COVID-19 Vaccine in Immunosuppressed Adults with Autoimmune rheumatic Diseases (COVIAAD): safety, immunogenicity and antibody persistence at 12 months following Moderna Spikevax primary series

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ABSTRACT

Objective To assess the safety, immunogenicity and cellular responses following the Moderna Spikevax primary series in rheumatic disease.

Methods We conducted a 12-month, prospective, non-randomised, open-label, comparative trial of adults with either rheumatoid arthritis (RA, n=131) on stable treatment; systemic lupus erythematosus (SLE, n=23) on mycophenolate mofetil (MMF); other rheumatic diseases on prednisone ≥10mg/day (n=8) or age-matched/sex-matched controls (healthy control, HC, n=58). Adverse events (AEs), humoral immune responses (immunogenicity: IgG positivity for anti-SARS-CoV-2 spike protein and its receptor binding domain, neutralising antibodies (NAbs)); cellular responses (ELISpot) and COVID-19 infection rates were assessed.

Results Frequency of solicited self-reported AEs following vaccination was similar across groups (HC 90%, RA 86%, SLE 90%); among them, musculoskeletal AEs were more frequent in RA (HC 48% vs RA 66% (95% CI 3 to 32.6)). Disease activity scores did not increase postvaccination. No vaccine-related serious AEs were reported. Postvaccination immunogenicity was reduced in RA and SLE (RA 90.2%, SLE 86.4%; for both, ΔCIs compared with HC excluded the null). Similarly, NAb was reduced among patients (RA 82.6%, SLE 81.8%). In RA, age >65 (OR 0.3, 95% CI 0.1 to 0.8) and rituximab treatment (OR 0.003, 95% CI 0.001 to 0.02) were negative predictors of immunogenicity. ELISpot was positive in 16/52 tested RA and 17/26 HC (ΔCI 11.2–53.3). During the study, 11 HC, 19 RA and 3 SLE patients self-reported COVID-infection.

Conclusion In COVID-19 Vaccine in Immunosuppressed Adults with Autoimmune Diseases, the Moderna Spikevax primary series was safe. MMF, RA age >65 and rituximab were associated with reduced vaccine-induced protection.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Registry data provide reassurance about the safety profile of SARS-CoV-2 vaccines in patients with autoimmune rheumatic diseases (RD).
⇒ Most patients with RD develop humoral and cellular responses to SARS-CoV-2 vaccines; however, concern exists that some specific treatments (ie, rituximab) may be associated with reduced immunogenicity.

INTRODUCTION

Immunosuppressed people living with autoimmune rheumatic diseases (RD) are at risk for prolonged SARS-CoV-2 replication, intra-host viral evolution of mutated variants and poor clinical outcomes.1 This underscores the importance of their vaccination. Phase 3 clinical trials of COVID-19 vaccines either excluded or had only small numbers of immunosuppressed patients.2,3 To ensure that recommendations for vaccination of immunocompromised adults were based on robust safety, immunogenicity and efficacy data, the Public Health Agency of Canada prioritised conducting clinical trials that included those patients.4

The trial ‘COVID-19 Vaccine in Immunosuppressed Adults with Autoimmune Diseases (COVIAAD)’ was mandated by the Quebec Ministry of Health and Social Services in February 2021. COVIAAD (NCT04806113) was designed as a 1-year prospective,
WHAT THIS STUDY ADDS

⇒ Our data provide direct evidence on the safety and immunogenicity related to three doses of mRNA-1273 SARS-CoV-2 vaccine in RD subgroups (ie, rheumatoid arthritis (RA), systemic lupus erythematosus (SLE)) as well as their COVID-19 infection risk over a 1-year period.
⇒ Age (over 65 years) and rituximab treatment are independent predictors of reduced Moderna Spikevax immunogenicity in RA.
⇒ After the third vaccine dose 10% of RA (including most rituximab treated RA) and 14% of SLE participants did not develop humoral vaccine-induced responses.
⇒ The frequency of COVID-19 infection among patients with RA and SLE in this trial was 15% and 13%, respectively. Their frequency was similar to that in healthy control (19%).

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Individuals can be reassured that the Moderna Spikevax primary vaccine series induces humoral responses in most patients with RA without an increase in disease activity.
⇒ The magnitude of antibody levels to each of the COVID-19 vaccine doses was reduced in RA compared with healthy controls, which could decrease protection; this argues for the need for boosters beyond the primary vaccine series.
⇒ Older patients with RA and those on rituximab should be aware that they may have reduced vaccine-induced responses.
⇒ Correlates of protection from SARS-CoV-2 vaccines in RD and their persistence overtime need to be defined.

multicentre, non-randomised, open-label, comparative clinical trial with pragmatic features. COVIAAD’s primary objective was to assess the safety of a two-dose vaccination schedule of an approved RNA-based COVID vaccine (mRNA-1273 SARS-CoV-2 vaccine), given 28 days apart to healthy controls (HCs), people with rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE).7

Given changes in public health recommendations, the trial was adapted to evaluate the safety of a third vaccine dose (ie, primary series). COVIAAD’s secondary objectives included vaccine-induced humoral and cellular responses, effect of age and treatment category on immunogenicity and COVID-19 infection rates.

METHODS

Study participants

COVIAAD took place at the CHU de Québec – Université Laval and McGill University Health Centre (MUHC), both in Canada. All patients provided written informed consent. Patients were enrolled if they had a diagnosis of RA fulfilling the American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) 2010 classification criteria6 or SLE according to the 2012 Systemic Lupus International Collaborating Clinics criteria and/or the 2019 EULAR/ACR criteria.7,8 Patients with RA were classified according to age (ie, ≤64 vs ≥65 years) and treatment (ie, methotrexate, non-rituximab biologics, rituximab or Janus kinase (JAK) inhibitors). Only those patients with SLE on mycophenolate mofetil (MMF) were included. Patients with RA and SLE were required to be on stable treatment defined as ≥3 months of DMARDs/biologics/JAK inhibitors or MMF prior to enrolment. A group of patients with other RDs (ORDs) requiring more than 10 mg of prednisone per day for >3 weeks prior to study entry was included. Age-matched and sex-matched HC without rheumatological diseases were recruited and enrolled from the community. Sample size calculations are presented in Section 15 of the Study Protocol. Inclusion/exclusion criteria are presented in online supplemental table 1.

Study procedures

mRNA-1273 SARS-CoV-2 vaccines (subsequently referred as Moderna Spikevax) were provided by the Quebec Ministry of Health and Social Services in February 2021 and delivered to the Vaccine Study Centre (VSC) of the CHUL and the MUHC. Both VSC are sites of the Canadian Immunisation Research Network and operate using similar harmonised protocols. Participants received the first two doses at the VSC and were given the option to receive the third dose either at the VSC or in the community. Vaccine administration followed the schedule of the original phase 3 Moderna trial (ie, two 100 µg doses intramuscularly given 28 days apart).9 The third dose was administered 4–6 months after the second vaccine dose according to the preference of the participant. Patients were not asked to discontinue any of their medications before vaccination. Prior to each vaccine dose, a blood sample was drawn, and a memory aid (online supplemental material) was given to each participant to record solicited AEs (solicited AEs=reactogenicity) as well as any other unsolicited self-reported AEs that occurred 28 days after each vaccine dose. Participants were asked to grade the intensity and duration of all AEs and whether they required medication changes, physician encounters and/or emergency room (ER) visits. Serious AEs (ie, those that resulted in death, were life-threatening, required in-patient hospitalisation or prolonged an existing hospitalisation or resulted in persistent or significant disability/incapacity9 were recorded throughout the study. Participants received a phone call 7 days post each vaccine dose, as a reminder to complete their memory aid, enquire about local and systemic AEs, disease flares, health changes requiring care (all ER visits and non-routine medical visits for any reasons) or changes in RA/SLE treatment. Memory aids were returned 28 days postvaccination at a visit in which an update of disease activity scores and medications was done, a blood sample was drawn and COVID-19 clinical events were recorded. Data were stored in the Research Electronic Data Capture system. Study procedures are presented in online supplemental figure 1.
Data and samples collection

At the initial visit, we collected demographic data, comorbidities and risk factors associated with COVID-19 infection and its complications. At each visit, we recorded all medications and patient-reported outcomes for disease activity and COVID infection. RA disease activity measures included the Routine Assessment of Patient Index Data (RAPID3), RA flare questionnaire (RA-FQ) and RA Disease Activity Index (RADAI-5). For SLE, we used the Systemic Lupus Activity Questionnaire. Patient-reported COVID infection required a positive COVID-19 rapid test and/or PCR.

Sera were collected at each time point (day 0–D0, d57, month 6-M6, post-dose 3-PD3 and M12), aliquotted and stored until tested. Humoral responses were evaluated in a custom automated high throughput ELISA platform following published protocols. A parallel detection of immunoglobulin (Ig)Gs against the spike trimer (anti-S) and its receptor binding domain (anti-RBD) and the nucleocapsid (anti-N) protein was done at each time point. The assays were calibrated to a reference standard from the WHO. Two dilutions of each sample were evaluated: 1/100 to determine seroprevalence calls and anti-N titres, and 1/2500 for anti-S and anti-RBD titres. Positivity thresholds were established for each antigen by determining a signal level resulting in a specific false positive rate in a cohort of prepandemic RA and SLE samples. Thresholds pertaining to 3%, 5% and 1% false positivity for Spike, N and RBD (respectively) were used to score individual samples for positivity. Postvaccination increases in both anti-S and anti-RBD, but not anti-N, defined vaccine-induced immunity.

The assessment of neutralising Abs (NAbs) to the original Wuhan strain was done using a microneutralisation assay as previously described. SARS CoV-2 (SARS 2 LSPQ(1)) virus was obtained from the Laboratoire de Santé Publique du Québec, and it was propagated and tittered. In the microneutralisation assay, the highest serum dilution that prevented infection corresponded to the 100% neutralisation titre. Titres of ≥20 were considered positive.

SARS-CoV-2-specific T-cell responses were detected using the IFN-γ ELISpotPLUS (3420-AST-2) kit from Mabtech inc (Cincinnati, Ohio, USA). In brief, peripheral blood mononuclear cells (PBMCs) were isolated from whole blood and stored at −150°C until tested. SARS CoV-2 Spike peptide pool was purchased from Mabtech while the cytomegalovirus, Epstein-Barr virus and influenza virus (CEF) peptide pool was obtained from JPT Peptide Technologies (Berlin, Germany). Peptides were added directly to the PBMCs, the mix was plated, incubated for 20 hours, washed and blotted dry. Detection Ab (7-B6-1-biotin) followed by Streptavidin-ALP and then substrate (BCIP/NBT-plus) were added. The spots present in the wells of each plate were counted using the 96 Ultimate Analyzer from Immunosop (Cleveland, Ohio). A T-cell response (cellular response) was positive when there was twice the number of spots to the SARS peptide following three vaccine doses compared with baseline.

Outcomes

COVIDAD’s primary outcome was the safety of Moderna Spikevax (ie, the frequency of solicited and unsolicited self-reported AEs including ‘significant’ disease flares) in RA/SLE participants versus HC. ‘Significant’ disease flares were defined as worsening clinical disease activity documented by the treating physician requiring intensification of therapy.

Secondary outcomes included immunogenicity rates and titres of anti-S and anti-RBD Abs; frequency of NAbs; effect of treatment and RA participants’ age on immunogenicity; vaccine induced T-cell responses, and frequency of COVID reported infection.

Statistical analysis

Analyses were conducted on observed data using the intention-to-treat population, including all enrolled participants. Baseline demographics and disease characteristics were summarised by group using descriptive statistics including the mean and SD for continuous variables and counts and percentages for categorical variables. The incidence of solicited and unsolicited self-reported AEs was described with the number and proportion of participants in each group with ≥1 event. In analyses of self-reported solicited AEs by severity, the highest severity was considered in participants who had ≥1 event in the same category. Immunogenicity, presence of NAbs, and cellular responses at baseline and following each dose were summarised by group using descriptive statistics. The correlation of anti-S and anti-RBD titres were assessed in linear regressions and the coefficient of determination (R²) was reported. Differences in titres of anti-S and anti-RBD Abs between RA or SLE and HC were assessed with one-way analysis of variance while differences in immunogenicity, NAbs positivity and T-cell responses with the differences in proportions and associated 95% CI based on Wilson’s method. Predictors of immunogenicity over time among patients with RA were explored with generalised estimating equations considering sex, age group (<64 vs ≥65 years), methotrexate use, rituximab use, rituximab biologic use, disease activity (RAPID-3) and visit. Agreement between immunogenicity and NAbs was assessed with percent (%) concordant pairs. Statistical analysis was conducted using SPSS Statistics V.24 (IBM).

Patient involvement

Participants were not directly involved in the conception, experimental design or in the conduct of the study. Preliminary study results were communicated to the Québec Immunisation Committee and shared with participants, and initial findings were presented at scientific meetings where patient representatives were in attendance.
**RESULTS**

**Participants demographics and disease characteristics**

Between 8 March 2021 and 10 April 2021, 220 participants (162 patients with RD and 58 HC; 110 per site) were enrolled and received a first dose of Moderna Spikevax. At D28, 218 (99.1%) participants received a second dose, and 4–6 months later 212 (96.4%) received a third one. The trial profile is presented in figure 1, baseline demographics in table 1, number of participants enrolled per cohort in online supplemental table.

![Trial profile diagram](image)

**Figure 1**  Trial profile. aBaseline—the Moderna Spikevax first dose was administered at this visit; bModerna Spikevax second dose was administered at this visit. *Twenty-five patients with RD received the third Moderna Spikevax dose at M6. **Twenty-four patients with RD (12 RA, 9 SLE and 3 ORD) received a booster dose (fourth dose) between 28 days post third dose and month 12. RD, rheumatic disease; HC, healthy control; 28D, 28 days.
Inflammatory arthritis

The overall frequency of solicited local and systemic self-reported AEs after each of the three vaccine doses did not increase in RA/SLE participants versus HC (figure 2). The cumulative frequency of solicited self-reported AEs following the primary series was similar in all study groups (HC 90%, RA 86%, SLE 90%). The most common local and systemic solicited self-reported AEs following any of the three doses were pain at injection site (HC=94.8%, RA=88.5%, SLE=100%, ORD=87.5%) and fatigue (HC=75.9%, RA=75.6%, SLE=65.2%, ORD=87.5%) (online supplemental table 4). The frequency of solicited musculoskeletal AEs was higher in patients with RA (HC 48.3% vs RA 66.4%, Δ 18.1% (95% CI 3% to 32.6%); arthralgias HC vs RA: dose 1: 10.3% vs 25.2%; dose 2: 21.1% vs 33.1%, dose 3: 17.9% vs 28.1%; swollen joints: dose 1: 0% vs 8.4%; dose 2: 3.5% vs 20.0%; dose 3: 1.8% vs 18.2%) (online supplemental table 5).

Table 1 COVIAAD participants' baseline characteristics

<table>
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<tr>
<th>Variable</th>
<th>Healthy controls (n=58)</th>
<th>Rheumatoid arthritis (n=131)</th>
<th>Systemic lupus (n=23)</th>
<th>Other* (n=8)</th>
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<tr>
<td>Age (years)</td>
<td>62±12</td>
<td>62±11</td>
<td>52±14</td>
<td>57±19</td>
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<td>Female sex</td>
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<td>100 (76.3)</td>
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<td>1 (12.5)</td>
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<td>118 (90.1)</td>
<td>22 (95.7)</td>
<td>7 (87.5)</td>
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<td>Race</td>
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<td>Caucasian</td>
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<td>119 (90.8)</td>
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<td>5 (62.5)</td>
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<td>3 (13.0)</td>
<td>1 (12.5)</td>
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<td>Asian/Native Hawaiian/Pacific Islander</td>
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<td>2 (1.6)</td>
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<td>Other†</td>
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<td>9 (6.9)</td>
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<td>COVID-19 infection‡</td>
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<td>0 (0)</td>
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<td>Current smoker</td>
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<td>22 (16.8)</td>
<td>1 (4.4)</td>
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<td>Body mass index (kg/m²)</td>
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<td>Charlson Comorbidity Index</td>
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<td>2.9±1.5</td>
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<td>Disease duration (years)</td>
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<td>15.2±12.8</td>
<td>14.3±12.1</td>
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<td>Comorbidities</td>
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<td>Myocardial infarction</td>
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<td>9 (6.9)</td>
<td>1 (4.3)</td>
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<td>Hypertension</td>
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<td>40 (30.5)</td>
<td>8 (34.8)</td>
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<td>Methotrexate</td>
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<td>1 (12.5)</td>
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<td>53 (40.5)</td>
<td>21 (91.3)</td>
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<td>Biologics§</td>
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<td>0 (0)</td>
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<td>15 (11.5)</td>
<td>6 (26.1)</td>
<td>8 (100)</td>
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</table>

*Idiopathic inflammatory myopathy, juvenile-onset interstitial lung disease with inflammatory arthritis, giant cell arteritis (n=2), antisynthetase syndrome, polymyalgia rheumatica (n=2), psoriatic arthritis.
† Multiracial, unknown or unobtainable, or free-text designations that included Philippine, Indian, Turkish, Armenian, El Salvadoran, Guatemalan, Brazilian, Nicaraguan, Peruvian, Colombian.
‡ COVID-19 infection prior to COVIAAD enrolment.
§ Biologic agents=abatacept, etanercept, adalimumab, tocilizumab, golimumab, certolizumab, sarilumab, secukinumab.
¶ Tofacitinib, upadacitinib.

COVIAAD, COVID-19 Vaccine in Immunosuppressed Adults with Autoimmune Diseases.
The frequency of unsolicited self-reported AEs confirmed by chart review was low and overall, not different in RD versus controls (online supplemental tables 6 and 7). One RA individual on rituximab had a non-disseminated ophthalmic herpes zoster 5 days after the second vaccine dose. Among AEs of special interest (self-reported AEs confirmed by chart review), there were five significant disease flares in patients with RA reported after the second vaccine dose (two within 7 days, one after 12 days, one 25 days and one 166 days postvaccination). Overall disease activity indexes did not increase postvaccination (online supplemental table 8).

Eight serious AEs occurred prior to M6 and were reported to the Public Health Agency of Canada (online supplemental table 9). None of these serious AEs were deemed to be causally related to the vaccine. No deaths were reported.

**Immunogenicity**

Immunogenicity postprimary vaccine series was reduced in RA and SLE (HC 100% vs RA 90.2%, Δ 9.8% (95% CI 2.3% to 16.4%); HC 100% vs SLE 86.4%, Δ 13.6% (95% CI 2.7% to 33.3%)) (table 2). Repeated-measures analysis with time-dependent covariates (D28–M12) found age >65 (0.3, 95% CI 0.1 to 0.8) and rituximab treatment (0.003, 95% CI 0.001 to 0.02) as negative predictors of immunogenicity in RA. (online supplemental table 10). At each specific time point, the levels of anti-S and anti-RBD Abs strongly correlated with each other (online supplemental figure 3). Anti-S levels were reduced in RA compared with HC after each vaccine dose (HC vs RA mean±SD BAU/mL, dose 1: 1283.4±1504.9 vs 240.2±402.0, Δ−1043.2 (95% CI −1305.6 to −780.9); dose 2: 1848.7±680.5 vs 1122.7±912.4 (Δ−726.0, 95% CI −995.5 to −456.5) p<0.05; dose 3: 5372.0±2069.7 vs 2954.3±2341.0, (Δ−1621.6, 95% CI −2142.8 to −1102.4) (figure 3 and online supplemental figure 4). Anti-S levels stratified per RA treatment are presented in figure 4.

Patients with RA on rituximab had the lowest anti-S levels irrespective of vaccine dose. The time between rituximab infusion and vaccine dose is presented in online supplemental table 11. In all groups, antibody levels decreased 4–6 months after the second vaccine dose (M6) prior to receiving the third dose. Eight patients with RA were anti-S/RBD positive at D57 and became negative at M6 (one on methotrexate (age <64) and seven on biologics (age <64 n=3). The immunogenicity rates at 12 months, irrespective of the number of vaccine doses received, were 100% in HC, 88.7% in RA, 90.9% in SLE and 100% in ORD. Twelve patients with RA, all of whom were sero-positive after the third dose, received a fourth dose before M12. The interval between third and fourth dose in those patients was 109.6±25.2 days (online supplemental table 12). Spike and RBD antibody levels increased post-fourth dose (28D post-third dose vs M12: anti-S: 3440.7±1754.8 vs 5278.0±2754.9 (Δ1837.3, 95% CI 118.2 to 3792.8); anti-RBD: 3667.8±2661.0 vs 13758.7±13022.9 (Δ10090.8, 95% CI 2133.2 to 18048.4)) (online supplemental figure 5).

**Neutralisation responses**

In all participants, the frequency of NAb positivity increased with each vaccine dose (D28, 13.3%; D57, 75.3%, D28 post-third dose, 87.6%) (online supplemental
Inflammatory arthritis

Inflammatory arthritis

Inflammatory arthritis

table 13). Among patients with RA, at each time point, the frequency of NAb positivity was lower than in HCs (HC vs RA: D28, 33.3% vs 5.4%, Δ27.9% (95% CI 15.9% to 41.2%); D57: 100% vs 68.5%, Δ31.5% (95% CI 21.9% to 40.0%); D28 post-third dose: 100% vs 82.6%, Δ17.4% (95% CI 8.8% to 25.1%)). In particular, patients with RA on rituximab were less likely to develop NAbs (D28, 0%; D57 6.3%; D28 post-third dose 14.3%). Patients with SLE on MMF also failed to produce NAbs (HC vs SLE: D28: 33.3% vs 4.3%, Δ28.9% (95% CI 9.1% to 42.4%); D57: 100% vs 47.8%, Δ52.2% (95% CI 32.0% to 70.8%); D28 post-third dose: 100% vs 81.8%, Δ18.2% (95% CI 5.6% to 38.5%)). The frequency of COVIAAD participants with dual positivity for anti-S/RBD and NAbs after the primary series was 87.6% (HC vs RA: 100% vs 82.6%, Δ17.4% (95% CI 8.8% to 25.1%); HC vs SLE: 100% vs 81.8%, Δ18.2% (95% CI 5.6% to 38.5%)) (online supplemental table 14). Similar to anti-S/RBD, at M6, NAb titres decreased both in RA and HC. At the end of the study (M12), 83.5% of participants were positive for NAbs (HC 100% vs RA 75.8%, Δ24.2% (95% CI for difference 15.1% to 32.4%)).

T-cell responses

ELISpot was done in a subgroup of COVIAAD participants (26 HC, 52 RA, 11 SLE and 5 ORD) at baseline and at D28 post-third dose. Among patients with RA, the primary vaccination series resulted in lower T-cell responses compared with HC (positive ELISpot, HC 65.4% vs RA 30.8%, Δ34.6% (95% CI 11.2% to 53.3%)). ELISpot was done in six patients with RA on rituximab treatment of whom three (50%) were positive. The relationship between vaccine-induced T-cell responses, immunogenicity and NAbs results is presented in online supplemental table 15.

Self-reported COVID-19 infection

During COVIAAD, 33 (15%) participants self-reported COVID-19 infection (11 HC (19% of HC), 19 RA (15.3% of RA), 3 SLE (13% of SLE)). Most infections occurred after the third dose of the vaccine (81.8%), corresponding with the appearance of Delta and Omicron COVID-19 variants in 2022. Most of the infected participants were positive for anti-S/RBD and NAbs at the visit prior to infection (90.9%). At the time of infection, four patients with RA visited the ER, but none were hospitalised. A description of participants who reported infections are presented in online supplemental table 16.

DISCUSSION

COVIAAD results confirm that the Moderna Spikevax primary vaccine series appears safe in immunosuppressed RA and SLE populations and does not trigger significant disease flares. The overall immunogenicity in RA was comparable to that in HC. Moreover, given that NAbs are a correlate of protection against COVID-19 in the general population, COVIAAD data are encouraging as 80% of participants who reported infections were positive for NAbs (HC vs RA, 100% vs 82.6%, Δ17.4% (95% CI 8.8% to 25.1%)). In particular, patients with RA on rituximab were less likely to develop NAbs (D28, 0%; D57 6.3%; D28 post-third dose 14.3%). Patients with SLE on MMF also failed to produce NAbs (HC vs SLE: D28: 33.3% vs 4.3%, Δ28.9% (95% CI 9.1% to 42.4%); D57: 100% vs 47.8%, Δ52.2% (95% CI 32.0% to 70.8%); D28 post-third dose: 100% vs 81.8%, Δ18.2% (95% CI 5.6% to 38.5%)).

Table 2  Participants with dual positivity for anti-S and receptor binding domain antibodies by visit and age group

<table>
<thead>
<tr>
<th>Visit</th>
<th>Health controls (n=58)</th>
<th>Rheumatoid arthritis (n=131)</th>
<th>Systemic lupus (n=23)</th>
<th>Other* (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>Age ≤65</td>
<td>n (%)</td>
<td>Age ≤65</td>
</tr>
<tr>
<td>Day 0†</td>
<td>1 (2.9)</td>
<td>1 (4.2)</td>
<td>2 (3.4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Day 28</td>
<td>34 (100)</td>
<td>23 (100)</td>
<td>57 (100)</td>
<td>55 (68.8)</td>
</tr>
<tr>
<td>Day 57</td>
<td>34 (100)</td>
<td>24 (100)</td>
<td>58 (100)</td>
<td>71 (88.8)</td>
</tr>
<tr>
<td>Month 6</td>
<td>34 (100)</td>
<td>24 (100)</td>
<td>58 (100)</td>
<td>66 (83.5)</td>
</tr>
<tr>
<td>28D post-dose 3</td>
<td>34 (100)</td>
<td>23 (100)</td>
<td>57 (100)</td>
<td>66 (90.4)</td>
</tr>
<tr>
<td>Month 12</td>
<td>34 (100)</td>
<td>24 (100)</td>
<td>58 (100)</td>
<td>66 (88)</td>
</tr>
<tr>
<td>*Idiopathic inflammatory myopathy, interstitial lung disease and arthritis, giant cell arteritis, antisynthetase syndrome, polymyalgia rheumatica, psoriatic arthritis.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>†Baseline — The first dose of the Moderna Spikevax was received at this visit.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>‡The second dose of the Moderna Spikevax was received at this visit.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Idiopathic inflammatory myopathy, interstitial lung disease and arthritis, giant cell arteritis, antisynthetase syndrome, polymyalgia rheumatica, psoriatic arthritis.
of patients with RA developed NAbs after the primary series. However, whether NAbs in RA is also a correlate of protection remains to be determined. Finally, it is reassuring that despite documenting COVID-19 infection rates of 15% among RA COVIAAD participants, none of them were hospitalised.

Similar to previous studies in patients with RD, in COVIAAD, the profile and frequency of AEs associated with Moderna Spikevax vaccine were comparable to those described in the general population. Self-reported solicited systemic AEs (ie, fever, chills, myalgia, feeling unwell, fatigue, headaches and nausea/vomiting) occurred in about 70% of participants regardless of disease status. Of relevance, we did not observe an increase in RA disease activity following any vaccine dose despite the increase in the frequency of musculoskeletal self-reported solicited AEs during the first week postvaccination. It is reassuring that despite five patients with RA having worsening of clinical disease activity documented by the treating physician and requiring intensification of therapy (ie, significant disease flares), the disease activity in the overall RA group was not affected by vaccination. Although SLE disease activity scores also remained stable postvaccination, the small number of patients in this group does not allow for firm conclusions. In COVIAAD, there were no serious AEs deemed to be related to the vaccine. Overall, vaccination was not associated with a safety signal of concern.

The overall immunogenicity rate in COVIAAD patients after the Moderna Spikevax primary vaccine series is consistent with previous reports (~90% seropositivity in RA). All HC in COVIAAD developed anti-S and anti-RBD antibodies that persisted throughout the 12 months of the study, in contrast, 10% of the patients with RA were seronegative even after all three vaccinations. Anti-S and anti-RBD antibody titres followed a similar pattern in HC and RA, with increased titres 28 days following each vaccine dose and with a reduction at M6 (postsecond dose). At each specific time point, antibody titres were consistently higher in HC than in RA. Among RA COVIAAD participants, older age (>65 years old) and rituximab treatment were associated with reduced immunogenicity. This highlights the need for additional efforts to enhance humoral responses in these subgroups (eg, assessment of additional booster doses, testing mix-and-match strategies, timing vaccine doses within rituximab scheduling to promote immunogenecity). Recent studies in rituximab-exposed individuals reported that the extent of B cell reconstitution at the time of vaccination (eg, presence of B cells in peripheral blood) and high frequency of naïve and transitional B-cells at time of vaccination predict vaccination response to mRNA COVID vaccines. These findings are not restricted to COVID-19 vaccine responses.
but extend to other vaccines (eg, influenza, pneumococcal). In COVIAAD, the rituximab-treated patients with RA who generated humoral responses had a greater interval between the last rituximab infusion and the third vaccine dose, suggesting higher likelihood of B-cell reconstitution (number of days between last rituximab infusion and third vaccine dose in patients with RA with positive versus negative anti-S/RBD, mean±SD: 344.3±186 vs 90.1±45.3). We acknowledge, as a limitation, that the actual number of B cells in these individuals was not assessed. Even in the absence of humoral responses, patients on rituximab can prime T cells, especially TH1 and CD8 T cells. Robust CD8 T cell responses are associated with improved survival in COVID-19 patients with haematological malignancies. Moreover, T cells can recognise emerging SARS-CoV-2 variants that can partially escape humoral-based immunity. In COVIAAD, over 50% of patients with RA had anti-S and anti-RBD with negative NAbs. The relevance of this with regards to future infection risk remains to be determined. Regardless, breakthrough infections in COVIAAD did not require hospital admission and were not more frequent among RA than HC.

The main limitation of COVIAAD is the relatively small number of participants, particularly in subgroup analyses. Previous studies showed that anti-SARS-CoV-2 antibody reactivity after COVID-19 infection was attenuated in antitumour necrosis factor (infliximab)-treated patients with inflammatory bowel disease versus those treated with vedolizumab, and it was further blunted in those with concomitant thiopurine or methotrexate. The reduced number of patients in the COVIAAD cohorts precludes drawing conclusions on vaccine-induced responses to specific drugs or treatment combinations. In addition, AEs (ie, reactogenicity and unsolicited) were self-reported and documented by participants in a memory aid (online supplemental material) that were reviewed by nurses at the next study visit. Self-report of outcomes could have led to over-reporting of specific AEs and/or misclassification (ie, reporting bias). COVIAAD patients were called by a study-nurse a week after each vaccine dose and followed up in person a month later at the vaccine ventre (online supplemental figure 1) to optimise data capture and reduce recall bias. Self-report of AEs also incorporates the patient experience, which is relevant given the emphasis today on patient-reported outcomes. Because most vaccine safety studies also use self-report AEs, our estimates should be comparable to similarly done studies. The lack of assessment of RA/SLE flares by a COVIAAD-rheumatologist using current definitions, is a study weakness. In COVIAAD, we only reported ‘significant flares’, all of which were documented either by the treating rheumatologist or the rheumatology nurse in the patient’s electronic medical

Figure 4

Titr es of anti-S antibodies in rheumatoid arthritis treatment cohorts and controls following each vaccine dose. In patients with RA on different treatment (MTX, Bio, JAKi) anti-S levels increase after each vaccine dose. The anti-S levels in patients with RA on RTX do not increase regardless of the number of vaccine doses. D0, baseline—first dose of the Moderna Spikevax was administered at this visit. D28, 28 days post-first dose—second dose of the Moderna Spikevax was administered at this visit; D57, 28 days post-second dose of Moderna Spikevax; M6, 6-month post-first dose of Moderna Spikevax; P-D3, 28 days post-third dose of Moderna Spikevax. Only statistically significant comparisons are shown. Bio, biologics; HC, healthy controls; JAKi, JAK inhibitors; MTX, methotrexate; RA, rheumatoid arthritis; RTX, rituximab. *p value <0.5; **p value <0.01, ***p value <0.001, **** p value <0.0001.
In summary, people with RDs are a heterogeneous population. Among them, there are subgroups with reduced responses to Moderna Spikevax primary vaccine series including those above age 65 and those on rituximab treatment. Accepted correlates of protection (ie, neutralising Abs) are reduced among patients with RA. Patients with SLE on MMF have reduced immunogenicity rates and vaccine-induced protective antibody levels. Patients with RD should be considered as a priority group in the context of future infectious threats. Further research in this area should be promoted to better define the determinants of increased infectious risk and reduced vaccine responses among specific RD subgroups.

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Contributors
All authors reviewed and contributed to this manuscript. SB, PRF, DM and IC contributed to the study design. ER, W and IC contributed to data analysis. ERL, M-AL and LF performed antibody measurements. VE, ER, MU, NA, SB, PRF and IC contributed to the first manuscript draft. MU, NA, LB, M-AL, EH, LM, PP and SB contributed to patient recruitment. PRF and IC had access to all the data, accept full responsibility for the work and conduct of the study and made the decision to publish. IC is the guarantor for this article.

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Disclaimer
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Competing interests
IC, VE, NA, MU, ER, LF, ER-L, M-AL, EH, DM, LM, PP, M-AL, SB, PRF—no competing interests. LB received grants or has contracts with Amgen, BMS, Janssen, UCB, AbbVie, Pfizer, Merck, Celgene, Sanofi, Lilly, Novartis, Gilead, JAMP Pharma.

Patient consent for publication
Not applicable.

Ethics approval
This study involves human participants and the study protocol and all relevant documents were approved as a multicentre study by the Research Ethics Board of the McGill University Health Centre in March 2021 (MP-37-2021-7562). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review
Not commissioned; externally peer reviewed.

Data availability statement
Data are available on reasonable request. Anonymous patient data are available under specific conditions. Proposals will be reviewed and approved by the sponsor, scientific committee and staff based on scientific merit and the absence of competing interests. Once the proposal has been approved, data can be transferred through a secure online platform after the signing of a data access agreement and a confidentiality agreement.

Supplemental material
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