

THE LANCET

Rheumatology

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed.
We post it as supplied by the authors.

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in patients with systemic lupus erythematosus: the international VACOLUP study.
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APPENDIX

Appendix methods

Dissemination of the study was facilitated by main national and international patients' associations through their websites as well as by the following social media: Twitter, Facebook, Instagram (see acknowledgements).

Patients reporting purely cutaneous lupus, non-medically confirmed SLE, or any other diagnosis than SLE were excluded.

Demographic characteristics (sex, age, country of residence); prior medical conditions and treatments; previous infection by SARS-CoV-2, if any; date and type of SARS-CoV-2 vaccine which was administered, were collected. Participants were asked to rate the intensity of side-effects as absent, minor, moderate or severe (the latter being defined as symptoms affecting the ability to do daily activities).

Patient and public involvement

Patients were not involved in the design of this study, however patient organizations were involved in its dissemination as well as in that of the study results to participants and to wider and relevant patient communities.

Statistics

Qualitative variables were described using numbers and percentages and quantitative variables as medians and the 25th-75th percentile interquartile range (IQR). The association between side effects and other study parameters was assessed using the relative risk (RR) and its 95% confidence interval (95%CI) when appropriate. Comparisons between groups were performed using the Chi-squared test, exact Fisher's test or logistic regression when appropriate. A p-value < 0.05 was considered as statistically significant and all tests were 2-sided. Statistical analysis was performed using JMP 13 (SAS institute, Cary, USA).

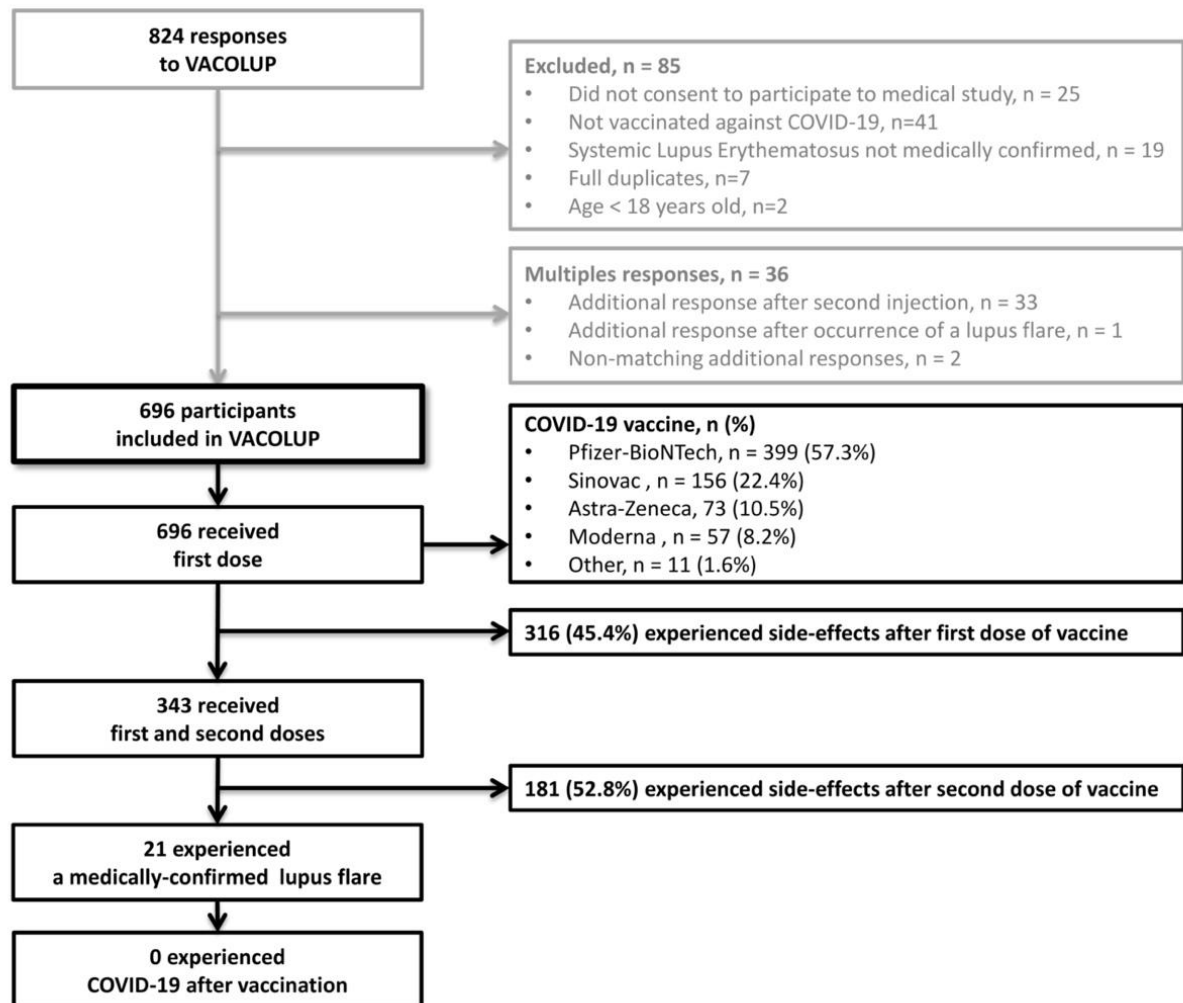
The data which support the findings of this study are available from the authors upon reasonable request.

Appendix discussion

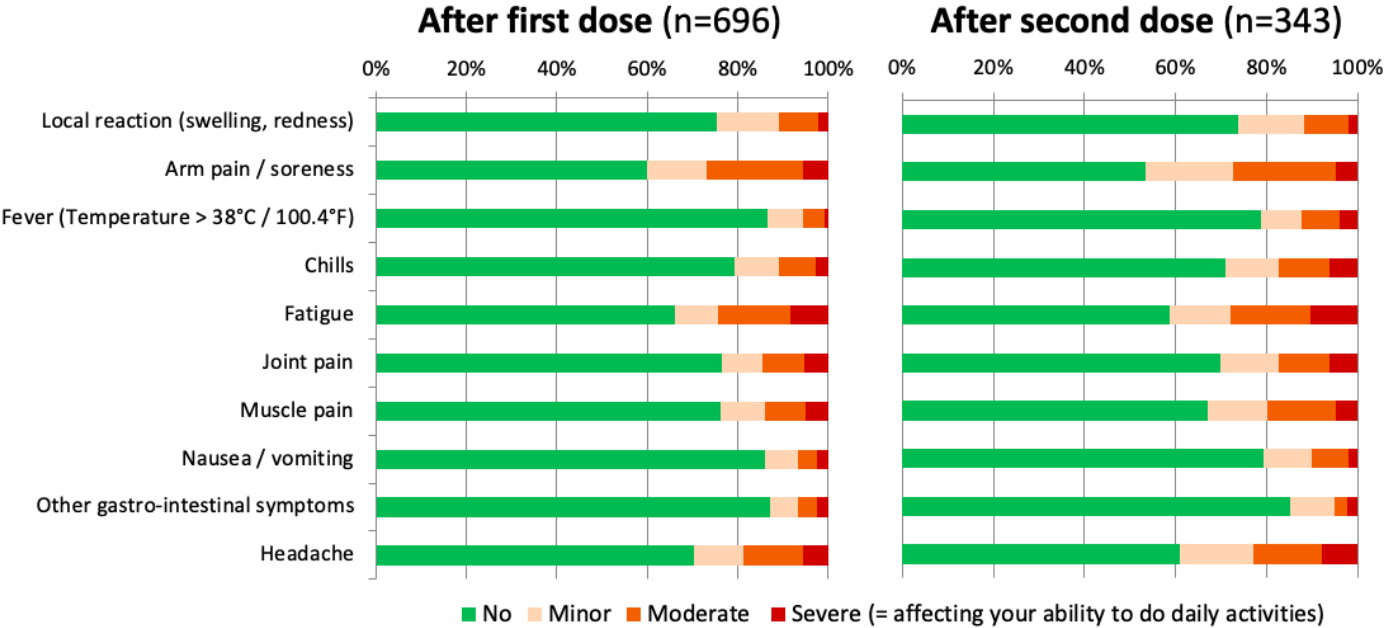
Additional limitations that are not addressed in the discussion section could include:

- Lack of data collection on ethnicity which is of importance for SLE patients.
- Subjective nature of data as they are self-declared by patient.
- No collection of timing of B cell depleting medications relative to COVID-19 vaccination, on the holding of immunosuppressive medications at the time of COVID-19 vaccination and no information on doses of medications including glucocorticoids.
- Participation bias that is inherent to surveys.

Appendix Figure 1. Flow chart



Appendix Figure 2. Type and intensity of side effects after COVID-19 vaccination



Cumulative plot showing the proportion of minor, moderate and severe reaction for each adverse event (as self-reported by patients, with severe manifestations defined as affecting the ability to do daily activity)

Appendix Table 1. Patient characteristics

	Patients
N	696
Age (years), median [IQR25-75]	42 [34-51]
Female, n (%)	669 (96.1%)
Male, n (%)	27 (3.9%)
Country, n (%)	
Italy	247 (35.5%)
Chile	190 (27.3%)
France	88 (12.6%)
USA	60 (8.6%)
UK	31 (4.5%)
Uruguay	14 (2.0%)
Other*	66 (9.5%)
Prior SLE manifestations, n (%)	n=695
Malar rash	301 (43.3%)
Discoid rash	134 (19.3%)
Photosensitivity	489 (70.4%)
Oral ulcers attributed to lupus	327 (47.1%)
Inflammatory joint pain / Arthritis	630 (90.6%)
Pleuritis or Pericarditis	188 (27.1%)
Lupus nephritis	240 (34.5%)
Seizure or psychosis	61 (8.8%)
Lupus treatments, n(%)	
Oral glucocorticoids	373 (53.6%)
Hydroxychloroquine / Chloroquine	542 (77.9%)
Immunosuppressive agents: Methotrexate / Leflunomide / Mycophenolate / Azathioprine / Cyclophosphamide	347(49.9%)
Belimumab (intravenous or subcutaneous)	76 (10.9%)
Rituximab	22 (3.2%)
Lupus flare during the past year, Yes, n (%)	217 (31.2%)
Lupus flare at the time of COVID vaccination, n (%)	49 (7.0%)
COVID-19 since the beginning of the pandemic before vaccination, Yes, n (%)	33 (4.7%)

* Other countries: Spain n=12, Canada n=9, Mexico n=7, Australia n=5, Belgium n=5, Argentina n=3, Finland n=3, Austria n=2, United Arab Emirates n=2, Germany n=2, Peru n=2, Venezuela n=2, Bolivia n=1, Colombia n=1, Denmark n=1, Dominican Republic n=1, El Salvador n=1, Guatemala n=1, Ireland n=1, Israel n=1, Netherlands n=1, Nigeria n=1, Philippines n=1, Poland n=1.

Appendix Table 2. Side effects and SLE flare according to countries and COVID vaccines

	Side effects after first dose of vaccine	Side effects after second dose of vaccine	SLE flare
Country*, n/N (%)			
Italy	96/247 (38.9%)	76/134 (56.7%)	1/247 (0.4%)
Chile	81/190 (42.6%)	39/96 (40.6%)	5/190 (2.6%)
France	28/88 (31.8%)	17/35 (48.6%)	1/88 (1.1%)
USA	40/60 (66.7%)	30/39 (76.9%)	7/60 (11.7%)
UK	26/31 (83.9%)	6/8 (75.0%)	2/31 (6.5%)
Uruguay	3/14 (21.4%)	1/9 (11.1%)	0/14 (0%)
Spain	7/12 (58.3%)	5/6 (83.3%)	1/12 (8.3%)
Canada	6/9 (66.7%)	0/1 (0%)	0/9 (0%)
Mexico	5/7 (71.4%)	0/1 (0%)	2/7 (28.6%)
Australia	4/5 (80.0%)	1/1 (100%)	1/5 (20.0%)
Belgium	4/5 (80.0%)	-	0/5 (0%)
COVID vaccine, n/N (%)			
Pfizer-BioNTech	169/399 (42.4%)	127/222 (57.2%)	8/399 (2.0%)
Sinovac	59/156 (37.8%)	27/80 (33.8%)	4/156 (2.6%)
Astra-Zeneca	47/73 (64.4%)	1/5 (20.0%)	4/73 (5.5%)
Moderna	35/57 (61.4%)	24/30 (80.0%)	5/57 (8.8%)
Janssen	3/5 (60%)	-	0/5 (0%)
Sinopharm	0/2 (0%)	1/1 (100%)	0/2 (0%)
Cansino	1/1 (100%)	-	0/1 (0%)
Curevac	0/1 (0%)	0/1 (0%)	0/1 (0%)
Sputnik V	1/1 (100%)	1/1 (100%)	0/1 (0%)
Unknown	1/1 (100%)	-	0/1 (0%)

* Countries with at least 5 participants

Appendix (VACOLUP questionnaire)

VACOLUP (Tolerance and consequences of VAccination against COVID-19 in LUPus patients)

Thank you for your participation in this study, which aims to assess the tolerance and consequences of vaccination against COVID-19 in SLE (systemic lupus erythematosus) patients.

The purpose of this questionnaire is to identify the potential side effects of the COVID vaccination in lupus patients and to provide all lupus patients throughout the world with a regularly updated summary.

Participation in this survey is anonymous and takes approximately 10 minutes.

The information collected in the questionnaire is anonymous and recorded in a computerized file by Renaud FELTEN and Laurent ARNAUD for the Rheumatology Department of Strasbourg & the National Reference Center for Rare Systemic Autoimmune Diseases (RESO). The legal basis of the treatment is the consent.

The data collected will be communicated to the following recipients only: Renaud FELTEN and Laurent ARNAUD for the Rheumatology Department of Strasbourg & the National Reference Center for Rare Systemic Autoimmune Diseases (RESO). They are kept for the duration of the study.

You can access your data, rectify them, request their deletion or exercise your right to limit the processing of your data. You may withdraw your consent to the processing of your data at any time.

Consult the cnil.fr website for more information on your rights.

To exercise these rights or if you have any questions about the processing of your data in this device, you can contact:

Dr Renaud FELTEN

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67098 STRASBOURG Cedex

1. I am answering this 'VACOLUP' survey...*

for the first time

for the second time AFTER second INJECTION of COVID-vaccine

for the Xth time to report a lupus flare which occurred since I filled-in the questionnaire for the first time

to report a medically confirmed COVID-19 after vaccination

2. I am*

a man

a woman

non-binary

Other...

3. How old are you? (e.g 34)*

4. In which country do you live?*

5. When did you get the FIRST INJECTION of the vaccination against COVID-19? (this question will be asked again later in the questionnaire for verification purposes)

Day, month, year

6. How did you hear about this survey?

via Internet / Twitter

via a patient association

via my doctor

via a relative / family member / friend

Other...

7. Do you agree to the use of your data for medical research purposes?*

Yes

No

8. DO YOU HAVE A MEDICALLY-CONFIRMED DIAGNOSIS OF SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)? (excluding Cutaneous Lupus Erythematosus (CLE), lupus-like disease, incomplete lupus, drug-induced lupus, SLE suspicion only).*

Yes

No

9. Since the beginning of the pandemic, have you contracted the SARS-CoV-2 / COVID (medically confirmed infection)?

Yes

No

I am not sure

10. Did you get the vaccination against COVID-19?*

Yes

No

11. Which of the following symptoms have you ever experienced during the follow-up of your LUPUS?*

Yes No I am not sure

Malar skin rash

Discoid skin rash

Photosensitivity

Oral ulcers attributed to lupus

Inflammatory joint pain / Arthritis

Pleuritis or Pericarditis

Lupus nephritis (renal involvement due to lupus)

Lupus seizure or psychosis

Hematologic Disorder due to lupus (Anemia OR Leukopenia OR Lymphopenia OR Thrombocytopenia)

Positive Anti-dsDNA and/or Anti-Sm and/or antiphospholipid antibodies

Positive Antinuclear Antibody

12. Which of the following treatments were you taking for your lupus at the time of your COVID-19 vaccination?*

Yes No

Oral glucocorticoids (prednisone / prednisolone)?

Hydroxychloroquine PLAQUENIL / Chloroquine NIVAQUINE

IMMUNOSUPPRESSIVE AGENTS: Methotrexate / Leflunomide / Mycophenolate (e.g Cellcept) / Azathioprine (Imuran)

Cyclophosphamide (intravenous)

Belimumab BENLYSTA (intravenous or subcutaneous)

Rituximab

13. Did you have a MEDICALLY CONFIRMED lupus flare during the past 12 months?

Yes

No

I am not sure

14. Did you have a medically confirmed lupus flare at the time of your vaccination against COVID-19?

Yes

No

I am not sure

15. Which vaccine did you get?*

Pfizer–BioNTech COVID-19 vaccine

Moderna COVID-19 vaccine

Oxford–AstraZeneca COVID-19 vaccine

Gam-COVID-Vac (Sputnik V)

BBIBP-CorV (Sinopharm)

CoronaVac (Sinovac)

Ad5-nCoV (Convidicea)

EpiVacCorona [ru]

BBV152 (Covaxin)

Ad26.COVS.S (Janssen Pharmaceutica [Johnson & Johnson])

NVX-CoV2373 (Novavax)

ZF2001 (RBD-Dimer)

Zorecimeran (CVnCoV) (CureVac)

ZyCoV-D (Cadila Healthcare)

I do not know

Other...

16. When did you get the FIRST INJECTION of the COVID vaccine?*

Day, month, year

17. Did you experiment any side effects after FIRST INJECTION of the COVID vaccine?*

Yes

No

Side effects after the FIRST INJECTION of the vaccination against COVID-19?

18. What kind of side effects did you experiment after the FIRST INJECTION of the vaccination against COVID-19? (Which intensity?)*

No Minor Moderate Severe (= affecting your ability to do daily activities)

Local reaction (swelling, redness)

Arm pain / soreness

Fever (Temperature > 38°C / 100.4°F)

Chills

Fatigue

Joint pain

Global muscle pain

Nausea / vomiting

Other gastro-intestinal symptoms (pain, diarrhea,...)

Headache

19. Did you experiment other symptoms after the FIRST INJECTION of the vaccination against COVID-19?

When did the side effects begin?

Day, month, year

20. Did you consult a doctor because of any of those symptoms?*

Yes

No

21. Did you go to the emergency because of any of those symptoms?*

Yes

No

22. Were you hospitalized because of any of those symptoms?*

Yes

No

23. Did you also get the SECOND INJECTION of the COVID vaccine?*

Yes

No

24. If yes, when did you get the SECOND INJECTION of the COVID vaccine?

Day, month, year

25. Did you experiment any side effects after the SECOND INJECTION of the COVID vaccine?*

Yes

No

26. What kind of side effects did you experiment after the SECOND INJECTION of the vaccination against COVID-19? (Which intensity?)*

No Minor Moderate Severe (= affecting your ability to do daily activities)

Local reaction (swelling, redness)

Arm pain / soreness

Fever (Temperature > 38°C / 100.4°F)

Chills

Fatigue

Joint pain

Global muscle pain

Nausea / vomiting

Other gastro-intestinal symptoms (pain, diarrhea,...)

Headache

27. Did you experiment other symptoms after the SECOND INJECTION of the vaccination against COVID-19?

When did the side effects begin?

Day, month, year

28. Did you consult a doctor because of any of those symptoms?*

Yes

No

29. Did you go to the emergency because of any of those symptoms?*

Yes

No

30. Were you hospitalized because of any of those symptoms?*

Yes

No

31. Did you experience a MEDICALLY CONFIRMED LUPUS FLARE following the vaccination?*

Yes

No

Yes but not medically confirmed

I don't know

32. Date of the beginning of your lupus flare following the COVID-19 vaccination*

Day, month, year

33. What kind of symptoms of lupus flare did you experiment AFTER COVID-19 vaccination?*

No I am not sure Yes

Fever (Temperature > 38°C / 100.4°F)

Cutaneous (skin) flare (medically confirmed)

Musculoskeletal symptoms (joint, arthritis, arthralgia, myalgia) (medically confirmed)

Pleuritis / pleurisy (medically confirmed)

Pericarditis (medically confirmed)

Renal involvement (medically confirmed)

Neuro-psychiatric manifestations (medically confirmed)

Cytopenia (anemia, thrombocytopenia, leukocytopenia) (medically confirmed)

Low complement (medically confirmed)

Increase in anti-dsDNA antibody titer (medically confirmed)

Fatigue

Other symptoms

34. Did you consult your doctor because of your LUPUS flare?*

Yes

No

35. Did you modify your treatment because of your LUPUS flare?*

Yes by myself

Yes after a medical consultation

No

36. Were you hospitalized because of your LUPUS flare?*

Yes

No

37. How was your COVID-19 AFTER COVID vaccine confirmed?

By RT-PCR nasopharyngeal test

By rapid COVID-19 nasopharyngeal test

By salivary test

I am not sure

38. Which vaccine did you get?*

Pfizer–BioNTech COVID-19 vaccine

Moderna COVID-19 vaccine

Oxford–AstraZeneca COVID-19 vaccine

Gam-COVID-Vac (Sputnik V)

BBIBP-CorV (Sinopharm)

CoronaVac (Sinovac)

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NVX-CoV2373 (Novavax)

ZF2001 (RBD-Dimer)

Zorecimeran (CVnCoV) (CureVac)

ZyCoV-D (Cadila Healthcare)

I do not know

Other...

39. When did you get the FIRST INJECTION of the COVID vaccine?*

Day, month, year

40. Did you get a SECOND INJECTION of the COVID vaccine?*

Yes

No

41. If yes, when did you get the SECOND INJECTION of the COVID vaccine?

Day, month, year

42. When did you infected by the COVID?

Day, month, year

43. How was your COVID-19 medically managed?

At home

Hospitalization in standard care with no need for oxygen

Hospitalization in standard care with a need for oxygen

Hospitalization in ICU

End of the survey...

Thank you very much for your kind participation.

As specified at the beginning, the purpose of this questionnaire is to identify the potential side effects of the COVID vaccination in lupus patients and to provide all lupus patients throughout the world with a regularly updated summary.

You can therefore access a brief summary of previous participations by following this link:

www.maladie-autoimmune.fr/vacolup/ (this data will be updated regularly).

Should you have a lupus outbreak as a result of your vaccination, even though you have already completed this questionnaire, we will give you the opportunity to answer again. To do so, you will have to answer the first question: "I am answering this survey to report a lupus flare which occurred since I filled-in the questionnaire for the first time". Then all you have to do is re-enter your gender, age and country and fill in the description of your lupus flare.

Renaud FELTEN and Laurent ARNAUD for the Rheumatology Department of Strasbourg & the National Reference Center for Rare Systemic Autoimmune Diseases (RESO)