Dear Editor,

Despite the morbidity and mortality associated with coronavirus disease 2019 (COVID-19) infection, vaccine hesitancy remains an ongoing clinical challenge for rheumatologists worldwide. As the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus has evolved, it has become apparent that additional vaccine doses are required to augment vaccine-induced protection [1, 2]. We previously reported that two-dose SARS-CoV-2 vaccination is well-tolerated among patients with rheumatic and musculoskeletal diseases (RMDs) [3]. Immune recall evokes a strong immune response following vaccine dose 3 (D3) [2], raising concern that additional immunological priming post-D3 could negatively impact disease activity among RMD patients. There is currently a paucity of data on the safety of D3 among RMD patients, thus we sought to evaluate disease flare and post-vaccination reactions (reactogenicity) following D3 SARS-CoV-2 vaccination in RMD patients.

Adult RMD patients who received three-dose SARS-CoV-2 vaccination (two-dose mRNA followed by single mRNA or adenoviral dose) completed questionnaires detailing local and systemic reactions experienced within 7 days of D3. Local reactions such as pain, redness and swelling, as well as systemic reactions including fever, fatigue, headaches, chills, vomiting, diarrhoea and myalgia were captured using an ordinal scale; these were graded per their impact on daily activity, ‘no interference with daily activity’, ‘some interference with daily activity’ and ‘prevention of daily activity’. One month following D3, participants completed an online questionnaire pertaining to the incidence and prior history of flare, incident flare as well as symptoms, duration and treatment; flare events were qualified as flares requiring treatment by a physician, as previously described [3]. Associations between participant characteristics and flare were examined using logistic regression. All tests were two-sided with an α level of 0.05; significant associations on univariate analysis were included in multivariable analysis.

A total of 645 RMD participants were included (Table 1). Thirty-five percent reported at least one flare in the 6 months preceding dose 1 (D1), while 10% reported flare following dose 2 (D2). D3 included BNT162b2 (52.7%), mRNA-1273 (46.7%) or J&J (0.6%) received at a median of 177 days [interquartile range (IQR) 145–203] post-D2. Almost half (49.3%) withheld peri-D3 immunosuppression.

Fifty-two (8.1%) patients reported flare post-D3. Flares occurred at a median of 8 days (IQR 2–28) post-D3, lasting to a median of 10 days (IQR 4–34). An increase in baseline symptoms was reported by a median of 66% (IQR 50–76) of participants, with the most frequent symptoms being worsening joint pain [36/52 (69%)], myalgia [20/52 (38%)] and joint swelling [19/52 (36.5%)]. Flares were mostly treated with oral corticosteroids [31/52 (59.6%)] for a median of 8 days (IQR 6–11), while more than one-third [19/52 (36.5%)] reported up-titration of baseline immunosuppressive therapy. No participant required hospital admission.

Younger age [odds ratio (OR) 1.05 (95% CI 1.03, 1.07)], flare pre-D1 [OR 1.28 (95% CI 1.08, 1.51)], flare post-D2 [OR 2.35 (95% CI 1.01, 5.63)] and overlap connective tissue disease [OR 1.93 (95% CI 1.06, 3.53)] were associated with flare. Age [adjusted OR (aOR) 1.06 (95% CI 1.02, 1.1)], P = 0.01 remained significant on multivariable analysis, while factors including flare after D2 [aOR 2.3 (95% CI 0.91, 5.87), P = 0.08], flare prior to vaccination [aOR 1.04 (95% CI 0.79, 1.36), P = 0.7] and overlap connective tissue disease [aOR 1.92 (95% CI 0.75, 4.92), P = 0.17] did not reach significance.

The most common local and systemic reactions included injection site pain (87%) and fatigue (75%); most did not interfere with daily activity (Supplementary Fig. S1, available at Rheumatology online). Reports of reactions that prevented daily activities were uncommon, with fatigue (13%) and myalgia (7%) most frequently reported (Supplementary Table S1, available at Rheumatology online). There were no post-vaccination reactions requiring hospitalization.

Limitations of this study include a lack of granularity on baseline disease control and physician verification of flare. In addition, the use of survey data may result in both recall and selection bias, while it may also underestimate severe outcomes. Strengths include a large, national sample with novel findings addressing an area in which there is currently a large knowledge deficit.

We provide novel data on post-D3 safety in a large cohort of RMD patients. Consistent with findings

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Safety of third-dose SARS-CoV-2 vaccination in patients with rheumatic and musculoskeletal disease

Rheumatology key message

- Third dose SARS-CoV-2 vaccination is safe, with low rates of disease flare in RMD patients

- Third dose SARS-CoV-2 vaccination is safe, with low rates of disease flare in RMD patients
following two-dose SARS-CoV-2 vaccination in both centre-based [4–6] and population-based studies [7], D3 was well tolerated with low rates of flare. There was an association between flare and younger age, with 6% higher odds of flare per decrease in year. While flare prior to vaccination and following two-dose vaccination was associated with flare following D3 on univariate analysis, these did not reach significance on multivariable analysis. Furthermore, we previously reported an association of pre-vaccination COVID-19 infection and flare [3], but we did not observe a relationship in this analysis, which is limited by its small size; these warrant additional evaluation in larger cohorts. In addition, modulation of perivaccination immunosuppression was not associated with an increased rate of flare, thereby providing reassurance regarding this strategy to augment the vaccine response among our vulnerable patients.

Our findings emphasize the safety of SARS-CoV-2 vaccines among RMD patients. Waning protection conferred by mRNA vaccines reinforces the importance of additional doses to improve protection [8] and will help

### Table 1

Characteristics of 645 RMD patients, stratified by presence/absence of disease flare requiring treatment and multivariable analysis of factors associated with post-D3 flare

| Characteristics                                      | Overall  | Disease flare | No disease flare | P-value |
|------------------------------------------------------|----------|---------------|-----------------|---------|
|                                                      | (N = 645)| (n = 52)      | (n = 593)       |         |
| Age, years, median (IQR)                             | 51 (41–62)| 43 (34–52)    | 50 (41–58)      | <0.001* |
| Female, n (%)                                        | 590 (91.5)| 52 (100)      | 538 (90.7)      |         |
| Non-white, n (%)                                     | 65 (10.1)| 4 (7.7)       | 61 (10.3)       | 0.55    |
| Diagnosis, n (%)                                     |          |               |                 |         |
| Inflammatory arthritis                               | 283 (43.9)| 14 (26.7)     | 269 (45.3)      | 0.66    |
| SLE                                                  | 105 (16.3)| 9 (17.3)      | 96 (16.2)       | 0.26    |
| Sjögren’s syndrome                                   | 24 (3.7)| 2 (3.8)       | 22 (3.7)        | 0.23    |
| Myositis                                             | 66 (10.2)| 2 (3.8)       | 64 (10.8)       | 0.13    |
| Vasculitis                                           | 32 (4.9)| 5 (9.6)       | 27 (4.6)        | 0.11    |
| Systemic sclerosis                                   | 22 (3.4)| 2 (3.8)       | 20 (3.4)        | 0.85    |
| Overlap connective tissue disease                    | 113 (17.5)| 18 (34.6)     | 95 (16)         | 0.03    |
| D2 vaccine, n (%)                                     |          |               |                 |         |
| BNT162b2                                             | 335 (51.9)| 28 (53.8)     | 309 (52.1)      | –       |
| mRNA-1273                                            | 310 (48.1)| 24 (46.2)     | 287 (48.4)      | 0.98    |
| Withheld IS pre-/post-D3                             | 318 (49.3)| 23 (44.2)     | 295 (49.7)      | 0.45    |
| Therapy, n (%)                                       |          |               |                 |         |
| Conventional DMARD                                   | 479 (74.3)| 34 (65.4)     | 445 (75.1)      | 0.11    |
| Biologic                                             | 367 (56.9)| 35 (67.3)     | 332 (55.9)      | 0.14    |
| Immunosuppressive therapy                            | 32 (4.9)| 3 (5.8)       | 29 (4.9)        | 0.77    |
| Combination therapy                                  | 384 (59.5)| 34 (65.4)     | 350 (59.1)      | 0.33    |
| Flare in 6 months prior to vaccination, n (%)        | 228 (37.2)| 32 (61.5)     | 196 (33.1)      | 0.01    |
| Flare after D2, n (%)                                | 66 (10.2)| 13 (25)       | 53 (9.9)        | 0.05    |
| Pre-vaccination COVID-19 infection, n (%)            | 22 (3.4)| 4 (7.7)       | 18 (3)          | 0.09    |

**Multivariable analysis of factors associated with post-D3 flare**

| Factor                                           | aOR (95% CI) | P-value |
|--------------------------------------------------|--------------|---------|
| Age                                              | 1.06 (1.02, 1.10) | 0.01    |
| Flare after D2                                   | 2.30 (0.91, 5.87) | 0.08    |
| Flare in 6 months prior to vaccination           | 1.04 (0.79, 1.36) | 0.70    |
| Overlap connective tissue disease                | 1.92 (0.75, 4.92) | 0.17    |

*Bold denotes significant (P < 0.05) associations on univariate analysis that were included in multivariable analysis. All participants who experienced post-D3 flare were female, thus the OR/P-value was not calculated. The denominators for these categories differ from the total N as 3 participants selected ‘prefer not to answer’ for race and 32 did not answer ‘flare prior to vaccination’. RA, AS, PsA, reactive arthritis and IBD-associated arthritis. Overlap denotes participants who selected more than one diagnostic category, including inflammatory arthritis, SLE, Sjögren’s syndrome, vasculitis, myositis or systemic sclerosis. AZA, HCQ, LEF, MTX, MMF, SSZ and tacrolimus. Abatacept, adalimumab, anakinra, baricitinib, belimumab, certolizumab, etanercept, golimumab, infliximab, ixekizumab, rituximab, secukinumab, tocilizumab, tofacitinib, upadacitinib and ustekinumab. IVIG or subcutaneous immunoglobulin. Denotes conventional DMARD and biologic and/or glucocorticoid, or biologic and glucocorticoid. Flare requiring treatment from a physician following D2.

https://academic.oup.com/rheumatology
address vaccine hesitancy related to additional vaccine doses in RMD patients.

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Data availability statement

Data are available upon reasonable request by any qualified researchers who engage in rigorous, independent scientific research and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). All data relevant to the study are included in the article.

Supplementary data

Supplementary data are available at Rheumatology online.

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References

1 Karaba AH, Zhu X, Liang T et al. A third dose of SARS-CoV-2 vaccine increases neutralizing antibodies against variants of concern in solid organ transplant recipients [published online ahead of print, 2021 Dec 24]. Am J Transplant 2021;22:1253–60.

2 Goel RR, Painter MM, Lundgreen KA et al. Efficient recall of Omicron-reactive B cell memory after a third dose of SARS-CoV-2 mRNA vaccine. Cell 2022;185:1875–87.e8.

3 Connolly CM, Ruddy JA, Boyarsky BJ et al. Disease flare and reactogenicity in patients with rheumatic and musculoskeletal diseases following two-dose SARS-CoV-2 messenger RNA vaccination. Arthritis Rheumatol 2022;74:28–32.

4 Sattui SE, Liew JW, Kennedy K et al. Early experience of COVID-19 vaccination in adults with systemic rheumatic diseases: results from the COVID-19 Global Rheumatology Alliance Vaccine Survey. RMD Open 2021;7:e001814.

5 Spinelli FR, Favalli EG, Garufi C et al. Low frequency of disease flare in patients with rheumatic musculoskeletal diseases who received SARS-CoV-2 mRNA vaccine. Arthritis Res Ther 2022;24:21.

6 Heshin-Bekenstein M, Ziv A, Toplak N et al. Safety and immunogenicity of BNT162b2 mRNA COVID-19 vaccine in adolescents with rheumatic diseases treated with immunomodulatory medications. Rheumatology (Oxford) 2022;doi: 10.1093/rheumatology/keac103.

7 Machado PM, Lawson-Tovey S, Strangeland A et al. Safety of vaccination against SARS-CoV-2 in people with rheumatic and musculoskeletal diseases: results from the EULAR Coronavirus Vaccine (COVAX) physician-reported registry. Ann Rheum Dis 2022;81:695–709.

8 Centers for Disease Control and Prevention. Waning 2-dose and 3-dose effectiveness of mRNA vaccines against COVID-19-associated emergency department and urgent care encounters and hospitalizations among adults during periods of delta and omicron variant predominance — VISION Network, 10 States, August 2021–January 2022. MMWR Morb Wkly Rep 2022;71:255–63.