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Humoral and cellular immunogenicity, effectiveness and safety of COVID-19 mRNA vaccination in patients with pediatric rheumatic diseases: A prospective cohort study

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ABSTRACT

Objectives: To evaluate immunogenicity, effectiveness and safety of COVID-19 vaccination in patients with pediatric autoimmune inflammatory rheumatic disease (pedAIIRD).
Methods: A prospective cohort study was performed at the pediatric rheumatology department of the Wilhelmina Children's Hospital in Utrecht, the Netherlands. Vaccination dates, COVID-19 cases and vaccine-related adverse events (AEs) were registered for all pedAIIRD patients during regular clinic visits from March 2021 – August 2022. SARS-CoV-2 IgG antibody levels and T-cell responses were measured from serum samples after vaccination, and clinical and drug therapy data were collected from electronic medical records. Rate of COVID-19 disease was compared between vaccinated and unvaccinated patients in a time-varying Cox regression analysis.
Results: A total of 157 patients were included in this study and 88 % had juvenile idiopathic arthritis (JIA). One hundred thirty-seven patients were fully vaccinated, of which 47 % used biological agents at the time of vaccination, and 20 patients were unvaccinated. Geometric mean concentrations (GMCs) of post-vaccine antibody levels against SARS-CoV-2 were above the threshold for positivity in patients who did and did not use biological agents at the time of vaccination, although biological users demonstrated significantly lower antibody levels (adjusted GMC ratio: 0.38, 95 % CI: 0.21 – 0.70). T-cell responses were adequate in all but two patients (9 %). The adjusted rate of reported COVID-19 was significantly lower for fully vaccinated patients compared to non-vaccinated patients (HR: 0.53, 95 % CI: 0.29 – 0.97). JIA disease activity scores were not significantly different after vaccination, and no serious AEs were reported.
Conclusions: COVID-19 mRNA vaccines were immunogenic (both cellular and humoral), effective and safe in a large cohort of pedAIIRD patients despite their use of immunosuppressive medication.

1. Introduction

Coronavirus disease 2019 (COVID-19) mRNA vaccines demonstrated (short-term) safety, immunogenicity and efficacy against severe COVID-19 in healthy adults and children and were authorized by the Food and Drug Administration (FDA) and the European Medicine Agency (EMA) [1–3]. In addition, these vaccines lead to a protective effect against a potentially fatal disease called pediatric inflammatory multisystem

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syndrome temporally associated with SARS-CoV-2 (PIMS-TS), also called multisystem inflammatory syndrome in children (MIS-C) [4,5].

In general, children with pediatric autoimmune inflammatory rheumatic disease (pedAIIRD) are at higher risk for infections due to their underlying disease and immunosuppressive treatments [6]. At the same time, vaccines pose a great challenge in this patient group due to decreased immunogenicity secondary to their underlying disease and immunosuppressive treatment, and the concern about disease flares following vaccination. Therefore, effective and safe immunization is crucial in the management of these groups of patients [7].

Studies of COVID-19 in pediatric patients with rheumatic diseases treated with disease-modifying antirheumatic drugs (DMARDs) do not report a higher risk of contracting COVID-19 or a more severe disease outcome compared to the general population [8–10]. Nevertheless, severe illness can occur in these patients as has been shown in adults, especially among those with underlying comorbidities such as obesity, chronic lung disease, cardiovascular disease or diabetes [11], and data show that the course of COVID-19 may be more severe in patients with systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS), progressive systemic sclerosis (pSS), vasculitis and congenital or acquired interferonopathies [12]. As with other viral infections, disease flares can occur after infection with acute respiratory syndrome coronavirus 2 (SARS-CoV-2), for example in patients with juvenile idiopathic arthritis (JIA) in remission or inactive disease on medication [13].

Several health authorities have developed guidelines for COVID-19 vaccines in autoimmune rheumatic diseases [14,15], and several studies report that immune-modulatory therapies, such as methotrexate (MTX), tumor necrosis factor (TNF)-blockers and rituximab, may impair the humoral response to vaccination and therefore interfere with vaccine efficacy [16,17]. Other studies found that pedAIIRD patients receiving immunomodulatory treatment were able to mount an effective humoral response while continuing their therapy [18–20], without serious adverse events (AEs) [21–23]. Studies including T-cell responses and efficacy of COVID-19 vaccinations in immunosuppressed children are scarce [24,25].

In this study, we aimed to evaluate immunogenicity, effectiveness and safety of COVID-19 mRNA vaccination in a large cohort of patients with pedAIIRD, including children using biological (b)DMARDs. We investigated the humoral and cellular immune response of COVID-19 mRNA vaccines, and compared vaccine effectiveness with unvaccinated patients from the same setting. In addition, we studied short and long-term disease activity and AEs after vaccination.

2. Methods

2.1. Study design and participants

A prospective observational cohort study was performed at the Pediatric Rheumatology department of the Wilhelmina Children's Hospital in Utrecht, the Netherlands. Between 2021 and 2022, all patients were invited to receive two COVID-19 mRNA vaccinations (Comirnaty/BioNTech-Pfizer or Spikevax/Moderna) – generally one month apart – via the Dutch national vaccination program. Data collection started in March 2021 and ended in August 2022. COVID-19 vaccination dates, vaccine-related AEs and symptomatic cases of COVID-19 were registered during regular clinic visits for all patients aged 12–21 years diagnosed with JIA, autoinflammatory syndromes, idiopathic uveitis and other rheumatic diseases. Serum samples for measuring IgG antibody levels and T-cell responses against SARS-CoV-2 were collected in combination with regular care blood sampling. Both fully vaccinated patients (i.e. who received two or more COVID-19 vaccinations) and unvaccinated patients were included. Patients who were partly vaccinated (i.e. who received < 2 vaccinations) or did not report a date of vaccination were excluded. Patients diagnosed with an immune deficiency disease or malignancy were not considered for inclusion.

This study was approved by the UMCU Medical Ethical Committee (METC number 22–643). T-cell responses were measured in patients who gave informed consent in the Pharmachild study (METC number 11-499c).

2.2. Outcome measures

2.2.1. Humoral immunogenicity

IgG antibody levels against SARS-CoV-2 were measured in serum samples collected from fully vaccinated patients at one or even two clinic visits (median 137 and 282 days after first vaccination date, and median 113 and 252 days after second vaccination date, respectively). For these determinations, the Abbott SARS-Cov-2 IgG anti-spike antibody chemiluminescent microparticle immunoassay (CMIA) was performed on the Alinity i platform according to the manufacturers instruction (SARS-CoV-2 IgG II Quant assay, Abbott Laboratories, Abbott Park, Illinois, U.S.A). Results are reported in arbitrary units (AU)/ml, and levels $\geq$ 50.0 AU/ml were considered positive. Humoral response was not measured in unvaccinated patients.

2.2.2. Cellular immunity

In addition, cellular immunity was measured in available samples that were obtained at maximum three months and at minimum one week after first vaccination date using the interferon (IFN)-γ enzyme-linked immune absorbent spot (ELISpot) assay. Results are reported as spot forming units (SFU) per well ($2x10^5$ peripheral blood mononuclear cells (PBMC)/well) and spots were analyzed with CTL software. Results of $>$ 2 SFU/$2x10^5$ PBMC, after background subtraction, were considered positive. More detailed procedures are reported elsewhere [26]. Cellular response was not measured in unvaccinated patients.

2.2.3. Effectiveness

Whereas vaccine efficacy refers to the performance of a vaccine in a controlled setting, such as a randomized controlled trial, vaccine effectiveness refers to the performance of a vaccine in an observational or real-world setting [27]. In the current study, COVID-19 cases were determined in both vaccinated and unvaccinated patients. A case of COVID-19 was defined as every acute illness confirmed with positive PCR or rapid antigen test for SARS-CoV-2 from nasal swabs.

2.2.4. Safety

Safety of the vaccine was evaluated in all patients by short-term physician-reported AEs (at maximum three weeks after vaccination). Furthermore, disease activity scores in JIA patients reported at one or even two clinic visits after vaccination (median 67 and 166 days after first vaccination date, and median 32 and 132 days after second vaccination date, respectively) were compared to disease activity scores at one or two visits prior to vaccination (median 62 and 168 days after first vaccination date, and median 102 and 215 days after second vaccination date, respectively). Disease activity components included the active joint count (AJC), physician global assessment of disease activity (PGA), patient-reported visual analogue scale (VAS) for well-being, and the composite clinical Juvenile Arthritis Disease Activity Score (cJADAS) [28]. Serious AEs were defined as any adverse reaction that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a birth defect [29].

Additional clinical characteristics and drug therapy data were collected from electronic medical records.

2.3. Statistical analysis

Characteristics of included patients were summarized separate for vaccinated and unvaccinated patients and compared using the χ^2 test, Fisher's exact test and Mann-Whitney *U* test.

Post-vaccine SARS-CoV-2 IgG antibody levels and T-cell responses were presented separately for patients with and without biological

therapy at vaccination, the former as geometric mean concentrations (GMC) with 95 % confidence interval. Antibody levels and T-cell responses were log-transformed for all subsequent analyses. Pairwise comparisons of post-vaccine antibody levels and T-cell responses between more specific drug therapy groups (biological monotherapy, MTX and biological combination therapy, MTX monotherapy and no immunosuppressants/NSAID) were performed using the *t*-test with Bonferroni correction. Proportions of positive antibody levels (>50 AU/mL) and T-cell responses (>2 SFU/2x10^5 PBMC) in the different drug therapy groups were compared using the Fisher's exact test.

In order to examine the independent effect of drug therapy on SARS-CoV-2 antibody levels, we performed linear mixed effects analyses with a random intercept per patient. Mixed effects analyses are commonly used to appropriately adjust for within-subject dependency of observations, as is common in repeated measures designs [30]. Missing data were handled by multiple imputation using chained equations [31]. All analyses were run for 20 imputed datasets and estimates were pooled using Rubin's rules. We performed both univariable and multivariable analyses adjusted for disease, age at disease diagnosis, gender, vaccine brand (constant variables), prior COVID-19 disease, disease duration and drug therapy (time-varying variables). For these analyses, regression coefficients were exponentiated to obtain (adjusted) GMC ratios (GMR) and 95 % CIs for the different drug therapy groups. No adjusted analyses were performed on the T-cell response data due to a limited sample size.

For examining the effect of full vaccination on the rate of COVID-19 disease, we performed a multivariable time-varying Cox regression analysis adjusted for prior COVID-19 disease. In order to eliminate immortal time bias [32], the start date of follow-up for this analysis was 1 October 2021, since by this time most children had had the opportunity to become fully vaccinated. Patients who were vaccinated after this date were accounted for in this time-varying analysis.

Proportions of physician-reported AEs for the total cohort were calculated. For JIA patients, VAS, PGA, active joint count and cJADAS scores at every study visit were presented as mean with 95 % confidence interval. An overall difference in disease activity scores between study visits was tested using the Skillings-Mack test for unbalanced dependent samples [33]. Subsequent pairwise comparisons were performed using the Wilcoxon rank sum test with Bonferroni correction. In order to examine the independent effect of COVID-19 vaccination on disease activity, we performed linear mixed effects analyses with a random intercept per patient. These analyses were adjusted for JIA subtype, age at JIA diagnosis, gender, vaccine brand (constant variables), prior COVID-19 disease, disease duration and drug therapy (time-varying variables).

A P-value of < 0.05 was considered statistically significant in all analyses. All analyses were performed with R version 4.0.3 using the mice, survival and lme4 packages.

3. Results

3.1. Cohort characteristics

Of the 160 patients identified, three were excluded from further analysis (two because of missing vaccination dates, one was only partly vaccinated). Of the remaining 157 patients, the majority had JIA (88 %) and were female (66 %), 137 patients (87 %) were fully vaccinated against COVID-19 and 20 patients (13 %) were unvaccinated (Table 1). Median age at vaccination was 16.5 years and 47 % of the vaccinated patients used biological agents at the time of vaccination. The most common vaccine brand was Comirnaty (Pfizer-BioNTech) (94 %). One patient had received the Jcovden (Janssen) vaccine and was therefore considered fully vaccinated after one vaccination. Serological and disease activity data post-vaccination were available for 104 (76 %) and 89 (65 %) patients, respectively (Supplementary Table 1). Eighty-three patients (53 %) reported COVID-19 disease (of whom 17 patients prior to first vaccination) and baseline characteristics were similar to patients who did not report COVID-19 disease (Supplementary Table 2).

Table 1
Baseline characteristics of included patients (n = 157).

Variable	Vaccinated (n = 137)	Unvaccinated (n = 20)	*P*
Female (n, %)	90 (65.7 %)	13 (65.0 %)	1.00
Disease (n, %)			0.56
JIA	120 (87.6 %)	18 (90.0 %)	
ERA	13 (9.5 %)	2 (10.0 %)	
Oligoarthritis	55 (40.1 %)	4 (20.0 %)	
RF- polyarthritis	19 (13.9 %)	5 (25.0 %)	
RF + polyarthritis	10 (7.3 %)	1 (5.0 %)	
Psoriatic arthritis	10 (7.3 %)	2 (10.0 %)	
Systemic arthritis	8 (5.8 %)	1 (5.0 %)	
Unknown	22 (16.1 %)	3 (15.0 %)	
Uveitis	5 (3.6 %)	0 (0.0 %)	
SLE/MCTD	5 (3.6 %)	1 (5.0 %)	
Other[1]	7 (5.1 %)	1 (5.0 %)	
COVID-19 vaccine characteristics			
Age at first vaccination in years (median, IQR)	16.5 (14.2 – 17.9)	NA	–
Disease duration at first vaccination in years (median, IQR)	5.3 (1.8 – 10.2)	NA	–
COVID-19 disease before vaccination (n, %)	17 (12.4 %)	NA	–
Vaccine brand (n, %)[2]			
Comirnaty (BioNTech/Pfizer)	90 (93.8 %)	NA	–
Spikevax (Moderna)	4 (4.2 %)	NA	–
Jcovden (Janssen)	1 (1.0 %)	NA	–
Vaxzevria (AstraZeneca)	1 (1.0 %)	NA	–
Drug therapy at first vaccination (n, %)			
NSAID/no immunosuppressant	50 (36.5 %)	NA	–
MTX monotherapy	18 (13.1 %)	NA	–
MTX + bDMARD	32 (23.4 %)	NA	–
bDMARD monotherapy	32 (23.4 %)	NA	–

bDMARD: biological disease-modifying antirheumatic drug, COVID-19: coronavirus disease 2019, ERA: enthesitis-related arthritis, IQR: interquartile range, JIA: juvenile idiopathic arthritis, MCTD: mixed connective tissue disease, MTX: methotrexate, n: number, NSAID: non-steroidal anti-inflammatory drug, RF: rheumatoid factor, SLE: systemic lupus erythematosus
*statistically significant
[1]Includes CREST syndrome, pyoderma gangrenosum, Behçet's disease, chronic recurrent multifocal osteomyelitis, primary angiitis of the central nervous system, localized scleroderma, polyarteritis nodosa and juvenile dermatomyositis
[2]there were 61 missing observations

3.2. Vaccine immunogenicity

3.2.1. Humoral immunogenicity

All but four patients (all JIA, one treated with NSAIDs, two with MTX and bDMARD and one with bDMARD monotherapy) had positive SARS-CoV-2 IgG antibody levels. Geometric mean concentrations were above the positive threshold of 50 AU/mL for patients with and without bDMARD therapy (Fig. 1) and all separate drug therapy groups (Supplementary Fig. 1). Absolute antibody levels and proportions of positive antibody levels post-vaccination did not differ significantly between patient groups who used NSAIDs, MTX and bDMARDs at the time of vaccination (Supplementary Table 3). On multivariable analysis, antibody levels post-vaccination were significantly lower in patients who used biological agents at the time of vaccination compared to those who did not use these agents (GMR: 0.38, 95 % CI: 0.21 – 0.70; Table 2). Similarly, antibody levels were significantly lower on multivariable analysis for patients who used bDMARD monotherapy compared to NSAIDs (GMR: 0.25, 95 % CI: 0.10 – 0.61; Supplementary Table 4).

3.2.2. Cellular immunity

A subset of 22 samples (all JIA, two treated with NSAIDs, one with MTX monotherapy, 14 with MTX and bDMARD and five with bDMARD monotherapy) could be analyzed for cellular immunity with a median

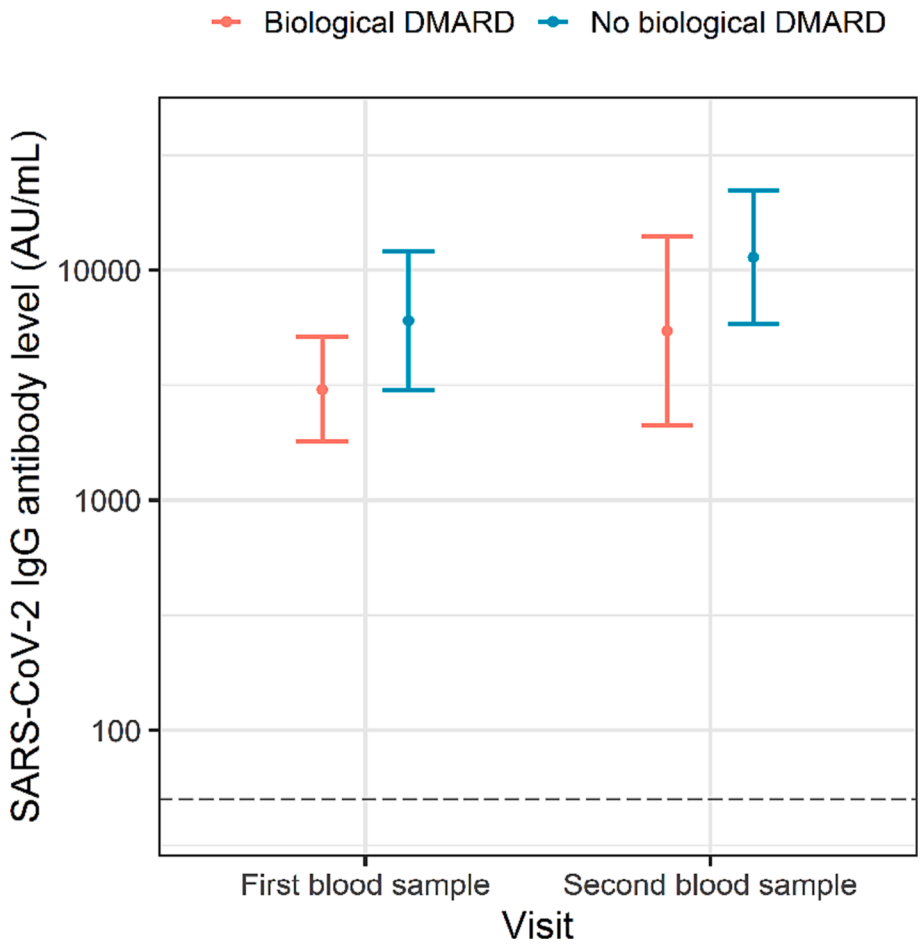

Fig. 1. Post-vaccine geometric mean concentrations of SARS-CoV-2 antibodies in patients with or without biological therapy at vaccination. Samples were drawn median 137 (first sample) and 282 days (second sample) after first vaccination date. Vertical bars indicate 95 % confidence interval, horizontal dashed line indicates positive threshold (50 AU/mL). DMARD: disease-modifying antirheumatic drug.

Table 2
Linear mixed effects analyses of log-transformed SARS-CoV-2 IgG antibodies post-vaccination in patients with and without biological therapy at vaccination.

Analysis	GMR	95 % CI
Crude		
No biological therapy	1	Reference
Biological therapy	0.54	0.25 – 1.16
Adjusted[1]		
No biological therapy	1	Reference
Biological therapy	0.38	0.21 – 0.70*

[1]adjusted for disease, age at disease diagnosis, gender, vaccine brand (constant variables), prior COVID-19 disease and disease duration (time-varying variables)
*statistically significant effect
CI: confidence interval, GMR: geometric mean ratio
Missing values were handled by multiple imputation.

time after first vaccination date of 58 days (IQR: 20 – 82). Of these, 15 patients had had two vaccinations and 7 had had one vaccination at the time of sampling. Two samples in total (2/22; 9 %) – from JIA patients who both used MTX and bDMARD combination therapy at vaccination (2/14; 14 %) – did not demonstrate a positive T-cell response (Fig. 2; Supplementary Fig. 2). These patients received combination therapy of MTX with tocilizumab and MTX with adalimumab. One of these two patients had had one vaccination at the time of sampling. Absolute T-cell responses and proportions of positive T-cell responses post-vaccination did not differ significantly between patient groups who used NSAIDs, MTX and bDMARDs at the time of vaccination (Supplementary Table 3). Two samples (9 %) were drawn from patients who reported COVID-19

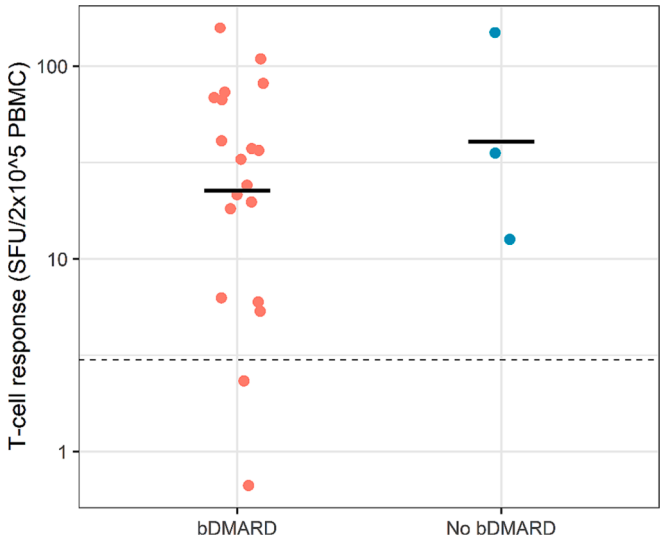

Fig. 2. Post-vaccine T-cell responses against SARS-CoV-2 in 22 patients with or without biological (bDMARD) therapy at vaccination (median 58 days after first vaccination date). Horizontal black lines indicate mean value per patient group. Horizontal dashed line indicated positive threshold (>2 SFU/2x10^5 PBMC). bDMARD: biological disease-modifying antirheumatic drug, PBMC: peripheral blood mononuclear cells, SFU: spot forming units.

infection prior to vaccination and both demonstrated a positive T-cell response.

A strong and positive correlation was observed between absolute SARS-CoV-2 IgG antibody levels and T-cell responses from the same blood sample ($r = 0.94$, $P = <0.01$), although this could only be determined from seven samples with both humoral and cellular data.

3.3. Vaccine effectiveness

After adjusting for prior COVID-19 disease, the rate of COVID-19 was significantly lower for fully vaccinated patients compared to patients who were not vaccinated (HR: 0.53, 95 % CI: 0.29 – 0.97; Fig. 3). After a survival time of 100 and 200 days, 4 and 12 unvaccinated patients developed COVID-19 (survival probability: 84 % and 45 %, respectively), compared to 7 and 48 vaccinated patients (survival probability: 95 % and 64 %, respectively). No significant difference was observed between patients vaccinated with and without bDMARD therapy (HR: 0.96, 95 % CI: 0.55 – 1.67; Supplementary Fig. 3). The total observation time for this analysis was 117 years (median 0.8 years per patient). No severe COVID-19 cases occurred, including in the patients using bDMARDs.

3.4. Vaccine safety

No statistically significant difference in JIA disease activity scores between study visits was observed (Fig. 4). Multivariable analyses also revealed no significant differences in JIA disease activity scores before and after vaccination (Table 3). In total, 20 patients who got vaccinated (15 %) reported 22 AEs. The most common AEs were arm pain (n = 12), myalgia (n = 4) and fatigue (n = 2). Other AEs were fever, flu-like symptoms, dyspnea and headache. No serious AEs were reported.

4. Discussion

Immunogenicity, effectiveness and safety data regarding COVID-19 vaccines among adolescents with AIIRDs are limited. In this long-term follow-up study, we found COVID-19 mRNA vaccines to be immunogenic, effective and not associated with an increase of disease activity. No serious AEs were reported in this study group.

Immunomodulatory treatments interfere with the immune system at multiple levels and may reduce COVID-19 vaccine responses to a variable extent [16,34–36]. Therefore, several guidelines recommend modification of the treatment plan at the time of COVID-19 vaccination [14–16]. In our clinical practice, children were instructed to continue their treatment around the time of vaccination. Despite continuing immunosuppressive/modulating treatment, all but four patients had positive SARS-CoV-2 IgG antibody levels in our study, even after a median follow-up of 282 days until the second blood sample. We did however observe a difference in antibody levels between pedAIIRD patients treated with bDMARDS and patients not treated with bDMARDs.

In line with our results, a recent prospective cohort study of 40 adolescents with rheumatic diseases – 60 % treated with bDMARDs – reported an adequate humoral immune response to the BNT162b2 (Comirnaty/Pfizer-BioNTech) mRNA vaccine after three weeks, which was similar to a healthy control group [25]. Another observational study reported that pediatric rheumatic disease patients receiving immunomodulatory treatment were able to mount an effective humoral response

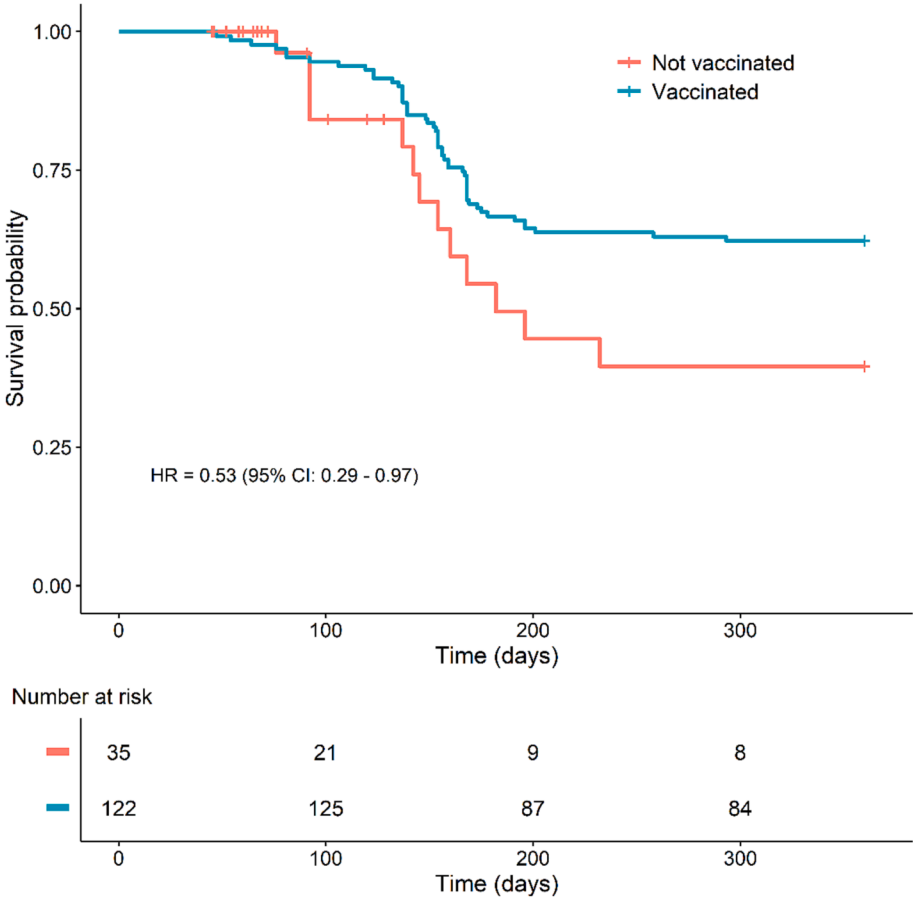

Fig. 3. Survival curves of time to symptomatic COVID-19 disease from 1 October 2021 – 26 August 2022. CI: confidence interval, HR: hazard ratio. Hazard ratio reflects the ratio of COVID-19 rates for vaccinated compared to non-vaccinated patients, adjusted for prior COVID-19 disease. Vertical bars indicate censored patients, i.e. unvaccinated patients who got vaccinated during follow-up.

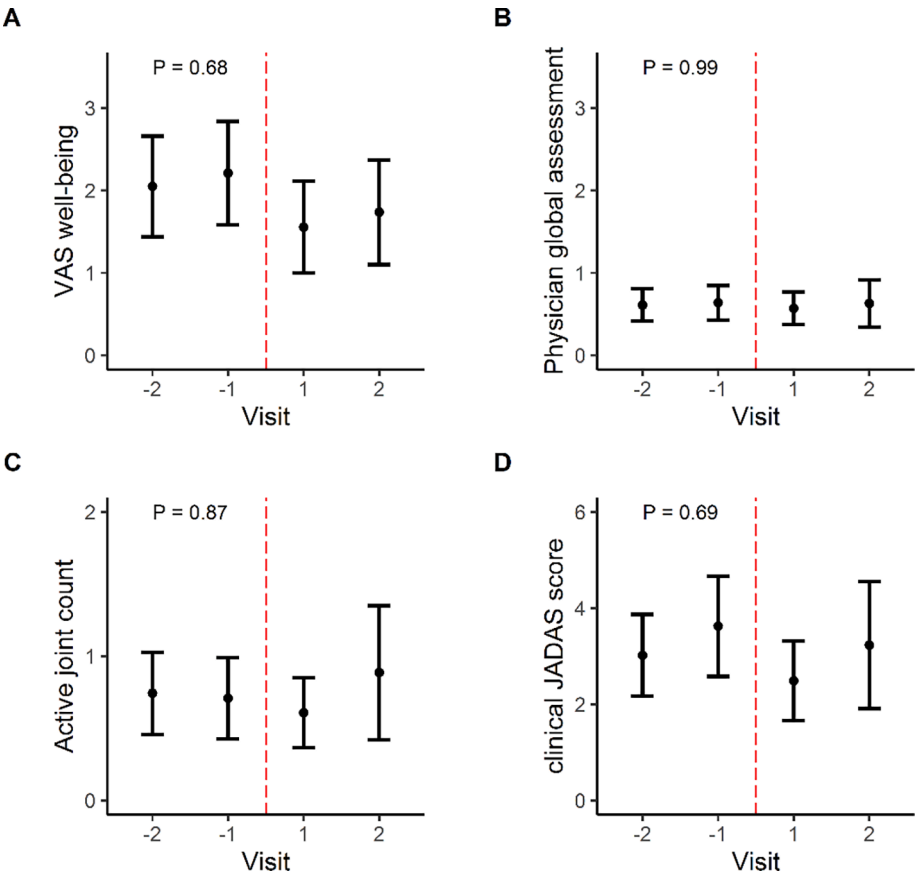

Fig. 4. Disease activity scores in included JIA patients (n = 120) before and after COVID-19 vaccination. A: mean VAS well-being at different study visits. B: mean physician global assessment of disease activity at different study visits. C: mean active joint count at different study visits. D: mean clinical JADAS score at different study visits. Vertical red line indicates moment of vaccination, vertical black bars indicate 95 % confidence intervals. *P*-values indicate overall difference between visits.

Table 3
Linear mixed effects analyses of disease activity in JIA patients before and after COVID-19 vaccination.

Analysis	Mean difference after vs. before COVID-19 vaccination	95 % CI
VAS well-being		
Crude	−0.42	−1.06 – 0.22
Adjusted[1]	−0.47	−1.20 – 0.26
Physician global assessment		
Crude	−0.10	−0.27 – 0.08
Adjusted[1]	−0.16	−0.40 – 0.08
Active joint count		
Crude	−0.15	−0.35 – 0.06
Adjusted[1]	−0.21	−0.50 – 0.09
clinical JADAS score		
Crude	−0.67	−1.43 – 0.09
Adjusted[1]	−0.80	−1.74 – 0.14

[1]adjusted for JIA subtype, age at JIA diagnosis, gender, vaccine brand (constant variables), prior COVID-19 disease, disease duration and drug therapy (time-varying variables)
CI: confidence interval, JADAS: juvenile arthritis disease activity score, JIA: juvenile idiopathic arthritis, VAS: visual analogue scaleMissing values were handled by multiple imputation.

following vaccination, although patients treated with both csDMARDs and bDMARDs (n = 11) had significantly lower titers than patients treated with csDMARDs (n = 14) only [18]. A multicenter prospective study of 91 juvenile-onset autoimmune inflammatory rheumatic disease (AIIRD) patients – 37 % treated with bDMARDs – reported a seropositivity rate of 97 % three months after vaccination, but significantly lower anti-spike antibody titers compared with healthy controls [19]. Similar results were observed in a cohort of adult chronic inflammatory disease patients [34] and a large cohort of adult autoimmune disease patients [37]. A study in adult AIIRD patients also reported that the BNT1262 mRNA vaccine was immunogenic in the majority of patients, even though treatment with immunosuppressive agents, including glucocorticoids, rituximab, mycophenolate mofetil and abatacept, was associated with a significantly reduced vaccine-induced immune response [38]. Furthermore, studies in adult patients with immune-mediated inflammatory diseases have also reported a reduced rate of adequate immunogenicity following COVID-19 vaccination in patients on MTX therapy [35,39]. Studies have also reported TNF-inhibitor therapy in chronic inflammatory disease patients to be associated with lower antibody levels against SARS-CoV-2 after vaccination [17,40]. Still, adequate immunogenicity of COVID-19 mRNA vaccines in adolescent JIA patients on TNF inhibitor therapy has been reported [20]. Thus, seropositivity rates in the current study are similar to those reported in previous studies in children, but higher compared to studies in adults with AIIRD. The good responses can be attributed to the relationship between a younger age and a better immunological response to COVID-19 vaccination [41]. In the current study, we could not analyze the effect of the anti-B-cell therapy drug rituximab. This drug is related to a decrease in humoral response in adults [36,42], but has

demonstrated an adequate cellular response in adolescents [19].

Importantly, we also studied cellular immunity, as this might be even more important in conferring protection against (severe) COVID-19 [6,43]. CD8 + T-cell responses were previously identified to be a correlate of protection in non-human primate studies of SARS-CoV-2 infection [44]. Other studies have highlighted that humoral immune measurements do not always correlate with T-cell responses, and observed heterogeneity in the magnitude of adaptive immune responses to SARS-CoV-2 persisting into the immune memory phase [43,45]. In our cohort, we did observe a correlation between absolute SARS-CoV-2 IgG antibody levels and T-cell responses from the same blood sample, but this could be determined only from seven samples. We observed no adequate T-cell response in two patients (9 %) who received combination therapy of MTX with tocilizumab and MTX with adalimumab. The remaining patients – including those who received bDMARD monotherapy and MTX monotherapy – demonstrated adequate T-cell responses. In a cohort of 51 adults with immune-mediated inflammatory diseases, patients on MTX (n = 18) did not demonstrate an increase in CD8 + T-cell activation after vaccination with the BNT162b2 mRNA COVID-19 vaccine. On the other hand, patients on anti-cytokine or non-MTX oral medications demonstrated similar levels of immunogenicity as healthy controls [35]. In a group of 40 adolescents with rheumatic diseases who were fully vaccinated with the BNT162b2 mRNA vaccine, of which 60 % where using bDMARDs, cellular response after three weeks did not differ from 24 healthy controls. The authors of this study concluded that children with rheumatic diseases under immunosuppressive therapy do not represent a high-risk group for severe forms of COVID-19, but are more likely to develop asymptomatic infections than healthy peers [25].

We observed a significantly lower adjusted rate of COVID-19 disease for fully vaccinated pedAIIRD patients compared to non-vaccinated patients. Also, none of the COVID-19 cases had a severe disease course requiring admission or further evaluation. Importantly, the effectiveness results in the current study apply to symptomatic COVID-19 disease, since vaccinated patients might have had unnoticed asymptomatic SARS-CoV-2 infections. A large observational cohort study by Ziv et al. also observed that the BNT162b2 mRNA vaccine was effective against COVID-19 in adolescents with and without juvenile-onset inflammatory or immune rheumatic disease [46]. The effectiveness was not affected by immunomodulatory therapy.

JIA disease activity scores before and after vaccination did not significantly differ in the current study. Furthermore, we observed no serious AEs, especially no myocarditis. Similarly, a multicenter observational study reported a good safety profile of the BNT162b2 vaccine in 91 adolescents with juvenile-onset autoimmune inflammatory rheumatic diseases, with 97 % of the patients reporting no or mild AEs and no worsening of disease activity [19]. In that study, three patients suffered from transient acute symptoms: two following the first vaccination (renal failure and pulmonary hemorrhage) and one following the second dose (mild lupus flare vs. viral infection). Another study describing 36 adolescents with inflammatory rheumatic and musculoskeletal diseases reported only one mild polyarthralgia flare and one serious AE (malaise) [21]. These numbers are in line with other studies reporting safety data in children with rheumatic diseases [18,20–22,25,34,47,48].

This study has strengths and limitations. The latter include its single center design, the emergence of multiple SARS-CoV-2 variants during the study period, incomplete serological and cellular samples (as these were collected combined with regular care blood sampling), possible underreporting of COVID-19 cases, and the lack of data regarding serology before vaccination. Also, the results of our study might not be generalizable to younger age groups and no control group of healthy (vaccinated) children was included. Furthermore, the authors are aware that other factors - not adjusted for in the current analyses - might have influenced disease activity scores, such as other infections. The main strengths of this research are its large population of pedAIIRD patients with a notable amount of bDMARD users, the relatively long-term prospective clinical and serological follow-up including cellular immune response data in addition to humoral responses, and the effectiveness data (documentation of symptomatic COVID-19) including a non-vaccinated control group of patients.

While most published studies only investigated humoral vaccine responses in pedAIIRD patients, T-cell responses – as included in the current study – may be more important in conferring viral immunity against SARS-CoV-2 [16,43]. Nevertheless, there is still limited evidence about correlation between vaccine-induced antibody titers and cell-mediated responses. Future studies should therefore focus on this relationship and possibly establish discriminatory cut-off values of protection for T-cell driven responses. Further research should also investigate immunogenicity after prolonged follow-up and the effect of booster doses.

In conclusion, COVID-19 mRNA vaccines were immunogenic (both cellular and humoral), effective and safe in a large cohort of pedAIIRD patients despite their use of immunosuppressive medication. Based on these results, we recommend that immunosuppressive treatments are not discontinued or adjusted at the time of COVID-19 vaccination.

CRediT authorship contribution statement

Mohamad Hamad Saied: Conceptualization, Investigation, Methodology, Resources, Supervision, Writing – original draft, Writing – review & editing. **Joeri W. van Straalen:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Sytze de Roock:** Conceptualization, Investigation, Methodology, Resources, Supervision, Writing – original draft, Writing – review & editing. **Frans M. Verduyn Lunel:** Formal analysis, Investigation, Resources, Software, Validation, Writing – original draft, Writing – review & editing. **Jelle de Wit:** Formal analysis, Investigation, Methodology, Resources, Software, Validation, Writing – original draft, Writing – review & editing. **Lia G.H. de Rond:** . **Erika Van Nieuwenhove:** Writing – original draft, Writing – review & editing, Conceptualization, Resources. **Bas J. Vastert:** Conceptualization, Writing – original draft, Writing – review & editing, Resources. **Joris M. van Montfrans:** Conceptualization, Writing – original draft, Writing – review & editing, Resources. **Annet van Royen-Kerkhof:** Conceptualization, Writing – original draft, Writing – review & editing, Resources. **Gerrie C.J. de Joode-Smink:** Conceptualization, Resources, Writing – original draft, Writing – review & editing. **Joost F. Swart:** Conceptualization, Methodology, Supervision, Writing – original draft, Writing – review & editing, Resources. **Nico M. Wulffraat:** Conceptualization, Funding acquisition, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing, Resources. **Marc H.A. Jansen:** .

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Ethics

This study was approved by the UMCU Medical Ethical Committee (METC number 22-643). T-cell responses were measured in patients who

gave informed consent in the Pharmachild study (METC number 11-499c).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2024.01.047.

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