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ORIGINAL RESEARCH

SARS-CoV-2 vaccine safety in adolescents with inflammatory rheumatic and musculoskeletal diseases and adults with juvenile idiopathic arthritis: data from the EULAR COVAX physician-reported registry

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ABSTRACT

Background There is a lack of data on SARS-CoV-2 vaccination safety in children and young people (CYP) with rheumatic and musculoskeletal diseases (RMDs). Current vaccination guidance is based on data from adults with RMDs or CYP without RMDs.

Objectives To describe the safety of SARS-COV-2 vaccination in adolescents with inflammatory RMDs and adults with juvenile idiopathic arthritis (JIA).

Methods We described patient characteristics, flares and adverse events (AEs) in adolescent cases under 18 with inflammatory RMDs and adult cases aged 18 or above with JIA submitted to the European Alliance of Associations for Rheumatology COVAX registry.

Results A total of 110 cases were reported to the registry. Thirty-six adolescent cases were reported from four countries, most with JIA (42%). Over half (56%) reported early reactogenic-like AEs. One mild polyarthralgia flare and one serious AE of special interest (malaise) were reported. No CYP reported SARS-CoV-2 infection postvaccination.

Seventy-four adult JIA cases were reported from 11 countries. Almost two-thirds (62%) reported early reactogenic-like AEs and two flares were reported (mild polyarthralgia and moderate uveitis). No serious AEs of special interest were reported among adults with JIA. Three female patients aged 20–30 years were diagnosed with SARS-CoV-2 postvaccination; all fully recovered.

Conclusions This is an important contribution to research on SARS-CoV-2 vaccine safety in adolescents with RMDs and adults with JIA. It is important to note the low frequency of disease flares, serious AEs and SARS-CoV-2 reinfection seen in both populations, although the dataset is limited by its size.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ There is a lack of data on SARS-CoV-2 vaccine safety in children and young people (CYP) with rheumatic and musculoskeletal diseases (RMDs) as they were excluded from SARS-CoV-2 vaccine clinical trials.

⇒ Although initial data in the wider CYP population and on SARS-CoV-2 vaccine immunogenicity in CYP with RMDs is reassuring, many questions regarding the safety and efficacy of SARS-CoV-2 vaccines in this population are unanswered.

WHAT THIS STUDY ADDS

⇒ In these data on 36 adolescents with inflammatory-RMDs and 74 adults with juvenile idiopathic arthritis (JIA), there were rare reports of RMD flare (adolescents: 2%, adults: 3%), only one report of serious adverse events (AEs) among adolescents, and no reports of serious AEs in adults with JIA.

⇒ The frequency and profile of early non-serious local and systemic reactions was similar to findings observed in the general population.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study will support discussions with patients and the public regarding the safety of SARS-CoV-2 vaccines and the development of recommendations by competent organisations.

⇒ These data should provide some reassurance to medical professionals, vaccine recipients and their families, and increase confidence in SARS-CoV-2 vaccine safety in CYP and adults with RMDs.

INTRODUCTION

While initial data on SARS-CoV-2 vaccines in children and young people (CYP) under 18 years of age are reassuring,[1] there is a lack of data on CYP with immune-mediated rheumatic and musculoskeletal diseases (RMDs),

as they were excluded from initial vaccine trials. Consequently, current CYP RMD vaccination advice is based on data from adults with RMDs, or CYP without RMDs.[2] Immunosuppressed adults are recommended to have third primary and booster doses of SARS-CoV-2 vaccines in some countries; in some countries such as the UK, this was extended to children aged 5 and over with severe immunosuppression,[3] again primarily based on research in adults.

Reduced SARS-CoV-2 vaccine immunogenicity[4–6] and breakthrough infections[7] have been documented in adult patients with RMD; as CYP with RMDs are often treated with similar medications to adults, it is vital to understand how they respond to SARS-CoV-2 vaccination. Limited data have now shown that adolescents with juvenile idiopathic arthritis (JIA) on tumour necrosis factor inhibitors (TNFi) have good immunogenicity, safety and tolerability to SARS-CoV-2 vaccines,[8 9] but many questions are yet unanswered.

Elucidating population-specific vaccine safety concerns are important to setting vaccination recommendations. RMD disease flares are of particular concern, and are documented in CYP with JIA who had SARS-CoV-2 infection.[10] Another essential consideration are influences on individual choices to get vaccinated; surveyed adults and parents of children with RMDs indicated SARS-CoV-2 vaccine hesitancy is due to lack of medical advice and information on vaccine safety/efficacy, concerns around medication contraindications and vaccine suitability for CYP.[11] Evaluating vaccine efficacy is also crucial for this age group as it could influence individual decisions regarding protective and social distancing measures (eg, mask-wearing and avoidance of face-to-face contact), which in turn could influence whether CYP have uninterrupted access to education. Further data are clearly needed to guide vaccination recommendations and improve public and clinical trust in vaccination in immunosuppressed CYP globally.

The European Alliance of Associations for Rheumatology (EULAR) launched a COVAX registry on 2 February 2021 to document SARS-CoV-2 vaccination and vaccine-associated flares and adverse events (AEs) among patients with RMD; AE of special interest were listed a priori based on prior knowledge of the vaccines. We describe the characteristics and outcomes of adolescents with inflammatory RMDs, and adults with JIA submitted to the EULAR Coronavirus vaccine (COVAX) physician-reported registry.

METHODS

Data were entered ad hoc by the treating clinical team directly into the data entry website or transferred from national COVID-19 registries. The EULAR COVAX Registry data were collected and managed using REDCap hosted at The University of Manchester, UK.[12] The EULAR COVAX registry was determined 'not human subjects' research' by the UK Health Research Authority and the University of Manchester and no consent to collect anonymised data was required.

Adolescent cases were included if under 18, 'partially vaccinated' (≥14 days after dose 1 to <14 days after dose 2) or 'fully vaccinated' (≥14 days after dose 2/single dose of Janssen) according to the Centers for Disease Control and Prevention definitions.[13] The Pfizer/BioNTech vaccine was approved for use in 5–11 years old in Europe on 25 November 2021,[14] and in the UK on 22 December 2021[15]—due to this, we do not yet have data on CYP under the age of 12. Adult JIA cases were included if aged 18 or above, had a RMD diagnosis of either non-systemic or systemic JIA (ns-JIA; s-JIA), 'partially vaccinated' or 'fully vaccinated' (according to prior definitions). Cases were included if reported before the cut-off date of 13 January 2022.

Flares were reported by the reporting clinician, who provided the date, type (eg, arthritis flare, cutaneous flare), and severity of the flare; flare type and severity are categorical variables in predefined lists. RMD disease activity is based on the reporting clinician's evaluation at the time of the first vaccine dose based on the data available to them (eg, medical records, direct patient reports, physical exams). The EULAR COVAX registry collects data on all adult and paediatric rheumatic diseases, therefore, a standardised measure of disease activity was not recorded, similar to the EULAR COVID-19 registry.[16]

RESULTS

Adolescents with inflammatory RMDs

Of 36 patients from Italy, Spain, France and the UK, 44% were fully and 56% partially vaccinated. Most (58%) were female and the median age was 15 (IQR: 14.5–17) (table 1). The most common RMDs were ns-JIA (28%), s-JIA (14%), systemic lupus erythematosus (14%) and spondyloarthritis/psoriatic arthritis (14%). The majority were in remission (64%) or had minimal (22%) disease activity at time of vaccination. The most frequent RMD medications were methotrexate (MTX; 36%), antimalarials (22%), TNFi (19%) and glucocorticoids (14%); median prednisolone-equivalent glucocorticoid dose at time of vaccination was 5 mg/day.

Ninety-two per cent received Pfizer/BioNTech vaccines, 6% Moderna and 2% AstraZeneca/Oxford. Most (67%) received two doses, 31% had received 1 dose and 2% three doses. All fully vaccinated cases received Pfizer vaccines. Median time between first and second vaccine doses was 24 days (IQR: 21–31). Median time from first and second dose to reporting was 50.5 days (IQR: 27–100.5) and 44 days (IQR: 6–79), respectively.

One fully vaccinated female patient aged 15–18 years old with reactive arthritis experienced a mild polyarthralgia flare post-vaccination. She was in remission and taking MTX which was not altered before or after vaccination. She received two Pfizer vaccine doses 30 days apart; the flare occurred the same day as the second dose suggesting reactogenicity rather than true disease flare.

Table 1 Characteristics of 36 adolescents with inflammatory RMDs from the EULAR COVAX registry, stratified by vaccination status

		All (N=36)	Fully vaccinated* (N=16)	Partially vaccinated† (N=20)
Sex	Female	21 (58)	9 (56)	12 (60)
	Male	15 (42)	7 (44)	8 (40)
Age (median (IQR))		15 (14.5–17)	17 (15–17)	15 (13–16.5)
Primary RMD diagnosis	Juvenile idiopathic arthritis, not systemic	10 (28)	3 (19)	7 (35)
	Juvenile idiopathic arthritis, systemic	5 (14)	3 (19)	2 (10)
	Systemic lupus erythematosus	5 (14)	2 (12)	3 (15)
	Spondyloarthritis/psoriatic arthritis	5 (14)	3 (19)	2 (10)
	Vasculitis/other RMD‡	11 (30)	5 (31)	6 (30)
RMD disease activity	Remission	23 (64)	8 (50)	15 (75)
	Minimal	8 (22)	6 (38)	2 (10)
	Moderate	2 (6)	1 (7)	1 (5)
	Severe	1 (2)		1 (5)
	Not applicable/missing	2 (6)	1 (7)	1 (5)
RMD medication	None	9 (25)	5 (31)	4 (20)
	Antimalarials (including hydroxycholoroquine, chloroquine and mepacrine/quinacrine)	8 (22)	3 (19)	5 (25)
	Rituximab	1 (2)		1 (5)
	Cyclosporine	1 (2)	1 (6)	
	Glucocorticoids—systemic	5 (14)	3 (19)	2 (10)
	IL-1 inhibitors (including anakinra, canakinumab, rilonacept)	1 (2)		1 (5)
	Methotrexate	13 (36)	5 (31)	8 (40)
	Held before vaccination	*1 (2)*		*1 (5)*
	Mycophenolate mofetil/mycophenolic acid	4 (11)	2 (12)	2 (10)
	Held before vaccination	*1 (2)*		*1 (5)*
	TNF inhibitors (including infliximab, etanercept, adalimumab, golimumab, certolizumab and biosimilars)	7 (19)	2 (12)	5 (25)
	Held before vaccination	*1 (2)*		*1 (5)*
COVID-19 vaccine type	Pfizer-BioNTech	33 (92)	16 (100)	17 (85)
	Moderna	2 (6)		2 (10)
	AstraZeneca/Oxford	1 (2)		1 (5)
COVID-19 vaccine doses	1	11 (31)		11 (55)
	2	24 (67)	15 (94)	9 (45)
	3	1 (2)	1 (6)	
RMD flare	Yes	1 (2)	1 (6)	
	No	35 (97)	15 (94)	20 (100)
Adverse event (AE)	Yes	20 (56)	8 (50)	12 (60)
	No	16 (44)	8 (40)	8 (40)
Early AE types	Pain at the site of injection	8 (22)	3 (19)	5 (25)
	Generalised muscle pain	6 (17)	3 (19)	3 (15)
	Generalised joint pain	1 (2)		1 (5)
	Headache	4 (11)	1 (6)	3 (15)
	Fever	9 (25)	5 (31)	4 (20)
	Chills	1 (2)	1 (6)	
	Fatigue	2 (6)	1 (6)	1 (5)
	Vomiting	1 (2)		1 (5)
AE of special interest	Malaise	1 (2)		1 (5)
	Syncope	1 (2)	1 (6)	

Continued

Table 1 Continued

		All (N=36)	Fully vaccinated* (N=16)	Partially vaccinated† (N=20)
AE seriousness	Non-serious	1 (2)	1 (6)	
	Serious—important medical event	1 (2)		1 (5)
AE outcome	Ongoing/continuing	1 (2)		1 (5)
	Recovered/resolved without sequelae	1 (2)	1 (6)	

All data are N (%) of the column unless stated otherwise.
*Fully vaccinated: ≥14 days after dose 2 at time of reporting.
†Partially vaccinated: ≥14 days after dose 1 to <14 days after dose 2 at time of reporting.
‡Other RMD includes Sjogren's syndrome, systemic sclerosis, undifferentiated connective tissue disease, non-monogenic autoinflammatory syndrome, chronic recurrent multifocal osteomyelitis and other inflammatory arthritis.
EULAR, European Alliance of Associations for Rheumatology; IL-1 inhibitors, interleukin-1 inhibitors; RMD, rheumatic and musculoskeletal disease; TNF-inhibitors, tumour necrosis factor inhibitors.

She had no previous SARS-CoV-2 infection and, at time of reporting 160 days after her second dose, reported no further AEs.

Over half (56%) of the adolescents reported AEs, primarily common early reactogenic-like AEs experienced within 7 days of vaccination including fever (25%), pain at injection site (22%) and muscle pain (17%). There was one serious (important medical event) AE in a female patient aged 15–18 years old with systemic sclerosis who received one Pfizer vaccine and had no SARS-CoV-2 infection before vaccination. She experienced severe malaise which started 11 days post-vaccination and was ongoing at time of reporting 14 days after vaccination. She was in remission and taking mycophenolate mofetil which was held 3 days pre-vaccination and restarted 8 days after.

No CYP had SARS-CoV-2 post-vaccination between vaccination and time of reporting. Nine were diagnosed with SARS-CoV-2 pre-vaccination, with a median of 257 days (IQR: 94–299) between previous infection and first vaccination. The proportion with AEs post-vaccination was equal independent of prior SARS-CoV-2 infection.

Adults with JIA

Of 74 cases from 11 countries, 77% were fully and 23% partially vaccinated. Most (73%) were female and the median age was 26 (IQR: 23–31) (table 2). Eighty-five percent had ns-JIA and 15% had s-JIA. Three-quarters were in remission (45%) or had minimal (28%) disease activity at time of vaccination. The most common RMD medications were TNFi (54%), MTX (26%), IL-6 inhibitors (8%) and glucocorticoids (8%); median prednisolone-equivalent glucocorticoid dose at time of vaccination was 5 mg/day.

Sixty-eight per cent received Pfizer/BioNTech vaccines, 14% Moderna and 14% AstraZeneca/Oxford. Most (82%) received two doses, 11% had received one dose and 7% had three doses. Median time between first and second doses was 25 days (IQR: 21–31). Median time from first and second dose to reporting was 120 days (IQR: 75–145) and 89 days (IQR: 43–122), respectively.

Sixty-two per cent of the patients reported AEs, primarily early reactogenic-like AEs within 7 days of vaccination including fever (35%), pain at injection site (22%) and fatigue (18%). There were no serious AEs reported among adults with JIA.

Two fully vaccinated female ns-JIA patients aged 20–30 years old experienced flares; both had two Pfizer doses 21 days apart and minimal disease activity. The first had a secondary RMD diagnosis of Ehlers-Danlos Syndrome and received non-steroidal anti-inflammatory drugs (NSAIDs) on demand but no disease modifying anti-rheumatic drug (DMARD) treatment. She experienced mild reactogenicity following vaccination and had a mild polyarthralgia flare 15 days after her second dose, resulting in a medication change. She had no previous SARS-CoV-2 infection and, as of 99 days after the second dose, experienced no further AEs. The second patient was taking MTX and TNFi, which were not changed due to vaccination. She had mild reactogenicity following vaccination, then a moderate uveitis flare 32 days after her second dose, requiring a change in medication. She had no previous SARS-CoV-2 infection, and, as of 122 days after the second dose, had no further AEs.

Four adults with JIA were diagnosed with SARS-CoV-2 pre-vaccination, a median of 140 days (IQR: 125–238) between previous infection and vaccination.

Three female patients aged 20–30 years old were diagnosed with SARS-CoV-2 post-vaccination—all fully recovered from the infection, had minimal disease activity and did not change their medication before or after vaccination. One with ns-JIA had two Pfizer doses 21 days apart and 140 days before her SARS-CoV-2 diagnosis. She had a secondary diagnosis of Ehlers-Danlos Syndrome and was taking abatacept. The second ns-JIA patient was taking MTX and TNFi and had two doses of Pfizer 21 days apart. She received one booster dose with Moderna 226 days after the second Pfizer dose. The SARS-CoV-2 infection was diagnosed 17 days after the booster. The other patient with s-JIA had two doses of CoronaVac/Sinovac 28 days apart; she was diagnosed with SARS-CoV-2 74 days later. She had a secondary RMD diagnosis of undifferentiated connective tissue disease and was taking antimalarials and colchicine.

Table 2 Characteristics of 74 adults with JIA from the EULAR COVAX registry, stratified by vaccination status

		All (N=74)	Fully vaccinated* (N=57)	Partially vaccinated† (N=17)
Sex	Female	54 (73)	43 (75)	11 (65)
	Male	20 (27)	14 (25)	6 (35)
Age (median (IQR))		26(23, 31)	26(23, 31)	27(22, 32)
Primary RMD diagnosis	Juvenile idiopathic arthritis, not systemic	63 (85)	50 (88)	13 (76)
	Juvenile idiopathic arthritis, systemic	11 (15)	7 (12)	4 (24)
RMD disease activity	Remission	33 (45)	23 (40)	10 (59)
	Minimal	21 (28)	17 (30)	4 (23)
	Moderate	12 (16)	12 (21)	
	Severe	1 (1)		1 (6)
	Not applicable/missing	7 (10)	5 (9)	2 (12)
RMD medication	None	3 (4)	3 (5)	
	Abatacept	2 (3)	1 (2)	1 (6)
	Antimalarials (including hydroxycholoroquine, chloroquine and mepacrine/quinacrine)	2 (3)	2 (4)	
	Colchicine		1 (2)	
	Glucocorticoids—systemic	6 (8)	6 (11)	
	IL-1 inhibitors (including anakinra, canakinumab, rilonacept)	2 (3)	1 (2)	1 (6)
	IL-6 inhibitors (including tocilizumab, sarilumab)	6 (8)	5 (9)	1 (6)
	Held after vaccination	*1 (1)*	*1 (2)*	
	JAK inhibitors (including tofacitinib, baricitinib, upadacitinib)	2 (3)	1 (2)	1 (6)
	Leflunomide	1 (1)	1 (2)	
	Methotrexate	19 (26)	16 (28)	3 (18)
	Held after vaccination	*3 (4)*	*3 (5)*	
	Mycophenolate mofetil/mycophenolic acid	1 (1)	1 (2)	
	Held before vaccination	*1 (1)*	*1 (2)*	
	Sulfasalazine	3 (4)	3 (5)	
	TNF inhibitors (including infliximab, etanercept, adalimumab, golimumab, certolizumab and biosimilars)	40 (54)	30 (53)	10 (59)
	Held before vaccination	*1 (1)*	*1 (2)*	
	Held after vaccination	*6 (8)*	*4 (7)*	*2 (12)*
COVID-19 vaccine type	Pfizer-BioNTech	50 (68)	42 (74)	8 (47)
	Moderna	10 (14)	8 (14)	2 (12)
	AstraZeneca/Oxford	10 (14)	5 (9)	5 (29)
	Janssen	1 (1)		1 (6)
	CoronaVac	2 (3)	1 (2)	1 (6)
	UNK	1 (1)	1 (2)	
COVID-19 vaccine doses	1	8 (11)		8 (47)
	2	61 (82)	52 (91)	9 (53)
	3	5 (7)	5 (9)	
RMD flare	Yes	2 (3)	2 (4)	
	No	67 (91)	51 (89)	16 (94)
	Unknown	5 (7)	4 (7)	1 (6)
Adverse event (AE)	Yes	46 (62)	39 (68)	7 (41)
	No	28 (38)	18 (32)	10 (59)

Continued

Table 2 Continued

		All (N=74)	Fully vaccinated* (N=57)	Partially vaccinated† (N=17)
Early AE types	Pain at the site of injection	16 (22)	11 (19)	5 (29)
	Redness	2 (3)	2 (4)	
	Generalised muscle pain	9 (12)	7 (12)	2 (12)
	Generalised joint pain	3 (4)	3 (6)	
	Headache	10 (14)	9 (16)	1 (6)
	Fever	26 (35)	22 (39)	4 (23)
	Chills	5 (7)	5 (9)	
	Fatigue	13 (18)	12 (21)	1 (6)
AE of special interest	Dizziness	1 (1)	1 (2)	
AE seriousness	Non-serious	1 (1)	1 (2)	
AE outcome	Recovered/resolved without sequelae	1 (1)	1 (2)	

All data are N (%) of the column unless stated otherwise. Data were reported from Belgium, France, Greece, Italy, Latvia, Portugal, Romania, Slovakia, Spain, Turkey and the UK.
*Fully vaccinated: ≥14 days after dose 2/single dose of Janssen at time of reporting.
†Partially vaccinated: ≥14 days after dose 1 to <14 days after dose 2 at time of reporting.
EULAR, European Alliance of Associations for Rheumatology; IL-1 inhibitors, interleukin-1 inhibitors; JIA, juvenile idiopathic arthritis; RMD, rheumatic and musculoskeletal disease; TNF-inhibitors, tumour necrosis factor inhibitors.;

DISCUSSION

To the authors' knowledge, this is the largest physician-reported dataset on SARS-CoV-2 vaccine safety in adolescents with RMDs and adults with JIA. Overall, these data present a reassuring picture of rare disease flares and AEs after full or partial SARS-CoV-2 vaccination. While 56% of adolescents with RMDs and 62% of adults with JIA reported early reactogenic-like AEs, this was not unexpected as they are considered normal minor early side effects in the general population.[17] The rare reports of SARS-CoV-2 infection post-vaccination are also encouraging, although most vaccinations collected in the database were reported within a few months of vaccination and we do not collect follow-up data so cannot firmly comment on COVID-19 vaccine efficacy.

For comparison, the US reports 75% of mRNA-based SARS-CoV-2 vaccine recipients experience local adverse reactions, and 69% systemic adverse reactions in the 7 days following vaccination; similar to this study, the most frequently reported reactions were injection site pain, fatigue, headache and myalgia.[18] Clinical trials of the Pfizer, Moderna, AstraZeneca, Sinopharm and CoronaVac vaccines in healthy children and adolescents also show similar results; predominantly mild to moderate reactogenic AEs in the first few days following vaccination and few reports of serious AEs related to the vaccine.[19–25] The WHO has determined the Pfizer and Moderna vaccines safe for use in children and adolescents, and now recommends children with existing health conditions be prioritised for vaccination.

Few cases reported disease flares following vaccination (2% in adolescents with RMDs, 3% in adults with JIA), a similar figure to the 4% of cases reporting disease flares post-vaccination observed in the wider population of adults with RMDs from the EULAR COVAX registry.[26] Existing data on adolescents with RMDs has also showed similarly low levels of vaccine AEs and disease flares across their cohort, as well as post-vaccine SARS-CoV-2 infection, although this was limited to a 3-month follow-up period.[27] Patient-reported survey data from Turkey on Pfizer/CoronaVac vaccine AEs among adolescents and young adults with RMDs also showed low levels of serious AEs and early reactogenic-like AEs, although reported higher levels of disease flare (11%).[28] The Global Rheumatology Alliance also conducted a survey among adults with RMDs to capture their early experiences of SARS-CoV-2 vaccination, again with similar proportions of common AEs and very few serious AEs, while 13% reported a post-vaccine disease flare,[29] perhaps related to the difficulty in distinguishing some reactogenic-like AEs from rheumatic disease flares (eg, arthralgia, myalgia, fatigue), and the tendency for these reactogenic-like AEs to be more often interpreted by patients as rheumatic disease flares.

Importantly, we had no reports of paediatric inflammatory multi-system syndrome or myocarditis AEs. Reported rates of myocarditis are 1.7 per 100 000 individuals vaccinated with two doses, range from 1.4 to 1.7 per 100 000 for the Pfizer/BioNTech vaccine, and 4.2–6.0 following the Moderna vaccine. For individuals under 18 who received the Pfizer/BioNTech vaccine, this rate ranges from 1.0 to 13.7 per 100 000.[22–24 30] Our lack of reports of myocarditis is therefore not unexpected, due to our small sample size and low numbers of individuals receiving the Moderna vaccine.

However, our study has important limitations. The EULAR COVAX registry relies on voluntary case submission. This means there is potential for selection bias in the data, and careful consideration is needed when assessing the generalisability of these results. This potential bias could mean over-reporting of disease flares and serious AEs, although it is encouraging that our observations of disease flare and serious AEs are very low and

not unusual in comparison to other studies. Additionally, data reported to the EULAR COVAX registry is based on reports from rheumatologists or other healthcare providers, not patients themselves, and no information is collected on levels of post-vaccine antibodies. Of note, this sample size is small and not enough to evaluate any associations between adolescent RMD/adult JIA population-specific factors and the safety of SARS-CoV-2 vaccination. Therefore, no causal conclusions can be drawn from this dataset, and the observations noted here should not be taken as an exact reflection of the wider CYP RMD population.

In summary, we observed reassuringly low frequencies of disease flares, serious AEs and SARS-CoV-2 reinfection following SARS-CoV-2 vaccination in adolescents with RMDs and adults with JIA, which should provide reassurance to paediatric vaccine recipients, their families, paediatric rheumatologists, and other health professionals, and promote confidence in the safety of SARS-CoV-2 vaccination in CYP with or without RMDs. Further research is needed to more deeply examine the safety and efficacy of SARS-CoV-2 vaccination in CYP with RMDs or other CYP taking immunomodulatory/immunosuppressive medications, particularly in those under the age of 12.

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REFERENCES

1 Frenck RW, Klein NP, Kitchin N, *et al*. Safety, immunogenicity, and efficacy of the BNT162b2 Covid-19 vaccine in adolescents. *N Engl J Med Overseas Ed* 2021;385:239–50.
2 PReS -- English. Guidelines and recommendations. Available: https://www.pres.eu/clinical-affairs/guidelines.html [Accessed 03 Dec 2021].

3 UK Health Security Agency. COVID-19: the green book, chapter 14A, 2022. Available: https://www.gov.uk/government/publications/investigation-of- [Accessed 15 Jun 2022].
4 Simon D, Tascilar K, Fagni F, *et al*. SARS-CoV-2 vaccination responses in untreated, conventionally treated and anticytokine-treated patients with immune-mediated inflammatory diseases. *Ann Rheum Dis* 2021;80:1312–6.
5 Geisen UM, Berner DK, Tran F, *et al*. Immunogenicity and safety of anti-SARS-CoV-2 mRNA vaccines in patients with chronic inflammatory conditions and immunosuppressive therapy in a monocentric cohort. *Ann Rheum Dis* 2021;80:1306–11.
6 Furer V, Eviatar T, Zisman D, *et al*. Immunogenicity and safety of the BNT162b2 mRNA COVID-19 vaccine in adult patients with autoimmune inflammatory rheumatic diseases and in the general population: a multicentre study. *Ann Rheum Dis* 2021;80:1330–8.
7 Lawson-Tovey S, Hyrich KL, Gossec L, *et al*. SARS-CoV-2 infection after vaccination in patients with inflammatory rheumatic and musculoskeletal diseases. *Ann Rheum Dis* 2022;81:145–50.
8 Dimopoulou D, Vartzelis G, Dasoula F, *et al*. Immunogenicity of the COVID-19 mRNA vaccine in adolescents with juvenile idiopathic arthritis on treatment with TNF inhibitors. *Ann Rheum Dis* 2022;81:592–3.
9 Dimopoulou D, Spyridis N, Vartzelis G, *et al*. Safety and tolerability of the COVID-19 messenger RNA vaccine in adolescents with juvenile idiopathic arthritis treated with tumor necrosis factor inhibitors. *Arthritis Rheumatol* 2022;74:365–6.
10 Hügle B, Krumrey-Langkammerer M, Haas J-P. Infection with SARS-CoV-2 causes flares in patients with juvenile idiopathic arthritis in remission or inactive disease on medication. *Pediatr Rheumatol Online J* 2021;19:163–5.
11 Beesley RP, Costello W, Angevare SP, *et al*. Survey of adult and paediatric rheumatology patients suggests information about COVID-19 vaccination will aid uptake. *Rheumatology* 2021;60:3474–5. doi:10.1093/rheumatology/keab169
12 Harris PA, Taylor R, Thielke R, *et al*. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009;42:377–81.
13 Cdc COVID-19 study shows mRNA vaccines reduce risk of infection by 91 percent for fully vaccinated people | CDC online Newsroom | CDC. Available: https://www.cdc.gov/media/releases/2021/p0607-mrna-reduce-risks.html [Accessed 16 Aug 2021].
14 Comirnaty COVID-19 vaccine. Ema recommends approval for children aged 5 to 11 | European medicines Agency. Available: https://www.ema.europa.eu/en/news/comirnaty-covid-19-vaccine-ema-recommends-approval-children-aged-5-11 [Accessed 13 Jan 2022].
15 GOV.UK. The MHRA concludes positive safety profile for Pfizer/BioNTech vaccine in 12- to 15-year-olds. Available: https://www.gov.uk/government/news/the-mhra-concludes-positive-safety-profile-for-pfizerbiontech-vaccine-in-12-to-15-year-olds [Accessed 03 Dec 2021].
16 Gianfrancesco M, Hyrich KL, Al-Adely S, *et al*. Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 global rheumatology alliance physician-reported registry. *Ann Rheum Dis* 2020;79:859–66.
17 COVID-19 vaccines advice. Available: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/covid-19-vaccines/advice [Accessed 16 Dec 2021].
18 Chapin-Bardales J, Gee J, Myers T. Reactogenicity following receipt of mRNA-based COVID-19 vaccines. *JAMA* 2021;325:2201.
19 Ali K, Berman G, Zhou H, *et al*. Evaluation of mRNA-1273 SARS-CoV-2 vaccine in adolescents. *N Engl J Med* 2021;385:2241–51.
20 Frenck RW, Klein NP, Kitchin N, *et al*. Safety, immunogenicity, and efficacy of the BNT162b2 Covid-19 vaccine in adolescents. *N Engl J Med* 2021;385:239–50.
21 Walter EB, Talaat KR, Sabharwal C, *et al*. Evaluation of the BNT162b2 Covid-19 vaccine in children 5 to 11 years of age. *N Engl J Med* 2022;386:35–46.
22 Revon-Riviere G, Ninove L, Min V, *et al*. The BNT162b2 mRNA COVID-19 vaccine in adolescents and young adults with cancer: a monocentric experience. *Eur J Cancer* 2021;154:30–4.
23 Han B, Song Y, Li C, *et al*. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine (CoronaVac) in healthy children and adolescents: a double-blind, randomised, controlled, phase 1/2 clinical trial. *Lancet Infect Dis* 2021;21:1645–53.
24 Xia S, Zhang Y, Wang Y, *et al*. Safety and immunogenicity of an inactivated COVID-19 vaccine, BBIBP-CorV, in people younger than 18 years: a randomised, double-blind, controlled, phase 1/2 trial. *Lancet Infect Dis* 2022;22:196–208.
25 Li G, Cappuccini F, Marchevsky NG, *et al*. Safety and immunogenicity of the ChAdOx1 nCoV-19 (AZD1222) vaccine in children aged 6-17 years: a preliminary report of COV006, a phase 2 single-blind, randomised, controlled trial. *Lancet* 2022;399:2212–25. doi:10.1016/S0140-6736(22)00770-X
26 Machado PM, Lawson-Tovey S, Strangfeld 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.
27 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* 2022. doi:10.1093/rheumatology/keac103. [Epub ahead of print: 18 Feb 2022].
28 Haslak F, Gunalp A, Cebi MN, *et al*. Early experience of COVID-19 vaccine-related adverse events among adolescents and young adults with rheumatic diseases: a single-center study. *Int J Rheum Dis* 2022;25:353–63.
29 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.
30 Husby A, Hansen JV, Fosbøl E, *et al*. SARS-CoV-2 vaccination and myocarditis or myopericarditis: population based cohort study. *BMJ* 2021;375:e068665.