	246 (5.2)	1 (0.2)	—	227 (7.4)	18 (1.7)
Leflunomide	155 (3.2)	8 (1.4)	—	144 (4.7)	3 (0.3)
Oral tacrolimus	49 (1.0)	18 (3.0)	—	24 (0.8)	7 (0.6)
Ciclosporin	24 (0.6)	4 (0.7)	—	16 (0.5)	4 (0.4)
IVIg	45 (1.0)	5 (0.9)	—	25 (0.8)	14 (1.3)
Cyclophosphamide	13 (0.2)	4 (0.7)	—	9 (0.3)	0 (0.0)
Glucocorticoids					
No glucocorticoids	3541 (74.8)	258 (44.2)	—	2309 (75.2)	958 (88.8)
<10 mg prednisone (or eq.)/day	961 (20.4)	269 (46.1)	—	615 (20.0)	75 (6.9)
10–20 mg prednisone (or eq.)/day	184 (3.8)	40 (6.8)	—	117 (3.8)	26 (2.4)
>20 mg prednisone (or eq.)/day	63 (1.4)	16 (2.7)	—	27 (0.9)	20 (1.9)

AIDs: autoimmune diseases; AIRDs: autoimmune rheumatic diseases (other than SLE or inflammatory myopathies); HC: healthy controls; NA: not applicable.  
<sup>a</sup> Others included open-ended responses in different languages.

**Table 2.** Comparison of vaccination-related AEs in patients with active vs inactive SLE

	Active SLE (n = 328) n (%)	Inactive SLE (n = 255) n (%)	Univariable		Multivariable	
			OR (95% CI)	P	OR (95% CI)	P
Any AEs	277 (84.5)	207 (81.2)	—	0.296	—	—
Injection site pain	229 (69.8)	186 (73.0)	—	0.409	—	—
Minor AEs						
Any minor AEs	277 (84.5)	207 (81.2)	—	0.296	—	—
Myalgia	55 (16.8)	36 (14.1)	—	0.382	—	—
Body ache	74 (22.6)	46 (18.0)	—	0.180	—	—
Fever	74 (22.6)	38 (14.9)	1.6 (1.1, 2.5)	<b>0.020</b>	1.6 (1.1, 2.5)	<b>0.026</b>
Chills	37 (11.3)	29 (11.4)	—	0.972	—	—
Nausea and vomiting	29 (8.8)	15 (5.8)	—	0.180	—	—
Headache	84 (25.6)	63 (24.7)	—	0.803	—	—
Rashes	12 (3.7)	3 (1.2)	—	0.060	—	—
Fatigue	102 (31)	60 (23.5)	1.4 (1.0, 2.1)	<b>0.043</b>	1.5 (1.1, 2.3)	<b>0.025</b>
Diarrhoea	9 (2.7)	10 (3.9)	—	0.427	—	—
Abdominal pain	9 (2.7)	4 (1.6)	—	0.340	—	—
Tachycardia	20 (6.0)	2 (0.8)	8.2 (1.9, 35)	<b>0.001</b>	8.0 (1.8, 35)	<b>0.006</b>
Rise in blood pressure	5 (1.5)	3 (1.2)	—	0.720	—	—
Fainting	0 (0.0)	1 (0.4)	—	0.256	—	—
Difficulty in breathing	6 (1.8)	1 (0.4)	—	0.114	—	—
Dizziness	26 (7.9)	15 (5.8)	—	0.338	—	—
Chest pain	10 (3.0)	1 (0.4)	7.9 (1.0, 62)	<b>0.019</b>	7.7 (0.9, 62)	0.054
Major AEs						
Any major AEs	12 (3.7)	3 (1.2)	—	0.060	—	—
Anaphylaxis	2 (0.6)	1 (0.4)	—	0.716	—	—
Marked dyspnoea	1 (0.3)	0 (0.0)	—	0.378	—	—
Throat closure	1 (0.3)	0 (0.0)	—	0.378	—	—
Severe rashes	1 (0.3)	0 (0.4)	—	0.858	—	—
Hospitalization	0 (0.0)	1 (0.4)	—	0.256	—	—

Factors included as covariates in multivariable binary logistic regression analysis included age, gender, ethnicity, country by human development index. Bold text highlights significant *P*-values. AEs: adverse events; OR: odds ratio.

Table 3, Supplementary Table S3 (available at *Rheumatology* online) and Fig. 2 provide an overview of vaccination-related AEs based on the type of vaccine received by patients with SLE. Overall, any AEs were reported more frequently by Pfizer-BioNTech (BNT162b2) vaccine recipients (OR: 2.2; 95% CI: 1.1, 4.2; *P*=0.016) compared with the rest. Any minor AEs followed similar trends. Injection site pain was reported more frequently by Pfizer-BioNTech (BNT162b2) vaccine recipients (OR: 2.9; 95% CI: 1.6, 5.0; *P*<0.001) and less frequently by Sinopharm (BBIBP-CorV) vaccine recipients (OR: 0.2; 95% CI: 0.1, 0.6; *P*=0.003) compared with the rest.

Major AEs were reported to be similar across recipients of different vaccine types. Hospitalization following vaccination was infrequent, with similar frequencies across recipients of the various vaccine types.

Systemic minor AEs such as fever, chills and body ache were more frequently reported by Oxford/AstraZeneca (ChAdOx1 nCoV-19) and Moderna (mRNA-1273) vaccine recipients (OR ranging between 2.5 and 3.0; *P*<0.05 for all instances). All other minor AEs were similar across recipients of different vaccine types (Table 3 and Supplementary Table S3, available at *Rheumatology* online).

Supplementary Tables S4 and S5, available at *Rheumatology* online, provide an overview of vaccination-related AEs stratified by the type of background immunosuppressive therapy. The vaccination-related AEs were similar across background treatment categories except for lower chills in SLE patients who were on antimalarial agents (OR: 0.5; 95% CI: 0.3, 0.9; *P*=0.042) compared with patients who were not on

antimalarials. The hospitalization frequencies were also similar across the various background treatment groups.

Figure 3, Supplementary Tables S2, S6 and S7, all available at *Rheumatology* online, provide an overview of vaccination-related AEs between patients with SLE and HC, between patients with SLE and patients with other AIRDs, and patients with SLE and patients with nrAIDs, respectively. Compared with HC, patients with SLE had similar overall AEs frequencies, frequencies of injection site pain, overall minor AEs, and hospitalization frequencies, except for higher frequencies of rashes (OR: 1.2; 95% CI: 1.0, 1.5; *P*=0.038) and anaphylaxis (OR: 8.7; 95% CI: 1.3, 57.0; *P*=0.024) in patients with SLE. In terms of absolute numbers, the patients with SLE who reported anaphylaxis were few (*n*=3; 0.5%). When compared with other AIRD patients, patients with SLE reported similar frequencies of overall AEs, minor AEs, major AEs and hospitalizations, except for lower frequencies of chills (OR: 0.6; 95% CI: 0.4, 0.8; *P*=0.005) in SLE patients. Similarly, when compared with nrAID patients, patients with SLE reported similar frequencies of overall AEs, minor AEs, major AEs and hospitalizations, except for chills (OR: 0.5; 95% CI: 0.3, 0.8; *P*=0.003) and fatigue (OR: 0.6; 95% CI: 0.4, 0.9; *P*=0.020) that were less frequent in the SLE population.

Supplementary Table S8, available at *Rheumatology* online, demonstrates that SLE patients with autoimmune comorbidities (*n*=92; 15.8%) reported similar frequencies of overall AEs, minor AEs, and major AEs compared with SLE patients without autoimmune comorbidities (*n*=491; 84.2%), with the exception of fatigue (OR: 2.1; 95% CI: 1.3, 3.4; *P*=0.002) and abdominal pain (OR: 3.6; 95% CI: 1.1, 12.1; *P*=0.033)

**Table 3.** Frequencies of vaccination-related AEs in SLE patients by vaccine type

	Pfizer-BioNTech (BNT162b2) (n = 250)	Oxford/AstraZeneca (ChAdOx1 nCoV-19) (n = 68)	Johnson & Johnson (J&J) (JNJ-78436735) (n = 16)	Moderna (mRNA-1273) (n = 59)	Covishield (Serum Institute India) (ChAdOx1 nCoV-19) (n = 46)	Covaxin (Bharat Biotech) (BBV152) (n = 10)	Sputnik (Gam-COVID-Vac) (n = 7)	Sinopharm (BBIBP-CorV) (n = 33)
Any adverse event	<b>219 (87.6)*</b>	60 (88.2)	15 (93.8)	55 (93.2)	31 (67.4)	7 (70.0)	7 (100.0)	28 (84.8)
Injection site pain	<b>202 (80.8)***</b>	53 (77.9)	12 (75.0)	51 (86.4)	19 (41.3)	6 (60.0)	6 (85.7)	<b>17 (51.5)*</b>
Minor AEs								
Any minor AEs	<b>219 (87.6)*</b>	60 (88.2)	15 (93.8)	55 (93.2)	31 (67.4)	7 (70.0)	7 (100.0)	28 (84.8)
Myalgia	38 (15.2)	11 (16.2)	3 (18.8)	15 (25.4)	7 (15.2)	0 (0.0)	1 (14.3)	5 (15.2)
Body ache	<b>33 (13.2)***</b>	<b>25 (36.8)***</b>	3 (18.8)	<b>19 (32.2)*</b>	8 (17.4)	1 (10.0)	2 (28.6)	7 (21.2)
Fever	38 (15.2)	<b>22 (32.4)**</b>	4 (25.0)	<b>23 (38.9)***</b>	10 (21.7)	0 (0.0)	0 (0.0)	8 (24.2)
Chills	25 (10.0)	<b>14 (20.6)*</b>	2 (12.5)	<b>19 (32.2)***</b>	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea and vomiting	19 (7.6)	7 (10.3)	2 (12.5)	6 (10.2)	0 (0.0)	0 (0.0)	2 (28.6)	2 (6.1)
Headache	51 (20.4)	25 (36.8)	8 (50.0)	22 (37.4)	5 (10.9)	2 (20.0)	3 (42.9)	8 (24.2)
Rashes	7 (2.8)	1 (1.5)	0 (0.0)	<b>5 (8.5)**</b>	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)
Fatigue	81 (32.4)	21 (30.9)	9 (56.3)	22 (37.3)	5 (10.9)	0 (0.0)	3 (42.9)	5 (15.2)
Diarrhoea	8 (3.2)	5 (7.4)	1 (6.3)	2 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Abdominal pain	4 (1.6)	3 (4.4)	1 (6.3)	3 (5.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
High pulse rate	10 (4.0)	4 (5.9)	1 (6.3)	5 (8.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.0)
Rise in blood pressure	3 (1.2)	1 (1.5)	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fainting	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Difficulty in breathing	4 (1.6)	1 (1.5)	0 (0.0)	2 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dizziness	<b>10 (4.0)*</b>	7 (10.3)	3 (18.8)	5 (8.5)	1 (2.2)	0 (0.0)	1 (14.3)	4 (12.1)
Chest pain	5 (2.0)	1 (1.5)	0 (0.0)	3 (5.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Others	31 (12.4)	7 (10.3)	1 (6.3)	2 (3.4)	2 (4.3)	1 (10.0)	0 (0.0)	7 (21.2)
Major AEs								
Any major AEs	9 (3.6)	1 (1.5)	0 (0.0)	3 (5.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Anaphylaxis	2 (0.8)	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Marked dyspnoea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Throat closure	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Severe rashes	1 (0.4)	1 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Others	6 (2.4)	0 (0.0)	0 (0.0)	2 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hospitalisation	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Results from binary logistic regression analysis. Comparisons are made between one drug vs the rest. Bold denotes increased risk (OR) compared with the rest, while bold underlined denotes decreased risk (OR) compared with the rest.

\* P < 0.05; \*\* P < 0.005; \*\*\* P < 0.001.

AEs: adverse events; OR: odds ratio.

that were more frequently reported by SLE patients with autoimmune comorbidities.

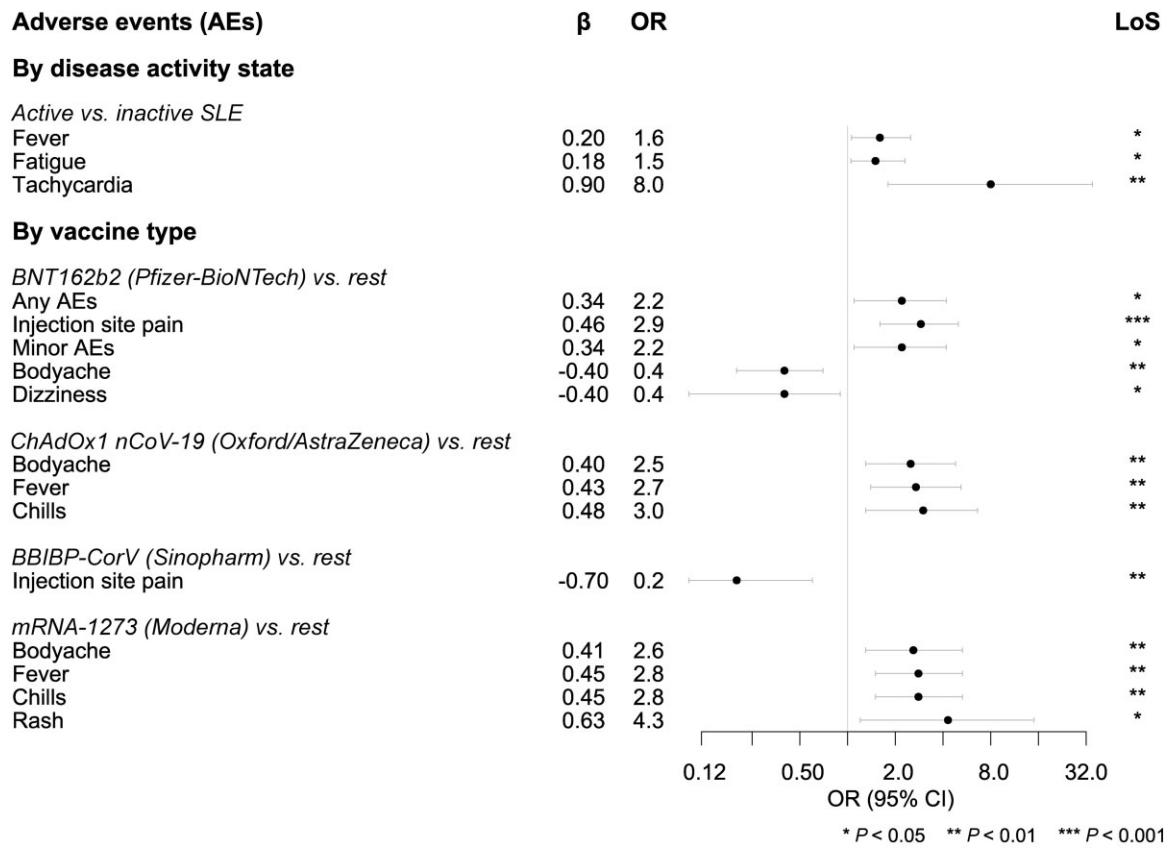
**Discussion**

Rapid production of vaccines against COVID-19 was necessitated by the pernicious impact of the pandemic on societies. However, the swift pace of vaccine development has resulted in hesitancy in a considerable proportion of the global population. This hesitancy has been even more prominent in patients with chronic diseases, particularly autoimmune diseases, patient groups not only considered more vulnerable to infections but also more prone to drug reactions [8, 9, 18]. Patients with SLE are often on immunosuppressant therapies and/or glucocorticoids, which may impact the biological responses to vaccines. In the present study, we evaluated patient-reported post-vaccination AEs in patients with SLE and found overall reassuring results; while 83.0% of patients reported AEs, these were typically minor and self-resolving. Nevertheless, major AEs were reported by 2.6% of SLE patients and included anaphylaxis, throat closure and severe rashes. To the best of our knowledge, this is the first study of this scale in terms of numbers, ethnic diversity and global reach, to address COVID-19 vaccination-related AEs over a

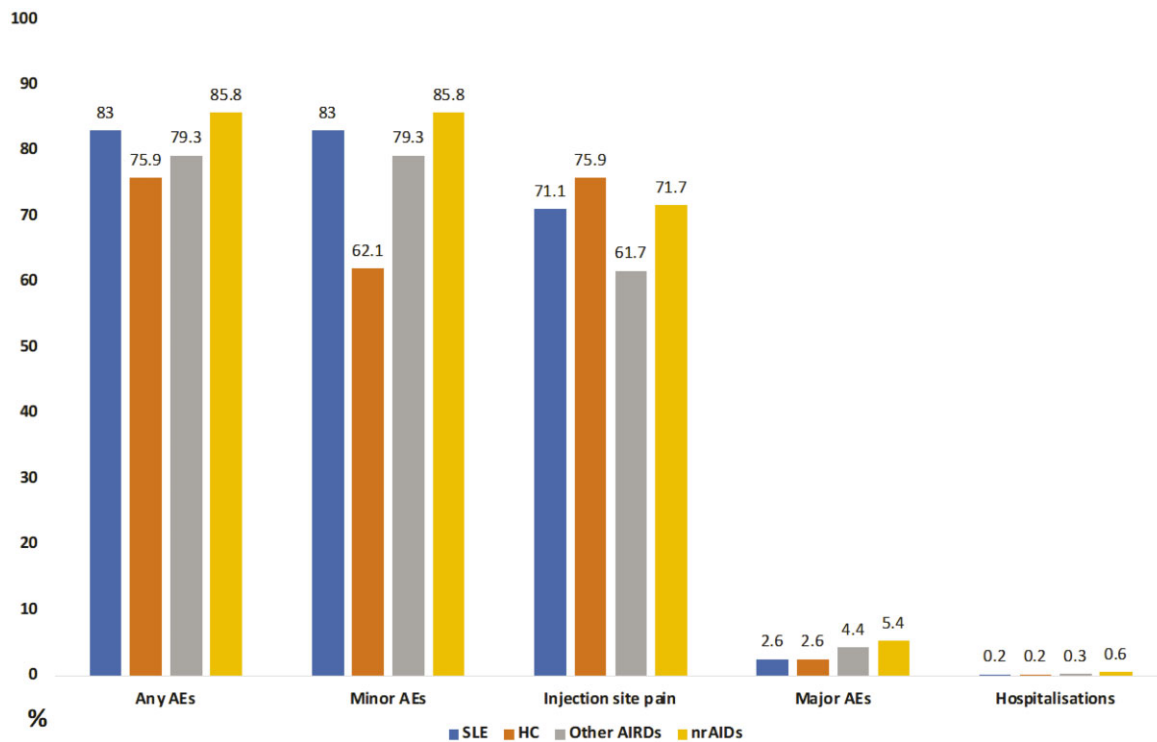
seven-day post-vaccination period, with a focus on patients with SLE and comparisons with patient populations with other AIRDs, nrAIDs, as well as healthy individuals.

In analysis stratifying SLE patients into patients with active and inactive disease, overall AE and hospitalization frequencies were similar between the groups. However, active SLE increased the chance for experiencing fever and fatigue by 1.6 and 1.5 times, respectively, and the chance for experiencing tachycardia by eight times. While the explanation underlying the observed association between active SLE and post-vaccination tachycardia is unclear and difficult to speculate upon, this is to the best of our knowledge the first time it is reported in the literature. The association persisted upon adjustments for glucocorticoid doses and intake of other immunosuppressive or immunomodulatory medications. Lastly, SLE patients with concurrent APS did not report thrombotic events post-vaccination, which is reassuring and concordant with previous reports on patients with APS [19–22].

In analysis stratified by vaccine type, AE frequencies reported by SLE patients were overall similar across the different vaccine types, except for Pfizer recipients who reported overall AEs and injection site pain at a 2-fold and 3-fold higher extent compared with recipients of other vaccine types, respectively, and Oxford/AstraZeneca and Moderna recipients who reported a



**Figure 2.** Selected vaccination-related AEs in patients with SLE. The forest plot illustrates selected results from multivariable logistic regression analysis. Circles denote odds ratios (ORs) and whiskers denote 95% confidence intervals. AEs: adverse events; LoS: level of significance; SLE: systemic lupus erythematosus



**Figure 3.** Frequencies of vaccination-related adverse events (AEs) across patients with various rheumatic diseases and healthy controls. AEs: adverse events; AIRDs: autoimmune rheumatic diseases (excluding SLE and IIM); HC: healthy controls; nrAIDs: non-rheumatic autoimmune diseases



higher probability of some minor AEs such as body ache, fever and chills. By contrast, Sinopharm recipients less frequently experienced injection site pain. Major AE and hospitalization frequencies were similar across recipients of different vaccine types. These findings were in line with those of the VACOLUP study, which reported similar frequencies of AEs across vaccine types, and irrespective of age or gender [13].

Lastly, we performed a subgroup analysis stratifying SLE patients based on background immunosuppressant or immunomodulatory therapy. In this analysis, AE frequencies did not differ across patient groups on different medications, with the exception of chills being less frequently reported by patients who were on antimalarial agents compared with patients who were not. Following conflicting initial signals, antimalarial agents were later disproved to be of efficacy in managing patients with COVID-19 infection [23, 24]. Patients with SLE who use antimalarials are recommended to continue the antimalarial treatment during a COVID-19 infection without any dose adjustment. There have been speculations about cardiotoxicity and electrocardiographic QTc prolongation with the use of antimalarials in COVID-19 infection, with a corroborating meta-analysis of several studies [5]. However, in many COVID-19 infection treatment protocols, patients were given higher doses of antimalarial agents compared with usual doses within rheumatology; for example, hydroxychloroquine loading with 800 mg [25]. Thus, SLE patients in the present study are anticipated to have received lower doses than those shown to induce cardiotoxicity; it is worth mentioning that the recommended daily hydroxychloroquine dose for patients with SLE is  $\leq 5$  mg/kg [26]. Moreover, many patients in the studies that showed hydroxychloroquine-induced cardiotoxicity also received azithromycin, another drug with potentiality to prolong the QTc [5]. Lastly, no signals were seen for B-cell depleting therapy regarding AE or hospitalization frequency.

Several limitations need to be acknowledged. Firstly, the study was entirely based on self-reported patient data, with no possibility for verification through medical charts or healthcare professionals. Secondly, online surveys introduce inherent recall bias, as well as selection bias due to an expected higher participation willingness in patients who experienced AEs, a potential lack of internet access for individuals of lower socioeconomic status, and the likely lower grade of data contribution by patients suffering severe disability. Thirdly, the focus of the study was on short-term safety of COVID-19 vaccination, thus not contributing to the knowledge on safety over a longer term. However, the study reaffirms the safety of COVID-19 vaccination in SLE patients and is in agreement with existing evidence on COVID-19 vaccine safety within SLE populations of different studies [19, 27–36]. Fourthly, it was beyond the scope of this study to explore humoral responses to vaccines, which may also have impact on the development of AEs. Nevertheless, the large number of study participants, the high frequency of complete survey responses, and the wide geographical spread of survey respondents constituted major strengths of the study. The anonymised and self-reported nature of the questionnaire may also be considered a strength, by facilitating direct and likely unbiased (without external influence) patient and HC representation.

In conclusion, the findings of the present study provide reassurance on the safety of COVID-19 vaccination for the SLE patient population, adding to the body of literature that

addresses concerns and controversies around COVID-19 vaccination. Most AEs reported were minor, self-resolving, and comparable in nature and frequencies to those reported by healthy controls. Our results will hopefully allow greater confidence and better uptake of COVID-19 vaccines in this particularly vulnerable group of individuals, as advocated by European [37] and American [7] guidelines.

## Supplementary material

Supplementary data are available at *Rheumatology* online.

## Data availability

The datasets generated during and/or analysed during the current study are not publicly available but are available from the corresponding author on reasonable request.

## Contribution statement

Conceptualisation: N.R., E.N., L.G., I.P. Data curation: All authors. Formal analysis: N.R. Funding acquisition: I.P. Investigation: N.R., E.N., L.G., I.P. Methodology: N.R., E.N., L.G., I.P. Software: L.G. Validation: V.A., R.A., J.B.L., H.C. Visualization: J.L., R.A., V.A., L.G. Writing—original draft: N.R., E.N., I.P. Writing—review and editing: All authors.

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## Funding

I.P. is supported by grants from the Swedish Rheumatism Association (R-941095), King Gustaf V's 80-year Foundation (FAI-2020-0741), Professor Nanna Svartz Foundation (2020-00368), Swedish Society of Medicine (SLS-974449), Ulla and Roland Gustafsson Foundation (2021-26), Region Stockholm (FoUI-955483) and Karolinska Institutet.

*Disclosure statement:* A.L.T. has received honoraria for advisory boards and speaking for Abbvie, Gilead, Janssen, Lilly, Novartis, Pfizer, UCB. E.N. has received speaker honoraria/participated in advisory boards for Celltrion, Pfizer, Sanofi, Gilead, Galapagos, AbbVie, Lilly and holds research grants from Pfizer and Lilly. H.C. has received grant support from Eli Lilly and UCB; consulting fees from Novartis, Eli Lilly, Orphazyme, Astra Zeneca; speaker for UCB, Biogen. I.P. has received research funding and/or honoraria from Amgen, AstraZeneca, Aurinia Pharmaceuticals, Elli Lilly and Company, Gilead Sciences, GlaxoSmithKline, Janssen Pharmaceuticals, Novartis and F. Hoffmann-La Roche AG. M.K. has received research grants and personal fees from AbbVie, AsahiKasei, Astellas, Boehringer Ingelheim, Chugai, Corbus, GlaxoSmithKline, Horizon, Kissei, MBL, Mitsubishi-Tanabe, Mochida, Nippon Shinyaku, and Ono Pharmaceuticals. J.D. has received research funding from CSL Limited. N.Z. has received speaker fees, advisory board fees and research grants from Pfizer, Roche, Abbvie, Eli Lilly, NewBridge, Sanofi-Aventis, Boehringer Ingelheim, Janssen, Pierre Fabre; none is related to this manuscript. O.D. has/had consultancy relationship with and/or has received research funding from or has served as a speaker for the following companies in the area of potential treatments for systemic

sclerosis and its complications in the last three years: Abbvie, Acceleron, Alcedim, Amgen, AnaMar, Arxx, Baecon, Blade, Bayer, Boehringer Ingelheim, ChemomAb, Corbus, CSL Behring, Galapagos, Glenmark, GSK, Horizon (Curzion), Inventiva, iQvia, Kymera, Lupin, Medac, Medscape, Mitsubishi Tanabe, Novartis, Roche, Roivant, Sanofi, Serodapharm, Topadur and UCB. Patent issued 'mir-29 for the treatment of systemic sclerosis' (US8247389, EP2331143). R.A. has/had a consultancy relationship with and/or has received research funding from the following companies-Bristol Myers-Squibb, Pfizer, Genentech, Octapharma, CSL Behring, Mallinckrodt, AstraZeneca, Corbus, Kezar, and Abbvie, Janssen, Alexion, Argenx, Q32, EMD-Serono, Boehringer Ingelheim, Roivant. The other authors have no conflict of interest relevant to this manuscript.

## Acknowledgements

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The authors are grateful to all respondents for filling out the questionnaire. The authors also thank The Myositis Association, Myositis India, Myositis UK, Myositis Support and Understanding, the Myositis Global Network, Deutsche Gesellschaft für Muskelkranke e. V. (DGM), Dutch and Swedish Myositis patient support groups, Cure JM, Cure IBM, Sjögren's India Foundation, Patients Engage, Scleroderma India, Lupus UK, Lupus Sweden (Riksföreningen för SLE), Emirates Arthritis Foundation, EULAR PARE, ArLAR research group, AAAA patient group, APLAR myositis special interest group, Thai Rheumatism association, PANLAR, NRAS, Anti-Synthetase Syndrome support group, and various other patient support groups and organizations for their contribution in the

dissemination of this survey. Finally, the authors wish to thank all members of the COVAD study group for their invaluable role in data collection.

H.C. is supported by the National Institution for Health Research Manchester Biomedical Research Centre Funding Scheme. The views expressed in this publication are those of the authors and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health.

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