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Research Article

Vaccine Safety and Immunogenicity in Pediatric Patients with Immune-mediated Inflammatory Diseases

Mireia Lopez Corbeto[1*], Irene Torrecilla Martínez[2], Estefanía Moreno Ruzafa[1], Laia Martínez Mitjana[1], José Ángel Rodrigo Pendás[2], Xavier Martínez Gómez[2]

[1]Department of Rheumatology, Pediatric Rheumatology Unit, Vall D'Hebron University Hospital, Barcelona, Spain; [2]Department of Preventive Medicine and Epidemiology, Hospital Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain

ABSTRACT

Immune-mediated Pediatric Rheumatic Diseases (IMPRD) is potentially serious diseases that can lead to a significant decrease in the child's quality of life. The use of immunosuppressive therapies necessary in IMPRD may contribute to an increased risk of infections. The objective is to describe the prevalence of susceptibility to vaccine-preventable diseases and the immunogenicity and safety of vaccines in patients with IMPRD. A prospective cohort study included 36 pediatric patients with an IMPRD who visited a large tertiary hospital. Pre-vaccination serological tests were performed, and a vaccination plan was developed for each patient. Blood samples were collected for study of the post-vaccination seroprotection when needed. Follow-up was performed to analyze the safety of the vaccines: local and systemic reactions were evaluated during 28 days after vaccination, while detection of flares was reviewed until 3 months after. The vaccination schedule was not completed in 6 patients (16.7%). A total of 146 vaccines were administered with a median of 2 vaccines per child and visit. Overall seroprotection rates at the inclusion were higher than 80%, being the highest proportion in varicella (94.5% (95CI%: 81.9-98.5)) and the lowest in hepatitis B (47.2% (95% CI: 32.0-63.0)). Seroprotection rate after vaccination was higher than 90% for all vaccines. There were 15 local and 1 systemic adverse events after vaccination. No flares were observed. Vaccination is safe and overall immunogenic in this population. We recommend assessing vaccination requirements in IMPRD as soon as their diagnosis is made.

Keywords: Vaccines; Pediatric rheumatology; Immunogenicity

INTRODUCTION

Immune-mediated Pediatric Rheumatic Diseases (IMPRD) is potentially serious diseases that can lead to a significant decrease in the child's quality of life. For this reason, it is very important to recognize children affected by these diseases such as Juvenile Idiopathic Arthritis (JIA), Juvenile Systemic Lupus Erythematosus (JSLE), Juvenile Dermatomyositis (JDM), Juvenile Scleroderma (JSC) or Auto-inflammatory Syndromes (AS) [1]. These conditions share a multifactorial etiological mechanism, in which genetic predisposition in interaction with environmental factors plays a role in its initiation and maintenance [2].In this sense, the therapeutic approach is similar, through the use of immunomodulatory and immunosuppressive therapies that may constitute important factors that increase risk of infections in children with IMPRD [3].

Furthermore, due to the immunosuppressive effect of these treatments, the immunogenicity of vaccinations might be reduced, and their safety profile may be different from healthy children. In this context, a correct evaluation of the vaccination schedule and control of post-vaccination serologies are of vital importance [4]. The European League Against Rheumatism (EULAR) task force for vaccination in pediatric patients with IMPRD recommends adhering to national vaccination guidelines. However, the low vaccination coverage observed in these patients is striking, despite consensus documents that 46 support the recommendation to vaccinate [5]. In our opinion, this could be related to several factors, such as the limited evidence on immunogenicity and vaccine safety in this population, the difficulty of finding the optimal time to vaccinate, or the reluctance to vaccinate due to historical doubts about the possible association between vaccines and flares.

Correspondence to: Mireia Lopez Corbeto, Department of Rheumatology, Pediatric Rheumatology Unit, Vall D'Hebron University Hospital, Barcelona, Spain, E-mail: mireia.lopez@vallhebron.cat

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Recently, communities and health-care workers have faced the negative impact of COVID-19 pandemic in childhood vaccinations because those which are routinely delivered in schools have been interrupted by school closures [6]. The regional office for Europe of the World Health Organization (WHO) has advised that routine immunization services should continue to aim for high population immunity [7,8]. In this context, patients with IMPRD should be prioritized and promptly update their vaccine schedule. Here we describe the prevalence of susceptibility to vaccine-preventable diseases and the immunogenicity and safety of vaccinations in a cohort of patients with IMPRD.

MATERIALS AND METHODS

Patient inclusion

We performed a prospective, longitudinal study of children from 2 to 17 years-old newly diagnosed with an IMPRD from March 2020 to January 2021 at our hospital by the Pediatric Rheumatology Unit and with immunosuppressive treatment or indication of it in the following 6 months after diagnosis. Diagnosis of the different IMPRD was performed according to the recommendations of the International League of Associations for Rheumatology (ILAR). Patients were included once and consecutively after the legal guardians signed informed consent. Exclusion criteria for this study studied acute infection at the time of vaccination, history of previous adverse reaction or anaphylaxis to chicken egg protein or any other vaccine, demyelinating disease or parents refusing to sign the informed consent. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Vall d'Hebron Barcelona Hospital Campus Ethics Committee (Reg. MLC-74 PRE-2020-01). Signed informed consent was obtained from all patients before study enrolment.

Clinical data and vaccine evaluation protocol

The vaccination records and the serological results were reviewed, and a vaccination plan was developed according to the characteristics of each patient. Pending vaccinations recommended for the patient's age and clinical circumstances were administered as soon as possible.

In addition to the inactivated vaccines recommended in the immunization schedule of Catalonia, each patient was recommended a sequential vaccination schedule against pneumococcus (doses of conjugate vaccine appropriate for their age (if not previously administered) plus a dose of polysaccharide vaccine 2 months after the previous ones if at least 2 years of age) and the seasonal flu vaccine. Regarding the hepatitis B vaccine, booster doses or full revaccination schedules were administered depending on vaccination records and serological results. In the case of live attenuated vaccines, an attempt was made to complete the vaccination regimen or to administer booster doses according to the results of the serology and before the start of pharmacological immunosuppression if possible.

No more than four vaccines were administered per day. All vaccines were administered following the official recommendations of the health authorities of Catalonia.

The volume, composition and manufacturing company of all the vaccines administered in the study is reported in the supplementary data Table 1.

Immunological assessment

Blood samples were collected from all the subjects at diagnosis booster dose, as appropriate. Antibody levels against each vaccine antigen were assessed using standardized, validated enzyme-linked immunosorbent assays with predefined cut offs.

Vaccine response was defined by the detection of antibody titers above the following cut-off points: >20 International Unit (IU)/L for Hepatitis A Virus (HAV), >10 IU/L for Hepatitis B Virus (HBV), >165 mIU/L for Varicella Zoster Virus (VZV), >16.5 Absorbance Units (AU)/mL for measles, >10 IU/L for rubella and >11 AU/mL for mumps.

Safety assessment

Solicited local injection-site reactions (pain, redness, swelling, and itchiness) and general symptoms (fever, myalgia, asthenia, and general malaise) were registered during the 14-day post vaccination period by a structured telephone questionnaire. The duration of the reactions was categorized according to whether they lasted up to 7 days or more. Unsolicited adverse events were recorded up to a 28-day period following vaccination. Serious Adverse Events (SAEs) were recorded from enrollment until the end of the follow-up period. A daily phone call was made by the treating physician for the first 7 days. Another telephone contact was made on day 14 by the lead investigator. A review of solicited and unsolicited adverse events was made on their next visit to rheumatology on day 28 after inclusion in the cohort. Subsequently, the medical history of the participants was reviewed every month until a 3-month follow-up and a last phone call was made to detect flares or worsening of the IMPRD. The absence of symptoms was recorded as grade 0, while minor reactions and those which interfered with normal day-to-day activities were recorded as grades 1 and 2, respectively. Grade 3 pain was defined as crying upon movement of the limb and/or pain at rest; grade 3 fever was defined as a temperature of 39°C (axillar, oral or tympanic) or 39.5°C (rectal), and grade 3 of other general symptoms was defined as preventing normal daily activities.

Variables

Demographic data (including age, gender, and body mass index), time at diagnosis, disease subtype, and disease activity defined by the rheumatologist as high or low based on joint pain or swelling with a JADAS index (Juvenile Arthritis Disease Activity Score) greater than 1 were collected 8. If the patient needed to start an immunosuppressive treatment due to the severity of the disease, the Disease Modifying Anti Rheumatic Drugs (DMARDs) were collected. Glucocorticoid treatment was considered immunosuppressive if the patient received the equivalent of 2 mg of prednisone/kg/day or more for at least 14 days. Immunosuppression was defined as receiving conventional DMARDs, biological DMARDs, and immunosuppressive doses of corticosteroids or combinations of the above treatments.

The main primary outcome for the analysis was seroprotection, defined as the number of patients with positive serology at diagnosis among the total of patients (per antigen), and was expressed as percentage with 95% confidence interval (95% CI). Secondary outcomes were seroconversion after vaccination (defined as the number of susceptible patients at diagnosis with positive serology after the appropriate vaccine among the total of susceptible patients vaccinated against each antigen) and safety (as the number of patients with any degree of adverse event among all vaccinated patients).

Statistical analysis

A descriptive statistical analysis was performed. Continuous

variables were described with the mean and the Standard Deviation (SD) or the median and Interquartile Range (IQR) if the variable was not normally distributed. Categorical variables were expressed with counts and percentages and their 95% CI. The association between seroprotection and independent variables was analyzed using the Wilcoxon rank-sum test for continuous variables and the odds ratio (OR) with its 95% CI for categorical variables. All the analysis was carried out with Stata/SE 14.2 for Windows (Stata Corp LLC. College Station, Texas, USA). Statistical significance was established as a p-value of <0.05. All reported p-values were based on two-tailed tests.

RESULTS

A total of 36 subjects were included in the study: 69.4% were girls (n=25), and the median age at diagnosis was 8.1 (± 5.3 SD) years. JIA was the most frequent diagnosis with 24 patients (66.7%) followed by JSLE (4 patients; 11.1%). High disease activity was present at diagnosis in 15 patients (41.7%) and prompt treatment at diagnosis before vaccination was indicated to 18 (50%) patients with conventional DMARDs and in 12 (33.3%) with biological DMARDs. Immunosuppressive glucocorticoid doses were also indicated to 7 (19.4%) patients. 25 patients were immunosuppressed (69.4%): 6 of them (24%) with 2 treatments and 3 (12%) with 3 or more treatments. No therapeutic changes were developed during the study. Baseline clinical parameters and demographic characteristics are shown in (Table 1).

Table 1: Baseline clinical parameters and demographic characteristics (n=36).

Variables	n (%)
Sex (Female)	25 (69.4%)
Age in years	8.14 (5.3)
BMI	19.22 (5)
Disease activity (high)	15 (42.7%)
Disease	
Juvenile Idiopathic arthritis (JIA)	24 (66.7%)
Systemic JIA	1 (2.8%)
RF positive polyarticular JIA	1 (2.8%)
RF negative polyarticular JIA	1 (2.8%)
Oligoarticular JIA	15 (41.7%)
Psoariatic JIA	4 (11.1%)
Enthesitis-related arthritis JIA	2 (5.6%)
Juvenil Systemic Lupus	4 (11.1%)
Juvenile Dermatomyositis	1 (2.8%)
Vasculitis	2 (5.6%)
Autoinflammatory syndrome	3 (8.3%)
Non-infectious uveitis	2 (5.6%)
Treatment	
DMARDs	
Methotrexate	14 (38.9%)
Hidroxycloroquine	1 (2.8%)
Azathioprine	1 (2.8%)
Mycophenolate	2 (5.6%)
bDMARDs	
Etanercept	5 (13.9%)
Adalimumab	3 (8.3%)
Anakinra	2 (5.6%)
Ruxolitinib	1 (2.8%)
Other	1 (2.8%)
Glucocorticoid (immunosuppressive dose)	7 (19.4%)
Immunosupression (present)	25 (69.4%)

Note: BMI: Body Mass Index; JIA: Juvenile Idiopathic Arthritis; DMARDs: conventional Disease-Modifying Antirheumatic Drugs; bDMARDs: biological Disease-Modifying Antirheumatic Drugs.

Vaccine evaluation protocol and immunological assessment

The immunization card was revised in all patients and 61 visits to the Preventive Medicine department were needed to complete the vaccination protocol. A second and a third visit were required in 18 (50%) and 7 (19.4%) of the children., respectively The vaccination schedule recommended for their age was not completed in 6 patients (16.7%): one patient had not received varicella vaccination, one patient had missed the second dose of measles-mumps-rubella vaccine, two patients only had the first dose of hepatitis A dose and another two patients had not received the quadrivalent ACWY meningococcal conjugate vaccine.

A total of 146 vaccines were administered with a median of 2 vaccines per child and visit (maximum 4 vaccines per day). The influenza vaccine was the most frequent vaccine administered (36 doses; 24.6%) followed by the pneumococcal conjugate (27 doses; 18.6%) and hepatitis B virus vaccines (17 doses; 11.7%) (Supplementary data Table 1).

Seroprotection rates at the inclusion were higher than 80%, being the highest proportion for varicella with a 94.5% seroprotection rate (95CI%: 81.9-98.5), and the lower for HBV where an adequate seroprotection rate was observed just in the 47.2% (95% CI: 32.063.0) of the patients. Seroprotection rates and susceptible patients for all the vaccines are presented in (Table 2).

The overall response after vaccination was excellent, achieving a 100% (95% CI: 90.3-100) in varicella, mumps, and rubella vaccines, 97.2% (95%CI: 85.8-99.5) in measles and 97.1% (95%CI: 85.1-99.9) in HAV and HBV.

Only three patients did not respond to vaccination: one patient did not respond to HAV (oligoarticular JIA without immunosuppressive treatment), another patient to HBV (negative RF polyarticular JIA with immunosuppressive treatment (adalimumab and methotrexate)), and the last one did not respond to measles (JSLE without immunosuppressive treatment).

Association between independent variables and seroprotection previous to vaccination was only analyzed for HBV because it was the only antigen with enough number of susceptible patients. No statistically significance was achieved for sex (OR of being female: 1.9 (95%CI: 0.5-7.79)), immunosuppression (OR of not being immunosuppressed: 2.6 (95%CI: 0.6-10.8)), type of disease (OR of AIJ: 2.4 (95%CI: 0.6-9.5)) or activity of disease (OR of low activity: 2.7 (95%CI: 0.7-10.2)). Age was the only variable statistically related to seroprotection: median age of seroprotected children was 4 (IQR: 2-6) compared to 11 (IQR: 9-14) in non-seroprotected children (p=0.002).

Table 2: Seroprotection rates and susceptible patients for all the vaccines.

	Pre vaccination			Post vaccination		
Vaccine	Antibody titer Median (IQR)	Seroprotection rate % (95% CI)	Susceptible patients	Antibody titer median (IQR)	Seroprotection rate % (95% CI)	Susceptible patients
Varicella	844.5 (410.1-2320)	94.45 (81.86-98.46)	2	962.15 (502.7-2320)	100 (90.3-100)	0
Mumps	143 (66.8-265.5)	86.11 (71.34-93.20)	5	159.5 (72.75-265.5)	100 (90.3-100)	0
Rubella	97.15 (32.45-404.15)	88.89 (74.69-95.60)	4	97.15 (35.45-437.8)	100 (90.3-100)	0
Measles	148 (32.4-300)	83.33 (68.10-92.13)	6	148 (43.65-300)	97.2 (85.8-99.5)	1
HAV	100 (39.4-100)	91.67 (78.17-97.12)	3	100 (39.4-100)	97.1 (85.1-99.9)	1
HBV	9 (3.1-420.84)	47.22 (31.99-62.99)	19	296. 1 (45.9-905.1)	97.1 (85.1-99.9)	1

Note: IQR: Interquartile Range; HAV: Hepatitis A Virus; HBV: Hepatitis B Virus.

Safety assessment

A total of 61 follow-up periods after vaccination were evaluated. No subject was lost to follow-up. Overall, no SAEs were observed. A total of 16 adverse events occurred in the 36 patients (44.4%). There were 15 local adverse events (24.5%) after vaccination, with 3 (20%) of them lasting more than 7 days. All local adverse events were categorized as grade 1. There was only 1 systemic adverse event (1.6%), consisting in fever >38.5°C that occurred in the first week after the pneumococcal polysaccharide vaccine (23 valent, PPSV23). Systemic and local reactions were more often reported after influenza (9 cases; 60%) and dTpa (2 cases; 13.3%), No patient had a flare based on the mentioned criteria for the next 3 months after each vaccination. Solicited symptoms are presented in (Table 3).

Table 3: Safety assessment and adverse events.

Safety assessment	n (%)
Local injection-site reactions ≤7 days	12 (19.7)
Local injection-site reactions more than 7 days	3 (4.9)
General symptoms ≤7 days	1 (1.6)
General symptoms more than 7 days	0 (0)
Flares	0 (0)

DISCUSSION

In this cohort of children with IMPRD visited during SARS-CoV-2 pandemic, vaccination was safe and immunogenic. Seroprotection rates after vaccination were higher than 90% for all vaccines and just 3 patients remained susceptible after measles, HAV and HBV vaccination.

However, 16.7% of the patients were not up to date regarding the official vaccine recommendations for their age. Serology tests were carried out in all the children, which made it possible to assess the need for booster doses or revaccinations.

Childhood vaccination coverage in Europe has been increasing for decades, and several countries have managed to achieve the 95% coverage goal [9]. In recent years, this trend has decreased in many regions: Bechini et al. have reported that coverages of vaccines like Poliovirus, Diphtheria-Tetanus-Pertussis, and Measles containing vaccines at 24 months of age have decreased in Europe as low as 70% for the first dose [10]. Because of the nature of the disease and treatments related, when an IMPRD is diagnosed it is advisable to assess and update the child's vaccination schedule.

The current recommendations of EULAR/PReS state that all routine vaccinations should be administered as scheduled, even during the COVID-19 pandemic [11].

There is currently no evidence that the COVID-19 pandemic poses any specific risk linked to vaccination, in fact, the interruption of immunization evokes outbreaks of preventable diseases [12]. Routine immunization sessions should have continued as far as possible and as the local context allowed, especially in IMPRD who have a risk of infections resulting primarily from the treatment used and high disease activity.

In our cohort, seroprotection rates measured for all the vaccines were higher than 80% except for HBV. Nineteen of our patients did not have protective anti-HBs titers at the moment of the diagnosis, as all of them were previously vaccinated. Seventeen patients received a booster dose, and all generated protective antibody titers, indicating a good humoral response to this booster dose. Decreased antibody titer due to the passing of time, may explain why younger patients in our cohort, who had received the primary course of HBV vaccination more recently, had higher seroprotection rates than older ones, as has been described [13].

Our results are in accordance with previous studies. For example, Kostik M et al. reported 170 JIA children diagnosed with JIA with a protective level of anti-HBs antibodies for just 50% [14]. The main predictors affecting antibodies against hepatitis B were a systemic-onset JIA and biologics treatment category. Similarly to our results, Çakmak et al. analyzed the anti-Hbs titers of 262 treatment-naive JIA patients and compared to 276 healthy control. In the JIA group, seropositivity rate was 59.1% while 72.9% of the control group were immune against HBV (p=0.002). However, when the different rates of previous seroprotection among the different JIA subtypes were analyzed, no significant differences were found (p=0.28) [15]. Currently, there is not enough scientific evidence to explain why patients with systemic JIA may have lower seroprotection coverage against HBV. The existing dysregulation of both the innate and adaptive immune systems in this subtype of JIA could be a hypothesis. Also, the nature of the vaccine has a crucial role: mainly live attenuated or virus-like particles vaccines induce

antibody responses that persist for several decades, if not lifelong, in the absence of subsequent antigen exposure and reactivation of immune memory [16].

Regarding safety assessment, in our study, vaccines were well tolerated as in only 12 of 61 follow-up periods (19.7%) was an adverse local reaction during the first 7 days, and none of them was serious. Similarly, Carrasco-Garrido et al. did not find a higher adverse event rate in 946 healthy children ranging in age from 0 to 14 years, and detected 19% of adverse events in vaccinated children, similar as in our study [17]. Also, the more frequently reported adverse events were injection-site oedema (12.2 per 1,000 doses) and pain at site of inoculation (10.3 per 1,000 doses).

Systemic and local reactions were more often reported after influenza and dTpa vaccines. As observed in our study, Carrasco-Garrido et al. found that injection-site edema was attributed to dTPa and Hib in 55% of cases (18.8 per 1000 doses), followed by 18.4% (n=7) attributable to Td vaccine (112 per 1000 doses) [17]. Regarding influenza vaccine, Camacho-Lovito et al. reported that 7 out of 41 (17%) children with JIA under biological treatment showed adverse local reactions (six with local skin inflammation and one hematoma). Most of these patients were naive to influenza vaccination, which may be one of the main issues to explain this vaccine reactogenicity. On the other hand, the high exposure to multiple vaccines containing diphtheria, tetanus, and pertussis antigens may explain the reactogenicity to dTpa [18].

Even though the number of patients included is limited, the systematic assessment and the follow-up time was enough for a flare to be detected. Although the mechanism of flare is not known, it could be explained by different facts, such as non-specific effects on the immunity of vaccine components, or the molecular mimicry between elements included in the vaccines and the patient's characteristics [19,20]. Worsening in disease activity after vaccination has always been a major concern, especially with live attenuated vaccines, but recent data from a systematic review, reported just one study where disease activity worsened in three of 39 children with JIA 4 to 6 weeks after VVZ vaccination [21,22]. Furthermore, it has to be taken into account that many of the IMPRDs are characterized by an intermittent and relapsing course even without triggers.

Since many pediatric rheumatologists as well as International vaccination guidelines recommend to vaccinate these children in a stable phase and often defer vaccination until lower disease activity is reached, it could have a coincidence in time with a relapse after vaccination due to the ordinary course of the disease. This reactivation could be misinterpreted as erroneously related to vaccination.

The present study's main limitations are related to the overall low number of patients included, which could limit the extent of the conclusions. Nevertheless, this study was conducted during the SARS-CoV-2 pandemic and the number of patients visited during this period decreased and consequently new diagnosis. Like us, other hospitals have experienced this decline in the number of visits during the pandemic: Ummusen et al. reported a decrease by approximately 40% of pediatric rheumatic visits during this period [23]. In another study evaluating admissions in 49 pediatric hospitals in 2020 compared with the prior decade, a decrease by 45.4% in April 2020 compared to the previous years was stated [24].

Another cause for concern may be different reporting biases. To minimize potential parental recall bias regarding reported adverse events, we contacted the patient's family during the first 7 days after vaccination, as well as a final call was made at the end of the follow-up period. In this way, with telephone calls, we tried to minimize recall bias. Even though younger children may have difficulties expressing these events, all parents were trained upon consultation about the requested adverse events. This, and the prospective collection of data using standardized questionnaires, increases the confidence in the high internal validity of the study. Furthermore, there was heterogeneity in the degree of immunosuppression in the treatment used at diagnosis as well as in the type of diseases included. Those are limitations inherent to the spectrum of immune-mediated inflammatory diseases and their treatment.

Nonetheless, some strength should be taken into consideration since there were no cases lost to follow-up of safety assessment, so the internal validity of the study was not reduced. Another strength is that our center is a pediatric referral hospital in Catalonia, so the pediatric rheumatologic population included is very broad and can be extrapolated to any other setting.

Even though additional studies with a higher number of participants are needed to increase our knowledge about the immunogenicity and safety of vaccines in rheumatologic pediatric immunosuppressed patients, our study has shown that vaccination is safe and immunogenic in this population, and we strongly recommend the assessment of vaccination requirements in pediatric patients with immune-mediated rheumatic diseases as soon as their diagnosed is made.

CONCLUSION

In conclusion, the findings of this study demonstrate that vaccination in children with Immune-mediated Pediatric Rheumatic Diseases (IMPRDs) during the SARS-CoV-2 pandemic was safe and effective in terms of immunogenicity. The seroprotection rates for all vaccines exceeded 90%, with only a small number of patients remaining susceptible after measles, hepatitis A, and hepatitis B vaccination. However, it is concerning that a significant proportion of patients were not up to date with the official vaccine recommendations for their age. The study emphasizes the importance of assessing and updating the vaccination schedule for children diagnosed with IMPRDs, as routine immunization is crucial for preventing outbreaks of preventable diseases. The current recommendations from EULAR/PReS support the administration of routine vaccinations even during the COVID-19 pandemic. The study also highlights the need for booster doses or revaccinations based on serology test results. The safety profile of the vaccines was generally favorable, with only a small percentage of adverse reactions reported, most of which were mild. While the study had limitations due to the small number of participants and heterogeneity in disease types and treatments, it provides valuable insights into the immunogenicity and safety of vaccines in immunosuppressed pediatric patients with rheumatic diseases. Further research with larger sample sizes is warranted, but based on the available evidence, vaccination should be strongly recommended and regularly assessed in pediatric patients with IMPRDs.

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