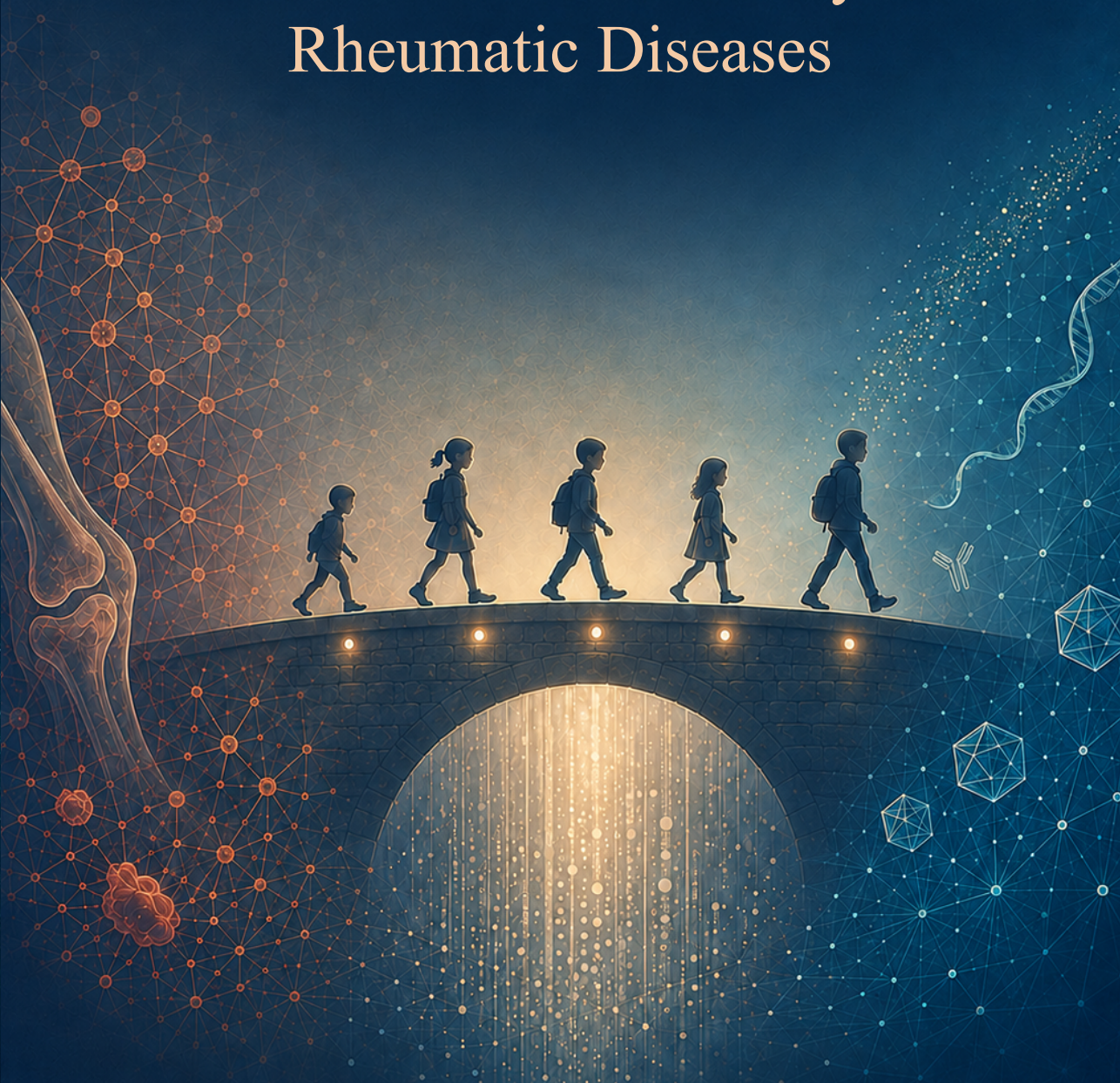
# Vaccination in Children with Paediatric Autoimmune and Autoinflammatory Rheumatic Diseases



Mohamad Hamad Saied

# Vaccination in Children with Paediatric Autoimmune and Autoinflammatory Rheumatic Diseases

Evidence on Safety, Immunogenicity and Effectiveness Across Live-Attenuated, mRNA and Recombinant Vaccines

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ISBN: 978-94-6534-614-4
DOI: https://doi.org/10.33540/3826
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Cover design and printing: ProefschriftMaken
The research described in this thesis was conducted at the Department of Paediatric Rheumatology and Immunology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, the Netherlands.
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**Vaccination in Children with Paediatric Autoimmune and Autoinflammatory Rheumatic Diseases**

Evidence on Safety, Immunogenicity and Effectiveness Across Live-Attenuated, mRNA and Recombinant Vaccines

**Vaccinaties in Kinderen met Autoimmuun en Autoinflammatoire Reumatische Ziekten**

Evidentie voor de veiligheid, immunogeniciteit en effectiviteit van levend verzwakte, mRNA- en recombinante vaccins

(with a summary in English)

**Proefschrift**

ter verkrijging van de graad van doctor aan de
Universiteit Utrecht
op gezag van de
rector magnificus, prof. dr. ir. W. Hazeleger,
ingevolge het besluit van het College voor Promoties
in het openbaar te verdedigen op

woensdag 7 oktober 2026 des middags te 2.15 uur

door

**Muhammad Hamad Said**

geboren op 19 maart 1983
te Haifa, Israël

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# Outline of the Thesis

# Outline of the Thesis

This thesis examines vaccination in children with paediatric autoimmune and autoinflammatory rheumatic diseases (pedAIIRDs), a patient group that carries a higher burden of infection than their peers. Their immune responses are further shaped by the drugs used to control their disease. Despite this double vulnerability, children with pedAIIRDs remain underrepresented in vaccine research. The five original studies at the heart of this thesis were each motivated by a specific unanswered clinical question, spanning three vaccine platforms: the live-attenuated MMR booster, COVID-19 mRNA vaccines, and the recombinant zoster vaccine.

**Chapter 1: General Introduction**
The opening chapter provides the clinical and scientific context for the research. It describes the spectrum of pedAIIRDs and explains how the immunosuppressive drugs used to treat these conditions both increase infection risk and have the potential to reduce vaccine responses.
The longstanding clinical culture of caution around live-attenuated vaccines in immunocompromised patients is critically examined. The 2021 EULAR/PRES vaccination recommendations for paediatric patients are also reviewed in detail.
The chapter concludes by outlining the rationale for the five studies and the specific aims of the thesis.

**Chapter 2: Safety of MMR Booster Vaccination in Children with JIA**
This chapter presents a retrospective cohort study of 186 children with JIA who received the measles-mumps-rubella (MMR) booster as part of the Dutch national immunisation programme. The cohort included children on biologic monotherapy and combination therapy.
Disease activity was measured at two clinic visits before and two after vaccination. No significant change in disease activity was observed at any time point, no serious adverse events occurred, and no cases of vaccine-strain viral infection were recorded.
This chapter provides real-world safety evidence supporting MMR booster vaccination in biologic-treated children.

**Chapter 3: Long-Term Immunogenicity of MMR Booster Vaccination in Children with JIA**
This chapter examines whether the MMR booster-induced immunity is maintained over time in children with JIA, including those treated with immunomodulatory drugs and biological therapies. Measles-, mumps-, and rubella-specific IgG concentrations were measured in stored serum from 182 JIA

patients at five years post-vaccination and at the most recent available follow-up visit, with a median follow-up of 6.9 years. Most patients retained seroprotection against all three antigens, but measles-specific protection at five years was significantly lower in those receiving biologic therapy compared with those who were not (60% versus 86%). This finding supports targeted serological monitoring at five years post-booster in biologic-treated patients, with a further vaccine dose offered to those who have lost protection, rather than a blanket revaccination policy for all patients.

**Chapter 4: The Protective Effect of COVID-19 Vaccination Against MIS-C: A Systematic Review and Meta-Analysis**

This chapter examines whether COVID-19 mRNA vaccination protects against multisystem inflammatory syndrome in children (MIS-C).

Thirteen eligible studies were identified; four large nationwide datasets from France, the United States, Denmark, and Israel, covering approximately 63 million children, were pooled in a meta-analysis. Vaccination was associated with a 96% reduction in MIS-C risk, with a rate of 2.9 MIS-C cases per million vaccinated children compared with 113.3 per million following natural infection.

**Chapter 5: Immunogenicity, Effectiveness, and Safety of COVID-19 mRNA Vaccination in Children with pedAIIRDs**

This chapter reports a prospective cohort study of 157 children with pedAIIRDs followed at the Wilhelmina Children's Hospital between March 2021 and August 2022.

Although biologic-treated patients had lower antibody concentrations, vaccine effectiveness was preserved. Fully vaccinated patients had a 47% lower risk of symptomatic COVID-19, and vaccine effectiveness did not differ significantly between biologic-treated and untreated patients.

T-cell responses were adequate in 91% of tested patients. No disease flares, myocarditis, or serious adverse events were identified.

**Chapter 6:Recombinant Zoster Vaccine in VZV-Naive Immunocompromised Children**

Children with pedAIIRDs on high-level immunosuppression cannot safely receive the live-attenuated varicella vaccine, leaving them unprotected against primary chickenpox. This chapter describes the first published evaluation of Shingrix, an adjuvanted recombinant zoster vaccine, off-label in ten VZV-naive children receiving immunosuppressive therapy as part of routine clinical care. Nine of ten children seroconverted after the two-dose schedule. Two children who were subsequently exposed to varicella at home developed mild breakthrough infections that resolved completely without antiviral treatment or hospitalisation.

This chapter provides the pilot safety and immunogenicity data needed to support a formal prospective evaluation of this approach.

**Chapter 7: General Discussion**
This chapter integrates the findings of all five studies and discusses their implications for clinical practice. The evidence now available to support MMR vaccination in biologic-treated children, the rationale for targeted serological monitoring, and the role of COVID-19 mRNA vaccines and Shingrix as vaccination options for immunocompromised children are examined in depth. Policy implications for the next revision of the EULAR/PRES paediatric vaccination recommendations are considered, including the persistent gap between available evidence and current clinical practice and the implementation strategies needed to close it. The chapter also outlines future research priorities, including extending the evidence base to non-JIA rheumatic diseases, other paediatric conditions managed with biologics such as inflammatory bowel disease and psoriasis, newer treatments including JAK inhibitors and rituximab, and children with primary or secondary immunodeficiency. The strengths and limitations of the thesis are considered in detail, and the chapter closes with a reflection on what the evidence generated here means for the care of children with pedAIIRDs today.

**Chapter 8: Summary**
Chapter 8 brings together the conclusions of the thesis in three forms: an English summary presenting the main findings and their clinical implications, a Nederlandse Samenvatting for a Dutch-speaking readership, and a Lay Summary written for patients, families, and members of the public.

**Chapter 9: Appendices**
The final chapter contains the List of Abbreviations and the Acknowledgements.

# Chapter 1

# General Introduction

# Chapter 1: General Introduction

## General Background: Paediatric Autoimmune and Autoinflammatory Rheumatic Diseases (pedAIIRDs) and Vaccinations

Paediatric autoimmune and autoinflammatory rheumatic diseases (pedAIIRDs) encompass a clinically heterogeneous group of chronic immune-mediated conditions arising in childhood, including juvenile idiopathic arthritis (JIA), systemic lupus erythematosus (SLE), juvenile dermatomyositis (JDM), scleroderma, Sjögren disease, mixed connective tissue disease (MCTD), systemic vasculitides, and a growing number of monogenic autoinflammatory syndromes such as Familial Mediterranean Fever (FMF), TNF receptor-associated periodic syndrome (TRAPS), and cryopyrin-associated periodic syndromes (CAPS). JIA is the most prevalent childhood rheumatic disorder, affecting approximately 1 in 1,000 children in Europe and accounting for the majority of paediatric rheumatology consultations worldwide (1,2). Other conditions are considerably rarer: childhood-onset SLE has a prevalence of approximately 3-9 per 100,000 children in European populations, juvenile dermatomyositis an incidence of 2-3 per million children per year, and monogenic autoinflammatory syndromes such as TRAPS and CAPS each affect fewer than 1 per 100,000 in Western European populations (3–5). FMF is an exception, with prevalence varying markedly by ethnicity, from approximately 2.5 per 100,000 in Western Europeans to several hundred per 100,000 among Sephardic Jews, Armenians, and Turks (6).

The pathogenesis of pedAIIRDs varies substantially across subtypes but uniformly involves a breakdown of immune tolerance. Autoimmune diseases such as JIA are characterised by dysregulated adaptive immunity, with aberrant T helper cell polarisation (predominantly Th1 and Th17), B-cell hyperactivation, autoantibody production, and impaired regulatory T-cell function all driving sustained synovial and systemic inflammation (7,8). Systemic autoimmune diseases (SLE, JDM, MCTD, Sjögren and scleroderma) are characterised by an aberrant B-cell response with disease specific auto-antibodies and a dysregulated interferon response (9). In contrast, autoinflammatory phenotypes, including systemic JIA (sJIA), are driven by innate immune dysregulation, often with excessive inflammasome activation and overproduction of cytokines including TNF-α, IL-1β, IL-6, and IL-18. In some autoinflammatory and autoimmune diseases, including sJIA and SLE, this innate hyperactivation can trigger macrophage activation syndrome (MAS), a life-threatening complication associated with markedly elevated concentrations of IL-1 and IL-18 and release of damage-associated molecular patterns such as S100 proteins (10,11).

Treatment of pedAIIRDs has been transformed by the introduction of biologic DMARDs (bDMARDs), including TNF inhibitors, IL-1 and IL-6 antagonists, anti

B-cell monoclonals, T-cell co-stimulation blockers, and more recently targeted synthetic DMARDs such as JAK inhibitors, alongside established conventional synthetic agents (csDMARDs) (2,12). While these therapies have substantially improved disease control and long-term outcomes, they modulate the same immune pathways that underpin protective vaccine responses. Depending on the targeted mechanism, they may impair antigen presentation, inhibit T- and B-cell activation and differentiation, suppress cytokine signalling, or reduce the generation of long-lived plasma cells, all of which make patients more vulnerable to infections.

To protect immunosuppressed children from infections, vaccination is the most effective and durable intervention available. Vaccination is therefore both more important and more difficult to implement in children with pedAIIRDs than in the general paediatric population. Clinicians must weigh three concerns: first, how prevalent and how severe is the infection we aim to prevent, and how will it evolve in an immunosuppressed host (13,14). Second: whether the vaccine is safe and does not precipitate disease flares or other immunological harm; third whether they remain immunogenic and effective against the background of ongoing immunosuppression. Systematic evidence addressing all three concerns exists but remains incomplete across most vaccine types and therapeutic combinations (15). In practice, this uncertainty has produced a culture of caution rooted in the principle of first do no harm: doctors are more fearful of the harms of action than of inaction, and anticipated regret favours withholding an intervention over administering one whose risks feel uncertain. The result is a bias toward inaction, leaving children with pedAIIRDs inadequately protected at the point of greatest need (16,17).

**Immunosuppression and Infection Risk in pedAIIRDs**

Children with pedAIIRDs generally face an elevated infection risk because of multiple causes. Immunosuppressive therapy pharmacologically blunts the pathways that normally combat infection; the underlying inflammatory disease itself further disrupts immune surveillance; and incomplete or delayed vaccination removes an important additional layer of protection. Hospitalisation rates for bacterial infection are approximately twice as high in children with JIA as in non-JIA controls, even independent of immunosuppressive therapy, rising further with escalation to bDMARD therapy (13,14,18). Among the infections documented in this population, vaccine-preventable diseases feature prominently. Severe and complicated courses have been well documented in immunocompromised children: measles can cause fatal pneumonitis and encephalitis even without the classical rash; varicella can disseminate to cause pneumonia, hepatitis, and encephalitis; invasive pneumococcal disease carries substantially higher rates of bacteraemia and meningitis in immunocompromised hosts than in healthy peers; and COVID-19 can trigger multisystem inflammatory syndrome in children (MIS-

C), a severe hyperinflammatory complication whose risk is substantially reduced by vaccination (18–21).

Live-attenuated vaccines present specific management difficulties. MMR, varicella, yellow fever, oral typhoid, rotavirus, and oral polio (OPV) vaccines all carry a theoretical risk of uncontrolled replication of the attenuated organism in an immunosuppressed host, and vaccine-strain infections, although rare, have been documented in profoundly immunocompromised patients. Live vaccines are therefore broadly considered contraindicated at moderate to high levels of immunosuppression, and their administration is frequently deferred when therapy is escalated. The practical implication is clear: live-attenuated vaccination should, where possible, be completed before immunosuppressive therapy commences. In clinical practice, however, diagnosis and treatment initiation often follow rapidly upon one another, and the vaccination window is frequently missed (15). Moreover, necessary treatment should not be postponed for vaccination (22).

Outbreaks of vaccine-preventable diseases have reinforced the public health dimension of these individual clinical decisions. Measles and mumps have re-emerged across Europe, including in the Netherlands, driven by heterogeneous vaccination coverage and waning population immunity (23–25). For immunocompromised children who have never been adequately vaccinated or who have lost seroprotection over time, such outbreaks represent a concrete and identifiable hazard. Unlike healthy peers, these children cannot rely on herd immunity to offset their individual vulnerability.

**Vaccine Classification and Relevance in pedAIIRDs**

Vaccines used in children with pedAIIRD fall into two principal categories, and the distinction between them is clinically consequential. Live-attenuated vaccines, including MMR, varicella, and oral polio and rotavirus, contain replication-competent organisms weakened to induce immunity in immunocompetent individuals without causing disease. Non-live vaccines, encompassing inactivated whole-pathogen preparations, protein subunit vaccines, conjugate vaccines, mRNA vaccines (as used for COVID-19), and recombinant vaccines (as used for herpes zoster), carry no risk of vaccine-strain infection and are considered safe in immunosuppressed patients regardless of treatment intensity, although post-vaccination disease flares have been reported in a subset of patients, particularly in those with periodic fever syndromes (26–30).

For live-attenuated vaccines, in principle the clinical question is not *whether* to vaccinate but *when*, and under which treatment conditions vaccination can be safely offered. For non-live vaccines, the questions shift to immunogenicity: whether the vaccine response with standard scheme vaccinations is sufficient to confer clinically relevant protection and how long that protection is maintained under ongoing immunosuppression. Answering either set of questions requires

disease-specific, treatment-stratified, prospective data, which remain scarce across most vaccine types and therapeutic combinations.

**Vaccination Challenges in Immunosuppressed Children**

The barriers to adequate vaccination in children with pedAIIRDs are multifactorial and interrelated, and addressing them in isolation rarely leads to sustainable improvement. A brief overview of the key barriers and their interactions is therefore necessary before outlining the research undertaken to address them.

Central to the problem is a **limited and heterogeneous evidence base**. Published data on vaccine safety and immunogenicity in pedAIIRDs are fragmented across diagnoses and vaccine types, largely retrospective in design, and constrained by limited follow-up duration. The clinical consequences are clear: when a treating rheumatologist lacks reliable, disease-specific or immunosuppressant-specific data for a given vaccine, they are forced to make decisions without the information needed to do so confidently. Surveys of paediatric rheumatologists have shown the result: considerable variation in vaccination practices across institutions and countries, with particularly pronounced hesitancy regarding live-attenuated vaccines in children receiving biologic therapies (16,17).

**Timing compounds the difficulty.** Vaccination is most straightforwardly managed before immunosuppressive therapy begins, but the clinical trajectory of newly diagnosed pedAIIRDs frequently demands rapid treatment escalation, leaving insufficient time for a full immunisation schedule. Once therapy has commenced, the appropriate interval before live-attenuated vaccines may be safely administered varies by immunosuppressant drug, dose, and mechanism of action. For agents with extended biological half-lives, such as rituximab, the required interval before live-attenuated vaccines may be six months or longer, and following high-dose IVIG, MMR vaccination should be delayed by up to 11 months depending on dose (22). Coordinating vaccination within these windows demands active communication between rheumatology, primary care, and public health services, coordination that is rarely formalised.

**Parental hesitancy** adds a further layer. Families who have seen their child suffer from severe inflammatory disease may resist any intervention that carries even a theoretical risk of provoking a flare. When clinicians themselves send inconsistent signals, recommending vaccination in one clinic and deferring it in the next, families understandably conclude that the risks are poorly understood and that caution is safer. This clinical uncertainty intersects with a broader erosion of public trust in vaccination, fuelled by misinformation on social media and declining familiarity with the diseases vaccines prevent (31). For families of children with pedAIIRDs, these influences represent an additional and

compounding barrier. Consistent, evidence-based communication across the multidisciplinary care team is therefore essential to support trust and informed decision-making.
Finally, even vaccinations that are successfully administered may provide shorter-lived protection than expected. Immunosuppressive therapy impairs immunological memory formation, and protective antibody concentrations have been found to wane more rapidly in children with pedAIIRDs than in healthy peers. The practical consequence, that periodic serological monitoring and selective revaccination may be necessary in biologic-treated children, is not yet reflected in routine clinical care (28).

**European and International Expert Recommendations (EULAR/PRES)**

In 2021, the European Alliance of Associations for Rheumatology (EULAR) and the Paediatric Rheumatology European Society (PRES) jointly published updated vaccination recommendations for children with autoimmune inflammatory rheumatic diseases, grounded in a systematic literature review and international expert consensus (22,32). The guidelines comprise six overarching principles and seven specific guidance points. Their publication established an important clinical framework, though their implementation has been constrained by the scarcity of the evidence they themselves identified as lacking.

The overarching principles establish that vaccination status should be reviewed annually by the treating specialist; that vaccines should preferably be administered during periods of low disease activity, though this is not an absolute requirement; and that treatment initiation and escalation should not be delayed to allow vaccination. For non-live vaccines, the guidance is permissive across all immunosuppressive regimens. Corticosteroids, csDMARDs, bDMARDs, and JAK inhibitors are not considered contraindications, and routine immunisation with inactivated, subunit, mRNA, and recombinant vaccines should continue without interruption of therapy.

Guidance on live-attenuated vaccines has moved away from blanket contraindication as a first principle. The MMR booster, administered in the Netherlands as part of the national immunisation programme, can be given safely to patients receiving methotrexate and may be considered in patients on low-dose glucocorticoids, TNF inhibitors, anti-IL-1, or anti-IL-6 agents, provided disease activity is controlled and there is no recent history of serious infection. Varicella vaccination should be considered in VZV-naive patients, including those on methotrexate, with individualised risk-benefit assessment when biologic therapy is present. Live vaccines remain contraindicated in patients on high-dose

corticosteroids, cyclophosphamide, rituximab, or two or more concurrent bDMARDs.

Several studies supporting these recommendations originated from Dutch research groups, with contributions from the University Medical Centre Utrecht (15,22,26). The 2021 EULAR/PRES guidelines were developed with direct involvement from the same centre, and the present research programme builds on that guideline framework, generating the prospective, disease-specific, real-world data that the guidelines identified as the main evidence gap limiting their full implementation.

**Public Health and Policy Considerations**

Vaccination practice in children with pedAIIRDs does not occur in a public health vacuum. In recent years, measles and mumps outbreaks have recurred across Europe, including in the Netherlands, driven by declining vaccination coverage and waning population immunity (23,24,33). This decline reflects several overlapping influences: erosion of institutional trust, the spread of conspiracy theories and vaccine misinformation, anthroposophical objections to vaccination, and lower uptake within several religious communities. Immunocompromised children who have lost seroprotection, or who were never adequately vaccinated, carry a disproportionate risk during such outbreaks. Because routine immunisation surveillance records vaccine coverage rather than current immune status, these children are often not identified as susceptible.

The COVID-19 pandemic sharpened these concerns. mRNA-based COVID-19 vaccines demonstrated protective efficacy in children with rheumatic diseases on immunosuppressive therapy (29,34), and COVID-19 vaccination substantially reduces the risk of multisystem inflammatory syndrome in children (MIS-C), a severe post-infectious hyperinflammatory complication, as shown in this thesis (35). Despite this, vaccination of children with chronic diseases was shaped by the same clinical hesitancy and institutional variability that characterises vaccination practice in pedAIIRDs more broadly (17).

At the policy level, the structural gaps are as important as the clinical ones. National immunisation programmes are designed around healthy children and rarely include specific considerations for those with immunocompromising conditions. Rheumatology departments and public health vaccination services seldom communicate systematically about individual patients. In practice, public health vaccination services may decline to administer vaccines to children on immunosuppressive therapy that the treating rheumatologist would consider both safe and indicated, without consulting the specialist, while immunisation records held in primary care may not be accessible to hospital teams. Closing these gaps

requires structured, bidirectional communication that goes beyond individual clinical encounters.

**Rationale for This Thesis**

Three specific evidence gaps shaped the research programme presented in this thesis.

First, long-term immunogenicity data for MMR booster vaccination in children receiving biologic therapy were absent. Short-term studies had reported acceptable safety, but whether vaccine-induced seroprotection persists over the years of continued bDMARD treatment that characterise modern JIA management had never been examined.

Second, the emergence of COVID-19 created an immediate clinical need for data on mRNA vaccine immunogenicity and effectiveness in children with rheumatic diseases. Such evidence was not required for regulatory authorisation and could not be generated rapidly enough through conventional research pathways to guide clinical decision-making during the pandemic.

Third, VZV-naive children on intensive immunosuppressive therapy had no evidence-based non-live alternative to the contraindicated live-attenuated varicella vaccine. The recombinant zoster vaccine (Shingrix), licensed in adults for the prevention of herpes zoster and with demonstrated immunogenicity in immunocompromised adult populations, had never been evaluated as a non-live alternative for varicella protection in paediatric patients.

The five studies were conducted in the real-world clinical setting of a tertiary paediatric rheumatology centre embedded within the EULAR/PRES guideline framework (22). Rather than generating isolated answers to isolated questions, the programme was structured to build a coherent body of evidence spanning vaccine types (live-attenuated and non-live) and clinical contexts (routine, pandemic, and off-label), sufficient to inform day-to-day clinical practice and future guideline revision.

**Aim and Objectives of this Thesis**

The overarching aim of this thesis is to generate clinically applicable, real-world evidence on the safety, immunogenicity, and effectiveness of vaccination in children with pedAIIRDs receiving immunosuppressive therapy, of sufficient quality and scope to reduce clinical uncertainty and inform future vaccination guidelines at national, European and international level.

The specific objectives are: (1) to assess vaccine safety, with particular attention to post-vaccination disease activity and adverse events in children receiving

biologic therapy; (2) to evaluate humoral and, where feasible, cellular immune responses following vaccination, and to characterise the extent and duration of any treatment-related attenuation; (3) to examine real-world vaccine effectiveness against clinically relevant endpoints, including measles, varicella, symptomatic COVID-19, and MIS-C; (4) to provide evidence supporting individualised vaccination decisions at the interface of rheumatology and infectious disease; and (5) to contribute to the evidence base that will underpin future revision of national, European, and international vaccination recommendations for immunocompromised children.

**Overview of the Five Original Studies presented in this thesis.**

The five studies in this thesis evaluate vaccination safety, immunogenicity, and effectiveness across three vaccine platforms. They encompass prospective and retrospective observational cohort designs and one systematic review with meta-analysis, reflecting the methodological range required to answer questions that are not feasible to study using randomised controlled trials in rare paediatric diseases.

**Study 1 (chapter 2)- Safety of MMR Booster Vaccination in JIA.**

A retrospective cohort study of 186 patients with JIA (51% receiving csDMARDs and 28% biologic therapy at the time of vaccination) assessed clinical disease activity and vaccine-related adverse events at two clinic visits before and two after vaccination. No significant increase in disease activity was observed on any measure, including composite cJADAS, active joint count, physician global assessment, or patient-reported wellbeing. Mild adverse events occurred in 7% of patients; no serious adverse events were identified. The study provided prospective real-world evidence that MMR booster vaccination is safe across a broad range of immunosuppressive regimens, including biologic therapy (36).

**Study 2 (chapter 3)- Long-Term Immunogenicity of MMR Booster in JIA.**

An observational longitudinal study of 182 patients measured measles, mumps, and rubella-specific IgG concentrations in stored serum at five years post-vaccination and at last available follow-up (median 6.9 years). Protective antibody levels were maintained in most patients; however, measles-specific seroprotection at five years was significantly lower in those who had been receiving biologic therapy at vaccination (60% versus 86% in non-biologic users, $P = 0.03$). The rate of antibody waning did not differ significantly between groups, suggesting that the difference reflects a reduced initial vaccine response rather than accelerated antibody waning. With follow-up of nearly seven years, this study reported the longest immunogenicity dataset for MMR vaccination in children with rheumatic diseases and provided the longitudinal basis for a targeted serological monitoring strategy in bDMARD-treated patients (37).

**Study 3 (chapter 4)- The Protective Effect of COVID-19 Vaccination Against MIS-C.**

A systematic literature review and meta-analysis of 13 studies evaluated whether COVID-19 vaccination reduces the risk of multisystem inflammatory syndrome in children (MIS-C). Four nationwide studies, encompassing approximately 63 million children, were pooled. The pooled odds ratio for MIS-C in vaccinated versus unvaccinated children was 0.04 (95% CI: 0.03-0.06), with no significant heterogeneity. The rate of MIS-C attributable to vaccination itself (2.9 per million vaccinated children) was approximately 39-fold lower than the rate following natural SARS-CoV-2 infection. Vaccination provided strong protection against this severe complication (35).

**Study 4 (chapter 5)- Immunogenicity, Effectiveness and Safety of COVID-19 mRNA Vaccination in** ped**AIIRDs.**

A prospective cohort study of 157 patients with paediatric rheumatic diseases (88% JIA) evaluated humoral and cellular immune responses, vaccine effectiveness, and safety following COVID-19 mRNA vaccination. All but four patients developed positive post-vaccination SARS-CoV-2 IgG antibodies. On multivariable analysis, biologic therapy was associated with significantly lower adjusted antibody concentrations (geometric mean ratio (GMR) 0.38, 95% CI: 0.21-0.70), though geometric mean concentrations remained above the positivity threshold in both groups. T-cell responses were adequate in 20 of the 22 patients tested (91%), including those receiving biologic therapy. Vaccine effectiveness against symptomatic COVID-19 was demonstrated (HR 0.53, 95% CI: 0.29-0.97), with no difference observed between patients with and without biologic treatment (HR 0.96, 95% CI: 0.55-1.67). No increase in disease activity, myocarditis, or serious adverse events was observed (38).

**Study 5 (chapter 6)- Recombinant Zoster Vaccine (Shingrix) in VZV-Naïve Immunocompromised Children.**

A retrospective case series of 10 VZV-naive immunocompromised children evaluated the off-label use of the adjuvanted recombinant zoster vaccine. Seroconversion was achieved in nine of ten patients after the two-dose schedule. Two patients developed mild breakthrough varicella following confirmed direct household exposure; both recovered without antiviral therapy or hospitalisation. No serious vaccine-related adverse events were attributed to the vaccine. This was the first published evaluation of off-label use of Shingrix in VZV-naive paediatric patients, and it provided the pilot data needed to design a formal prospective study (39).

**To Conclude**

Vaccination in children with pedAIIRDs lies at the intersection of several persistent challenges: an increased risk of infection and severe infectious complications in immunocompromised hosts, potentially reduced vaccine responses, a limited and fragmented evidence base, and a clinical culture that has often defaulted to caution in the absence of disease-specific data. The 2021 EULAR/PRES recommendations (22) provide a structured framework to address these challenges; however, their translation into consistent clinical practice has been gradual, in part because significant gaps in knowledge remain. The five studies presented in this thesis were designed to address these gaps by generating clinically relevant evidence across the vaccine types and clinical scenarios most relevant to current paediatric rheumatology practice.

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**Chapter 2**

# Safety of MMR Booster Vaccination in Children with JIA

## Chapter 2: Safety of MMR Booster Vaccination in Children with JIA

# Safety of measles-mumps-rubella booster vaccination in patients with juvenile idiopathic arthritis: a long-term follow-up study

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**Vaccine. 2023 May 2;41(18):2976-2981.**

## 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.

**Keywords:** vaccination, measles-mumps-rubella booster, juvenile idiopathic arthritis, immunosuppressive therapy

## 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 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.

## METHODS

### 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.

### 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.

### 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.

### 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 nineth 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.

## RESULTS

### 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 csDMARD and bDMARD combination therapy. Thirty-seven percent did not receive systemic therapy at the time of MMR booster vaccination.

### 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 (Figure 1). Results were similar for patients using a bDMARD at the time of MMR booster vaccination and patients who did not (Figure 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 Table2), and patients with a reported exact vaccination date (Supplementary Table 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%) |

[1]csDMARD and bDMARD therapy

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,

**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 |

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

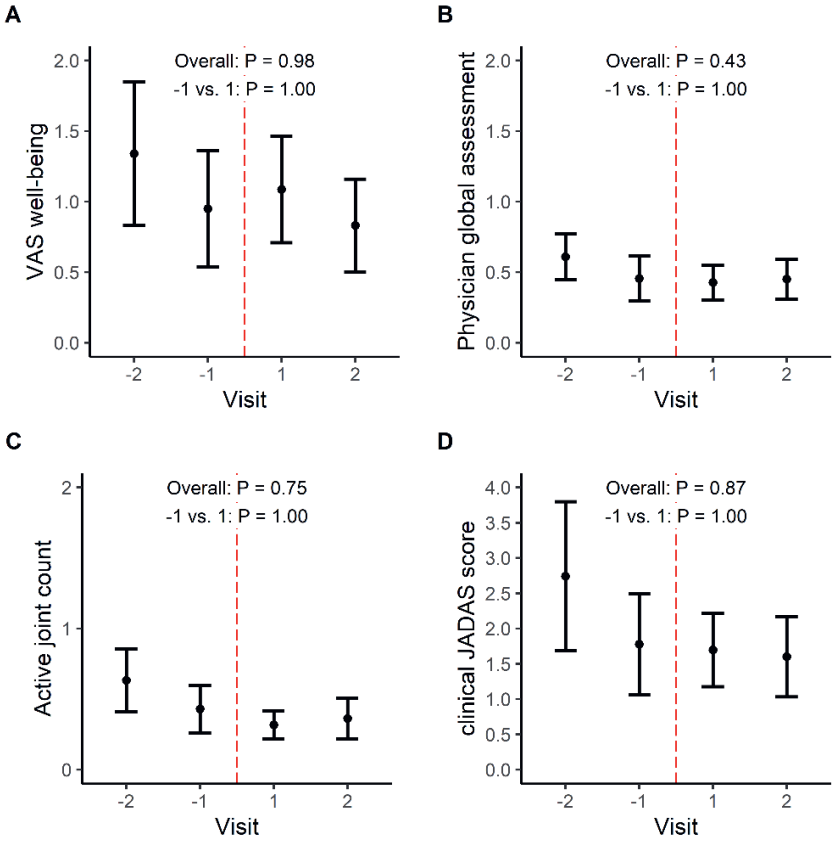



**Figure 1. Disease activity scores before and after MMR booster vaccination.**
A: mean patient-reported visual analogue scale (VAS) well-being at different study visits. B: mean physician global assesment (PGA) of disease activity at different study visits. C: mean active joint count (AJC) at different 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.

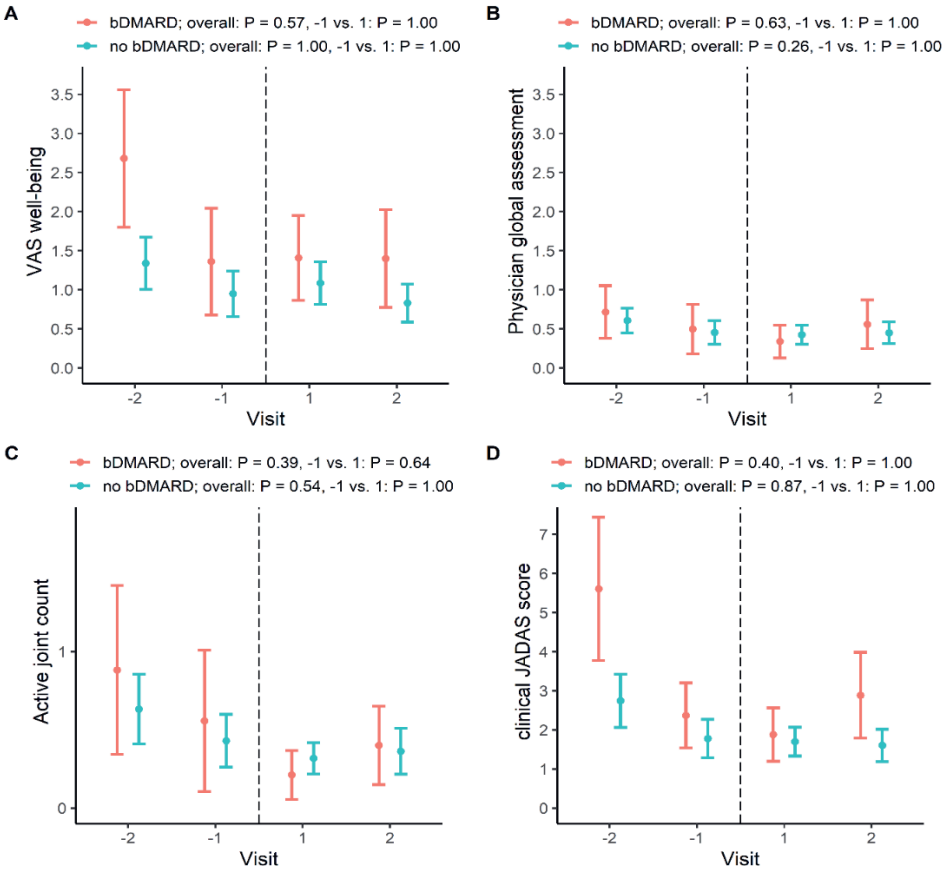



**Figure 2. Disease activity scores before and after MMR booster vaccination for bDMARD use at vaccination.** A: mean patient-reported visual analogue scale (VAS) well-being at different study visits. B: mean physician global assessment (PGA) of disease activity at different study visits. C: mean active 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.

## 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. 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-naive 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.

**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.

## STATEMENTS

### Disclosure statement
All authors declare no conflicts of interest.

### 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.

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**SUPPLEMENTARY MATERIAL**

**Supplementary Table 1. *P*-values for pairwise comparisons of diseases activity scores at different study visits.**

| Score | Visit | Visit -2 | Visit -1 | Visit 1 |
|---|---|---|---|---|
| VAS well-being | Visit -1 | 1.00 | - | - |
| | Visit 1 | 1.00 | 1.00 | - |
| | Visit 2 | 1.00 | 1.00 | 1.00 |
| PGA | Visit -1 | 0.22 | - | - |
| | Visit 1 | 0.36 | 1.00 | - |
| | Visit 2 | 0.78 | 1.00 | 1.00 |
| Active joint count | Visit -1 | 0.47 | - | - |
| | Visit 1 | 0.27 | 1.00 | - |
| | Visit 2 | 0.20 | 1.00 | 1.00 |
| cJADAS | Visit -1 | 1.00 | - | - |
| | Visit 1 | 1.00 | 1.00 | - |
| | Visit 2 | 1.00 | 1.00 | 1.00 |

cJADAS: clinical juvenile arthritis disease activity score, PGA: physician global assesment of disease activity, VAS: visual analogue scale

**Supplementary Table 2. Linear mixed effects analyses of disease activity before and after MMR booster vaccine for patients who received bDMARD therapy at the time of vaccination (n = 52).**

| Analysis | Mean difference after vs. before MMR booster | 95% CI | *P*-value |
|---|---|---|---|
| VAS well-being | | | |
| *Crude* | -0.22 | -1.16 – 0.72 | 0.65 |
| *Adjusted*[1] | 0.12 | -1.04 – 1.27 | 0.84 |
| Physician global assessment | | | |
| *Crude* | -0.16 | -0.44 – 0.13 | 0.28 |
| *Adjusted*[1] | -0.17 | -0.52 – 0.18 | 0.34 |
| Active joint count | | | |
| *Crude* | -0.41 | -0.84 – 0.01 | 0.06 |
| *Adjusted*[1] | -0.39 | -0.88 – 0.10 | 0.11 |
| clinical JADAS score | | | |
| *Crude* | -0.77 | -1.20 – 0.44 | 0.21 |
| *Adjusted*[1] | -0.40 | -1.88 – 1.07 | 0.59 |

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

bDMARD: biologic disease-modifying antirheumatic drugs 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.

**Supplementary Table 3. Linear mixed effects analyses of disease activity before and after MMR booster vaccine for patients with known exact vaccine date (n = 39).**

| Analysis | Mean difference after vs. before MMR booster | 95% CI | *P*-value |
|---|---|---|---|
| VAS well-being | | | |
| *Crude* | -0.16 | -0.70 – 0.39 | 0.56 |
| *Adjusted*[1] | -0.21 | -0.79 – 0.38 | 0.48 |
| Physician global assessment | | | |
| *Crude* | -0.23 | -0.64 – 0.18 | 0.27 |
| *Adjusted*[1] | -0.11 | -0.53 – 0.31 | 0.62 |
| Active joint count | | | |
| *Crude* | -0.44 | -1.09 – 0.20 | 0.18 |
| *Adjusted*[1] | -0.22 | -0.89 – 0.45 | 0.51 |
| clinical JADAS score | | | |
| *Crude* | -0.77 | -2.05 – 0.52 | 0.24 |
| *Adjusted*[1] | -0.49 | -1.82 – 0.83 | 0.46 |

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

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.

# Chapter 3

# Long-Term Immunogenicity of MMR Booster Vaccination in Children with JIA

# Chapter 3: Long-Term Immunogenicity of MMR Booster Vaccination in Children with JIA

## Long-term immunogenicity after live attenuated measles, mumps and rubella booster vaccination in children with juvenile idiopathic arthritis

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**Vaccine. 2023 Aug 23;41(37):5477-5482.**

## ABSTRACT

### Introduction

Vaccines, especially live-attenuated vaccines, in children with JIA pose a great challenge due to both potential lower immunogenicity and safety as a result of immunosuppressive treatment. For many years, in the Netherlands, JIA patients receive a measles, mumps and rubella (MMR) booster vaccine at the age of nine years as part of the national immunization program.

### Objectives

To study long-term humoral immunogenicity in a large cohort of JIA patients who received the MMR booster vaccine while being treated with immunomodulatory therapies at the Wilhelmina Children's Hospital in Utrecht, the Netherlands.

### Methods

MMR-specific IgG antibody concentrations in stored serum samples of vaccinated JIA patients were determined with chemiluminescent microparticle immuno assays (CMIA). Samples were analysed five years after MMR booster vaccination and at last available follow-up visit using both crude and adjusted analyses. Additional clinical data were collected from electronic medical records.

### Results

In total, 236 samples from 182 patients were analysed, with a median duration between vaccination and last available visit of 6.9 years (IQR: 2.8 – 8.8). Twenty-eight patients were using bDMARDS of whom 96% anti-TNF agents and 4% tociluzimab. Percentages of protective antibody levels against measles after five years were significantly lower for patients who used bDMARD therapy at vaccination compared to patients who did not: 60% versus 86% ($P = 0.03$). For mumps (80% versus 94%) and rubella (60% versus 83%) this difference was non-significant ($P = 0.11$ and $P = 0.07$, respectively). Antibody levels post-vaccination decreased over time, albeit not significantly different between bDMARD users and non-bDMARD users.

### Conclusion

The MMR booster vaccine demonstrated long-term immunogenicity in the majority of children with JIA from a large cohort, although lower percentages of protective measles antibody levels were observed in bDMARD users. Hence, it might be indicated to measure antibody levels after MMR booster vaccination in the latter group and advice an extra booster accordingly.

**KEY MESSAGES**

* The MMR booster vaccine demonstrated long-term immunogenicity in the majority of children with JIA.
* The percentages of protective MMR antibody levels against measles were lower in bDMARD users compared to non-bDMARD users.
* Clinicians should consider to measure antibody levels after MMR booster vaccination in bDMARD users and advice an extra booster accordingly.

## INTRODUCTION

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease in childhood (1,2). Clinical outcomes have dramatically improved over the last three decades, and clinical inactive disease can be obtained in most patients by treating them with immunomodulatory agents. Commonly used drugs in the treatment of JIA are conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), particularly methotrexate, and biologic disease-modifying antirheumatic drugs bDMARDs), most commonly anti-TNF agents (1,3–5).

JIA patients both have an increased risk for infections due to their underlying disease and due to the use of immunomodulatory or immunosuppressive drugs. Therefore, safe and effective immunization is crucial in the management of these groups of patients (6–8). However, vaccine immunogenicity might be impaired due to treatment (9,10).

In the Netherlands, the live attenuated measles, mumps and rubella (MMR) booster vaccination is routinely administered via the national immunization program at the age of nine years. In the University Medical Centre Utrecht, the Netherlands, JIA patients are advised to take the booster MMR vaccine – also when receiving immunomodulatory drug therapy – according to the new PRES and EULAR recommendations for vaccination of paediatric patients with autoimmune inflammatory rheumatic diseases (11,12).

Long-term follow up data on immunogenicity after MMR booster vaccination in children with JIA is limited in this era of bDMARDs therapy. In this study, we describe long-term immunogenicity in a large cohort of JIA patients who received the live-attenuated MMR booster vaccine and were simultaneously treated with csDMARDs and/or bDMARDs therapy.

## METHODS

### Study design and participants

A monocentre observational cohort study was performed in the paediatric rheumatology department of the Wilhelmina Children's Hospital in Utrecht, the Netherlands. All JIA patients born between 2002 - 2012 that met the International League of Associations for Rheumatology (ILAR) criteria for JIA (13) at the time of MMR booster vaccination and were enrolled in the international Pharmachild register (14) were included into the current study. Clinical and drug therapy data were collected from electronic medical records for the time of MMR booster vaccination, which was defined as the 9$^{th}$ birthday for all patients. The cut-off date for data collection was 17 September, 2022.

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.

**Outcome measure**

The primary outcome measure was the long-term humoral immunogenicity. MMR antibodies were measured five years after booster vaccination (range 5 – 6 years) and in the most recent sample, for which the time from MMR booster vaccination varied per patient. Since the incidence of naturally occurring MMR infections is low in the Netherlands (15), immunogenicity was used as surrogate measure of efficacy, An immune response that substitutes for the true immunologic correlate of protection(16).

MMR-specific immunoglobulin G (IgG) antibody concentrations in stored serum samples were determined with chemiluminescent microparticle immuno assays (CMIA). Antibodies for mumps and measles were analysed using Vircia IgG monotest (Vircell, Granada, Spain). Results were expressed as indexes, where an index >1.1 is considered protective. Previous carried in-house evaluation showed that an IgG anti-measles index >1.1 corresponded with >150 international units/l. Antibodies for rubella were analysed using the Alinity i Rubella IgG (Abbott Laboratories, Ireland). Results were given in IU/ml where results of ≥ 10 IU/ml were considered protective.

**Statistical analysis**

Characteristics of included patients were presented as frequency and percentage for categorical variables and median and interquartile range (IQR) for numerical variables. To study the effect of bDMARD use at the time of MMR booster vaccination on antibody levels after five years (both absolute and the percentage of protective levels), we performed linear and logistic regression analyses. For these analyses, absolute rubella-specific IgG antibody levels were log-transformed and bDMARD use was defined as the use of bDMARD monotherapy or combination therapy of a bDMARD and csDMARD. In addition, we performed multivariable analyses in which we adjusted for JIA subtype, age at JIA diagnosis and sex. We performed the same analyses on samples from last available visits to study the effect of time after vaccination on antibody levels, and whether or not this effect is different for bDMARD and non-bDMARD users. For the latter analysis, an interaction term between bDMARD use and time after vaccination in years was added to the regression models. All analyses were performed with R version 4.0.3 and a *P*-value of 0.05 was considered statistically significant.

## RESULTS

### Cohort characteristics

Serological samples were analysed from 182 patients with a diagnosis of JIA at the time of MMR booster vaccination. The majority of included patients were girls (67%) and had oligoarthritis (57%) (Table 1). Median age at JIA diagnosis was 5.1 years (IQR: 3.0 – 7.0). Fifty patients (28%) used MTX monotherapy at the time of MMR booster vaccination and 11 (6%) used bDMARD monotherapy, which were all anti-TNF agents. Seventeen patients (9%) used a combination of csDMARD and bDMARD monotherapy, of whom 96% used anti-TNF agents. Fifty-one percent of the patients used no immunosuppressive therapy or NSAIDs.

### Long-term humoral immunogenicity

In total 236 samples were analysed, which included 67 samples five years post-vaccination (Figure 1; Supplementary Table 1) and an additional 169 samples at last available visit (median follow-up: 6.9 years, IQR: 2.8 – 8.8).

On both crude and adjusted analysis, antibody levels five years post-vaccination were significantly lower in patients who used bDMARDs at vaccination than in patients who did not for measles, but not for mumps and rubella (Table 2). Percentages of protective antibody levels against measles after five years were significantly lower for bDMARD users compared to non-bDMARD users: 60% versus 86% ($P = 0.03$) (Table 3). For mumps (80% versus 94%) and rubella (60% versus 83%) this difference was non-significant ($P = 0.11$ and $P = 0.07$, respectively). On adjusted analysis, no statistically significant difference in protective antibody levels was observed. MMR antibody levels in samples from last visits decreased over time (Figure 2), but this decrease was not significantly different between bDMARD and non-bDMARD users (Supplementary Table 2).

## DISCUSSION

Concerns about the safety and immunogenicity of immunizing patients with JIA with live attenuated vaccines, especially those who are treated with immunosuppressive therapy, have persisted for years. In this study, the long-term humoral immunogenicity was assessed for MMR. Our study shows that the MMR booster vaccine is immunogenic in the majority of JIA patients after long-term follow-up, although percentages of protective antibody levels against measles are significantly lower in patients using anti-TNF agents.

We evaluated the long-term humoral immunogenicity of the MMR booster vaccine as a surrogate outcome for vaccine efficacy(16). We observed that antibody titres post-vaccination were above the protective threshold in the majority of included patients and tended to decline over time. Antibody levels five years post-vaccination were significantly lower in patients who used bDMARDs at vaccination than in patients who did not for measles, but not for mumps and

rubella. Patients who used a bDMARD, of whom 96% anti-TNF agents, at the time of booster vaccination had lower MMR antibody levels compared to patients who did not use a bDMARD including patients who used MTX or no immunosuppressive treatment, but the decrease in antibody levels was not significantly different.

A randomized trial reported no effect of MTX and bDMARDs on humoral response against measles, mumps and rubella in JIA patients 12 months after booster vaccination, although low patient numbers precluded definite conclusions (11). A cross-sectional study concluded that JIA patients had lower antibody concentrations and seroprotection rates compared to healthy controls against mumps and rubella, but not measles. In JIA patients, the use of glucocorticosteroids and MTX did not influence antibody concentrations and seroprotection rates (17). Other studies in patients with JIA and other paediatric rheumatic diseases also concluded that bDMARDs did not interfere with levels of MMR virus-specific IgG antibodies following booster vaccination (18,19). One study in children with enthesitis-related arthritis (ERA) using adalimumab investigated the persistence of measles and rubella specific-IgG antibodies one and three years after booster vaccination and compared this with healthy age-matched children (20). At both time points, the response was lower in ERA patients on adalimumab therapy compared with healthy children. Here, no difference was found between children with adalimumab therapy only and children who received an additional DMARD. A study of 30 children and adolescents with SLE reported that measles-specific antibody levels were similar to a healthy age-matched control group, despite use of glucocorticosteroids and/or other immunosuppressive drugs (21).

Safety of the MMR booster vaccine in JIA patients is confirmed by the available literature. A randomized trial of 137 booster vaccinated JIA patients, which included 60 patients using MTX and 15 patients using TNF-inhibitors, reported no worsening of disease activity (11). In a multicentre retrospective study including 211 booster vaccinated JIA patients of which 124 received csDMARDs and/or bDMARDs, none of the patients developed a disease flare, including those with high disease activity (22). Two systematic literature reviews also concluded that disease activity does not worsen following MMR booster vaccination in children with autoimmune rheumatic diseases (8,23). Furthermore, the 2021 PRES and EULAR recommendations for vaccination of paediatric patients with autoimmune inflammatory rheumatic diseases support the principle that the MMR booster vaccine can be safely administered in patients on MTX and can be considered in patients treated with low-dose glucocorticosteroids, TNF-inhibitors, anti-IL1 and anti-IL6 therapy (12). Other studies in children with rheumatic diseases also conclude that the MMR vaccine is generally well-tolerated and rarely associated with serious adverse events, and that postponing the MMR booster vaccination is often not required (10,11,18,22,24,25).

Waning of vaccine-induced immunity is considered to play a central role in the re-emergence of infections, especially among immunosuppressed patients with rheumatic or other diseases. In the last few years, an increasing number of measles and mumps outbreaks has been registered worldwide (26–28). A study of healthy adults who received two doses of the measles vaccine found that neutralizing antibody titres tended to decline over time, inversely correlated with the time elapsed between the two vaccinations (29). A third dose of the MMR vaccine was found to improve immunity against mumps in young adults and is expected to be a good and safe intervention for controlling outbreaks (30). A third MMR vaccine dose is recommended in the United States for persons at increased risk for mumps during outbreaks, and has demonstrated to be safe and tolerable (31). These results may indicate that periodic vaccination against MMR is required to prevent sporadic infections, especially in patients who are seronegative years after vaccination.

We are aware of the limitations of this study, which includes its retrospective and single centre design with varying time between MMR booster vaccination and last available visit. Also, it was not possible to retrieve the exact date of MMR booster vaccination for all patients, although all children in the Netherlands are vaccinated in their ninth year of life. Finally, because of the large number of samples from our cohort and the prolonged periods of follow up, our study could only assess humoral responses to vaccination and not provide data on T-cell responses, which may also be important in conferring viral immunity.
In the current study we only included patients with JIA. Recently, there is sufficient data to assume that MMR booster vaccination is also safe and immunogenic in other paediatric rheumatic diseases, including children receiving MTX , low dose glucocorticoids, anti TNF, anti-IL-1 and anti-IL-6 therapy(8,12,23,32,33). Further large multicentre studies are needed to shed light on these groups of patients and on patients with a primary immunodeficiency. Larger cohort studies and ideally RCTs should also be performed in order to increase the strength of future recommendations and to obtain more knowledge on vaccine efficacy and safety in patients receiving bDMARDs.

**In conclusion**, our study shows that the MMR booster vaccine is immunogenic in the majority of JIA patients, although percentages of protective antibody levels against measles after five years were significantly lower in bDMARD users. Clinicians should consider to measure antibody levels after MMR booster vaccination, especially in bDMARD users, and advice an extra booster accordingly.

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## STATEMENTS

### Funding
No funding was received for this research.

### Ethics
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.

### Disclosures
All authors declare no conflict of interest.

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

## TABLES AND FIGURES

**Table 1. Characteristics of included patients.**

| Characteristic | Total cohort (n = 182) |
|---|---|
| **Girls, n (%)** | 121 (66.5%) |
| **JIA subtype, n (%)** | |
| *Oligoarthritis* | 103 (56.6%) |
| *Persistent oligoarthritis* | 28 (15.4%) |
| *Extended oligoarthritis* | 25 (13.7%) |
| *Unknown* | 50 (27.5%) |
| *Polyarthritis* | 46 (25.3%) |
| *RF+ polyarthritis* | 1 (0.5%) |
| *RF- polyarthritis* | 40 (22.0%) |
| *Unknown* | 5 (2.7%) |
| *Psoriatic arthritis* | 8 (4.4%) |
| *Enthesitis-related arthritis* | 1 (0.5%) |
| *Systemic arthritis* | 24 (13.2%) |
| **Age at JIA diagnosis, median (IQR)** | 5.1 (3.0 – 7.0) |
| **Drug therapy at MMR booster vaccination, n (%)** | |
| *No immunosuppressive therapy/NSAIDs* | 92 (50.5%) |
| *Systemic corticosteroids* | 6 (3.3%) |
| *csDMARDs* | |
| *Methotrexate monotherapy* | 50 (27.5%) |
| *Azathioprine monotherapy* | 1 (0.5%) |
| *Leflunomide monotherapy* | 1 (0.5%) |
| *bDMARDs* | |
| *Adalimumab monotherapy* | 1 (0.5%) |
| *Etanercept monotherapy* | 10 (5.5%) |
| *csDMARD and bDMARD combination therapy*[1] | 17 (9.3%) |

[1]bDMARDs: ADA (n = 13), ETN (n = 3) and tocilizumab (n = 1)

IQR: interquartile range, JIA: juvenile idiopathic arthritis, MMR: measles mumps rubella, NSAID: non-steroidal anti-inflammatory drug, RF: rheumatoid factor

**Table 2. Crude and adjusted linear regression analyses for the association between bDMARD therapy at the time of booster vaccination and absolute MMR IgG antibody levels after five years.**

| Virus | Analysis | Mean difference for bDMARD use vs. no bDMARD use (95% CI) | *P*-value |
|---|---|---|---|
| Measles (index) | Crude | -0.45 (-0.83 – 0.08)* | 0.02* |
| | Adjusted[1] | -0.49 (-0.89 – -0.09)* | 0.02* |
| Mumps (index) | Crude | -0.30 (-1.12 – 0.51) | 0.47 |
| | Adjusted[1] | -0.34 (-1.22 – 0.55) | 0.46 |
| Rubella (IU/ml)[2] | Crude | -0.14 (-1.14 – 0.85) | 0.78 |
| | Adjusted[1] | -0.37 (-1.46 – 0.72) | 0.51 |

*statistically significant effect

[1]adjusted for gender, JIA subtype and age at JIA diagnosis

[2]antibody levels were log-transformed

**Table 3. Crude and adjusted logistic regression analyses for the association between bDMARD therapy at the time of booster vaccination and a protective MMR IgG antibody concentration after five years.**

| Virus | Analysis | Odds ratio for bDMARD use vs. no bDMARD use (95% CI) | *P*-value |
|---|---|---|---|
| Measles | Crude | 0.23 (0.06 – 0.87)* | 0.03* |
| | Adjusted[1] | 0.25 (0.05 – 1.07) | 0.06 |
| Mumps | Crude | 0.24 (0.04 – 1.46) | 0.11 |
| | Adjusted[1] | 0.18 (0.02 – 1.50) | 0.11 |
| Rubella | Crude | 0.31 (0.09 – 1.13) | 0.07 |
| | Adjusted[1] | 0.32 (0.07 – 1.38) | 0.12 |

*statistically significant effect

[1]adjusted for gender, JIA subtype and age at JIA diagnosis

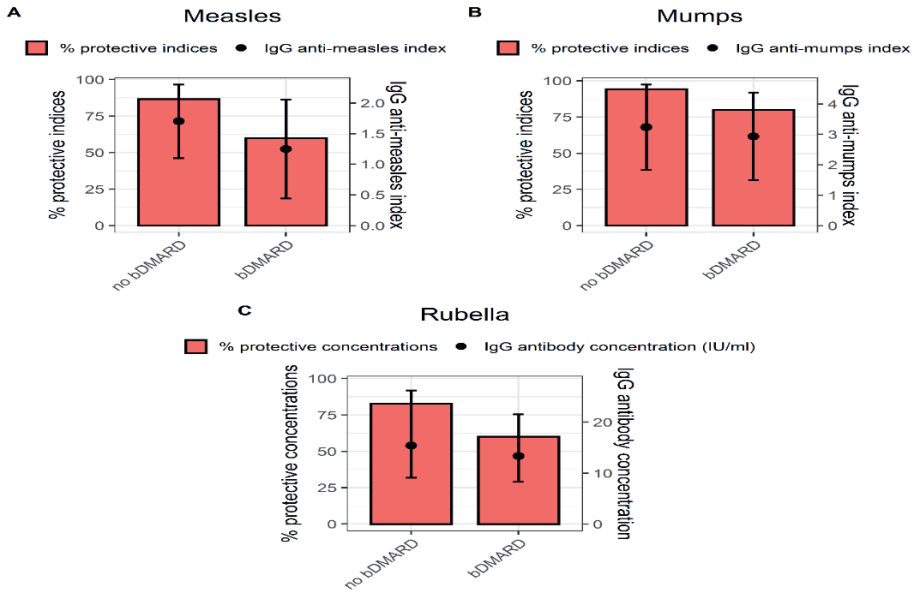



**Figure 1. MMR-specific IgG antibody assays five years post-booster vaccination (n = 67).** Data are presented separately for JIA patients who did and did not receive bDMARD therapy at the time of booster vaccination. A & B: red bars indicate % protective indices >1.1. Black dots indicate mean indices with standard deviation. C: red bars indicate % protective concentrations ≥10 IU/ml. Black dots indicate geometric mean concentrations with 95% confidence interval.

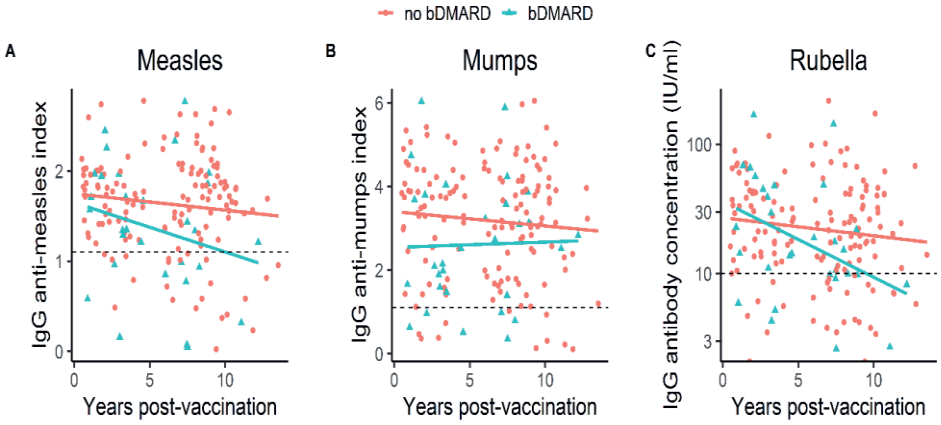



**Figure 2. Scatter plot with linear trend of MMR antibody levels in last collected samples (n = 169) over time as a function of bDMARD use at the time of booster vaccination.** Horizontal dotted line indicates protective threshold.

**SUPPLEMENTARY MATERIAL**

**Supplementary Table 1. Results (n, %) of MMR-specific IgG antibody assays five years post-booster vaccination (n = 67).**

| Virus | Outcome | No bDMARD at vaccination (n= 52) | bDMARD at vaccination (n = 15) |
|---|---|---|---|
| Measles | Positive | 45 (85.6%) | 9 (60.0%) |
| | Inconclusive | 2 (3.8%) | 0 (0.0%) |
| | Negative | 5 (9.6%) | 6 (40.0%) |
| Mumps | Positive | 49 (94.2%) | 12 (80.0%) |
| | Inconclusive | 0 (0.0%) | 1 (6.7%) |
| | Negative | 3 (5.8%) | 2 (13.3%) |
| Rubella | Positive | 43 (82.7%) | 9 (60.0%) |
| | Inconclusive | 4 (7.7%) | 4 (26.7%) |
| | Negative | 5 (9.6%) | 2 (13.3%) |

**Supplementary Table 2. Linear regression analyses for a difference in adjusted association between follow-up time post-MMR booster vaccination and IgG antibody levels between biological and non-biological users at vaccination.**

| Virus | Variable[1] | Mean difference (95% CI) | *P*-value |
|---|---|---|---|
| Measles | Follow-up time (years) | -0.02 (-0.05 – 0.01) | 0.13 |
| | Follow-up time (years)*bDMARD use | -0.04 (-0.11 – 0.04) | 0.32 |
| Mumps | Follow-up time (years) | -0.02 (-0.08 – 0.04) | 0.51 |
| | Follow-up time (years)*bDMARD use | 0.06 (-0.12 – 0.23) | 0.53 |
| Rubella | Follow-up time (years) | -0.10 (-2.41 – 0.50) | 0.20 |
| | Follow-up time (years)*bDMARD use | -2.85 (-6.98 – 1.28) | 0.18 |

[1]adjusted for gender, JIA subtype and age at JIA diagnosis

# Chapter 4

# The Protective Effect of COVID-19 Vaccination Against MIS-C

# The protective effect of COVID-19 vaccines on developing multisystem inflammatory syndrome in children (MIS-C): a systematic literature review and meta-analysis.

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**Pediatrics Rheumatology Journal 2023 Aug 7;21(1):80.**

**ABSTRACT**

**Objective**: To review whether the current COVID-19 vaccines can prevent the occurrence of multisystem inflammatory syndrome in children (MIS-C) and adolescents.

**Methods**: A systematic literature review and meta-analysis were performed. The data were abstracted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Primary outcome was the efficacy of COVID-19 vaccination in preventing MIS-C development. The search was performed in PubMed and Embase.

**Results**: The review yielded 13 studies, which were included for critical appraisal and data extraction. The available studies showed a reduced incidence of MIS-C after mRNA COVID-19 vaccination in children aged 12-18 years. Four studies were eligible for meta-analysis and the pooled odds ratio for MIS-C in vaccinated children compared to unvaccinated children was 0.04 (95% confidence interval: 0.03 – 0.06). Additionally, the risk of MIS-C as an adverse effect of vaccination was much lower compared to the risk of MIS-C post-infection.

**Conclusions**: Our systematic review highlights the current available evidence on the efficacy of COVID-19 vaccination in preventing MIS-C. The published studies so far – mainly conducted during the Delta wave – indicate that (original strain) COVID-19 mRNA vaccines in children are safe and associated with significantly less development of MIS-C. These findings further reinforce the recommendation for COVID-19 vaccination in children, which should be promoted and largely supported.

**Keywords**: MIS-C, PIMS-TS, COVID-19, mRNA vaccine.

## BACKGROUND

Coronavirus disease 2019 (COVID-19) mRNA vaccines demonstrated safety, immunogenicity, and efficacy against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in adults, adolescents (12 – 18 years) and children (5 – 11 years), and were therefore authorized by the Food and Drug Administration (FDA) and at the end of 2021 by the European Medicine Agency (EMA) for use in children aged 5-11 years (1–3). There has been debate on whether children should be vaccinated, as the pediatric population generally shows a milder and non-fatal course of COVID-19 compared to adults (4). However, in some children, COVID-19 can have severe consequences. There has been an increasing number of reported cases of pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS), also called multisystem inflammatory syndrome in children (MIS-C). This severe hyperinflammatory syndrome, which shares some similarities with Kawasaki disease and some unique clinical features with serious complications, occurs approximately three weeks (range 2-6 weeks) after SARS-CoV-2 infection (5). It is defined by the Centers for Disease Control and Prevention (CDC) as a severe illness requiring hospitalization in individuals aged <21 years, with fever for ≥24 hours, elevated inflammatory markers with multisystem (≥ 2) organ involvement and a suspected or confirmed SARS-CoV-2 infection within the last four weeks (6). Even though MIS-C and Kawasaki disease show phenotypic similarities, there are important differences regarding morbidity and mortality. MIS-C is more associated with gastrointestinal symptoms and cardiovascular system involvement (7). Cardiac involvement, including diminished ventricular function, coronary artery dilatation and diffuse myocardial oedema, are more prevalent and severe in MIS-C than in Kawasaki disease and cardiogenic shock is observed in MIS-C in 40-80% of the patients compared to 2-7% in Kawasaki (7,8). Additionally, more than 60% of the MIS-C patients are admitted to the pediatric intensive care unit (PICU) (7–9). Mortality rates for MIS-C are estimated to be around 1% in high-income countries, but significantly higher in developing countries (reported up to 9 %) (10) and overall higher than in Kawasaki disease, which has a mortality rate of 0.1-0.3% in patients treated with intravenous immunoglobulin (IVIG) (11,12). MIS-C patients are currently treated with IVIG, glucocorticosteroids, aspirin, supportive treatments, and refractory cases with additional biological DMARDs (13).

As of May 2022, a total of 8,525 MIS-C patients have been reported in the United States, of whom 69 patients have died (14). Available estimates of cases worldwide are lacking. Most MIS-C patients were healthy children, not known to

have an underlying medical disorder at time of infection and MIS-C. Until now, the pathophysiology of MIS-C remains largely unknown (15), but it has been hypothesized that MIS-C is a dysregulated immune response characterized by a cytokine storm associated with a superantigen-like activation of T-cells (16–19).

Currently, it is not clear if available COVID-19 vaccines are able to prevent these serious complications of SARS-CoV-2 infection in children. The purpose of this paper is therefore to perform a systematic literature review and meta-analysis on whether current COVID-19 vaccines have a protective effect on the development of MIS-C in children and adolescents aged 5-18 years.

## METHODS

### Literature search and data extraction

We conducted a systematic review of the literature on the protective effect of the COVID-19 vaccine on developing multisystem inflammatory syndrome in children (MIS-C). The systematic review protocol was designed in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) (20). The research question was: “does the COVID-19 vaccine have a protective effect on developing multisystem inflammatory syndrome in children (MIS-C)?”. The primary endpoint was efficacy and the secondary endpoint was safety. Efficacy was defined as the capacity of COVID-19 vaccines to prevent the development of MIS-C and safety by evaluating the data on COVID-19 vaccination as a trigger for MIS-C development.

The research question was adapted into search terms according to the PICO method (patient-intervention-comparison-outcome). Participants: children and adolescents 5-18 years old; intervention: COVID-19 vaccination; comparison: children who did not receive a COVID-19 vaccination; outcome: MIS-C, as per the CDC/WHO case definition or ICD-10 diagnosis codes for MIS-C (DB972B and DB972B1). Search terms were combined and are shown in Supplementary Data S1.

LvdG and MHS were in charge of the systemic literature review, removal of duplicates, independently reviewing abstracts of each reference to identify articles for a full review, reviewing the full articles of eligible abstracts and determined each article’s eligibility for inclusion independently. Discrepancies were resolved by consensus, with additional input from MJ as required. The search was performed in June and July 2022. Searched databases included Medline (via PubMed) and Embase. The list was further extended by reviewing the reference lists of identified papers to check for studies that might have been missed in the search strategy, i.e. the “snowballing” method. All original studies, including cohort studies, surveys and surveillance studies published up to June, 2022 were eligible for inclusion. Exclusion criteria were case-report and case

series studies, literature or systematic reviews, non-English papers, papers focusing on adults or patients with comorbidities, articles focusing on MIS-C without reference to vaccination, and articles with other primary endpoints. Papers focusing on the effect of vaccination on SARS-CoV-2 infection rather than MIS-C were excluded as well. LvdG and MJ assessed the quality of the included studies.

**Meta-analysis**

A meta-analysis was performed in order to quantify the effect of COVID-19 vaccination on the occurrence of MIS-C. For this analysis, only nationwide observational studies without overlapping cases of MIS-C were eligible. If missing from the included studies, frequency of age-matched vaccinated and unvaccinated children without MIS-C were obtained from national COVID-19 dashboards and censuses for similar time periods (21–26). Pooled odds ratios (OR) with corresponding 95% confidence intervals (CI) were calculated using a common (i.e. fixed) and random effects model with Mantel-Haenszel weighting. Heterogeneity of included studies was quantified using the $I^2$ and $\tau^2$ measures and tested using the Cochran's Q test. Publication bias was visually assessed using a funnel plot.

## RESULTS

**Included studies**

The systemic literature review yielded 13 studies that met the criteria and these were included for data extraction. The studies included two case-control studies, two randomized controlled trials (RCTs), two surveillance studies, two cohort studies, one project report, one survey, one risk-benefit analysis (outline of a CDC presentation), one brief report and one editorial letter. The brief report and editorial letter were used for background information since no new results were presented in these articles. Most studies researched the original strain vaccine during the COVID-19 Delta variant dominant era, but some studies compared results from this period time with cases during a period dominated by the Omicron variant.

The PRISMA flow chart for this study is shown in Figure 1. A summary of all the included studies including the quality of the studies, using standardized critical appraisal criteria and levels of evidence of the Oxford Centre for Evidence-Based Medicine (27), is shown in Table 1.

**Efficacy of current vaccines in preventing MIS-C development**

Recent research by Levy et al. in France and Zambrano et al.in the United States showed, in a cohort study and case-control study respectively, that COVID-19 mRNA vaccination is associated with a lower incidence of MIS-C in children aged

12-18 years compared to unvaccinated and incompletely vaccinated children (28,29).
Levy et al. reported a hazard ratio for the risk of MIS-C of 0.09 (95% CI: 0.04-0.21) for adolescents after the first vaccine dose compared with unvaccinated adolescents. Pediatric patients diagnosed with MIS-C were included during the Delta wave, between September 1 and October 31, 2021. The vaccine status of patients was known; >95% were vaccinated with BNT162b2 (Pfizer-BioNTech), <5% with mRNA-1273 (Moderna) and <1% with other COVID-19 vaccines. During the observational period, 107 MIS-C cases were reported. Among them were 33 (31%) adolescents eligible for vaccination with median age of 13.7 years. None of these children were fully vaccinated (i.e. received two doses), seven children received one dose and 26 children with MIS-C were unvaccinated (28). Similar results were observed in the study by Zambrano et al. They conducted their research in the era that the Delta variant of SARS-CoV-2 was most prevalent as well, from July 1 to December 9, 2021. The adolescents median age was 14.5 years and 102 MIS-C cases were reported; 95% of the cases had not been vaccinated and 5% were fully vaccinated children. Importantly, 37% of the MIS-C patients, all of them unvaccinated, needed life support including invasive mechanical ventilation, vasoactive infusions and extracorporeal membrane oxygenation (ECMO). Authors concluded that two doses of the Pfizer-BioNTech vaccine lead to a protective effect against MIS-C with an effectiveness of 91% (29).

Nygaard et al. aimed to determine the incidence of MIS-C in the Danish population after infection during the Delta era in children aged 0-17 years old between August 1, 2021 and February 1, 2022 (30). During this period, 52 MIS-C cases were reported. One MIS-C patient was fully vaccinated among 9,855 vaccinated individuals and 51 patients were unvaccinated among 175,458 unvaccinated individuals infected with SARS-CoV-2. Of these patients, 48 had PCR-confirmed SARS-CoV-2 infection with the Delta variant. Based on these observations, the incidence of MIS-C in unvaccinated individuals was estimated to be 1 in 3,400 unvaccinated children (183 per 1,000,000 unvaccinated person-years) compared to an incidence of MIS-C in fully vaccinated children of 1 in 9,900 individuals (11 per 1,000,000 vaccinated person- years). The rate of vaccination in October 2021 was 72% for children aged 12-15 years and 88% for children aged 16-17 years in Denmark (31). Nygaard et al. concluded that the vaccine efficacy against MIS-C is 94% (30), comparable with the findings of Zambrano et al.

Miller et al. aimed to compare the incidence of MIS-C cases during Delta and Omicron circulation in the United States in vaccinated and unvaccinated children (32). A total of 3,554 patients were reported between October 18, 2020 and July

8, 2021 during the third, Delta predominant, wave. However, during the fourth wave, when Omicron was in circulation between July 9, 2021 and January 31, 2022, a total of 2,116 MIS-C cases were reported. This was a clear reduction in incidence, and during this wave, the proportion of patients aged 5-11 years was significantly higher compared with the third wave ($p<.001$). This could be explained by a protective effect of the vaccine, which was given to children aged 12-18 years during the Delta wave, or merely the new Omicron variant. Overall, 763 MIS-C patients aged 5-20 years were eligible to be assessed for full vaccination status before MIS-C onset; 697 (91%) of these patients had no vaccine doses reported and 23 (3.0%) were fully vaccinated. ICU-level care was reported in a higher proportion of patients with no vaccination compared to fully vaccinated patients (61% vs. 48%). All 15 patients who received ECMO and 17 who died were reported to be non-vaccinated (32).

Additionally, a recent study of MIS-C in Israel in which 6% and 15% of patients in the Delta and Omicron waves, respectively, had received two doses of COVID-19 vaccine at least two weeks before admission, reported that MIS-C incidence was lower during the Omicron wave compared with the Alpha and Delta variant waves, and the proportion of cases with ICU admission decreased during successive waves (33).

**Meta-analysis of protective effect**

Four studies were eligible for a meta-analysis on the effect of COVID-19 vaccination on MIS-C development (Figure 2). Frequency of vaccinated and unvaccinated children without MIS-C were obtained from national COVID-19 dashboards and censuses for the studies of Nygaard et al. (age group: 10-17 years old), Miller et al. (age group: 5-17 years old) and Stein et al. (34) (age group: 0-19 years old)(30,32,34). These data are provided in Supplementary Table S1. The pooled OR for MIS-C in vaccinated children compared to unvaccinated children was 0.04 (95% confidence interval: 0.03 – 0.06). Pooled ORs were significantly protective in both the common and random effects model. There was no indication for heterogeneity of included studies ($p = 0.23$). The funnel plot was asymmetric indicating a possibility of publication bias (Figure 3).

**Safety data on COVID-19 vaccination as a trigger for MIS-C development**

The previously discussed studies have concluded that COVID-19 mRNA vaccines are safe and effective in preventing MIS-C in children aged 12-18 years. Because MIS-C is considered an auto-immune or abnormal immune reaction after a SARS-CoV-2 infection, it is of great importance to monitor whether MIS-C can occur after COVID-19 vaccination as well.

A recent study by Yousaf et al. stated, following an integrated surveillance study in the United States with data from December, 2020 - August, 2021, that MIS-C

after a COVID-19 vaccination is very rare (35). Using two surveillance systems, they identified 21 MIS-C cases. The mean age of the patients was 16 years and 62% were male. Fifteen MIS-C patients received BNT162b2 (Pfizer-BioNTech) and ten of them had only received one dose before disease onset. The median time between the last injection and disease onset was eight days when children had received one dose (11 MIS-C cases), and five days when they were fully vaccinated (10 MIS-C cases). Importantly, 15 out of these 21 patients had evidence of a past or recent SARS-CoV-2 infection (35).

Similar observations were seen in France (36). A post-authorization national population-based surveillance study was performed in children aged 12-17 years with data from June, 2021 till January, 2022. During this time, 102 cases of myocarditis or pericarditis and 12 cases of MIS-C were reported as the authors agree that those are likely different entities. The median age of the patients was 12 years; 83% were male. Ten patients had received BNT162b2 (Pfizer-BioNTech) and two patients had received mRNA-1273 (Moderna). The median time from vaccination to the onset of illness ranged from 1-42 days. Six cases occurred following the first dose and six following the second dose. In the French study, 4 out of 12 patients had evidence of a recent SARS-CoV-2 infection. The reporting rate of MIS-C was 2.9 per 1,000,000 vaccinated children aged 12-17 years. To compare, a MIS-C rate of 113.3 per 1,000,000 matched age infected children was determined. Furthermore, a lower rate of PICU transfer was seen for post-vaccine MIS-C (4/12, 33%) compared to post-SARS-CoV-2 MIS-C (143/199; 72%). It was concluded that the risk of MIS-C as a side effect of the mRNA vaccine is much lower than the risk of MIS-C post-infection, and very few vaccine-related adverse events were reported (36).

In addition, data from Hoste et al. from an international cross-sectional survey showed that children who had a history of MIS-C could be vaccinated safely and effectively. Two hundred seventy-three patients with a history of MIS-C were vaccinated with mRNA vaccine and all reported cases did not report relapses of MIS-C or other severe inflammatory side effects after SARS-CoV-2 (37).

## DISCUSSION

In this systemic literature review and meta-analysis, the effect of the mRNA COVID-19 vaccine on the development of MIS-C has been addressed. This systematic review lends supportive evidence that vaccination of children and adolescents is highly associated with reduced MIS-C development and underscores the importance of vaccination of all eligible children. In our meta-analysis, we found that the pooled OR for MIS-C in vaccinated children compared to unvaccinated children was 0.04 (95% confidence interval: 0.03–0.06).

Studies conducted in France and the United States during the Delta wave have shown a reduced incidence of MIS-C after mRNA COVID-19 vaccination in children aged 12-18 years, with a hazard ratio for the risk of MIS-C of 0.09 after one vaccine dose compared with unvaccinated adolescents in France (28). Two doses of the Pfizer-BioNTech vaccine led to a protective effect against MIS-C with an effectiveness of 91% in the US cohort (29). In addition, in Denmark, the Pfizer–BioNTech vaccine was protective against MIS-C in 94% during the Delta wave (30).

Altogether, it can be concluded that the protective effect of vaccination outweighs the triggering effect of vaccination on MIS-C, as the risk of developing MIS-C as an adverse effect of vaccination is much lower (2,9 per 1,000,000 children), compared to the risk of MIS-C post-infection (113 per 1,000,000 children) (36). Furthermore, based on the literature so far, it remains unknown if COVID-19 vaccination really can cause MIS-C or whether vaccinated children who developed MIS-C had a recent (sometimes unnoticed) SARS-CoV-2 infection.

It is noteworthy that the conclusions from our systemic review are based mostly on children in the age category of 12-18 years old. On October, 2021 the Pfizer-BioNTech vaccine was approved by the FDA for children aged 5-11 years (2,3). Therefore, the preventive effect seen in adolescents has not yet been evaluated in these younger children (38). In 2021, the CDC mentioned that MIS-C was most frequent among children 5-11 years, with 2,316 cases of MIS-C reported in the United States at that time (39). However, a plausible explanation for this would be that adolescents were already vaccinated during this period and since this has a protective effect, the number of MIS-C patients among the younger children increased. Based on a benefit-risk analysis from the CDC using recent epidemiological data for both 5-11 years old males and females, 130 MIS-C cases could be prevented for every million Pfizer-BioNTech vaccinations. Thus, the number needed to vaccinate (NNV) was 1,1226, indicating that in order to prevent one MIS-C case in children aged 5-11 years, 1,1226 children should be vaccinated (39). In addition to avoiding the development of MIS-C, COVID-19 vaccination also decreases the morbidity and mortality associated with the disease with low numbers of adverse events associated with the vaccination (40,41). In the upcoming months, data should be gathered to make a similar evidence-based conclusion about vaccination and MIS-C in children younger than 12 years.

The exact pathophysiology of MIS-C remains unknown, but recent research showed that patients with MIS-C have a different type of host immune response compared to patients with acute COVID-19. This immune response includes superantigen-like activation of T-cells with expansion of polyclonal expansion of TCR Vbeta 21.3$^{+}$ CD4$^{+}$ and CD8$^{+}$ T-cells, something which is not seen in toxic

shock syndrome, Kawasaki disease or COVID-19 in general. In addition, host genetics might alter the susceptibility to develop MIS-C (16–19,42–44).
Possible explanations for a protective mechanism of the vaccine on MIS-C include the prevention of COVID-19, since MIS-C is a complication of this disease and the vaccine does not seem to induce the super-antigen driven T-cell clone, whereas the wildtype infection does. A second hypothesis is that the vaccine could have a direct immune protective effect, preventing a hyper inflammatory condition (30,44).

The epidemiology of the COVID-19 virus is changing constantly, and the Omicron variant may lead to a milder disease course but might be also more contagious (38). It is not known yet if the Omicron variant is more or less associated with MIS-C compared to other variants (45). Future COVID-19 variants may affect the clinical course and may influence the incidence of MIS-C cases.
The studies included in this systematic review were conducted during a period when the Delta variant was dominant and Omicron was looming (38). The question arises, whether the conclusions that were made about the Delta era can be translated to the Omicron era. The CDC reported that Omicron has a higher transmission rate (38). Since Omicron has become dominant, researchers have focused on comparing COVID-19 and MIS-C cases between the Delta and Omicron era. Following an observational retrospective study that was performed in Rio de Janeiro with children aged 0-18 years, it was concluded that fewer hospital admissions occurred during the Omicron wave (46). Besides an increased number of children with acquired immunity due to prior (asymptomatic) SARS-CoV-2 infection and the fact that the Omicron variant is less pathogenic, another explanation for this reduction in hospital admissions could be the increased number of vaccinated children. Miller et al. aimed to compare the incidence of MIS-C cases during the Delta and Omicron waves in the United States and found a clear reduction in incidence and less often severe organ damage during the latter wave (32). However, they observed an increase in children aged 5-11 years with MIS-C. Similar observations were observed in Israel (33). This could again indicate that the COVID-19 vaccine, which was given to children aged 12-18 years during the Delta wave, has a protective effect on developing MIS-C. These findings might also indicate the importance of COVID-19 vaccination in children aged 5-11 years, although the number of studies in the current systematic review that included this age group was limited. Other possible explanations for the reduced number of (severe) MIS-C cases during the Omicron wave include lower pathogenicity of the Omicron variant, prior SARS-CoV-2 infection and improvement in the treatment of MIS-C.

This systematic review has some limitations. These findings reflect the current reality in the complicated situation of a global pandemic, multiple variant

outbreaks (Omicron variant had not been studied in most of the articles) and continuing vaccination processes all over the world with gradual addition of further age groups. Furthermore, the main limitation of the included studies is their small group size and heterogeneous study designs. However, MIS-C is a rare complication and the small group size can therefore still be seen as realistic, especially because the studies are based on national data which enhances statistical power. Another limitation concerns the virus variant, as the studies were conducted during the SARS-CoV-2 Delta wave. It has not yet been investigated whether the mRNA vaccine will also show a high vaccine efficacy against MIS-C during the SARS-CoV-2 Omicron wave or other future variants, and this also cannot be concluded with certainty from this systematic review. This generalization might be complicated even further since an increased number of children around the world will have currently already experienced a SARS-CoV-2 infection. Besides the low number of patients in some studies, there were few reports about regional variation and individual risks factors for MIS-C, such as sex, race/ethnicity, and comorbidities. Miller et al mention a predominance of males in MIS-C and an increasing proportion of non-Hispanic White and non-Hispanic Black patients during successive COVID-19 waves (32). The studies by Levy et al, Zambrano et al, and Nygaard et al. also report a male to female predominance in MIS-C (of 81%, 71% and 73%, respectively) (28–30).This analysis was not designed to evaluate waning immunity or duration of protection against MIS-C. Regarding the safety profile studies, there could be some bias related to recall or notification of adverse events. Nevertheless, it seems unlikely that healthcare providers would not have been notified of important inflammatory complications or MIS-C relapses. Regarding the meta-analysis, not all studies reported information about the number of vaccinated and unvaccinated children without MIS-C and these data had to be collected from national dashboards and censuses. This resulted in some slight discrepancies between age groups of children with and without MIS-C and hence we could not present risk ratios and a NNV, but merely ORs. Also, the funnel plot indicated a possibility of publication bias, but because of the low number of included studies this is uncertain. Nevertheless, the forest plot, $I^2$ statistic and Cochran's Q test indicated no heterogeneity of study results and we performed both fixed and random effects meta-analyses with similar results. Finally, it is well possible that some reported cases of MIS-C after a COVID-19 vaccination were related to unnoticed or undiagnosed SARS-CoV-2 infections with false negative infectious investigations.

This review could become an important contribution for discussion whether or not to vaccinate children against COVID-19. Eventually, the review can help to increase international COVID-19 vaccination rates in children from the age of 5 years. Currently, in the United States, only 29% of eligible children have been

fully vaccinated in the age group of 5-11 years, and 59% in the age group of 12-17 years (47).

In the coming period, data collection will have to be continued in order to monitor the incidence of MIS-C, the vaccine efficacy in younger children (<12 years old) and possible side effects. The epidemiology of SARS CoV-2 infection is changing rapidly and a possible new wave may present. With the small number of cases of MIS-C globally, establishing an international research collaboration would be of great value to combine studies and data effectively (5). Finally, more research will be needed to compare MIS-C cases triggered by the Delta, Omicron, and possible future unknown variants (45).

## CONCLUSIONS

Our systematic literature review and meta-analysis indicate that COVID-19 mRNA vaccines in children are safe and associated with significantly less development of MIS-C during the Delta wave. MIS-C after COVID-19 vaccination in children is rare and significantly less common than after SARS-CoV-2 infection in the same age-group. These findings form the most comprehensive review and analysis of the available evidence, further reinforcing the recommendation for COVID-19 vaccination children, and could greatly contribute to evidence-based guidelines. Still, further larger studies are needed to make an evidence-based statement on the protective effect of COVID-19 vaccination on developing MIS-C, addressing children <12 years of age and comparing MIS-C cases triggered by the Delta, Omicron and other SARS-CoV-2 variants.

## ABBREVIATIONS

CDC: Centers for Disease Control and Prevention
COVID-19: coronavirus disease 2019
ECMO: extracorporeal membrane oxygenation
EMA: European Medicine Agency
FDA: Food and Drug Administration
MIS-C: multisystem inflammatory syndrome in children
NNV: number needed to vaccinate
PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analysis
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

## DECLARATIONS

### Ethics approval and consent to participate
Not applicable.

### Consent for publication
Not applicable.

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

### Competing interests
All authors declare no conflicts of interest.

### Funding
No funding was received for this research.

### Authors' contributions
LvdG and MHS were in charge of the systemic literature review and drafted the final manuscript. LvdG and MJ assessed the quality of the included studies. Statistical analyses were performed by JvS. NW, SV and MJ conceptualized and designed the study. All authors critically reviewed, revised and approved the final manuscript.

**Acknowledgements**
Not applicable.

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# TABLES AND FIGURES

**Table 1** Characteristics of the studies selected in the systematic review and meta-analysis

| | Authors | Date | Study design | Vaccine | Viral variant | Study population | Patients (age) | Adverse events | Level of evidence (MIS-C) | Level of evidence (safety) |
|---|---|---|---|---|---|---|---|---|---|---|
| **Studies focusing on effectiveness of COVID-19 vaccination against MIS-C.** | | | | | | | | | | |
| 1 | Zambrano et al. (29) | 2022, January | Case-control study | BNT162b2 (Pfizer-BioNTech); 2 doses | Delta | 102 MIS-C cases, 5 fully vaccinated, 97 unvaccinated. United States. | 12–18 years | - | 2B | NA |
| 2 | Levy et al. (28) | 2021, December | Cohort study | BNT162b2 (Pfizer-BioNTech; > 95%), mRNA-1273 (Moderna; < 5%), and other COVID-19 vaccines (< 1%) | Delta | 33 MIS-C cases, none fully vaccinated, 7 partially vaccinated, 26 unvaccinated. France. | 12–18 years | - | 2B | NA |
| 3 | Nygaard et al. (30) | 2022, May | Cohort study | BNT162b2 (Pfizer-BioNTech) | Delta | 52 MIS-C cases, 1 fully vaccinated, 52 unvaccinated. Denmark. | Unvaccinated: < 18 years Vaccinated: 12–18 years | - | 2 C | NA |
| 4 | Miller et al. (32) | 2022, June | Case-control study | mRNA vaccine | Delta; Omicron | 763 MIS-C cases, 23 fully vaccinated, 40 partially vaccinated, 697 unvaccinated. United States. | 5–20 years | - | 2B | NA |
| 5 | Oliver et al. (39,48) | 2021, December | Risk-benefit analysis | BNT162b2 (Pfizer-BioNTech) | - | 130 MIS-C cases prevented. United States. | 5–11 years | - | 2 C | NA |
| 6 | Stein et al. (34) | 2022, January | Project report | BNT162b2 (Pfizer-BioNTech) | - | 220 MIS-C cases, 1 fully vaccinated. Israel. | Unvaccinated: < 18 years Vaccinated: 12–18 years | - | 2 C | NA |
| **Studies focusing on MIS-C as a possible side effect of COVID-19 vaccination.** | | | | | | | | | | |
| 7 | Ouldali et al. (36) | 2022, April | Population-based surveillance | BNT162b2 (Pfizer-BioNTech); mRNA-1273 (Moderna) | - | 12 cases of hyper-inflammation syndrome. | 12–17 years | - | 2 C | NA |
| 8 | Yousaf et al. (35) | 2022, February | Surveillance study | BNT162b2 (Pfizer-BioNTech); mRNA-1273, Ad26.COV2.S | Delta | 1 MIS-C case per million individuals receiving one or more doses. | 12–20 years | - | 2 C | NA |
| 9 | Hoste et al. (37) | 2022, May | Cross-sectional survey | mRNA vaccine | - | 273 patients with a MIS-C history, no relapse. | - | No relapses in individuals with history of MIS-C. | 2 C | NA |
| **Studies about COVID-19 vaccine safety, immunogenicity and efficacy.** | | | | | | | | | | |
| 10 | Creech et al. (3) | 2022, May | RCT | mRNA-1273 (Moderna) | Delta | - | 6–11 years | No cases of MIS-C were reported. | NA | 1B |
| 11 | Walter et al. (2) | 2022, April | RCT | BNT162b2 (Pfizer-BioNTech) | Delta | - | 5–11 years | No cases of MIS-C were reported. | NA | 1B |
| **Other.** | | | | | | | | | | |
| 12 | Curatola et al. (45,49) | 2022, February | Brief report | - | Omicron | - | - | - | - | - |
| 13 | Mangat et al. (38) | 2022, March | Editorial letter | - | Omicron | - | - | - | - | - |

*Level of evidence per the Oxford Centre for Evidence-Based Medicine; (MIS-C): level of evidence for preventing MIS-C, (safety): level of evidence for vaccine safety. NA: not applicable.*

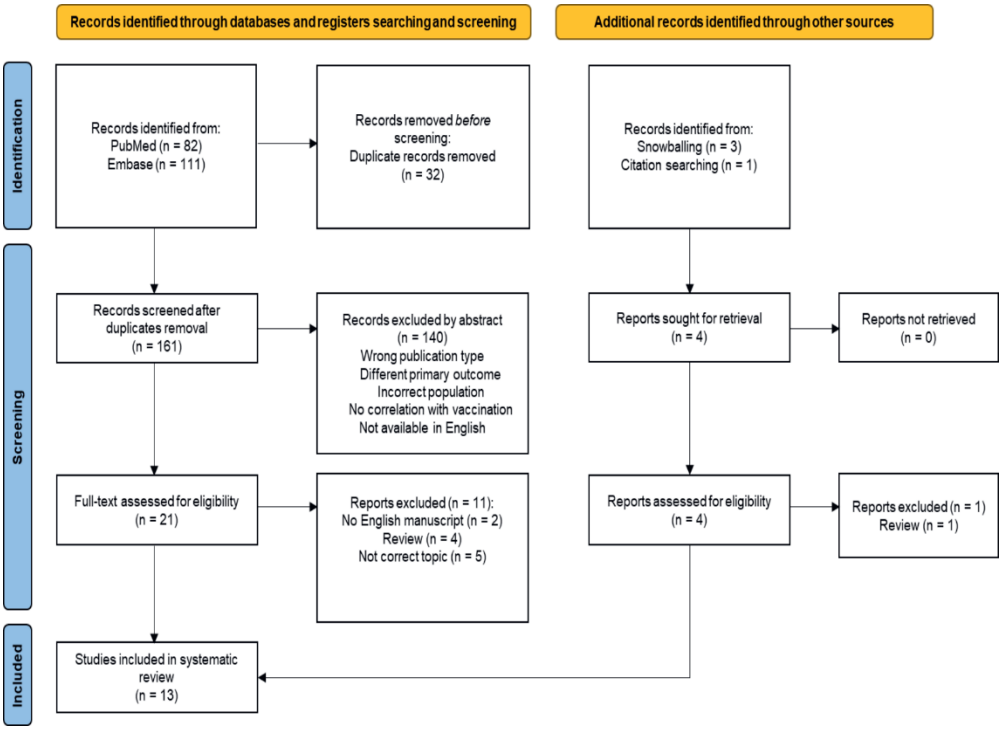



Figure 1. **PRISMA flow diagram for the search of databases**.

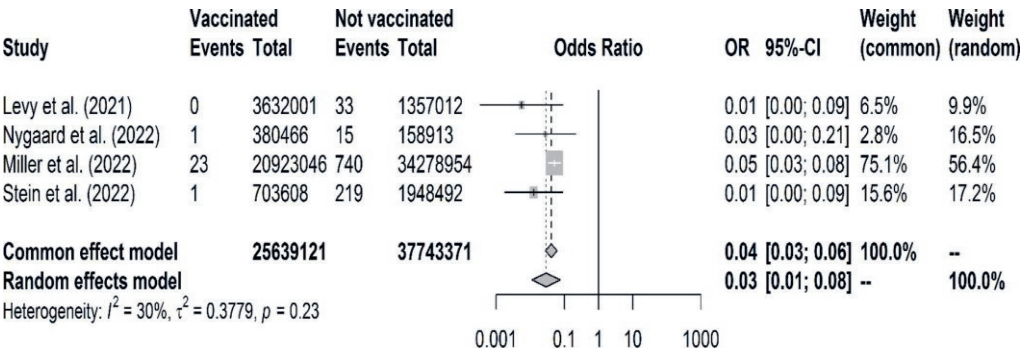



**Figure 2. Forest plot of meta-analysis for the effect of COVID-19 vaccination on the number of MIS-C events.** Boxes around study effect estimates reflect relative weight in the analysis. P-value reflects Cochran's Q test of heterogeneity. CI: confidence interval, OR: odds ratio.

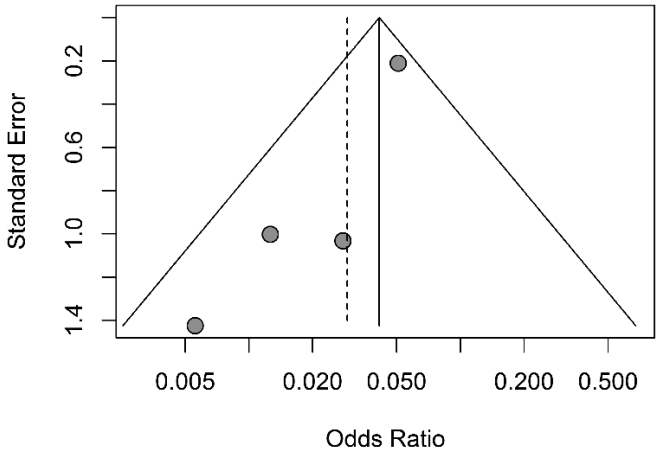



**Figure 3. Funnel plot of studies included in meta-analysis**. Vertical line indicates pooled common effects estimate. Vertical dashed line indicates pooled random effects estimate.

**SUPPLEMENTARY MATERIAL**

**Supplementary Data S1. Search strings used for identifying relevant studies.**

**Search string in PubMed**

(child*[Title/Abstract] OR adolescent*[Title/Abstract] OR young adult*[Title/Abstract]) AND (vaccin*[Title/Abstract] OR (active immunisation[Title/Abstract] OR active immunization[Title/Abstract])) OR (vaccination[MeSH Terms]) AND (MIS-C[Title/Abstract] OR PIMS-TS[Title/Abstract] OR (pediatric multisystem inflammatory disease[Title/Abstract]) OR (paediatric multisystem inflammatory syndrome[Title/Abstract]) OR (paediatric multi-system inflammatory syndrome[Title/Abstract]) OR (paediatric inflammatory multisystem syndrome[Title/Abstract]) OR (multi system inflammatory syndrome in children[Title/Abstract]) OR (pediatric multisystem inflammatory syndrome[Title/Abstract]) OR (pediatric multi-system inflammatory syndrome[Title/Abstract]) OR (pediatric inflammatory multisystem syndrome[Title/Abstract]))

**Search string in Embase**

(child*:ti,ab,kw OR adolescent*:ti,ab,kw OR young adult*:ti,ab,kw) AND (vaccin*:ti,ab,kw OR (active immunisation:ti,ab,kw OR active immunization:ti,ab,kw)) OR ('vaccine'/exp) AND (MIS-C:ti,ab,kw OR PIMS-TS:ti,ab,kw OR (pediatric multisystem inflammatory disease:ti,ab,kw) OR (paediatric multisystem inflammatory syndrome:ti,ab,kw) OR (paediatric multi-system inflammatory syndrome:ti,ab,kw) OR (paediatric inflammatory multisystem syndrome:ti,ab,kw) OR (multi system inflammatory syndrome in children:ti,ab,kw) OR (pediatric multisystem inflammatory syndrome:ti,ab,kw) OR (pediatric multi-system inflammatory syndrome:ti,ab,kw) OR (pediatric inflammatory multisystem syndrome:ti,ab,kw) OR ('pediatric multisystem inflammatory syndrome'/exp))

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**Chapter 5**

# Immunogenicity, Effectiveness, and Safety of COVID-19 mRNA Vaccination.

## Chapter 5: Immunogenicity, Effectiveness, and Safety of COVID-19 mRNA Vaccination.

# 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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**Vaccine. 2024 Feb 15;42(5):1145-1153.**

## 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.

### Keywords

COVID-19, mRNA vaccines, Vaccine safety, Vaccine effectivity, Humoral immunogenicity, Cellular immunogenicity, Pediatric rheumatic diseases, uvenile idiopathic arthritis, Epidemiology, Cohort study.

## 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 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.

## METHODS

### 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).

### Outcome measures

#### 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 ≥50.0 AU/ml were considered positive. Humoral response was not measured in unvaccinated patients.

**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.

**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.

**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.

**Statistical analysis**

Characteristics of included patients were summarized separate for vaccinated and unvaccinated patients and compared using the $\chi^2$ 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/2x$10^5$ 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.

## RESULTS

### 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).

### Vaccine immunogenicity

#### 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 (Figure 1) and all separate drug therapy groups (Supplementary Figure 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).

**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 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 (Figure 2; Supplementary Figure 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 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.

**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; Figure 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 Figure 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.

**Vaccine safety**

No statistically significant difference in JIA disease activity scores between study visits was observed (Figure 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.

## 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 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(16,43). 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.

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## STATEMENTS

**Acknowledgements**
The authors thank Marjan Bogaard-van Maurik and Petra J. Molenaar for executing the T-cell ELISpot assays.

**Funding**
No funding was received for this research.

**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).

**Disclosures**
All authors declare no conflict of interest.

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

## TABLES AND FIGURES

**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

**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.

**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 scale
Missing values were handled by multiple imputation.

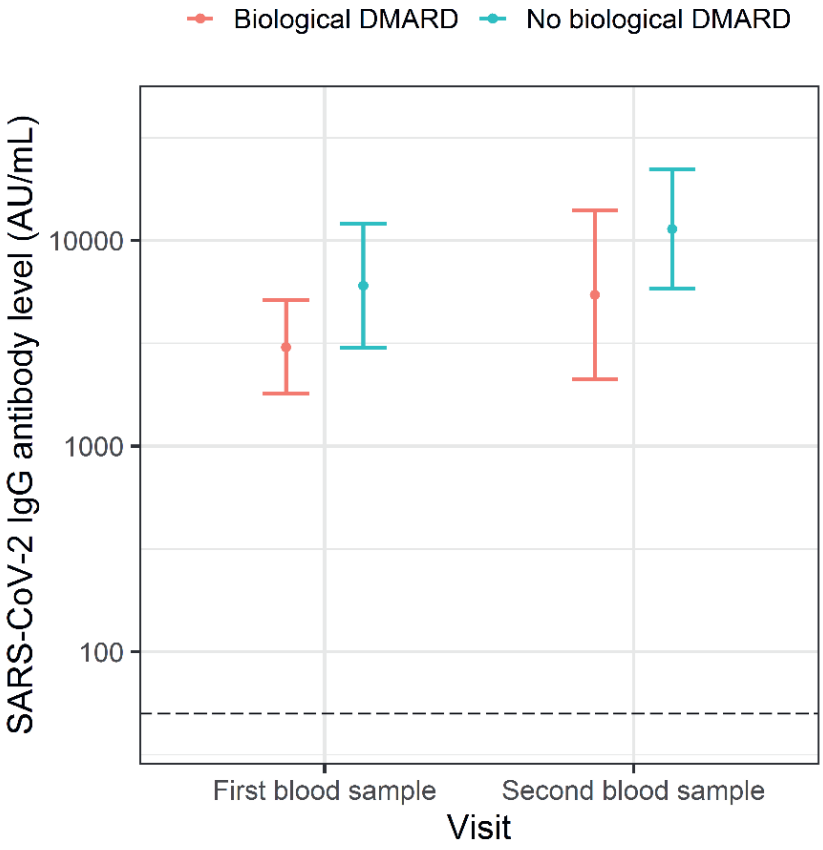



**Figure 1. Post-vaccine geometric mean concentrations of SARS-CoV-2 antibodies in patients with or without biological therapy at vaccination.** Samples were drawn median 137 (first sample) and 282 days (second sample) after first vaccination date. Vertical bars indicate 95% confidence interval, horizontal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

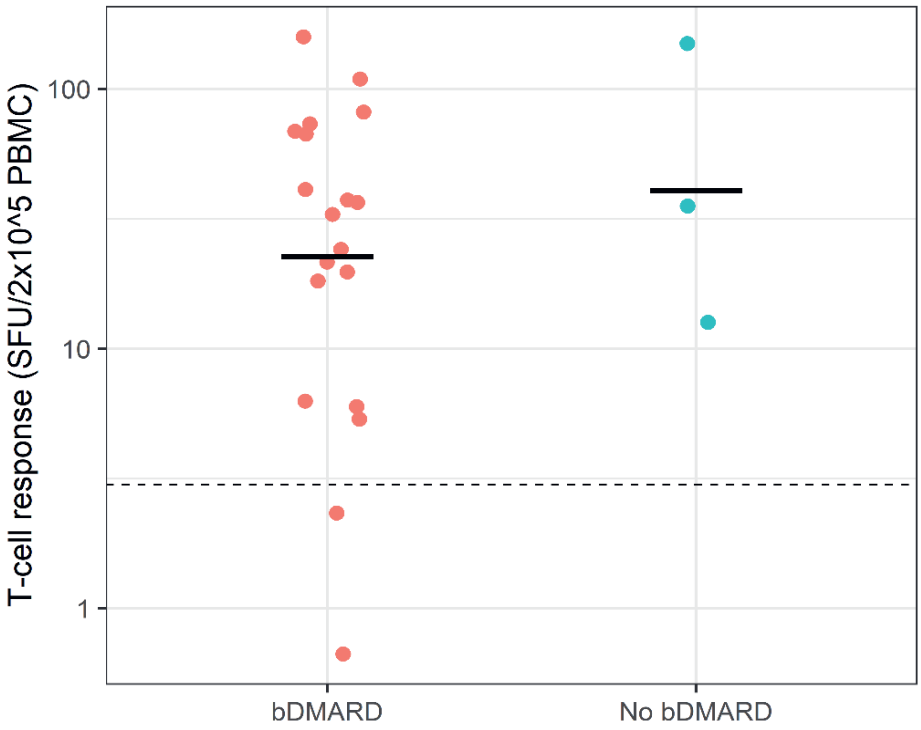



**Figure 2. Post-vaccine T-cell responses against SARS-CoV-2 in 22 patients with or without biological (bDMARD) therapy at vaccination (median 58 days after first vaccination date).** Horizontal black lines indicate mean value per patient group. Horizontal dashed line indicated positive threshold (>2 SFU/2x$10^5$ PBMC). bDMARD: biological disease-modifying antirheumatic drug, PBMC: peripheral blood mononuclear cells, SFU: spot forming units.

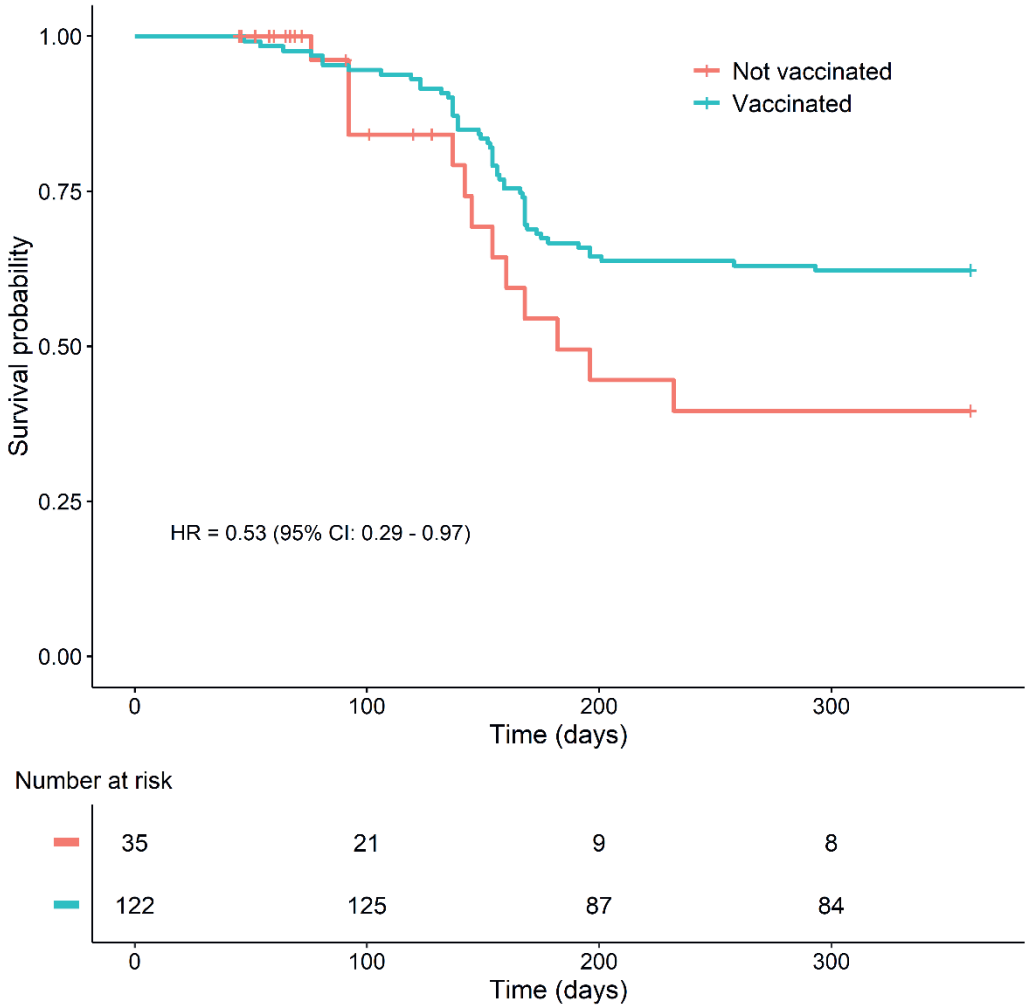



**Figure 3. Survival curves of time to symptomatic COVID-19 disease from 1 October, 2021 – 26 August, 2022.** CI: confidence interval, HR: hazard ratio. Hazard ratio reflects the ratio of COVID-19 rates for vaccinated compared to non-vaccinated patients, adjusted for prior COVID-19 disease. Vertical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

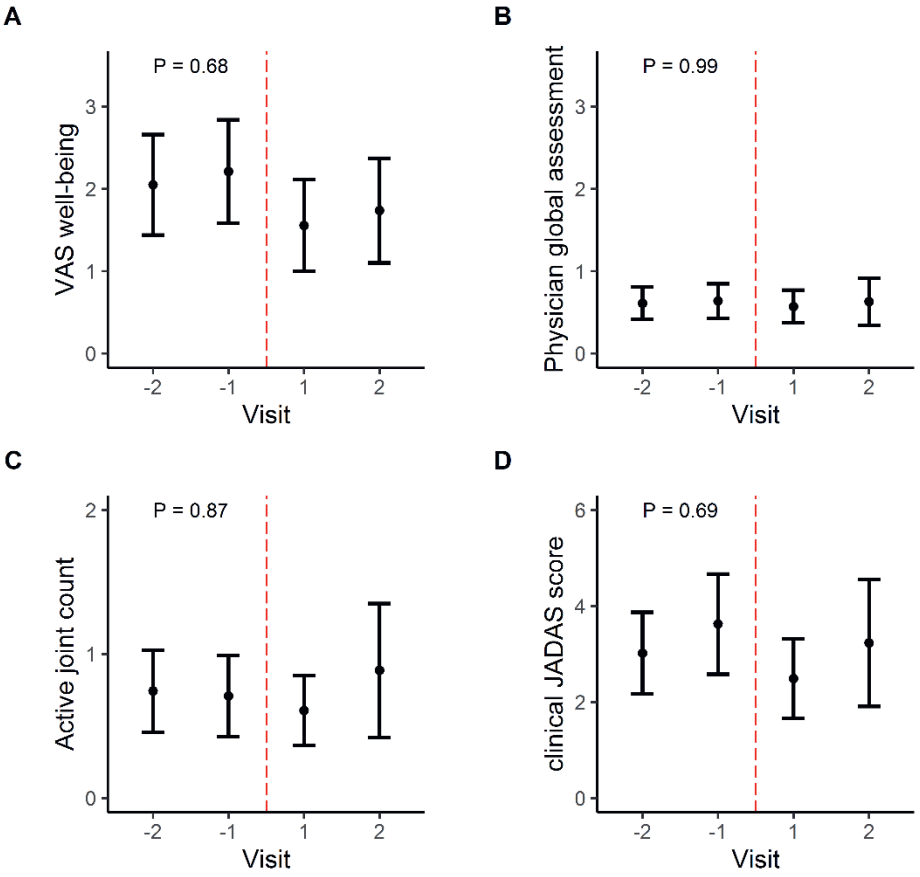



**Figure 4. Disease activity scores in included JIA patients (n = 120) before and after COVID-19 vaccination.** A: mean VAS well-being at different study visits. B: mean physician global assessment of disease activity at different study visits. C: mean active joint count at different study visits. D: 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.

**SUPPLEMENTARY DATA**

**Supplementary Table 1. Characteristics of study visits for vaccinated patients.**

| Study characteristics | Vaccinated cohort (n = 137) |
|---|---|
| **Days from study visit to vaccination** (median, IQR) | |
| *Visit -2* | 168 (122 – 316) n = 101 |
| *Visit -1* | 62 (31 – 151) n = 106 |
| *Visit 1* | 67 (35 – 100) n = 89 |
| *Visit 2* | 166 (118 – 231) n = 70 |
| **Days from vaccination to blood sample** (median, IQR) | |
| *First blood sample* | 137 (107 – 210) n = 104 |
| *Second blood sample* | 282 (209 – 329) n = 25 |

**Supplementary Table 2. Baseline characteristics of patients who reported COVID-19 disease and patients who did not.**

| Variable | Total cohort (n = 157) | No COVID-19 (n = 74) | COVID-19 (n = 83) | *P* |
|---|---|---|---|---|
| **Female (n, %)** | 103 (65.6%) | 49 (66.2%) | 54 (65.1%) | 1 |
| **Disease (n, %)** | | | | 0.07 |
| JIA | 138 (87.9%) | 64 (86.5%) | 74 (89.2%) | |
| *ERA* | 15 (9.6%) | 8 (10.8%) | 7 (8.4%) | |
| *Oligoarthritis* | 59 (37.6%) | 34 (45.9%) | 25 (30.1%) | |
| *RF- polyarthritis* | 24 (15.3%) | 8 (10.8%) | 16 (19.3%) | |
| *RF+ polyarthritis* | 11 (7.0%) | 6 (8.1%) | 5 (6.0%) | |
| *Psoriatic arthritis* | 12 (7.6%) | 3 (4.1%) | 9 (10.8%) | |
| *Systemic arthritis* | 9 (5.7%) | 3 (4.1%) | 6 (7.2%) | |
| *Unknown* | 8 (5.1%) | 2 (2.7%) | 6 (7.2%) | |
| Uveitis | 5 (3.2%) | 5 (6.8%) | 0 (0.0%) | |
| SLE/MCTD | 6 (3.8%) | 3 (4.1%) | 3 (3.6%) | |
| Other[1] | 8 (5.1%) | 2 (2.7%) | 6 (7.2%) | |

COVID-19: coronavirus disease 2019, CREST: calcinosis, Raynoud's phenomenom, esophageal dysfunction, sclerodactyly, teleangiectasia, ERA: enthesitis-related arthritis, IQR: interquartile range, JIA: juvenile idiopathic arthritis, MCTD: mixed connective tissue disease, n: number, 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

**Supplementary Table 3. Proportion of positive SARS-CoV-2 antibody levels (>50 AU/mL) and T-cell responses (>2 SFU/2x10$^5$ PBMC) in samples of vaccinated patients.**

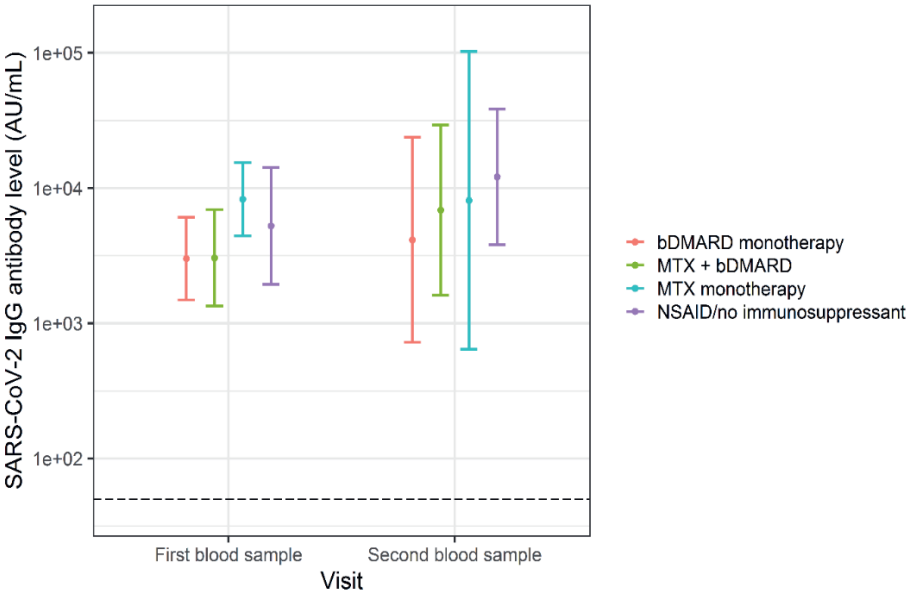
| Analysis | NSAIDs/ no drugs | MTX monotherapy | MTX + bDMARD | bDMARD monotherapy | *P* |
|---|---|---|---|---|---|
| Antibody levels (first sample) | 97% (34/35) | 100% (13/13) | 93% (25/27) | 96% (25/26) | 0.90 |
| Antibody levels (second sample) | 100% (7/7) | 100% (3/3) | 100% (7/7) | 100% (6/6) | 1.00 |
| T-cell response | 100% (2/2) | 100% (1/1) | 86% (12/14) | 100% (5/5) | 1.00 |

bDMARD: biological disease-modifying antirheumatic drug, MTX: methotrexate, n: number, NSAID: non-steroidal anti-inflammatory drug, PBMC: peripheral blood mononuclear cells, SFU: spot forming units.

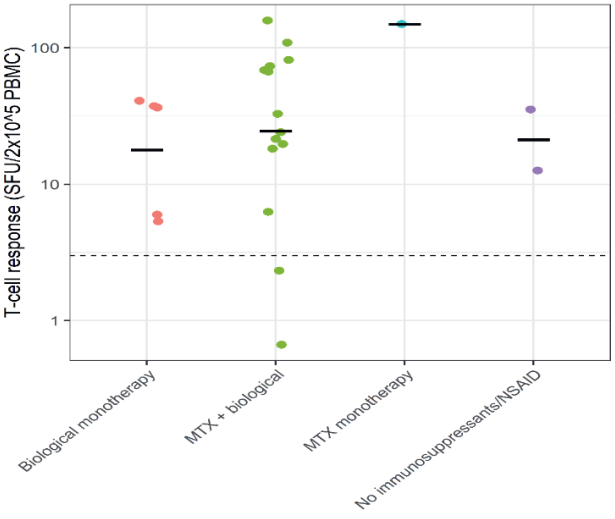
**Supplementary Table 4. Linear mixed effects analyses of log-transformed SARS-CoV-2 IgG antibodies post-vaccination in patients with different drug therapies at vaccination.**

| Analysis | GMR | 95% CI |
|---|---|---|
| Crude | | |
| *NSAIDs/no immunosuppressants* | 1 | Reference |
| *MTX monotherapy* | 1.44 | 0.42 – 4.89 |
| *MTX + bDMARD* | 0.61 | 0.23 – 1.67 |
| *bDMARD monotherapy* | 0.58 | 0.21 – 1.61 |
| Adjusted[1] | | |
| *NSAIDs/no immunosuppressants* | 1 | Reference |
| *MTX monotherapy* | 0.95 | 0.36 – 2.49 |
| *MTX + bDMARD* | 0.51 | 0.24 – 1.11 |
| *bDMARD monotherapy* | 0.25 | 0.10 – 0.61* |

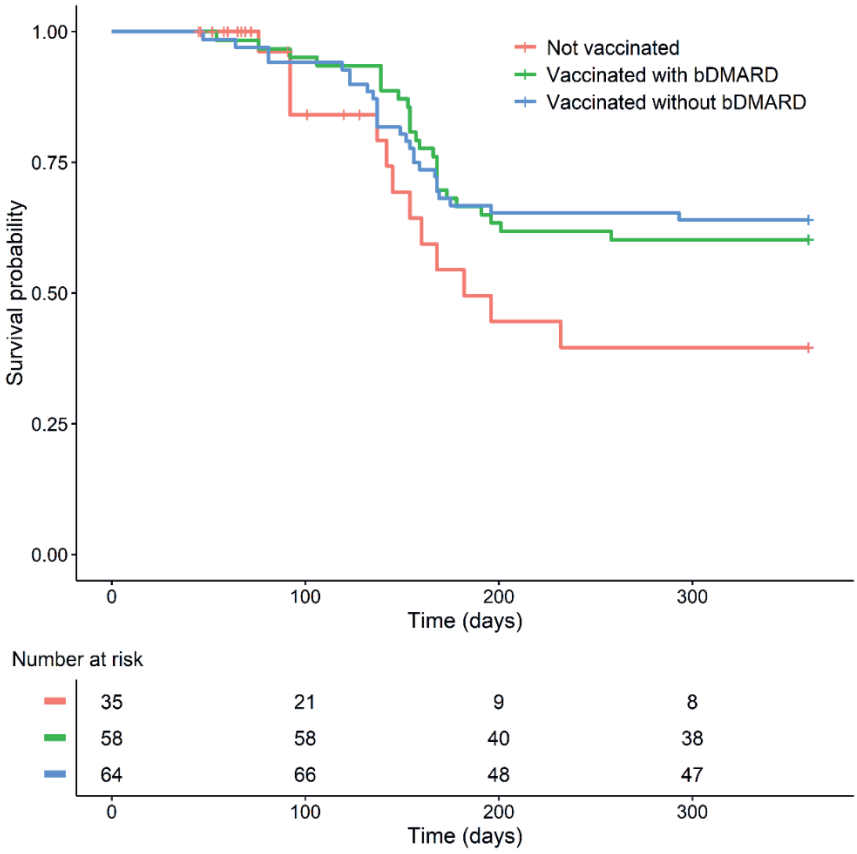
[1]adjusted for disease, age at disease diagnosis, gender, vaccine brand (constant variables), prior COVID-19 disease and disease duration (time-varying variables)
*statistically significant effect
bDMARD: biological disease-modifying antirheumatic drug, CI: confidence interval, GMR: geometric mean ratio, MTX: methotrexate, NSAID: non-steroidal anti-inflammatory drug.
Missing values were handled by multiple imputation.




**Supplementary Figure 1. Post-vaccine geometric mean concentrations of SARS-CoV-2 antibodies in patients with different drug 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).




**Supplementary Figure 2. Post-vaccine T-cell responses against SARS-CoV-2 in 22 patients with different drug therapy at vaccination (median 58 days after first vaccination date).** Horizontal black lines indicate mean value of different drug therapy groups. Horizontal dashed line indicates positive threshold (>2 SFU/2x$10^5$ PBMC).




**Supplementary Figure 3. Survival curves of time to COVID-19 disease from 1 October, 2021 – 26 August, 2022 as a function of vaccination status and bDMARD use.** bDMARD: biological disease-modifying antirheumatic drug. Vertical bars indicate censored patients, i.e. unvaccinated patients who got vaccinated during follow-up.

# Chapter 6

# Recombinant Zoster Vaccine in VZV-Naïve Immunocompromised Children

# Chapter 6: Recombinant Zoster Vaccine in VZV-Naive Immunocompromised Children

## Safety, immunogenicity and efficacy of the Shingrix vaccine in immunocompromised Varicella Zoster virus naïve pediatric patients.

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**Vaccine 2025 Oct 3;64:127708.**

**ABSTRACT**

**Background:** Pediatric patients with autoimmune and inflammatory diseases often require immunosuppressive therapy, which increases their susceptibility to infections, including varicella-zoster virus (VZV). While the live attenuated varicella vaccine is contraindicated in most immunocompromised children, the recombinant subunit vaccine, Shingrix, may offer an alternative preventive strategy. However, data on its safety, immunogenicity, and efficacy in pediatric VZV-naïve patients remain limited.

**Objective:** To evaluate the safety, immunogenicity, and efficacy of the Shingrix vaccine administered to VZV-naïve pediatric patients receiving immunosuppressive therapy.

**Methods:** We conducted a monocenter, real-world retrospective cohort study at the Pediatric Rheumatology Department of Wilhelmina Children's Hospital, Netherlands. Ten VZV-naïve pediatric patients (median age: 2 years 11 months) on immunosuppressive treatment who received the Shingrix vaccine were included. Safety was evaluated based on adverse events recorded within three months post-vaccination. Immunogenicity was assessed by measuring VZV IgG antibody levels pre- and post-vaccination. Efficacy was determined by the occurrence and clinical severity of breakthrough varicella infections. The median follow-up period from the first Shingrix dose to data collection was 7.6 months.

**Results:** Nine of ten patients developed VZV-specific IgG antibodies post-vaccination. One patient who received only a single dose remained seronegative. Two mild breakthrough varicella infections were observed without complications. One severe adverse event was recorded, likely attributable to concurrent viral infection rather than the vaccine itself.

**Conclusion:** To our knowledge, this is the first report on the use of Shingrix in VZV-naïve, immunocompromised pediatric patients. Shingrix demonstrated an acceptable safety profile in immunocompromised pediatric patients and elicited a humoral immune response in all but one cases. The vaccine appeared to provide protection against varicella, although mild breakthrough infections were observed. Prospective studies with larger cohorts and longer follow-ups are warranted to confirm its long-term efficacy and optimal vaccination strategies in this vulnerable population.

## 1. INTRODUCTION

Pediatric autoimmune and autoinflammatory disease encompass a diverse group of conditions that can affect specific organs or present with systemic involvement. These disorders arise from an overactive immune response and likely occur in genetically predisposed children (1). Among the most prevalent conditions worldwide are pediatric inflammatory bowel disease (IBD) and juvenile idiopathic arthritis (JIA) (2). Treatment typically involves immunosuppressive therapy, which, while essential for disease control, can increase susceptibility to infections due to immune system impairment (3).

One of the common childhood infectious diseases is varicella, commonly known as chickenpox. While varicella is typically a self-limiting disease, it can lead to more severe complications and hospitalization. These complications include bacterial sepsis, pneumonia, streptococcal group A infections, necrotizing fasciitis and encephalitis (4). Children receiving immunosuppressive therapy such as glucocorticoids, conventional disease modifying anti-rheumatic drugs (DMARDs), biologic DMARDs or small molecule targeted DMARDs are at an increased risk of serious complications and mortality from varicella infection (5,6). For children who are seronegative for Varicella-Zoster Virus (VZV), vaccination with a varicella vaccine is recommended at least three weeks prior to initiating immunosuppressive therapy (5,7).

Seroprevalence increases in childhood with age: about 70% of three-year-olds have antibodies against varicella, and by age six 95% have developed immunity to the virus. Children that did not visit daycare or nursery school had lower VZV seropositivity. Varicella vaccination is not included in the National Immunization Program in the Netherlands (8). After the COVID-19 pandemic and the reopening of schools and day-cares there was a huge catch-up in varicella cases amongst the children. Unfortunately, this steep increase in primary VZV infections was accompanied by a high incidence of serious streptococcal group A infections in these patients in the Netherlands (9).

Currently, there are two vaccines available in the Netherlands for healthy older adults against herpes zoster disease, a live attenuated VZV vaccine (Zostavax) and a recombinant adjuvanted VZV glycoprotein E subunit no live vaccine (Shingrix) (10). Zostavax, which is given in a single dose, is contraindicated in immunocompromised individuals and patients younger than 50 years. Shingrix, on the other hand, is administered in a two-dose schedule, with a minimum interval of one month between doses. Typically, the second dose is given 2 to 6 months after the first. Since it is a recombinant vaccine, it is not contraindicated in immunocompromised patients (6,10,11).

Shingrix is approved for use in adults aged 18 years and older for the prevention of shingles. Its safety and efficacy have not been established in individuals under 18 years of age, and it is not approved for use in children. In addition, it has not been evaluated, nor indicated for prevention of primary varicella infection (12).

While previous studies have shown that the recombinant VZV vaccine elicit significant humoral and cellular responses in VZV naïve immunocompromised adults (13–16), information on the Shingrix vaccine in naïve immunocompromised children is lacking.

In this observational, retrospective, real-world cohort study, we aimed to evaluate the safety, immunogenicity, and efficacy of the Shingrix vaccine in VZV-naive pediatric patients with autoimmune diseases who received the vaccine off label as part of routine clinical care while undergoing immunosuppressive treatment.

## 2. METHHODS

### *2.1. Study Design and Participants*

A monocenter, observational, retrospective real-world cohort study was conducted at the Pediatric Rheumatology Department of Wilhelmina Children's Hospital in the Netherlands. All patients (or their parents) provided informed consent for anonymous use of their data. Data collection from the electronic medical records began in October 2024 and concluded in December 2024. The study included pediatric VZV-naïve patients who were receiving immunosuppressive medication at the time of Shingrix vaccination in 2023 and 2024. Data were retrospectively extracted from electronic patient records, including clinical status, diagnosis, therapy, and vaccination details. Patients who were not VZV seronegative or received the vaccine as a booster were excluded from the analysis. Serum samples for measuring IgG antibody levels against VZV were collected in conjunction with routine blood sampling.

It should be noted that Shingrix vaccination was administered in full dose (50mcg/0.5ml) as part of routine clinical care, not within the context of a clinical trial. Immunocompromised children who could not receive a live attenuated vaccine were offered Shingrix to prevent wild-type varicella infection, which children in the Netherlands are very likely to be exposed to.

### 2.2. *Outcome measure*

The primary outcome of the study was to evaluate the safety of the Shingrix vaccine in pediatric patients receiving immunosuppressive therapy by measuring the occurrence of vaccination-related adverse events. The secondary outcomes

included assessing the presence of positive VZV IgG antibody levels following vaccination and evaluating the occurrence of breakthrough varicella infections at last follow-up.

### 2.2.1 *Safety*

All adverse events occurring from the first vaccine dose until three months after the second dose were extracted from electronic patient records and deemed possibly related to the vaccination. Adverse events were categorized as either mild, moderate or severe. Severe adverse events were defined as those requiring hospitalization or involving severe VZV vaccine strain infections: such as pneumonia, or encephalitis. All other events were classified as moderate or mild.

### 2.2.2 *Immunogenicity*

Data on pre- and post-vaccination VZV IgG levels, vaccination timing, and related vaccination details were extracted from electronic patient records. Post-vaccination samples were collected between two and seven months after vaccination. The hospital laboratory defined a positive VZV IgG threshold as ≥100 arbitrary units (AU)/mL.

For patients without a pre-vaccination serology sample, parental reports were used whether the child had a prior history of varicella infection.

### 2.2.3 *Efficacy*

Efficacy was assessed based on the occurrence of breakthrough varicella and potential exposure to the virus, as reported by parents in electronic patient records. Breakthrough cases were classified as mild or severe. Severe cases were defined by hospitalization due to illness or the presence of severe complications described in the introduction. Cases without severe complications or hospitalization were classified as mild.

## 3.RESULTS

### 3.1 Patient characteristics

A total of 10 patients were included in this study, each of whom is presented individually. Exact vaccination dates were available for all the patients. Baseline characteristics are summarized in Table 1. Five patients (50%) were female. The study cohort comprised patients with various diagnoses and corresponding immunosuppressive therapies. At vaccination participants had a median age of 2 years and 11 months (IQR: 2 years and 5 months – 3 years and 2 months) with a minimum age of 8 months and a maximum of 9 years. The time from the first

Shingrix dose to data collection ranged from 3 to 32 months, with a median of 7.6 months, reflecting real-world variability in vaccination timing and follow-up.

Pre-vaccination IgG levels were available for seven patients: all but one tested negative. The exception was an 8-month-old infant who had positive pre-vaccination IgG despite no history of chickenpox, which was thought to be of maternal origin. For three patients without pre-vaccination IgG data, parental confirmation indicated no prior history of chickenpox (table 1).

Ultimately, eight patients received both doses of the Shingrix vaccine, while two received only one dose.

### 3.2 Safety

#### *Adverse events*

One serious adverse event was reported in a single patient (Patient ID 09). This event was a reactivation of macrophage activation syndrome (MAS) and subsequent hospital admission. During the MAS reactivation, the patient had confirmed rhinovirus and enterovirus infections. The patient was hospitalized and treated with methylprednisolone, ultimately recovering and being discharged.

#### *Moderate and mild adverse events*

One patient (Patient ID 06) experienced worsening his underlying IBD. He was diagnosed at the age of 2 years with IBD one month before vaccination and had started biological therapy only two weeks prior. Nearly three months after receiving his first and only dose of Shingrix, he developed a disease flare and started with prednisolon and Azathioprine one month later. He did not respond to this therapy and had ongoing disease activity two months later at duodeno-colonoscopy. The prednisolone was tapered and infliximab was started. (7 months after the Shingrix vaccination).

Three patients developed bacterial infections: one with acute otitis media, one with a urinary tract infection, and one with tonsillitis. All were treated with antibiotics and recovered.

Three patients developed new skin rashes. One had a small patch of eczema on an extremity, another developed a facial rash, and the third had a rash suspected to be either scarlet fever or erythema infectiosum. The latter patient's sibling was recently diagnosed with scarlet fever, so he was treated with Amoxicillin-Clavulanate and recovered. The patient with the malar rash was suspected of having sun sensitivity due to medication or a parvovirus infection, as his sibling had a confirmed case. He was managed with watchful waiting.

Two minor adverse events occurred immediately following vaccination. One patient developed a fever of 38.0°C the day after receiving the vaccine, while another developed an injection site reaction after the second dose.

### 3.3 Immunogenicity

Pre- and post-vaccination IgG levels are shown in Figure 1. Nine out of ten patients developed positive VZV IgG antibody levels after vaccination.

One patient with JIA, treated with methotrexate and adalimumab, remained VZV IgG-negative post-vaccination (Patient ID 10). This patient received only one dose of Shingrix. A year later, the patient was vaccinated with a live varicella vaccine. Testing one year after the live attenuated vaccine confirmed positive VZV IgG antibody levels; however, the patient subsequently developed mild chickenpox despite both vaccinations during JAKi therapy later on.

### 3.4 Efficacy

The median follow-up was 7.6 months (range: 3–32 months), during which no moderate or severe varicella cases were reported, underscoring the vaccine's potential efficacy in this high-risk population. Although two of these patients had known direct contact with infected chickenpox patients, they showed primary prevention of VZV and did not develop any symptoms.

Two patients (Patient ID 09 and 10) were reported to have had mild chickenpox during. Both developed mild rash with no other signs or symptoms. Both recovered without complications without being treated with anti-viral drugs nor needed discontinuation of immunosuppressive therapy.

## 4. DISCUSSION

In this observational retrospective cohort study, we evaluated the safety, immunogenicity, and efficacy of the Shingrix vaccine in VZV-naïve pediatric patients receiving immunosuppressive therapy. Our findings provide valuable insights into the potential use of this recombinant vaccine in a highly vulnerable population, for whom live varicella vaccines are contraindicated.

In this pilot study, the Shingrix vaccine appeared safe in highly immunosuppressed pediatric patients. Most adverse events were mild and self-limited. The one SAE occurred in a single patient with systemic JIA and a prior history of MAS, who was concurrently infected with a rhinovirus and enterovirus, rendering a causal relationship with the vaccine uncertain (17). An exacerbation of IBD was also observed; however, a direct association with vaccination could not be established due to the patient's recent very-early onset IBD diagnosis.

Moderate adverse events were fever, rash (probably non-vaccine-related) and local side reactions. These are consistent with known side effects of Shingrix and resolved within a few days (10,18). The Shingrix vaccine has a clinically acceptable safety profile in adults (18,19) and has also been proven safe for those with autoimmune rheumatic diseases (20). However, data on its safety in pediatric patients are lacking. While currently approved only for adults aged 18 and older, our findings suggest that it has an acceptable safety profile in immunosuppressed pediatric patients as well, these results highlight the need for larger studies to further evaluate its safety in pediatric populations and explore its potential for broader use in this group.

Shingrix demonstrated strong immunogenicity, with 9 out of 10 VZV naïve patients developing positive VZV IgG levels post-vaccination, suggesting its ability to elicit an immune response even in immunocompromised children—sometimes even after a single dose. This aligns with data from immunocompromised adult patients showing robust humoral responses to the recombinant vaccine (11–14).

Another patient demonstrated pre-vaccination IgG seropositivity at 8 months of age, possibly due to transplacental transfer of maternal antibodies (21), and subsequently exhibited a strong immunogenic response following vaccination , as evidenced by high post-vaccination IgG titers.

One patient remained IgG-negative after a single dose and later seroconverted following a live-attenuated varicella vaccine yet still developed mild chickenpox. This highlights the difficulty of achieving effective immunity in this severely immunosuppressed population.

Although preliminary, our efficacy findings are encouraging: eight of ten patients remained protected from varicella, including two with direct exposure. Given that 95% of Dutch children contract chickenpox by age six (8), the likelihood of VZV exposure in this cohort was very high. These results suggest that Shingrix may offer effective real-world protection in immunocompromised children.

Both breakthrough cases were mild and easily managed despite their continued immunosuppression, indicating potential for reduced disease severity. Notably, one occurred after only a single dose, highlighting the importance of completing the full two-dose schedule for optimal protection.

Further larger prospective studies are needed to confirm the findings of our study and determine whether booster doses may be required for immunosuppressed children after a certain period post-vaccination or post-VZV infection. Additionally, future research should explore the optimal timing of vaccination in relation to immunosuppressive therapy to maximize efficacy.

Several limitations of this study should be acknowledged. The small sample size and single-center design limit the generalizability of the findings. Additionally, the retrospective nature of the study means that some adverse events may have been underreported, and the follow-up period varied among patients.

## 5. CONCLUSION

This study provides preliminary evidence supporting the safety, immunogenicity, and potential efficacy of Shingrix in VZV-naïve pediatric patients receiving immunosuppressive therapy. While mild and transient adverse events were observed, most patients demonstrated a serological response. The occurrence of mild breakthrough infections warrants further investigation into long-term protection.

Given the increased risk of severe varicella complications in immunocompromised children, Shingrix represents a promising vaccination strategy, but additional studies are required to fully establish its role in pediatric immunization protocols.

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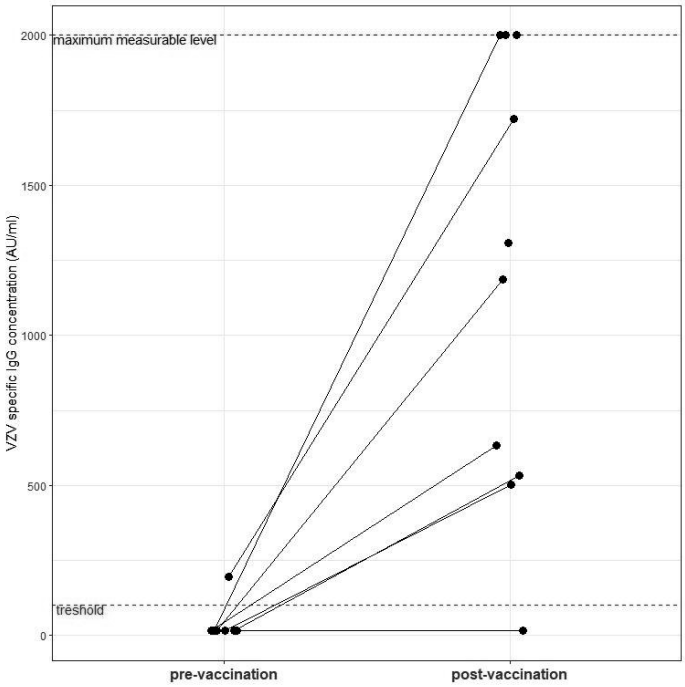
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**Table 1** Baseline patient characteristics at first dose of vaccination and follow-up duration.

| Patient Number | Age at first dose (years) | Biological sex | Diagnosis | Medication* | Nr of doses | Pre-vaccination serology | Follow-up duration (months)** |
|---|---|---|---|---|---|---|---|
| 01 | 2.5 | Male | JIA | Adalimumab Methotrexate | 2 | <15/Neg | 5 |
| 02 | 3.2 | Female | JIA | Canakinumab Methotrexate | 2 | <15/Neg | 4 |
| 03 | 1 | Male | Aicardi-Goutières syndrome | Baricitinib | 2 | <15/Neg | 7 |
| 04 | 8.7 | Male | linear scleroderma | Methotrexate | 2 | Missing † | 14 |
| 05 | 2.11 | Female | JIA | Adalimumab Methotrexate | 2 | Missing | 6 |
| 06 | 2.5 | Male | Crohn's disease | Infliximab Azathioprine | 1 | <15/Neg | 5 |
| 07 | 0.8 | Male | Aicardi-Goutières syndrome | Baricitinib | 2 | 196.5/Pos | 5 |
| 08 | 5.4 | Female | Systemic onset JIA | Tofacitinib Canakinumab | 2 | Missing | 3 |
| 09 | 3 | Female | Systemic onset JIA | Canakinumab Cyclosporine | 2 | <15/Neg | 13 |
| 10 | 3.3 | Female | JIA | Adalimumab Methotrexate | 1 | <15/Neg | 32 |

**Figure 1: Level of IgG in AU/ml pre-vaccination versus post-vaccination**



# Chapter 7

# General Discussion and future perspectives

## Chapter 7 – General Discussion and future perspectives

### Summary of Main Findings

Vaccination in children with paediatric autoimmune and autoinflammatory rheumatic diseases (pedAIIRDs) exists for one fundamental reason: to prevent infection. These children carry a higher burden of infection than their peers, driven by the combination of disease-related immune dysregulation and the immunosuppressive drugs needed to control it, and when they contract a vaccine-preventable disease they are at greater risk of a severe or complicated course (1). This is what makes vaccination both critically important and more challenging in this population than in healthy children.

Vaccination decisions in this population require careful consideration of both risks and benefits. Potential risks include disease flares following vaccination and vaccine-strain infection after a live-attenuated vaccine. A separate concern is immunological: immunosuppressive therapy may blunt the initial vaccine response, and may also shorten the duration of protection, so that an initially adequate response wanes faster than in healthy children. The primary benefit is a reduced risk of acquiring vaccine-preventable infections. These considerations raise a central clinical question: does vaccination confer protection that is both adequate and durable in this population?

This balance has become more urgent as vaccination coverage declines and herd immunity erodes worldwide (2). Because vaccine-preventable diseases have become uncommon in many settings, families and clinicians may underestimate their potential consequences. However, children with pedAIIRDs are particularly vulnerable to the consequences of declining herd immunity, as they are less able to rely on indirect protection and are at greater risk of severe or complicated disease if infected. A further complication is the longstanding clinical culture of caution around live-attenuated vaccines in immunocompromised patients, which has frequently led to unnecessary deferral instead of evidence-based, individualised decision-making.

The five studies in this thesis were specifically designed to address these critical knowledge gaps, covering the live-attenuated MMR booster vaccination, the COVID-19 mRNA vaccination, and the recombinant zoster vaccine. Each study in this thesis was motivated by a specific unanswered question, and together they generate a body of evidence that is relevant for and directly applicable to the care of these children. Taken together, these studies move the field beyond generalized caution towards a more precise, evidence-based approach to vaccination in children with pedAIIRDs.

The first study (chapter 2) addressed a question of direct clinical importance. The safety of the live-attenuated MMR booster in JIA was already supported for patients on methotrexate, and the multicentre study of Uziel et al. and the 2021 EULAR/PRES recommendations had extended cautious support to biologic-treated patients (3,4). Systematic real-world data with structured disease-activity assessment in biologic-treated children nonetheless remained limited. The study evaluated disease activity and adverse events in 186 children with JIA who received the MMR booster as part of the Dutch national immunisation programme (5). At the time of vaccination, 51% of patients were receiving conventional synthetic DMARDs (csDMARDs), predominantly methotrexate, and 28% were receiving biologic therapy, comprising 11% on biologic monotherapy and 17% on a csDMARD–biologic combination; 37% were receiving no systemic immunosuppressive treatment. Disease activity was measured across two clinic visits before and two after the booster vaccine, using active joint count, physician global assessment, patient visual analogue scale for wellbeing, and the composite cJADAS score. There was no statistically significant change in any of these measures, either across the full cohort or in the biologic-treated subgroup specifically. Mild adverse events occurred in 7% of patients and resolved without intervention. No serious adverse events and no vaccine-strain infections were reported at any point during follow-up, including in patients receiving combination immunosuppression.(5) This long-term safety profile, observed in a real-world cohort that included biologic-treated patients and those on combination immunosuppression who are typically excluded from controlled trials, is the central finding of chapter 2 and provides a direct evidence base for counselling families about the safety of MMR vaccination in the context of biologic therapy.

The second study, in chapter 3, addressed a question that safety data alone cannot answer: not whether the MMR booster is safe, but whether it induces durable protective immunity in children with JIA in the biologic era. Long-term humoral immunity was assessed in stored serum samples from 182 patients with JIA, obtained five years after the booster and again at the most recent available follow-up, with a median follow-up of 6.9 years (IQR 2.8–8.8) (6). Protective antibody concentrations against measles, mumps, and rubella were maintained in most patients. However, lower seroprotection rates were observed among patients receiving biologic therapy at the time of vaccination, almost all of whom were treated with anti-TNF agents. Five-year seroprotection against measles was significantly lower in biologic-treated patients than in those not receiving biologics at vaccination, including patients receiving csDMARDs or no systemic treatment (60% versus 86%, P = 0.03). Similar, although non-significant, trends were observed for mumps (80% versus 94%) and rubella (60% versus 83%).

Importantly, the rate at which antibody concentrations declined over time was not significantly different between the two groups. This points to where the deficit arises. Because biologic-treated patients were already less protected by five years but did not lose antibody faster thereafter, the gap was established within the years immediately following vaccination rather than through accelerated waning over the longer term. The most likely explanation lies in the first years after vaccination rather than in long-term loss: anti-TNF agents, which accounted for almost all biologic use in this cohort, together with methotrexate, impair the germinal-centre reaction, B-cell class switching, and the formation of long-lived plasma cells, as shown for vaccine-specific responses by Ingelman-Sundberg et al. and Haberman et al. (7,8). Whether this manifests as a lower initial peak or as faster early waning, the study cannot formally distinguish, since the first measurement was at five years; in either case the difference reflects how well protection was built and retained in the first years rather than an ongoing accelerated loss. Repeated boosting of all patients would therefore not address the problem; the rational response is to identify the specific patients who have not retained protection and offer them a further dose.

No previous study had followed MMR-specific antibody concentrations in children with rheumatic diseases for this length of time (8–12). Earlier reports were largely confined to one to three years of follow-up, sufficient to confirm initial seroconversion but not to reveal the gradual decline that becomes clinically relevant in the years after vaccination. Study 2 is the first to characterise this longer trajectory and to show that a substantial proportion of patients who were receiving biologic therapy at the time of vaccination lose measles seroprotection, and to a lesser extent mumps and rubella seroprotection, within five years. The clinical implication is directly actionable: measuring MMR-specific IgG at five years post-booster in patients who were receiving biologic therapy at the time of vaccination, and offering a further dose to those who have lost seroprotection, rather than applying a blanket revaccination schedule.

There are two important considerations when interpreting these serological findings. A measured antibody concentration above the protective threshold is a validated surrogate but not a perfect correlate of clinical protection, since immunological memory can contribute to defence even after circulating antibody has fallen below the threshold. The proportion of biologic-treated patients classified as unprotected at five years may therefore overestimate true susceptibility, because anamnestic memory B- and T-cell responses on re-exposure could rescue some seronegative children. This does not weaken the case for serological monitoring; rather, it suggests that a low antibody concentration should prompt further assessment and selective revaccination rather than be interpreted as evidence of certain vulnerability. Future studies should therefore evaluate recall responses and

cellular immunity, particularly because T-cell responses were not assessed in this cohort.

The third study (chapter 4) addressed a key clinical question that arose during the COVID-19 pandemic: beyond preventing severe acute SARS-CoV-2 infection, seen predominantly in adults, do mRNA SARS-CoV-2 vaccines also protect against multisystem inflammatory syndrome in children (MIS-C), the severe post-infectious complication typically seen in children? At the same time, concerns were raised regarding the theoretical possibility that vaccination itself could trigger hyperinflammatory responses resembling MIS-C. Addressing both aspects was essential before recommending widespread paediatric vaccination, particularly for children with pedAIIRDs, whose underlying immune dysregulation could potentially influence both susceptibility to MIS-C and vaccine responses. A systematic literature review identified 13 eligible studies(13). Four large nationwide observational studies from France, the United States, Denmark, and Israel, covering approximately 63 million children, were pooled in a meta-analysis. The pooled odds ratio for MIS-C in vaccinated compared with unvaccinated children was 0.04 (95% CI: 0.03–0.06), with no significant heterogeneity (P = 0.23), demonstrating a 96% reduction in MIS-C risk for vaccinated children (14–17) The rate of MIS-C attributable to vaccination itself was 2.9 per million vaccinated children, compared with 113.3 per million following natural infection, a nearly 40-fold difference (18). These vaccine-associated cases were defined as MIS-C specifically, counted separately from the more common post-vaccine myocarditis and pericarditis, and were less severe than post-infectious MIS-C: about a third required intensive care, compared with nearly three-quarters of post-infection cases. Some had evidence of recent SARS-CoV-2 infection, so it remains uncertain whether these cases were genuinely vaccine-triggered or instead post-infectious. The biological explanation is that mRNA vaccines encode only the spike protein, without the structural viral elements that appear to drive the superantigen-mediated polyclonal T-cell expansion underlying MIS-C(19), whereas natural infection activates this pathway. A separate study from our group reported that children on biologic or targeted synthetic therapies had a lower observed risk of developing MIS-C (20). If confirmed in larger cohorts, this would suggest that their treatment may also dampen the post-infectious inflammatory response. Together, these findings provide a compelling rationale for COVID-19 vaccination in all eligible children, including those with rheumatic disease.

The fourth study (chapter 5) addressed another question that was especially important to clinicians caring for children with pedAIIRDs during the pandemic: do COVID-19 mRNA vaccines provide safe and effective protection for these children despite pharmacologically induced immunosuppression? The study followed 157 patients (88% JIA)

prospectively at the Wilhelmina Children's Hospital between March 2021 and August 2022 (21). Both arms of the adaptive immune response were assessed: anti-spike IgG was measured in 104 patients with available samples, at one or two clinic visits after vaccination, and IFN-γ ELISpot assays were performed in a subset of 22 patients. All but four patients achieved a positive seroprotective antibody level after full vaccination. However, biologic-treated patients had significantly lower adjusted antibody concentrations than those not on biologics (geometric mean ratio (GMR) 0.38, 95% CI: 0.21–0.70). This reflects the known effects of TNF-alpha and IL-6 pathway inhibition, which impair B-cell class switching and plasma-blast differentiation and so reduce the quantity of high-affinity antibody generated in response to vaccination (22,23) The critical question was whether this serological reduction translated into more clinical COVID-19 infections. It did not. The rate of symptomatic COVID-19 was 47% lower in fully vaccinated patients (HR 0.53, 95% CI: 0.29–0.97), indicating a substantial reduction in infection risk, and this protective effect did not differ significantly between biologic-treated and untreated patients (HR 0.96, 95% CI: 0.55–1.67). The lower concentrations in biologic-treated patients remained above the seroprotective threshold in almost all cases, so a reduced titre did not mean an unprotected child. T-cell responses were adequate in 91% of those tested, and this preserved cellular immunity offers an additional explanation for why clinical protection was maintained even where antibody concentrations were lower (24–26). No worsening of disease activity, no myocarditis, and no serious adverse events were identified. COVID-19 mRNA vaccines are safe, immunogenic, and clinically effective in children with pedAIIRDs, and immunosuppressive therapy (including biologics) should not be interrupted at the time of vaccination.

The fifth study in chapter 6 addressed a major unmet clinical need in the real-world care of children with pedAIIRDs: how to protect VZV-naïve immunocompromised children in clinical scenarios where live-attenuated varicella vaccination is contraindicated due to high-level immunosuppression. For immunocompromised children, primary chickenpox carries a substantially higher risk of severe complications, including bacterial superinfection, pneumonitis, and encephalitis. This concern is heightened in children treated with JAK inhibitors, a drug class that blunts the cell-mediated and interferon-dependent antiviral responses controlling VZV and is associated with an increased risk of herpes zoster (27). JAK inhibitors such as tofacitinib were registered for polyarticular JIA only recently (28) and are now used in progressively younger children, precisely the group for whom the live-attenuated varicella vaccine is contraindicated. The adjuvanted recombinant zoster vaccine (Shingrix) offered a biologically and clinically compelling non-live alternative: it is a recombinant subunit vaccine, carries no risk of vaccine-strain infection, and has shown strong immunogenicity

against herpes zoster in immunocompromised adults. Vaccination against VZV is not part of the Dutch National Vaccination Program (RVP) and is not otherwise offered to healthy children. Ten VZV-naïve children (median age 2 years 11 months) receiving high-level immunosuppressive therapy including JAK inhibitors received Shingrix off-label as part of routine clinical care (29). Nine of ten developed positive VZV IgG; the single non-responder had received only one dose. Two children later developed mild varicella following confirmed direct household exposure but recovered completely without antiviral treatment or hospitalisation, suggesting that vaccine-induced immunity attenuated disease severity. The single serious adverse event, a MAS relapse in a child with systemic JIA who was simultaneously infected with rhinovirus and enterovirus, could not be attributed to the vaccine on temporal or virological grounds. This provides first-in-field clinical evidence supporting a non-live vaccination strategy for VZV-naïve immunocompromised children and opens a route to varicella prevention in this high-risk population that did not previously exist.

## Discussion

Vaccination coverage is declining in many countries, and the consequences are already visible. As uptake falls below the thresholds needed to sustain herd immunity, diseases that had become rare are returning, with measles outbreaks reported across the Netherlands, Europe, and beyond (2,30,31). Vaccination remains the single most effective tool for preventing these infections and the severe complications and deaths they still cause, and its value grows as coverage erodes and the diseases circulate again. For most children a fall in coverage is a population-level concern, but for children with pedAIIRDs it is an individual one. They are less able to rely on the indirect protection of those around them, they are more likely to suffer a severe or complicated course if infected, and the immunosuppressive therapy that controls their disease can blunt the protection their own vaccinations provide.

The five studies in this thesis were designed to address exactly this problem: how to vaccinate these children safely, how durable that protection is, and where it needs to be reinforced. The sections below discuss what each study adds and what the findings mean for clinical practice.

### MMR Booster Vaccination in pedAIIRDs

Live-attenuated vaccines represent a uniquely challenging category in immunocompromised patients because they introduce a replication-competent organism, however weakened, to a vulnerable host (the

pedAIIRD patient). In Studies 1 and 2 of this thesis, we demonstrated both the safety and characterised the long-term immunogenicity of an MMR booster in patients with JIA receiving immunosuppressive therapy, including biologic agents. These findings allow precaution to be replaced by evidence-based clinical guidance regarding which patients require an MMR booster, whether it can be administered safely, and when post-vaccination seroprotection should be assessed and a further dose considered.

On the safety side, the presented evidence is consistent and reassuring. The Dutch randomised controlled trial was the first rigorously designed study to show that the MMR booster does not worsen disease activity in JIA patients, confirming both the safety and the short-term immunogenicity of the vaccine including against measles (32). Earlier safety data from the same group showed that the MMR vaccine does not exacerbate disease in JIA even in patients with active disease(33). A retrospective multicentre study across 13 centres in 10 countries, in which 101 of the 234 children were receiving biologic therapy (39 on biologic monotherapy and 62 on a methotrexate plus biologic combination), found no disease flares and no vaccine-induced infections(4) A retrospective single-centre study reported no disease exacerbations and only mild adverse events in 14 children with rheumatic diseases treated with biologic therapy who received the MMR booster without interrupting treatment (34). A systematic review by Keller et al. and a scoping review by Cunninghame et al. both concluded that the available safety evidence does not support blanket contraindication of live vaccines in children with rheumatic diseases on immunosuppression(35,36). The 2021 EULAR/PRES recommendations reflected this consensus, supporting MMR vaccination in patients on methotrexate and, with individualised assessment, in those on TNF inhibitors, anti-IL-1, and anti-IL-6 therapy(3). Study 1 strengthens this evidence base substantially. This study is among the largest real-world safety cohorts for MMR vaccination in biologic-treated JIA patients with 186 patients, of whom 62% were on immunosuppressive therapy and 28% on biologic agents, assessed across four clinic visits spanning approximately fifteen months. No serious adverse event, no disease flare, and no case of vaccine-strain viral infection was identified at any point, including in patients on combination therapy. The conclusion is clear and clinically decisive: concern about vaccine-induced disease exacerbation or vaccine-virus replication in biologic-treated children is not supported by the evidence and should no longer justify deferring MMR vaccination.

The immunogenicity findings from chapter 3 require careful interpretation and consideration. A seroprotection rate of 60% against measles at five years in biologic-treated patients sounds alarming at first reading, but three qualifications are important. The majority of biologic-treated patients were still protected. The rate of antibody decline was not significantly different

between biologic-treated and untreated patients, meaning the deficit was established at the time of vaccination rather than accumulated during the years that followed. Earlier cross-sectional work had already shown that immunosuppression broadly reduces vaccine-specific antibody persistence in children with rheumatic diseases, supporting the biological plausibility of these findings and indicating that they are not unexpected(10). Ingelman-Sundberg et al. demonstrated diverse effects of methotrexate and anti-TNF therapy on vaccine-specific serum IgG titres and memory B-cell responses, with methotrexate exerting a particularly pronounced inhibitory effect(8). Kopsidas et al. similarly found that children with oligoarticular JIA on methotrexate had significantly lower measles-specific IgG concentrations at one and two years after vaccination compared with healthy controls, further supporting the inhibitory effect of methotrexate on long-term measles immunity(9) Maritsi et al. found lower measles and rubella IgG concentrations in children with enthesitis-related arthritis on adalimumab compared with healthy age-matched controls at both one and three years after booster vaccination(11). Borte et al. showed adequate short-term seroconversion after MMR revaccination in JIA on methotrexate and etanercept, but follow-up was limited to a few months and could not address the longer-term durability(12). Study 2 is the first to follow this effect longitudinally over nearly seven years and to quantify its clinical consequence: approximately 40% of biologic-treated patients had lost measles sero-protection by five years, with a similar trend, although non-significant, for mumps and rubella. The appropriate clinical response is targeted, strategy-driven serological monitoring: measuring MMR-specific IgG at five years post-booster in biologic-treated patients allows those who have lost protection to be identified and offered a further booster dose. A measured antibody concentration below the threshold does not by itself prove susceptibility, since an anamnestic memory response on exposure may still protect some children; it is best read as a trigger for assessment and selective revaccination rather than as evidence of certain vulnerability.

The epidemiological context makes this recommendation urgent. Measles has re-emerged across the Netherlands, Europe and the United States in recent years (31,37,38), and the virus has a basic reproduction number of approximately 15, meaning population immunity must be very high (around 95%) to interrupt transmission. Immunocompromised children who gradually lose seroprotection are invisible to routine surveillance and cannot rely on herd immunity for protection. Study 2 provides the longitudinal evidence to detect and close this gap proactively, within the framework of routine clinical blood sampling, rather than reactively after a case of vaccine-preventable disease.

**COVID-19 Vaccination in pedAIIRDs**

The COVID-19 pandemic created an unprecedented clinical challenge for paediatric rheumatology: vaccines were being rolled out to children at unprecedented speed, while data on their safety and effectiveness in immunocompromised patients were almost entirely absent. Studies 3 and 4 were designed to fill this gap from two different angles. Study 3 addressed whether COVID-19 vaccination prevents MIS-C, the most dangerous and possibly fatal paediatric complication of SARS-CoV-2 infection. Study 4 examined whether the vaccine is immunogenic, effective against symptomatic COVID-19 infection, and safe in pedAIIRD patients themselves.

The meta-analysis in Study 3 (chapter 4) produced a clear and clinically important finding in this thesis. A pooled odds ratio of 0.04 for MIS-C in vaccinated compared with unvaccinated children was consistent across four independent nationwide datasets from France, the United States, Denmark, and Israel, covering approximately 63 million children with no significant heterogeneity (14–17). This represents a 96% reduction in MIS-C risk for vaccinated children. The rate of MIS-C attributable to vaccination itself (2.9 per million) was approximately 39-fold lower than the rate following natural infection (113.3 per million) (18), effectively resolving the question of whether the vaccine might paradoxically trigger this syndrome. The biological explanation is mechanistically sound: mRNA vaccines encode the spike protein but lack the structural viral elements that drive the superantigen-like polyclonal T-cell expansion underlying MIS-C pathogenesis (19), while natural infection activates this pathway. The study by Khoury et al. adds a dimension specific to children with pedAIIRDs: biologic and targeted synthetic therapies were associated with a lower risk of developing MIS-C (20) suggesting that the pharmacological immunosuppression these children receive may additionally dampen the post-infectious inflammatory response responsible for MIS-C. This does not diminish the importance of vaccination; rather, it reinforces that if infection occurs despite vaccination, ongoing treatment may limit the severity of the inflammatory response. Both vaccination and immunosuppressive treatment act in the same protective direction.

Chapter 5 (Study 4) confirms that this population-level protection translates into individual benefit. The central finding is that vaccine effectiveness was preserved even in biologic-treated patients, who had lower antibody concentrations on average but remained protected. This pattern is well-established in the literature. Heshin-Bekenstein et al. reported 97% seropositivity three months after vaccination in 91 adolescents with juvenile-onset AIIRD, with lower but positive titres compared with healthy controls

(39). Akgun et al. observed adequate humoral responses across treatment groups in children with rheumatic diseases (40). Udaondo et al. demonstrated both humoral and cellular immune responses after mRNA vaccination in adolescents with rheumatic diseases, with adequate T-cell responses in most patients despite biologic use (41) Katoto et al. in a systematic review confirmed high seropositivity rates in immunocompromised adolescents despite treatment-related antibody attenuation(42). Geisen et al. and Boekel et al. both observed antibody attenuation with preserved directional protection in adults with chronic inflammatory diseases(22,23). Haberman et al. identified methotrexate specifically as the agent most responsible for attenuating humoral responses to BNT162b2 (7). Study 4 is consistent with all of these findings and extends them with real-world effectiveness data and cellular immunity assessment, which most earlier paediatric studies lacked. Together with guidance from the ACR and EULAR(25,26), these observations strongly support continuing immunosuppressive therapy at the time of COVID-19 vaccination rather than interrupting it.

Two factors explain why clinical effectiveness was maintained despite lower antibody concentrations in biologic-treated patients. First, those concentrations, although reduced, remained above the seroprotective threshold in almost all patients, so a lower titre did not mean an unprotected child. Second, cellular immunity was preserved: T-cell responses were adequate in 91% of tested patients in Study 4, and the strong correlation between IgG and T-cell responses ($r = 0.94$) supports antibody measurement as a practical surrogate. $CD8^+$ T-cell activation has been confirmed as a key correlate of protection against severe SARS-CoV-2 disease(43), and T-cell memory is more durable and more cross-reactive across viral variants than antibody-mediated neutralisation(44) The two patients who failed to mount adequate T-cell responses were both on combination methotrexate plus biologic therapy (tocilizumab and adalimumab), consistent with the synergistic immunosuppressive effect of this combination on adaptive immune responses(7). This identifies a subgroup warranting closer monitoring but does not change the overall conclusion.

Study 4 was conducted during the Delta-variant era. Omicron and its sublineages have substantially greater capacity to escape antibody neutralisation(45), and the specific effectiveness estimate cannot be applied to the current epidemiological context without caution. However, T-cell responses are more cross-reactive across variants, and the fundamental conclusion that vaccination benefits pedAIIRD patients remains sound.

**Recombinant Zoster Vaccine in pedAIIRDs**

Chapter 6 addresses a clinically significant and under-recognized unmet need. In the Netherlands, varicella is not part of the national immunization program, and children ordinarily acquire immunity through natural childhood exposure. For immunocompromised children, primary chickenpox carries substantially higher risk of serious complications, including pneumonitis, bacterial superinfection, and encephalitis (46). The live-attenuated varicella zoster vaccine is the standard preventive option, but it is contraindicated in children receiving high-level immunosuppression, including high-dose corticosteroids, cyclophosphamide, rituximab, JAK inhibitors, or combination biologic therapy, and requires careful individual risk-benefit assessment in patients on lower-level immunosuppression such as methotrexate or TNF inhibitors(3,47). This leaves a substantial and highly vulnerable group of children, those at highest infectious risk precisely because of their treatment intensity, without a safe and approved vaccination option. The adjuvanted recombinant zoster vaccine (Shingrix), developed to boost waning VZV immunity and prevent herpes zoster in older adults who acquired VZV earlier in life, is a non-live recombinant subunit vaccine and therefore carries no risk of vaccine-strain infection in immunocompromised hosts.

The 90% seroconversion rate of Shingrix in our VZV-naïve patients is worth noting, since Shingrix was designed as a booster for adults with existing VZV immunity rather than for primary immunisation of VZV-naïve individuals. That a subunit zoster vaccine produced seroconversion in nine of ten immunosuppressed, antigen-naïve children is encouraging. The two breakthrough infections that occurred were mild and self-limiting, and the single MAS relapse was attributable to concurrent rhinovirus and enterovirus infection rather than to the vaccine. This pattern fits with the responses Shingrix produces in other immunocompromised adult populations. In haematological malignancy patients, Shingrix elicited substantial humoral and cellular responses despite ongoing chemotherapy or bone marrow transplantation (48) In renal transplant recipients, it demonstrated both immunogenicity and acceptable safety post-transplant (49). A phase 4 randomized trial of Shingrix in adults with autoimmune rheumatic diseases is now underway (50).

The most directly comparable paediatric evidence comes from Bizjak et al., who studied the live-attenuated varicella vaccine in 17 children with JIA on biologic therapy (51). In that cohort, 14 of 17 (82%) were seropositive after the second dose, 3 of 17 (18%) had an increase in disease activity, and 4 of 17 (24%) developed mild breakthrough varicella four months to 4.5 years later, with cellular immunity that persisted longer than antibody and no severe disease. Our results are comparable on the measures that can be matched: a similar breakthrough rate (2 of 10, 20% versus 24%), with mild disease in

both cohorts and no vaccine-attributable serious events. The key difference is the vaccine: Bizjak et al. used the live-attenuated vaccine, which is registered and effective but contraindicated under high-level immunosuppression, and their patients were on TNF, IL-6, or IL-1 inhibitors, for whom EULAR/PRES considers it acceptable. The children in Study 5 were more heavily immunosuppressed, including on JAK inhibitors. Study 5 therefore does not suggest Shingrix should replace the live vaccine, but that it fills the gap the live vaccine cannot (51).

Study 5 is, to our knowledge, the first published report of Shingrix use in VZV-naïve immunocompromised children. Its contribution lies not in statistical precision but in providing first-in-field clinical evidence supporting a non-live vaccination strategy for this group. It shows that the approach is feasible, that seroconversion is achievable in most patients despite immunosuppression, that breakthrough infections are mild and manageable, and that the safety profile supports prospective evaluation. Three children in the cohort were receiving JAK inhibitors, representing the first paediatric experience with Shingrix in this treatment class. JAK inhibitors interfere broadly with cytokine signalling through mechanisms distinct from anti-TNF or anti-IL-6 therapy, and their interaction with vaccine immunogenicity in children deserves specific investigation. This study supports incorporating Shingrix into the clinical toolkit as a clinically important non-live alternative for VZV-naïve immunocompromised children who cannot safely receive a live vaccine.

Beyond the specific gap Study 5 addresses, how these two options should be positioned relative to each other remains an open question it cannot resolve**.** One view is that the live-attenuated vaccine should remain the first choice wherever the level of immunosuppression permits it, as EULAR/PRES currently allows for patients on TNF, IL-6, or IL-1 inhibitors, with Shingrix reserved for VZV-naïve children who cannot receive a live vaccine at all, those on high-dose corticosteroids, rituximab, cyclophosphamide, combination biologic therapy, or JAK inhibitors. An alternative view is that a non-live vaccine carrying no risk of vaccine-strain infection may be preferable across a broader range of immunosuppressed children, not only those for whom the live vaccine is contraindicated. Resolving this will require a direct comparison of the two strategies, including cellular immunity and long-term breakthrough rates, which Study 5 was not designed to provide.

**Policy Implications for the clinical care of children with pedAIIRDs**

The findings from all five studies have direct relevance to the next revision of the EULAR/PRES paediatric vaccination recommendations (3,52) The 2021 update was an important step forward, but its guidance on biologic-concurrent vaccination, particularly for live vaccines, was constrained by an evidence base that the authors themselves described as limited. The present work directly addresses several critical evidence gaps. For the MMR booster, we now have real-world safety data in a large biologic-treated cohort and longitudinal immunogenicity data extending nearly seven years, sufficient to support both a clear safety recommendation and a new recommendation for targeted serological monitoring. For COVID-19 mRNA vaccines, we have population-level evidence of substantial MIS-C risk reduction and prospective effectiveness and safety data in pedAIIRD patients. For VZV, we have the first evidence in paediatric patients, sufficient to justify its inclusion as a clinical option for VZV-naïve immunocompromised children who cannot receive a live vaccine.

We hope the evidence from this thesis can help to increase vaccination rates throughout the world, although more effort is needed. Vaccination rates in children with rheumatic diseases remain lower than in the general paediatric population, and practice varies widely between centres. A survey by de Souza et al. documented substantial inconsistency across CARRA member institutions, with live vaccine hesitancy especially in biologic-treated patients (53). Similar patterns of suboptimal vaccination coverage have been reported in other international cohorts (54,55). The studies in this thesis provide the specific, quantitative evidence needed to move beyond generalized caution and towards individualized, data-driven vaccination decisions in this patient group. When children with rheumatic diseases remain unvaccinated because the evidence for vaccine safety or efficacy is judged unconvincing, they are left exposed to the wild-type viruses themselves: measles (31,38), mumps, rubella, varicella (46), and COVID-19 (13). These are not hypothetical risks: measles has re-emerged across the Netherlands, Europe and the USA, varicella incidence complicated by group-A streptococcal superinfections has risen sharply in the wake of pandemic-related disruptions to natural childhood exposure (46), and COVID-19 continues to cause serious paediatric illness including MIS-C. The evidence generated by this thesis makes the clinical path forward clear: vaccination in children with pedAIIRDs is safe, generally immunogenic, and effective, and the default position should be to vaccinate, not to defer.

The strengths and limitations of this thesis follow from its design as real-world clinical research in a rare paediatric population

**Strengths**

**Duration of follow-up.** The median 6.9-year immunogenicity follow-up in Study 2 exceeds that of any previously published cohort study of MMR vaccination in children with rheumatic diseases. Earlier work was limited to short-term or one-to-three-year follow-up (Heijstek et al.(10) and Borte et al. (12)), sufficient to demonstrate initial seroconversion but not to detect the gradual decline of antibody concentrations that becomes clinically relevant over years of continued biologic therapy and that has direct implications for decisions about serological monitoring and revaccination. The post-COVID-19 vaccination follow-up in Study 4, extending to 282 days after first vaccination, similarly allows antibody waning to be observed over time rather than captured at a single point.

**Real-world clinical design.** All five studies were conducted within routine clinical practice at a tertiary paediatric rheumatology centre. Patients with active disease and those on combination immunosuppression, who would typically be excluded from controlled trials, were included here. This is particularly important for safety data: the adverse events that matter most clinically are often those that occur in patients who would have been ineligible for a trial, and their inclusion here makes the safety conclusions directly applicable to the children seen in everyday practice.

**Dual-compartment immunological assessment.** Most comparable studies measure antibody levels alone. Study 4 additionally assessed cellular immunity by IFN-γ ELISpot, which provided the mechanistic explanation for the preserved vaccine effectiveness despite lower antibody levels in biologic-treated patients. Without T-cell data, this finding would have been difficult to interpret and might have been misread as evidence that vaccination is less effective in biologic-treated patients, potentially discouraging vaccination in the group that needs it most.

**Methodological range.** The five studies together span a retrospective safety cohort (Study 1), a longitudinal serological cohort (Study 2), a systematic review and meta-analysis (Study 3), a prospective immunogenicity and effectiveness cohort (Study 4), and a real-world observational retrospective study (Study 5). This range allowed each question to be addressed with the design best suited to it, from real-world safety surveillance to prospective immunogenicity assessment and quantitative evidence synthesis.

**First-in-field contribution.** Study 5 is the first published evaluation of Shingrix in VZV-naive immunocompromised children. The vaccine was administered off-label as part of routine clinical care, reflecting a real-world decision made in the absence of any existing evidence or approved alternative. This context strengthens rather than weakens the contribution: it demonstrates that the approach is not only scientifically promising but

already being tried in clinical practice by physicians facing an unmet need. The study demonstrates feasibility, acceptable preliminary safety, and immunogenicity sufficient to support a further prospective evaluation. In a field where eligible patient populations are small and controlled trials are rarely possible, careful observation of real-world practice can be a practical way to generate first evidence

**Limitations**

**Sample size.** The biologic-treated subgroups in Studies 1 and 2, the cellular immunity subset in Study 4 (n = 22), and the entire cohort of Study 5 (n = 10) are small. Power to detect differences between treatment subgroups is limited, rare adverse events cannot be ruled out, and confidence intervals around many estimates are wide. These are inherent constraints of single-centre research in uncommon diseases and do not invalidate the findings, but define the level of certainty that can be claimed.

**Observational design.** None of the five studies used randomization, which means we cannot be certain that the groups being compared were identical in all relevant respects. In Study 4, for example, patients who chose to be vaccinated may have differed from those who did not in ways that were not fully captured by the statistical adjustments made, even though the analysis accounted for prior COVID-19 infection and used a time-varying approach to avoid counting time before vaccination as protected time. In Studies 1 and 2, children with more active or severe disease may have been less likely to receive the MMR booster, which could have influenced the disease activity scores measured before and after vaccination. This is the consequence of conducting pragmatic research in a vulnerable paediatric population where the rarity of the diseases makes large randomized trials logistically impractical.

**Single-centre recruitment.** Studies 1, 2, 4, and 5 were all conducted at a single tertiary university hospital. The patient population, treatment thresholds, and vaccination practices of a tertiary referral centre in the Netherlands may not be representative of paediatric rheumatology centres in other countries or healthcare systems. Children referred to a tertiary centre also tend to have more severe or complex disease than the broader population of children with pedAIIRDs, which may limit the generalizability of some findings. External validation in other centres and countries, particularly for Study 5, is therefore needed before the conclusions can be applied with confidence across different clinical settings.

**Absence of T-cell data for MMR and Shingrix.** T-cell responses were not assessed in Studies 1, 2, or 5. For MMR vaccination, $CD8^+$ T-cell memory may maintain clinical protection even after antibody concentrations fall below conventional seroprotective thresholds, meaning Study 2 may overestimate

the true proportion of patients who are clinically unprotected. For Shingrix in Study 5, VZV-specific T-cell immunity is thought to be the principal mechanism of durable protection against herpes zoster in immunocompromised adults (48,49). Because this was not measured in Study 5, the full protective response elicited by Shingrix in these children remains incompletely characterised. Future prospective studies evaluating both MMR and VZV in this population should incorporate standardised T-cell assays alongside serology to address this gap directly.

**Temporal limitations of the COVID-19 data.** Studies 3 and 4 were conducted predominantly during the period when the Delta variant of SARS-CoV-2 was dominant. Since then, the virus has evolved substantially. Omicron and its sublineages are considerably better at escaping the antibody responses generated by the original mRNA vaccines (45), which means the specific effectiveness estimate from Study 4 cannot be directly applied to the current situation. The MIS-C picture has also shifted: Miller et al. observed that during the Omicron wave, more MIS-C cases occurred in younger children who had not yet been vaccinated, suggesting that the pattern of risk has changed as vaccination coverage in older children increased (16). What has not changed is the fundamental conclusion: vaccination protects children with pedAIIRDs, and the risks of withholding it outweigh the risks of giving it. The specific numbers, however, will need to be revisited as new variants emerge and updated vaccines are introduced.

Taken together, the strengths and limitations of this thesis reflect the realities of conducting vaccination research in rare paediatric diseases. The study designs were shaped by practical and ethical constraints that are inherent to this field rather than specific to this work, and the findings were obtained from the patient populations and clinical settings in which vaccination decisions are actually made. What matters is that each study was designed to extract the maximum clinically useful information from the available data, and that the conclusions, considered together, are consistent, biologically plausible, and directly applicable to practice. The appropriate response to the limitations described above is not to discount what has been found, but to identify knowledge gaps that can be solved by larger, multicentre, prospective studies.

## Future Directions

**Larger and controlled studies.** The observational studies in this thesis provide the foundation for larger, prospective work that can now be designed with greater precision. For Shingrix, Study 5 has generated safety and immunogenicity pilot data that support further prospective evaluation in immunosuppressed paediatric cohorts, now ongoing within the PRES vaccination working group. A formal efficacy trial against primary VZV infection, an indication for which the vaccine was not developed, is unlikely to be undertaken given the small eligible population. For MMR vaccination, a multicentre longitudinal study across European paediatric rheumatology centres would provide the sample sizes needed to analyse immunogenicity outcomes by specific biologic agent, JIA subtype, and duration of therapy. Randomization is not feasible in this setting because withholding a recommended vaccine from a control group is not justifiable, but drawing control safety and efficacy data from existing Phase IV registries such as Pharmachild and BIKER offers a feasible alternative.

**Extending beyond JIA: other rheumatic diseases, inflammatory conditions, and immunodeficiency.** JIA, as the most prevalent paediatric rheumatic disease, dominated recruitment across the cohort studies. The findings nonetheless point towards a broader principle: for vaccine safety and immunogenicity, the immunosuppressive treatment a child receives appears to matter far more than the underlying diagnosis. This argues for vaccination recommendations organised primarily by treatment rather than by disease. Findings from children with JIA cannot, however, be directly extrapolated to children with SLE, systemic vasculitis, juvenile dermatomyositis, or monogenic autoinflammatory syndromes, whose patterns of immune dysregulation differ and who are frequently treated with agents not represented in the present studies, including B-cell depleting agents, cyclophosphamide, azathioprine, and mycophenolate mofetil. The scoping review by Cunninghame et al. identified the near-absence of vaccination data in non-JIA diagnoses as a critical gap that remains largely unaddressed (35) and a systematic review by Keller et al. reached the same conclusion across a broader range of vaccine types and rheumatic conditions (36). A recent prospective study by Maritsi et al. found accelerated rubella antibody loss in children with juvenile localized scleroderma on methotrexate, suggesting that the immunogenicity deficit observed in JIA extends to other paediatric rheumatic diseases treated with csDMARDs (56). Beyond rheumatic diseases, the same evidence gap applies to other paediatric conditions managed with biologics and csDMARDs, including inflammatory bowel disease, psoriasis, and atopic dermatitis. Children with these conditions receive the same classes of drugs, face the same questions about vaccine safety and immunogenicity, and are largely absent from the vaccination

literature. A treatment-based framework would allow these children to be studied and counselled together, across diagnoses and specialties. The feasibility of such cross-disease, cross-specialty recruitment is supported by MenACWY vaccination studies, which together enrolled adolescents with JIA, inflammatory bowel disease, and a range of primary and secondary immunodeficiencies across several clinical specialties (57,58). A further group deserving specific attention is children with primary immune dysregulation and immunodeficiency, the one setting where the underlying defect, rather than treatment, is the dominant factor. These patients face the greatest risk from vaccine-preventable disease yet are managed on a case-by-case basis with almost no supporting evidence. Understanding how underlying immune defects interact with vaccine responses, and whether standard seroprotective thresholds retain their predictive value in this setting, requires dedicated studies incorporating detailed immunological phenotyping alongside serological measurement. Progress in all of these areas will require collaboration between paediatric rheumatology, clinical immunology, gastroenterology, and dermatology, moving beyond diagnostic silos towards a shared evidence base for vaccination in children on immunosuppressive therapy.

**Emerging treatments.** Equally important is research in patients receiving newer treatments. Targeted synthetic DMARDs, specifically JAK inhibitors (JAKi), now used increasingly in paediatric rheumatology for JIA, systemic autoinflammatory diseases, and interferonopathies, interfere broadly with cytokine signalling pathways that are central to both innate and adaptive vaccine responses. With the recent expiry of the tofacitinib patent and the approval of generic versions, its price is expected to fall considerably, which could lead to earlier and wider prescribing. Nonetheless, the effect of JAKi on vaccine immunogenicity in children has barely been studied. Three of the ten children in Study 5 were already receiving JAK inhibitors, constituting the first available evidence on Shingrix immunogenicity in paediatric patients receiving JAK inhibitor therapy (29), but this is far from sufficient to draw conclusions. A different challenge is posed by B-cell depleting agents such as rituximab since humoral vaccine responses may take six months or longer to recover after treatment, and current guidance recommends timing vaccination accordingly (24,59), yet evidence specific to children remains limited. JAK inhibitors, B-cell depleting agents, and a growing range of targeted therapies with distinct mechanisms of immune modulation are being used in increasingly younger and more complex patients. For all of these agents, drug-specific vaccination data in children are either absent or very limited, making their systematic study an urgent clinical priority rather than a future aspiration.

**Vaccine-induced protection: beyond antibody titters.** Underlying the immunogenicity studies in this thesis is an assumption that seroprotective thresholds developed in healthy children apply equally to children with pharmacologically modified immune systems. For measles, the conventional threshold of 150 IU/L was established in populations with intact memory B-cell and T-cell biology; whether it reliably predicts clinical protection in children whose B-cell or T-cell function is suppressed by immunosuppressive therapy is not known. For mumps and rubella, validated correlates of protection are similarly uncertain, and the seroprotective thresholds in current use were not derived from immunocompromised populations. For COVID-19 and VZV, paediatric correlates of protection do not exist at all. Until these thresholds are properly established for this patient group, a positive antibody result cannot be confidently interpreted as protective, and a negative serological result cannot be taken to mean a child is clinically unprotected. Establishing paediatric-specific correlates of protection will require multinational studies that combine quantitative serology with functional assays and a reliable international registration of breakthrough infections, including plaque reduction neutralisation for measles and VZV-specific T-cell assays for zoster immunity, linked to clinical outcome data and stratified by disease, treatment intensity, and age. A systematic review by Keller et al. identified this as one of the most pressing evidence gaps in the field (36). Addressing it will require coordinated investment at the European or international level, but it is the foundational work on which all future vaccination guidance for this population ultimately depends.

**Building better systems for tracking vaccination outcomes.** A recurring challenge in this thesis was the lack of infrastructure for routine monitoring of outcomes in immunocompromised children following vaccination. When a child with JIA receives an MMR booster, there is generally no systematic follow-up beyond monitoring disease activity. As a result, it is not routinely assessed whether they experienced adverse effects, whether protective antibody levels persist five years later, or whether they subsequently develop measles, mumps, or rubella. This information is scattered across rheumatology clinic records, general practice notes, and public health systems that do not communicate with each other. Standardizing the electronic health record so that vaccination status is routinely recorded and updated, together with any vaccine side effects and any episodes of the diseases the vaccine is intended to prevent, is the next logical step. The European Health Data Space is designed to enable precisely this kind of secondary use of health data. From this foundation it would be straightforward to build a dedicated registry that would transform the quality of evidence around vaccination in this field. It would allow safety

signals to be detected earlier, waning immunity to be tracked systematically, and the effectiveness of different vaccination strategies to be compared across treatment groups. The COVID-19 pandemic showed what is achievable even in the absence of such infrastructure, when international collaboration generated vaccine safety and effectiveness data at unprecedented speed. A connected system would make such evidence generation routine.

**Improving vaccination uptake in practice.** Generating evidence and changing clinical behaviour are different challenges. The 2011 EULAR/PRES recommendations were shaped by an evidence base acknowledged to be limited, and it was this uncertainty that allowed hesitancy to become the default position in many centres. In 2021 the evidence base was extended, but it remained incomplete. Despite this progress, both caregivers and paediatric rheumatology providers continue to underutilise vaccines in this patient group, driven by safety concerns and uncertainty that the studies in this thesis directly address (54,55). The evidence generated by this thesis and by new studies provides a substantially stronger foundation for confident clinical decision-making. The task is to ensure this evidence reaches practice consistently. This requires structured shared decision-making frameworks that allow clinicians to discuss risk and benefit clearly with families, accessible patient-facing materials that can be read and understood before a clinic appointment, and provider education programmes that translate research findings into practical day-to-day guidance (60). We are already providing international webinars on this topic. In addition, the PRES Vaccination Working Party has produced multilingual vaccination recommendations for patients with paediatric rheumatic diseases on immunosuppressive drugs, which we are currently editing and translating. A logical extension of this work would be the development of a digital clinical decision support tool that integrates patient-specific variables: diagnosis, disease activity, current therapy, and vaccination history, to generate individualised, evidence-based vaccination recommendations at the point of care, bridging the persistent gap between guideline recommendations and consistent clinical practice. Systematic implementation of the available evidence into clinical practice deserves dedicated attention and monitoring.

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Chapter 8

# Summary

## Chapter 8: Summary

This thesis aimed to strengthen the evidence base for vaccination as a means of protecting immunocompromised children from preventable infection by addressing key unanswered questions regarding vaccine safety, immunogenicity, and effectiveness. To achieve this, it investigated five specific clinical questions that practitioners encounter in daily practice but often cannot answer with confidence, because the available evidence is limited or absent. Together, the five studies presented in this thesis provide a body of evidence across three vaccine platforms, obtained in real-world populations and in clinical settings where these decisions are actually made, and of sufficient scope and consistency to inform individual patient care, guideline revision and future research.

The most consistent finding across all five studies is that vaccination in this patient group is safer than the prevailing culture of caution has assumed. The MMR booster caused no significant change in disease activity and no serious adverse events in a large real-world cohort that included biologic-treated children, the very patients most commonly advised to avoid live attenuated vaccines. COVID-19 mRNA vaccines were safe and well-tolerated too, with no disease flares and none of the feared vaccine-triggered events such as myocarditis or MIS-C. The recombinant zoster vaccine Shingrix, used off-label in selected VZV-naïve immunocompromised children, represents the first published evaluation of this approach in paediatric patients and showed an acceptable preliminary safety profile despite the vulnerability of the study population. Safety did not appear to be the barrier it has been feared to be.

The findings describing immunogenicity tell a more complex story. Biologic-treated patients mounted lower antibody responses to both MMR and COVID-19 than children not on biologics, and a substantial proportion of patients had lost measles seroprotection within five years of the MMR booster. For COVID-19, however, those lower antibody levels still protected children against infection, whereas the loss of measles seroprotection leaves some children unprotected. These findings are not arguments against vaccination, rather they are arguments for more tailored and more effective vaccination strategies. A targeted approach, measuring MMR-specific IgG at an appropriate interval post-booster in biologic-treated patients and offering a booster dose to those who have lost seroprotection, is both clinically practical and directly supported by the longitudinal data generated in this thesis.

One of the most clinically important findings in this work comes from chapter 5: lower antibody levels did not translate into less protection. Biologic-treated children had significantly lower anti-spike IgG concentrations after COVID-19 mRNA vaccination than children not on biologics, though in almost all cases these remained above the seroprotective threshold, and their rate of symptomatic infection was no higher. Adequate T-cell responses in 91% of tested patients likely help maintain protection when antibody levels are lower. This has direct implications for how isolated serological results in immunocompromised children should be interpreted: a lower-than-expected antibody level does not necessarily mean the vaccine has failed.

The meta-analysis on the incidence of MIS-C after vaccination in chapter 4 produced clear quantitative evidence: a pooled odds ratio of 0.04 (95% CI 0.03–0.06) for MIS-C in COVID-19 vaccinated children compared with unvaccinated children, representing a 96% reduction in risk that was consistent across four independent nationwide datasets covering approximately 63 million children. The rate of MIS-C following COVID-19 vaccination itself was 2.9 per million, compared with 113.3 per million following natural infection. This finding, combined with evidence that biologic and targeted synthetic therapies are themselves associated with a lower risk of MIS-C, suggests that vaccinated children with pedAIIRDs receiving immunomodulatory treatment have multiple layers of protection against this severe complication.

Chapter 6 is the first published evaluation of Shingrix in VZV-naïve immunocompromised children. The vaccine was administered off-label as part of routine clinical care in selected significantly immunocompromised patients, in the absence of any approved alternative, reflecting a real-world decision made by clinicians facing an unmet need. It provides preliminary evidence that this approach is feasible, that seroconversion is achievable in most patients despite ongoing immunosuppression, that breakthrough infections when they occur are mild and manageable, and that no safety signal emerged that would preclude a larger study. For a patient group that currently has no approved vaccination option against primary varicella when high-level immunosuppression precludes the live vaccine, this represents a clinically important first step toward filling that gap.

The practical conclusions are clear. In children with pedAIIRDs, vaccination status should be systematically assessed at diagnosis and re-evaluated at each significant treatment transition. Biologic-treated patients should have MMR-specific IgG levels measured at an appropriate interval after the booster dose, with a further dose offered to those who have lost seroprotection. COVID-19 vaccination can generally be administered without interruption of immunosuppressive therapy. VZV-naïve children on high-level

immunosuppression should be considered for Shingrix as a non-live alternative. And in the most complex cases, children on multiple immunosuppressants or with features of primary immunodeficiency, the vaccination decision should be made jointly with clinical immunology and infectious disease colleagues, and should not be deferred indefinitely on grounds of uncertainty.

The evidence is not complete, and this thesis is explicit about what remains unknown: the validity of seroprotective thresholds in immunocompromised children, the vaccine responses to newer treatments including JAK inhibitors, B-cell depleting agents, and other advanced targeted therapies, the extension of these findings beyond JIA to children with other autoimmune and inflammatory conditions such as inflammatory bowel disease, psoriasis, and primary immunodeficiency, and the long-term correlates of protection for COVID-19 and recombinant zoster vaccines in paediatric patients. These limitations do not change the overall conclusions of this thesis. Instead, they identify important priorities for future research. They simply mark the point where this thesis ends and the next phase of work begin. The children who fall outside the current evidence base deserve the same quality of evidence that this thesis has begun to generate, and each gap identified here points towards a research programme that is now within reach.

What this thesis demonstrates, above all, is that the **default position in the care of children with pedAIIRDs should be to vaccinate** rather than to defer, and that the evidence now exists to make that position specific, defensible, and safe.

## Nederlandse Samenvatting

Sommige kinderen lijden aan aandoeningen waarbij hun eigen immuunsysteem het lichaam aanvalt. Ziekten zoals juveniele idiopathische artritis (JIA), systemische lupus erythematosus (SLE), juveniele dermatomyositis, systemische vasculitiden en monogene auto-inflammatoire syndromen, waaronder Familiaire Middellandse Zeekoorts (FMF) en TNF-receptor-geassocieerd periodiek syndroom (TRAPS), kunnen vanaf jonge leeftijd zorgen voor gewrichtsontsteking, koorts en ernstige orgaanschade. Om deze ziekten onder controle te houden, worden medicijnen gebruikt die het immuunsysteem bewust onderdrukken: klassieke middelen zoals methotrexaat, maar ook nieuwere biologische preparaten die gericht zijn op specifieke ontstekingseiwitten zoals TNF, IL-1 en IL-6, en meer recentelijk de JAK-remmers.

Deze medicijnen werken goed. Voor veel kinderen betekenen zij het verschil tussen een jeugd die gedomineerd wordt door ziekte en een zo normaal mogelijk dagelijks leven. Maar ze roepen ook een vraag op die ouders stellen en artsen bezighoudt: als het immuunsysteem van een kind door de behandeling wordt onderdrukt, kan het dan nog veilig worden gevaccineerd? En zo ja, werkt het vaccin dan ook echt?

Dit zijn geen eenvoudige vragen. Vaccins werken door het immuunsysteem te trainen een specifieke ziekteverwekker te herkennen en te bestrijden voordat een echte infectie optreedt. Als dat immuunsysteem door medicatie wordt geremd, bestaat de zorg dat het vaccin mogelijk onvoldoende bescherming biedt, of, bij levende vaccins die een verzwakte vorm van het echte virus bevatten, de infectie zelf kan veroorzaken. Dit heeft in de klinische praktijk geleid tot wijdverbreide terughoudendheid. Veel kinderen met reumatische aandoeningen kregen te horen dat vaccinatie moest worden uitgesteld, of dat bepaalde vaccins voor hen niet geschikt waren. Soms was die voorzichtigheid terecht. In veel gevallen echter niet, en het gevolg was dat kinderen onbeschermd bleven tegen infectieziekten die ernstig of zelfs levensbedreigend kunnen zijn wanneer de afweer verminderd is.

Dit proefschrift werd geschreven om meer onderbouwde antwoorden te geven op deze vragen. Er werden vijf studies uitgevoerd, elk gericht op een specifieke onbeantwoorde vraag over vaccinatie bij kinderen met reumatische aandoeningen. Vier studies werden uitgevoerd bij patiënten van het Wilhelmina Kinderziekenhuis in Utrecht, terwijl één studie gegevens uit meerdere landen samenbracht.

De eerste twee studies richtten zich op de bof-mazelen-rodehond (BMR)-boostervaccinatie. Mazelen zijn de afgelopen jaren opnieuw opgedoken in Nederland en in andere Europese landen, mede door dalende

vaccinatiegraad en afnemende groepsimmuniteit. Kinderen die niet beschermd zijn, lopen een reëel risico. De eerste studie toonde aan dat de BMR-boostervaccinatie veilig was bij 186 kinderen met JIA, inclusief degenen die biologische medicijnen gebruikten: er was geen toename van ziekteactiviteit, geen ernstige bijwerkingen en geen enkel geval waarbij het vaccin een infectie veroorzaakte. De tweede studie volgde 182 kinderen gedurende gemiddeld bijna zeven jaar na vaccinatie, de langste immunogeniciteitsopvolging in dit vakgebied tot nu toe. De meeste kinderen behielden beschermende antistofniveaus. Bij kinderen die biologische therapie gebruikten, was de bescherming tegen mazelen op vijf jaar echter significant lager dan bij kinderen zonder biologische therapie (60% versus 86%). De praktische conclusie is concreet: bij kinderen op biologische therapie dienen de mazelenantistoffen circa vijf jaar na vaccinatie te worden gemeten, en bij verlies van bescherming dient een extra dosis te worden aangeboden.

De derde en vierde studies richtten zich op COVID-19-vaccinatie. Een van de zorgen tijdens de pandemie was dat een zeldzame maar ernstige complicatie van COVID-19 bij kinderen, het multisysteeminflammatoir syndroom (MIS-C), mogelijk zou kunnen worden uitgelokt door het vaccin zelf. De derde studie, een systematische review en meta-analyse waarbij gegevens werden samengebracht uit vier grote nationale studies met tientallen miljoenen kinderen in Frankrijk, de Verenigde Staten, Denemarken en Israël, toonde het tegendeel aan: vaccinatie verlaagde het risico op MIS-C met 96%. Het risico op MIS-C na vaccinatie bedroeg 2,9 per miljoen gevaccineerde kinderen, vergeleken met 113,3 per miljoen na een natuurlijke infectie. Het vaccin veroorzaakt dit syndroom dus niet, het voorkomt het. De vierde studie liet vervolgens zien dat COVID-19-vaccins ook effectief zijn bij kinderen met reumatische aandoeningen. Hoewel de antistofniveaus bij kinderen op biologische therapie iets lager waren, bleef de bescherming tegen symptomatisch COVID-19 behouden: gevaccineerde kinderen hadden 47% minder kans op een symptomatische infectie, ongeacht of ze biologische therapie gebruikten of niet. De T-celrespons bleek bij 91% van de geteste kinderen adequaat, wat de verklaring biedt voor deze behouden bescherming ondanks lagere antistofspiegels. Er werden geen ziekte-opvlammingen, geen myocarditis en geen ernstige bijwerkingen vastgesteld.

De vijfde studie richtte zich op een probleem waarvoor nergens ter wereld een gepubliceerde oplossing bestond. Sommige kinderen met reumatische aandoeningen gebruiken zo intensieve immunosuppressie dat het standaard waterpokken-vaccin, dat een levend, verzwakt virus bevat, gecontra-indiceerd is. Dit laat hen onbeschermd tegen waterpokken, een infectie die bij immuungecompromitteerde kinderen ernstig kan verlopen. Een niet-levend vaccin genaamd Shingrix, normaal gebruikt ter voorkoming van gordelroos bij volwassenen, werd off-label toegediend aan tien VZV-naïeve

immuungecompromitteerde kinderen in het Wilhelmina Kinderziekenhuis. Negen van de tien ontwikkelden een meetbare immuunrespons. Twee kinderen die nadien thuis in contact kwamen met waterpokken, ontwikkelden een milde infectie die volledig genas zonder antivirale behandeling of ziekenhuisopname, wat erop wijst dat het vaccin de ziekte had verzacht, ook al had het deze niet volledig voorkomen. Dit was de eerste gepubliceerde evaluatie van deze aanpak bij kinderen en het legt de basis voor toekomstig formeel onderzoek.

Samen wijzen deze vijf studies in dezelfde richting: kinderen met reumatische aandoeningen kunnen en moeten worden gevaccineerd, en de onderbouwing bestaat nu om te begeleiden hoe, wanneer en met welke monitoring dit het beste kan worden gedaan. Vaccinatie is voor deze kinderen veel veiliger dan vaak werd gevreesd. De gevolgen van niet vaccineren, in een wereld waar mazelen opnieuw circuleren, waterpokken vaker voorkomen na de verstoringen door de COVID-19-pandemie, en COVID-19 ernstige ziekte blijft veroorzaken, zijn reëel en vermijdbaar. Dit proefschrift is bedoeld om ervoor te zorgen dat geen enkel kind onbeschermd blijft doordat het bewijs ontbrak om artsen en ouders gerust te stellen. Dit proefschrift draagt bij aan het leveren van dat bewijs.

## Lay Summary

For some children, the immune system that should protect them from infection becomes the source of the problem itself. These children live with autoimmune or autoinflammatory diseases, conditions in which the immune system mistakenly attacks the body's own tissues. Diseases like Juvenile Idiopathic Arthritis (JIA), lupus, and other rare rheumatic and inflammatory disorders can cause joint swelling, pain, fever, and serious organ damage from a very young age. To bring these diseases under control, doctors use medications that deliberately dampen the immune system, drugs like methotrexate, or newer biological treatments that target specific proteins involved in the inflammatory process.

These medications work well. For many children, they mean the difference between a childhood defined by illness and one that is as normal as possible. But they raise a question that parents and doctors alike cannot avoid: if a child's immune system is being suppressed by treatment, can they still be safely vaccinated? And if they are vaccinated, will the vaccine actually work?

These are not simple questions. Vaccines work by training the immune system to recognise and fight a specific infection before it arrives. If that immune system is being quieted by medication, there is a reasonable concern that the vaccine might not work well enough to be useful, or, in the case of live vaccines that contain a weakened form of the actual virus, that it might cause the very infection it is meant to prevent. The result, in everyday clinical practice, has been widespread hesitancy. Many children with rheumatic diseases have been told to wait, or not to have certain vaccines at all. Sometimes this caution has been justified. Often it has not, and it has left children unprotected against diseases that can be serious, or even fatal, in anyone whose immune defences are reduced.

This thesis was designed to provide the evidence needed to answer these questions more precisely. Five studies were conducted, each addressing a specific unanswered question about vaccination in children with rheumatic diseases. Four studies followed children treated at the Wilhelmina Children's Hospital in Utrecht, while one brought together data from millions of children across several countries.

The first two studies looked at the measles-mumps-rubella (MMR) booster vaccination. Measles has returned to the Netherlands and across Europe in recent years, and children who are not protected face a genuine risk. The first study, which followed 186 children with juvenile idiopathic arthritis, found that the MMR booster was safe even in those receiving biological medications: no child experienced a worsening of their disease, and no child developed the vaccine virus as an infection. The second study

followed 182 children for nearly seven years after vaccination, the longest follow-up of its kind in this field. Most children maintained protective antibody levels throughout this period. However, children on biological therapy were more likely to lose measles protection over time, not because their antibodies declined faster, but because the protection they built in the first years was somewhat lower. The practical implication is targeted: these children should have their measles antibody levels checked around five years after vaccination, and if protection has been lost, a further dose should be offered.

The third and fourth studies focused on COVID-19. One of the concerns during the pandemic was that a rare but severe complication of COVID-19 in children, called multisystem inflammatory syndrome in children, or MIS-C, might be triggered by the vaccine itself. The third study pooled data from four large national studies covering tens of millions of children across France, the United States, Denmark, and Israel, and found the opposite: vaccination reduced the risk of MIS-C by 96%. For every child who developed MIS-C after vaccination, roughly 40 developed it after natural infection. The vaccine did not cause the syndrome, it prevented it. The fourth study then showed that COVID-19 vaccines were effective in children with rheumatic diseases specifically, even in those receiving immunosuppressive treatment. While antibody levels were somewhat lower in children on biological therapy, overall protection against symptomatic COVID-19 was preserved, most likely because those antibody levels, although lower, generally stayed high enough to protect, and because a different part of the immune response, involving T-cells, also remained intact.

The fifth study addressed a group of children for whom routine vaccination against chickenpox was either not possible due to intensive immunosuppression, or not part of the national vaccination programme. Some children with rheumatic diseases are on such intensive immunosuppression that even the standard chickenpox vaccine, which contains a live, weakened virus, is not safe for them. This leaves them without a licensed vaccine option against an infection that can be dangerous in immunocompromised children. A non-live vaccine called Shingrix, normally used to prevent shingles in adults, was given off-label to ten such children at the Wilhelmina Children's Hospital. Nine of the ten developed a measurable immune response. Two children who were subsequently exposed to chickenpox at home developed a mild infection but recovered completely without needing antiviral treatment or hospitalisation, suggesting that the vaccine had softened the illness even if it had not fully prevented it. This was the first published evaluation of this approach in children, and it opens a path that future research can now follow.

Taken together, these five studies point clearly in the same direction: children with rheumatic diseases can and should be vaccinated, and the

evidence now exists to guide how, when, and with what monitoring this should be done. Vaccination is far safer for these children than has often been feared. The consequences of not vaccinating, in a world where measles is circulating again, chickenpox has become more common following pandemic-era disruptions to childhood exposure, and COVID-19 continues to cause serious illness, are real and avoidable. This research exists to ensure that no child is left unprotected simply because the evidence needed to guide doctors and reassure families was lacking. This thesis contributes to providing that evidence.

## List of Abbreviations

| | |
|---|---|
| **ACR** | American College of Rheumatology |
| **AE** | Adverse Event |
| **AJC** | Active Joint Count |
| **bDMARD** | Biologic Disease-Modifying Anti-Rheumatic Drug |
| **CAPS** | Cryopyrin-Associated Periodic Syndrome |
| **CARRA** | Childhood Arthritis and Rheumatology Research Alliance |
| **CDC** | Centres for Disease Control and Prevention |
| **CI** | Confidence Interval |
| **cJADAS** | Clinical Juvenile Arthritis Disease Activity Score |
| **COVID-19** | Coronavirus Disease 2019 |
| **csDMARD** | Conventional Synthetic Disease-Modifying Anti-Rheumatic Drug |
| **DMARD** | Disease-Modifying Anti-Rheumatic Drug |
| **ECMO** | Extracorporeal Membrane Oxygenation |
| **ELISpot** | Enzyme-Linked Immunospot Assay |
| **EULAR** | European Alliance of Associations for Rheumatology |
| **FDA** | Food and Drug Administration |
| **FMF** | Familial Mediterranean Fever |
| **GMR** | Geometric Mean Ratio |
| **HR** | Hazard Ratio |
| **IBD** | Inflammatory Bowel Disease |
| **IFN-γ** | Interferon Gamma |
| **IgG** | Immunoglobulin G |
| **IL** | Interleukin |
| **ILAR** | International League of Associations for Rheumatology |
| **IQR** | Interquartile Range |
| **IVIG** | Intravenous Immunoglobulin |
| **JAK** | Janus Kinase |
| **JAKi** | Janus Kinase Inhibitor |

| | |
|---|---|
| **JDM** | Juvenile Dermatomyositis |
| **JIA** | Juvenile Idiopathic Arthritis |
| **MAS** | Macrophage Activation Syndrome |
| **MCTD** | Mixed Connective Tissue Disease |
| **MIS-C** | Multisystem Inflammatory Syndrome in Children |
| **MMR** | Measles-Mumps-Rubella |
| **mRNA** | Messenger Ribonucleic Acid |
| **MTX** | Methotrexate |
| **NNV** | Number Needed to Vaccinate |
| **NSAID** | Non-Steroidal Anti-Inflammatory Drug |
| **OPV** | Oral Polio Vaccine |
| **OR** | Odds Ratio |
| **PBMC** | Peripheral Blood Mononuclear Cell |
| **pedAIIRDs** | Paediatric Autoimmune and Autoinflammatory Rheumatic Diseases |
| **PGA** | Physician Global Assessment |
| **PRES** | Paediatric Rheumatology European Society |
| **RZV** | Recombinant Zoster Vaccine |
| **SAE** | Serious Adverse Event |
| **SARS-CoV-2** | Severe Acute Respiratory Syndrome Coronavirus 2 |
| **sJIA** | Systemic Juvenile Idiopathic Arthritis |
| **SLE** | Systemic Lupus Erythematosus |
| **TNF** | Tumour Necrosis Factor |
| **TRAPS** | TNF Receptor-Associated Periodic Syndrome |
| **VZV** | Varicella Zoster Virus |
| **WHO** | World Health Organization |

## ACKNOWLEDGMENTS

A PhD thesis is rarely the work of one person alone, and this one is no exception. Over the years that this research took shape, I was fortunate to be surrounded by people who gave their time, expertise, and encouragement generously and without reservation. I am grateful to all of them.

My supervisory **team at the Wilhelmina Children's Hospital**, University Medical Centre Utrecht, made this work possible in the most direct sense. **Dr. Joris van Montfrans**, thank you for your steady support, your thoughtful guidance, and for always making time when it mattered most. You helped me navigate the difficult moments of this journey with patience and good judgement, and I am deeply grateful**. Dr. Marc Jansen**, your scientific sharpness, your hands-on involvement in every study, and your willingness to think carefully and creatively about every problem shaped this thesis more than you may realise. Working with you has been both a privilege and an education**. Prof. Joost Swart**, your clinical rigour, your commitment to your patients, and the quiet professionalism with which you approach everything you do set a standard I will carry with me long after this thesis is finished. **Prof. Bas Vastert**, thank you for your leadership of the Paediatric Rheumatology and Immunology departments, for championing this research from its earliest stages, and for creating an environment in which ambitious work is not only possible but expected.

The entire paediatric rheumatology and immunology teams at the Wilhelmina Children's Hospital deserve my sincere thanks. This research was built on clinical data collected during real patient care, and the quality of that data reflects the quality of the people who collected it. Special thanks to **Dr. Erika van Nieuwenhove, Dr. Annet van Royen-Kerkhof,** and **Dr. Sytze de Roock,** as well as to the nurses, research coordinators, and administrative staff whose daily work makes research like this possible.

**Dr. Joeri van Straalen,** your friendship and collaboration were woven through every stage of this project. Thank you for the conversations, the encouragement, and for making the work considerably more enjoyable than a PhD thesis has any right to be.

**Prof. Nico Wulffraat** welcomed me into the Wilhelmina Children's Hospital family and encouraged me to pursue this doctorate when it was still nothing more than an idea. His generosity, vision, and belief in what this research could achieve helped create the conditions for everything that followed, and I remain deeply grateful for his support.

From my home institution, I owe a particular debt of gratitude to **Prof. Giora Pillar**, Head of Department at Carmel Medical Centre. His confidence in me and his willingness to support my academic development while I continued my clinical responsibilities made it possible to conduct this work across two

countries and two institutions simultaneously. That kind of mentorship is rare, and I do not take it for granted.
None of this would have been possible, or worth doing, without my family. To my wife **Lina**, your patience, your understanding, and your unwavering belief in me carried me through the moments when I doubted myself. This thesis is dedicated to you. To our daughters, **Lara and Dima**, you are the reason all of this matters. **To my parents**, everything I have achieved is built on the foundation you gave me, through your sacrifices, your values, and your example. This achievement belongs to you as much as it does to me.
Finally, I gratefully acknowledge **the Graduate School of Life Sciences** at Utrecht University and the Infection and Immunity PhD Programme for providing the institutional home and intellectual community in which this research could flourish. Conducting this work within the Wilhelmina Children's Hospital and the broader environment of UMC Utrecht has been both a privilege and an honour.

# CURRICULUM VITAE

Mohamad Hamad Saied was born on 19 March 1983 in Kabul, Israel. He studied medicine at the Technion, Israel Institute of Technology, in Haifa, where he obtained his Bachelor of Science degree summa cum laude in 2008 and his medical degree in 2010.

After qualifying as a doctor he trained in paediatrics at Carmel Medical Center in Haifa, and went on to complete a fellowship in paediatric rheumatology at Schneider Children's Medical Center in Petah Tikva between 2016 and 2018. In 2018 he joined the Paediatric Rheumatology Unit at Carmel Medical Center as a consultant paediatric rheumatologist. He was later appointed Head of the Paediatric Rheumatology Unit and also served as Deputy Head of the Paediatric Department.

From 2022 to 2023 he undertook a further fellowship in paediatric rheumatology at the Wilhelmina Children's Hospital, University Medical Center Utrecht, the Netherlands. During this period he began the research presented in this thesis, carried out under the supervision of Dr J.M. van Montfrans, Dr S.J. Vastert, Dr J.F. Swart, and Dr M.H.A. Jansen. His doctoral work addressed the safety, immunogenicity, and effectiveness of vaccination in children with paediatric autoimmune and autoinflammatory rheumatic diseases, spanning the measles-mumps-rubella booster, COVID-19 mRNA vaccines, and the recombinant zoster vaccine.

He is currently Head of the Paediatric Rheumatology Unit at Carmel Medical Center and Assistant Professor at the Technion, Israel Institute of Technology, Faculty of Medicine. His clinical and research interests include juvenile idiopathic arthritis, the autoinflammatory diseases familial Mediterranean fever and PFAPA syndrome, and vaccination in children with immune-mediated disease.

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# LIST OF PUBLICATIONS

## Publications in this thesis

**Chapter 2** **Mohamad Hamad Saied**, van Straalen JW, de Roock S, de Joode-Smink G, Swart JF, Wulffraat NM, Jansen MHA. Safety of Measles-Mumps and Rubella booster vaccination in patients with Juvenile Idiopathic Arthritis: a long-term follow-up study. Vaccine. 2023 May.

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