

Safety of Measles–Mumps–Rubella booster vaccination in patients with juvenile idiopathic arthritis: A long-term follow-up study



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ABSTRACT

Objectives: To study short and long-term disease activity and vaccine-related adverse events in a cohort of JIA patients who received the live attenuated measles-mumps-rubella (MMR) booster vaccine while being treated with immunosuppressive and immunomodulatory therapies.

Methods: A retrospective study was performed in the UMC Utrecht, clinical and therapeutic data were collected from electronic medical records for two visits before and two visits after the MMR booster vaccine of JIA patients. Drug therapy was collected and adverse events related to the vaccine were requested from the patients during clinical visits or by short phone interviews. Associations between MMR booster vaccination and the active joint count, physician global assessment of disease activity, patient-reported visual analogue scale (VAS) for well-being and clinical Juvenile Arthritis Disease Activity Score (cJADAS) were analyzed using multivariable linear mixed effects analyses.

Results: A total of 186 JIA patients were included in the study. At the time of vaccination, 51% of the patients used csDMARD and 28% used bDMARD therapy. Overall, adjusted disease activity scores after MMR booster vaccination were not significantly different compared to pre-vaccination. Mild adverse events related to the MMR booster were reported for 7% of the patients. No serious adverse events were reported.

Conclusion: MMR booster vaccination was safe and did not worsen disease activity during long-term follow-up in a large cohort of JIA patients being treated with both csDMARDs and biological DMARDs.

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1. Introduction

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease in childhood. This disease encompasses several disease subtypes, each of which has distinct methods of presentation, clinical signs, symptoms, and, in some cases, genetic background [1–2]. Substantial progress in JIA treatment has been made over the last three decades. Clinical outcomes have dramatically improved since the introduction of biologic disease-modifying anti-rheumatic drugs (bDMARDs), with disease control and even possibility of remission in the majority of patients. Systemic immune modulatory drug therapy used in JIA can be divided

into two main categories: conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), particularly methotrexate (MTX), and bDMARDs [1,3].

Children with JIA are at higher risk for infections due to their underlying disease but also because they are often on immunosuppressive treatment [4–6]. Safe and effective immunizations are crucial in the management of these groups of patients. Vaccinations, especially live attenuated vaccines, pose a great challenge in immunocompromised patients, due to the hypothetical risk of infection with the live attenuated pathogen, lower immunogenicity due to treatment, and the fear that it may lead to a JIA flare [7–8]. A Dutch randomized controlled trial showed that administration of the live attenuated measles-mumps-rubella (MMR) booster vaccine – as is routinely administered via the National Immunization Program at age nine years in the Netherlands – was safe in JIA patients on csDMARDs [9]. In the University Medical Center Utrecht, patients are advised to take the MMR booster vaccine also while taking bDMARDs. The new PRES and EULAR recom-

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recommendations also summarized that MMR booster vaccination can be administered to patients on MTX and can be considered in patients treated with low-dose glucocorticosteroids or bDMARDs [10]. However, apart from a retrospective multicenter study of 234 children with rheumatic diseases [20], firm scientific data for the efficacy and safety of MMR booster vaccination in JIA patients on bDMARDs are still limited.

In this large retrospective cohort study, we aim to investigate the safety of the live attenuated MMR booster vaccine in JIA while being treated with immunomodulatory drug therapy including bDMARDs.

2. Methods

2.1. Study design and participants

A single-center retrospective long-term follow-up study was performed at the Pediatric Rheumatology department of the Wilhelmina Children's Hospital in Utrecht, the Netherlands. All patients meeting the International League of Associations for Rheumatology (ILAR) criteria for JIA who were born between 2002 and 2012 and received a MMR booster vaccine at their local municipal health service as part of the National Immunization Program were enrolled. Clinical status and drug therapy data were collected two visits prior and two visits after the MMR booster vaccine from electronic medical records. Patients without data for at least one visit before and one visit after vaccination were excluded. The clinical status was assessed using the active joint count (AJC), physician global assessment of disease activity (PGA), patient-reported visual analogue scale (VAS) for well-being and clinical Juvenile Arthritis Disease Activity Score (cJADAS). Exact dates of MMR booster vaccination and frequency of patient-reported adverse events (AEs) related to vaccination were determined from electronic medical records, clinical visits or by short phone interviews.

2.2. Ethics statement

Patients were included from the ongoing observational Pharmachild register. Pharmachild obtained approval from the institutional review board of University Medical Center Utrecht (11-499c) and is carried out in accordance with the Declaration of Helsinki. All patients provided written informed consent/assent.

2.3. Outcome measures

The primary outcome measure was JIA disease activity as measured by AJC, PGA, patient-reported VAS for well-being and the calculated cJADAS27 [11]. The secondary outcome measure was the occurrence of (serious) AEs related to the MMR booster vaccine.

2.4. Statistical analysis

Categorical variables for the total cohort were presented as frequencies with valid percentages and numerical variables were presented as median with interquartile range. For every visit before and after MMR booster vaccination, VAS, PGA, active joint count and cJADAS scores were presented as mean with 95 % confidence interval. In case the exact date of vaccination could not be determined from electronic medical records, clinical visits or phone interviews, we adhered to the ninth birthday as all children in the Netherlands are vaccinated with the MMR booster at this age. The overall difference in disease activity scores between study visits was tested using the Skillings-Mack test for unbalanced dependent samples [12]. Subsequent pairwise comparisons were

performed using the Wilcoxon rank sum test with Bonferroni correction. A P -value of < 0.05 was considered statistically significant in all analyses. To examine the effect of MMR booster vaccination on disease activity, we performed linear mixed effects analyses with a random intercept per patient and a random slope for the MMR booster effect. This analysis is commonly used to appropriately adjust for within-subject dependency of observations, as is common in repeated measures designs [13]. Missing data were handled by multiple imputations using chained equations [14]. 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 JIA disease duration, drug therapy (time-varying variables), age at JIA diagnosis and JIA subtype (constant variables). As a sensitivity analysis to evaluate the robustness of our results, we performed the mixed effects analyses in a sub-cohort of patients who used bDMARDs at the time of MMR booster vaccination, and a sub-cohort of patients with known exact MMR booster vaccination dates. All analyses were performed with R version 4.0.3 using the mice and lme4 packages.

3. Results

3.1. Patient characteristics

A total of 186 JIA patients were included in the study. Exact vaccine dates could be retrieved for 39 patients. Baseline characteristics of patients including demographic, clinical characteristics and drug therapy are shown in Table 1. One hundred twenty patients (65 %) were female and 98 patients (53 %) had the oligoarticular subtype of JIA. The median disease duration at the moment of MMR booster vaccination was 3.8 years. At the time of vaccination, 32 % of the patients used MTX monotherapy, 11 % used bDMARD monotherapy and 17 % used cDMARD and bDMARD combination therapy. Thirty-seven percent did not receive systemic therapy at the time of MMR booster vaccination.

3.2. Disease activity

Overall, disease activity scores, including AJC, PGA, patient-reported VAS for well-being and the calculated cJADAS27, did not differ significantly across study visits (Fig. 1). Results were similar for patients using a bDMARD at the time of MMR booster vaccination and patients who did not (Fig. 2). Furthermore, no significant differences in disease activity were observed upon pairwise comparison of study visits (Supplementary Table 1). Likewise, the adjusted association of MMR booster vaccination on disease activity scores was non-significant (Table 2). Similar results were observed when restricting the analyses to patients who used bDMARDs at the time of vaccination ($n = 52$; Supplementary Table 2), and patients with a reported exact vaccination date (Supplementary Table 3).

3.3. Safety and reported adverse events

No serious AEs (SAEs) or infections with the attenuated viruses were reported and 12/186 (7 %) patients reported mild adverse events related to the MMR booster (five of whom received bDMARD therapy). These included pain, swelling or redness at the injection site ($n = 6$, 3 %; three of whom received bDMARD therapy), fever and/or flu-like symptoms ($n = 5$, 3 %; two of whom received bDMARD therapy), and joint pain ($n = 1$, 1 %).

Table 1
Characteristics of the total cohort.

Variable	Total cohort (n = 186)
Female, n (%)	120 (64.5 %)
Age in years at JIA diagnosis, median (IQR)	5.2 (2.8–7.2)
JIA subtype, n (%)	
Oligoarticular JIA	98 (52.7 %)
Polyarticular JIA	50 (26.9 %)
Systemic JIA	24 (12.9 %)
Psoriatic arthritis	11 (5.9 %)
Enthesitis-related arthritis	2 (1.1 %)
Undifferentiated arthritis	1 (0.5 %)
Number of months before MMR booster at different study visits, median (IQR)	
Visit -2	7.3 (13.3–4.3) n = 174
Visit -1	2.6 (5.1–1.1) n = 186
Number of months after MMR booster at different study visits, median (IQR)	
Visit 1	2.7 (1.0–5.3) n = 186
Visit 2	7.3 (4.8–11.2) n = 171
Disease duration at first visit in years, median (IQR)	3.0 (1.1–5.1)
Disease duration at time of MMR booster, median (IQR)	3.8 (1.8–6.3)
Disease duration at last visit in years, median (IQR)	4.7 (2.7–7.0)
Drugs used at time of MMR booster, n (%)	
Methotrexate monotherapy	59 (31.7 %)
Other csDMARD monotherapy	5 (2.7 %)
Adalimumab monotherapy	2 (1.1 %)
Etanercept monotherapy	12 (6.5 %)
Other bDMARD monotherapy	7 (3.8 %)
Combination therapy ¹	31 (16.7 %)
Low dose systemic corticosteroids (≤ 5 mg)	3 (1.6 %)
Drug history at last study visit, n (%)	
Intraarticular corticosteroids	12 (6.5 %)
Low dose systemic corticosteroids (≤ 5 mg)	9 (4.8 %)
Methotrexate	103 (55.4 %)
Other csDMARDs	10 (5.4 %)
Adalimumab	29 (15.6 %)
Etanercept	20 (10.1 %)
Other bDMARDs	13 (7.0 %)

bDMARDs: biologic disease-modifying antirheumatic drugs, csDMARDs: conventional synthetic disease-modifying antirheumatic drugs IQR: interquartile range, JIA: juvenile idiopathic arthritis, MMR: measles-mumps-rubella, n: number.

¹ csDMARD and bDMARD therapy.

4. Discussion

Concerns about the safety of vaccinating immunocompromised children with live attenuated vaccines are persistent, widespread and were of renewed interest with the introduction of bDMARDs [6,15–18]. In this current long-term follow-up study, the safety of the MMR booster vaccination was evaluated in JIA patients largely on immunosuppressive treatment (including 28 % on bDMARD therapy) by measuring disease activity before and after the booster vaccine and vaccine-related AEs. MMR booster vaccination was not associated with a worsening in any clinical measure of disease activity including AJC, PGA, patient-reported VAS for well-being and the calculated cJADAS27. No SAEs were reported and mild adverse events related to the MMR booster were only reported by 7 % of the patients including local reactions at the injection site, fever, flu-like symptoms and arthralgia. Importantly, no infections with the attenuated viruses were reported. It has to be mentioned that most of the patients included in this study had an active joint count of zero at the last visit prior to vaccination. Disease activity might therefore be a factor to consider when discussing the right timing for receiving the MMR booster vaccine.

Our results are in line with a randomized trial including 137 JIA patients with 60 using MTX and a small number of patients using

bDMARD (15 on a TNF inhibitor) [9]. Furthermore, a retrospective observational multicenter cohort study was performed on 314 patients with JIA including patients using methotrexate, but not including bDMARDs, which showed that the MMR booster does not aggravate disease activity [8]. A small prospective nested case-control study performed in 15 patients with JIA, treated with either low-dose MTX therapy alone or in combination with etanercept, found no increase in disease activity or medication use within six months after MMR booster as well [19]. In a multicenter, retrospective data-collection study from thirteen pediatric rheumatology centers in ten countries, including 234 patients (90.2 % JIA), 124 patients had received the MMR booster or measles-mumps-rubella-varicella (MMR/V) booster while on MTX, MTX and bDMARDs (n = 62), or a combination of two DMARDs (n = 9) or bDMARDs (n = 39). None of the patients developed a disease flare, including those with a high disease activity score. None had moderate or serious AEs and no vaccine-induced infections were observed [20]. Based on these studies, the 2021 PRES and EULAR recommendations for vaccination of pediatric patients with autoimmune inflammatory rheumatic diseases support the principle that the MMR booster can be administered safely in patients on MTX and can be considered in patients treated with low-dose glucocorticosteroids, TNF inhibitors, anti-IL1 and anti-IL6 therapy.

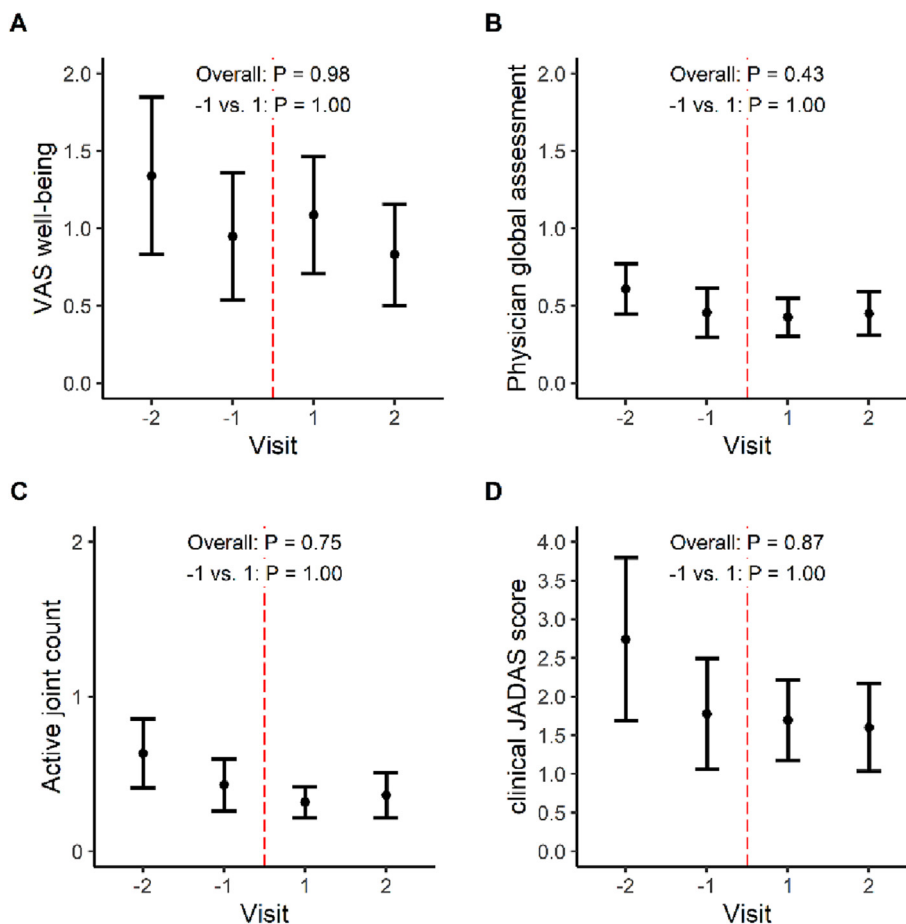


Fig. 1. Disease activity scores before and after MMR booster vaccination. A: mean patient-reported visual analogue scale (VAS) well-being at different study visits. B: mean physician global assessment (PGA) of disease activity at different study visits. C: mean active joint count (AJC) at different study visits. D: mean clinical JADAS27 score at different study visits. The vertical red line indicates the moment of MMR booster vaccination, vertical black bars indicate 95% confidence intervals. *P*-values indicate the overall difference between visits, and difference between visit –1 and 1. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Thus, postponing the MMR booster vaccination in JIA is often not required [10,21].

The MMR vaccine is well-tolerated and rarely associated with SAEs. AEs logically occur more frequently following the first dose than following the second [22–23]. Similar percentages to our results were also described in healthy young adults who received a third dose of the MMR vaccine and reported no SAEs [24]. Joint symptoms, as described in one patient from our study population, are associated with the rubella component of the MMR vaccine and occur more frequently among adults than children [25]. In the previously mentioned randomized trial among JIA patients, five children who received a MMR booster and eleven children in the control group were reported to have SAEs. Most of the AEs were elective hospitalization and surgeries, unlikely related to the vaccine. No disease due to infections with the attenuated viruses was observed [9]. In other published studies, no vaccine-induced infections or SAEs were documented indicating that MMR vaccines can be safely administered in JIA [6,19].

We are aware of the limitations of this study, including its retrospective single-center design with varying time between visits and the fact that some mild AEs could have been missed due to recall bias. Furthermore, we could not retrieve the exact date of

MMR booster vaccination for all patients. However, our results proved to be robust when performing a sensitivity analysis in the subset of patients who reported an exact vaccination date. Also, these study data do not apply to primary MMR vaccinations which are usually admitted at the age of one year, although this is generally also before JIA onset. Lastly, this study evaluated MMR booster vaccines without a combined varicella vaccine according to the Dutch National Immunization Program. The combined vaccine was found to be immunogenic with a high safety profile in children with rheumatic diseases using immunosuppressive treatment [7,20]. Furthermore, it was recently recommended to strongly consider varicella vaccination in varicella infection and vaccination-naïve patients on MTX, low-dose glucocorticosteroids and bDMARDs [10].

In our study, we included only patients with JIA. Recently, there is sufficient data to conclude that MMR booster vaccination is safe and does not affect disease activity in other pediatric rheumatic diseases as well, except for children receiving high-dose steroids or cyclophosphamide and probably rituximab, although these data do not come from studies on MMR [6,10,18,26–27]. Further large multicenter studies are needed to shed light on this group of patients and other diseases of (primary) immunodeficiency.

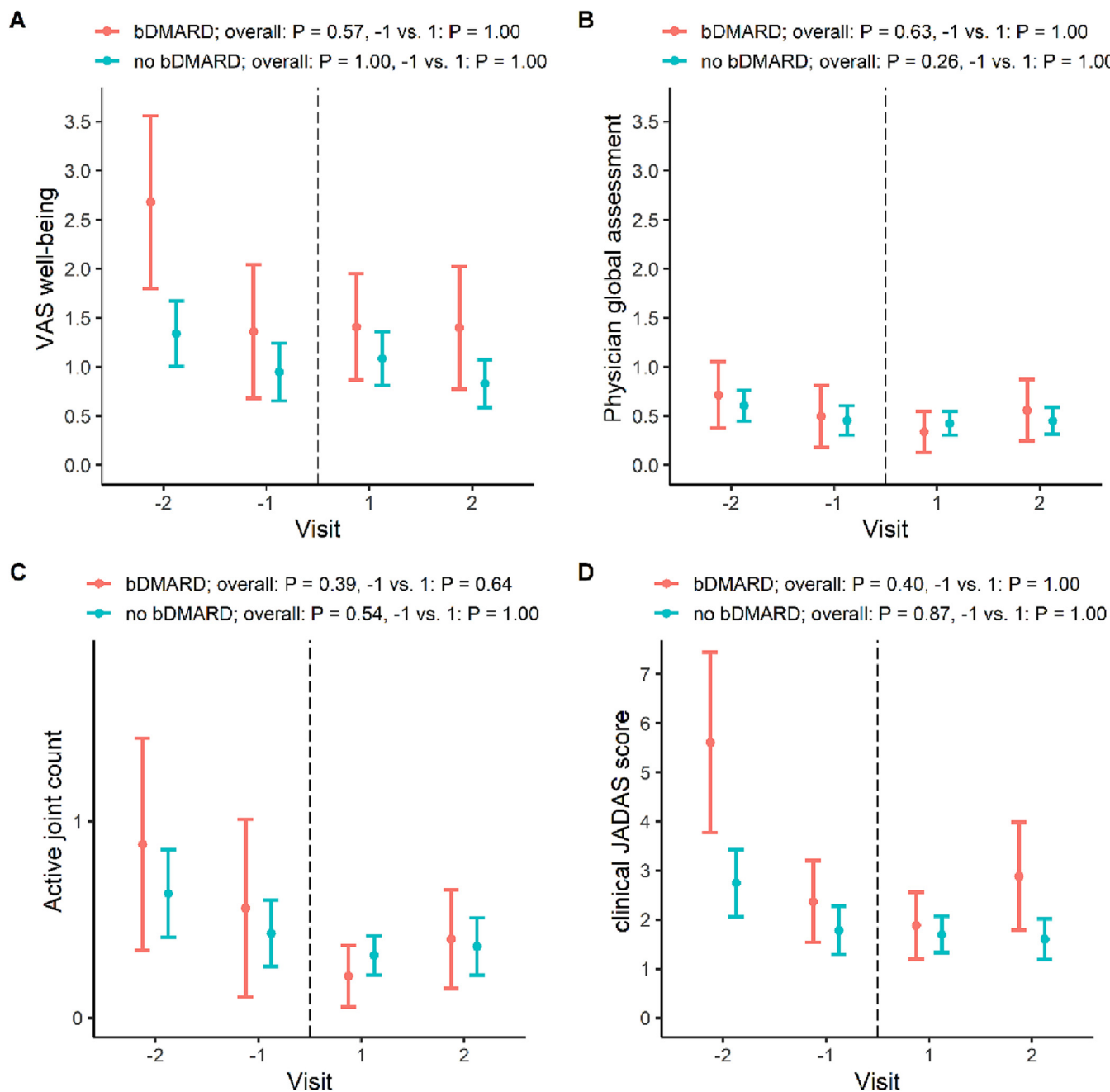


Fig. 2. Disease activity scores before and after MMR booster vaccination for bDMARD use at vaccination. A: mean patient-reported visual analogue scale (VAS) well-being at different study visits. B: mean physician global assessment (PGA) of disease activity at different study visits. C: mean active joint count (AJC) at different study visits. D: mean clinical JADAS27 score at different study visits. Vertical dotted line indicates the moment of MMR booster vaccination, vertical bars indicate 95% confidence intervals. *P*-values indicate overall difference between visits within the drug therapy group, and difference between visit -1 and 1.

In conclusion, our results show that administration of the MMR booster vaccine did not result in worsening of disease activity and was safe in a large cohort of JIA patients under immunomodulatory treatment, including biological therapy, during long-term follow-up.

Data availability statement

All relevant data are reported in the article. Additional details can be provided by the corresponding author upon reasonable request.

Funding

No funding was received for this research.

Ethics statement

Patients were included from the ongoing observational Pharmachild register. Pharmachild obtained approval from the institutional review board of University Medical Center Utrecht (11-499c) and is carried out in accordance with the Declaration of Helsinki. All patients provided written informed consent/assent.

Table 2
Linear mixed effects analyses of disease activity before and after MMR booster vaccine.

Analysis	Mean difference after vs before MMR booster	95 % CI	P-value
VAS well-being			
Crude	−0.08	−0.47–0.31	0.70
Adjusted ¹	−0.01	−0.50–0.48	0.96
Physician global assessment			
Crude	−0.11	−0.26–0.04	0.14
Adjusted ¹	−0.09	−0.27–0.08	0.29
Active joint count			
Crude	−0.19	−0.36–−0.02*	0.03*
Adjusted ¹	−0.12	−0.33–0.07	0.21
Clinical JADAS score			
Crude	−0.38	−0.90–0.14	0.15
Adjusted ¹	−0.24	−0.88–0.40	0.47

*Statistically significant.
CI: confidence interval, JADAS: juvenile arthritis disease activity score, JIA: juvenile idiopathic arthritis, MMR: measles-mumps-rubella, VAS: visual analogue scale.

Missing values were handled by multiple imputation.

¹ adjusted for JIA disease duration, drug therapy (time-varying variables), age at JIA diagnosis and JIA subtype (constant variables).

Data availability

Data will be made available on request.

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.

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.vaccine.2023.03.074>.

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