EULAR/PRES recommendations for vaccination of paediatric patients with autoimmune inflammatory rheumatic diseases: update 2021

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ABSTRACT

Objectives Recent insights supporting the safety of live-attenuated vaccines and novel studies on the immunogenicity of vaccinations in the era of biological disease-modifying antirheumatic drugs in paediatric patients with autoimmune/inflammatory rheumatic diseases (pedAIIRD) necessitated updating the EULAR recommendations.

Methods Recommendations were developed using the EULAR standard operating procedures. Two international expert committees were formed to update the vaccination recommendations for both paediatric and adult patients with AIIRD. After a systematic literature review, separate recommendations were formulated for paediatric and adult patients. For pedAIIRD, six overarching principles and seven recommendations were formulated and provided with the level of evidence, strength of recommendation and Task Force level of agreement.

Results In general, the National Immunisation Programmes (NIP) should be followed and assessed yearly by the treating specialist. If possible, vaccinations should be administered prior to immunosuppressive drugs, but necessary treatment should never be postponed. Non-live vaccines can be safely given to immunosuppressed pedAIIRD patients. Mainly, seroprotection is preserved in patients receiving vaccinations on immunosuppression, except for high-dose glucocorticoids and B-cell depleting therapies. Live-attenuated vaccines should be avoided in immunosuppressed patients. However, it is safe to administer the measles–mumps–rubella booster and varicella zoster virus vaccine to immunosuppressed patients under specific conditions. In addition to the NIP, the non-live seasonal influenza vaccination should be strongly considered for immunosuppressed pedAIIRD patients.

Conclusions These recommendations are intended for paediatricians, paediatric rheumatologists, national immunisation agencies, general practitioners, patients and national rheumatology societies to attain safe and effective vaccination and optimal infection prevention in immunocompromised pedAIIRD patients.

INTRODUCTION

Patients with autoimmune/auto-inflammatory rheumatic diseases (AIIRD) have an increased risk of infections caused by the disease itself and/or by the treatment with immunomodulating or immunosuppressive drugs.[1–5] Infection prevention is therefore vital in the management of patients with AIIRD.

Vaccinations play an important role in infection prevention.[6–8] Paediatric patients with AIIRD (pedAIIRD) are offered vaccines via National Immunisation Programmes (NIPs) in order to prevent infections. However, a one-size-fits-all NIP is suboptimal for infection prevention in pedAIIRD patients because additional vaccinations may be required due to specific infection risks, whereas live-attenuated vaccines might be contraindicated in specific circumstances. Also, vaccinations may be less effective and timing of vaccination in relation to treatment and disease activity may be warranted. Therefore, pedAIIRD patients require a tailor-made vaccination schedule, taking their disease activity, treatment, infection risk, vaccine safety and efficacy into account.

The EULAR developed the first set of recommendations for the vaccination of pedAIIRD patients in 2011.[9] These recommendations were based on 27 manuscripts specifically addressing paediatric patients. No data were available on the human papillomavirus (HPV) vaccine, only one paper was available on pneumococcal vaccine[10] and information on the safety and immunogenicity of live-attenuated vaccines was scarce.[11] In addition, there were hardly any studies on the effect of biological disease-modifying antirheumatic drugs (bDMARDs) on the immunogenicity of vaccinations. Most of the recommendations were based on extrapolation of data from adult AIIRD patients to the paediatric population. Since 2011, the amount of evidence on the safety and immunogenicity of vaccinations in pedAIIRD patients has doubled and the level of evidence (LoE) has increased. The safety of the live-attenuated measles–mumps–rubella (MMR) and varicella zoster virus (VZV) vaccines has been studied in pedAIIRD patients, including patients using methotrexate (MTX) and bDMARDs. Also, data on the safety and immunogenicity of the HPV vaccine in pedAIIRD patients has been published, as well as data on long-term immunogenicity of certain vaccines. The use of bDMARDs has increased, for example, up to 25% of the patients with JIA[12] and up to 100% of patients with systemic JIA use

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bDMARDs nowadays.[13 14] Therefore, data on immunogenicity in relation to biologicals (mainly tumour necrosis factor inhibitors (TNFi)) have become available. This new evidence and the emergence of new drugs (targeted synthetic (ts)DMARDs) urged us to update the EULAR recommendations for the vaccination of pedAIIRD.

Recent studies on the safety and immunogenicity of COVID-vaccinations have been published in adults with AIIRD and in healthy adolescents.[15 16] Studies on the safety, efficacy and immunogenicity of the recently introduced COVID-19 vaccination in children with pedAIIRD are in progress. It is planned to develop separate recommendations specific on COVID-19 vaccines in pedAIIRD in the near future.

The target-users for these updated EULAR recommendations are healthcare professionals involved in the management and vaccination of pedAIIRD patients, including paediatricians, paediatric rheumatologists, general practitioners, nurses, pharmacists and primary healthcare professionals involved in the execution of the NIPs. These recommendations also aim to inform patients and families as an integral part of informed/shared decision-making.

METHODS

Steering committee and task force

The present update of the EULAR recommendations was a partially combined project for paediatric and adult patients with AIIRD. It was constructed using the updated EULAR standard operating procedures from 2016, including adherence to the Appraisal of Guidelines for Research & Evaluation II recommendations.[17] After approval of the EULAR executive committee, the convenor (NMW) and methodologist (MWH) of the recommendations for vaccination of pedAIIRD patients along with the convenor of the recommendations for adult AIIRD patients (OE) formed a steering committee to update the 2011 EULAR recommendations. The steering group outlined the methodology to be used for these novel recommendations and assembled two Task Forces; one to establish the recommendations for the paediatric AIIRD patients described in the current paper and one for the adult AIIRD patients described elsewhere.[4] The paediatric Task Force consisted of 20 international experts (expert paediatric and adult rheumatologists, biologists, epidemiologists, immunologists and multiple patient representatives overall representing 9 countries.

MJ, MWH and CR were in charge of the systematic literature research (SLR). The results of the SLR are being published separately (manuscript accepted by Frontiers). The search focused on the safety, immunogenicity and efficacy of vaccinations in pedAIIRD patients and the effect of (b)DMARDS and glucocorticoids. The steering committee organised a 1-day meeting of the Task Force. Prior to this meeting, all experts independently graded literature on methodological quality and LoE. Each paper was evaluated by at least three experts. Data were extracted and LoE were determined using the standards of the Oxford Centre for Evidence-Based Medicine. During the 1-day meeting, the Task Forces on paediatric and adult AIIRD jointly discussed available evidence gathered from the systematic literature reviews, since the results of studies in adult patients may sometimes be extrapolated to paediatric patients and vice versa. Subsequently, separate recommendations were formulated for paediatric and adult patients. For pedAIIRD, six overarching principles and seven recommendations were formulated.

Each of the recommendations was graded based on the data from the SLRs following the standards of the Oxford Centre for Evidence Based Medicine. Subsequently, a second meeting was held at the end of 2021 to perform a closed Delphi voting procedure. In this meeting the final version of the principles and recommendations was formulated. Additionally, the level of agreement was determined with a reach from 0 (no agreement) to 10 (absolute agreement) for each recommendation. Recommendations on which the agreement was below 7.5 were removed.

The final manuscript was drafted after the second online meeting, reviewed, revised and approved by all Task Force members, followed by final review and approval by the EULAR Executive Committee before submission to the journal.

Definitions

It should be kept in mind that most studies evaluate the immunogenicity of vaccines (ability to induce humoral and cellular immune responses after vaccination) rather than efficacy, meaning the effect of vaccination on infection rates (ie, vaccine efficacy). In the current SLR, some studies describe the occurrence of vaccine-preventable infections after vaccinations. Still, most studies evaluate the immunogenicity of vaccines as a surrogate primary endpoint. For some vaccines there is a good correlation between pathogen-specific antibody levels and protection against infection (measles, rubella, tetanus, meningococci, hepatitis A and B), but for other vaccines this correlate of protection is less clear, for example, HPV and pertussis.[18]

Safe vaccination implies that vaccines have no severe adverse effects, do not aggravate the underlying disease and do not cause infections in case of live-attenuated vaccines. These three aspects of vaccine safety will be discussed throughout the recommendations.

Terminology of medications has changed in comparison to the previous recommendations. It was decided to use the same terminology for DMARDs as proposed recently, including conventional synthetic (cs)DMARDs, tsDMARDs and bDMARDs.[19] Also, not all DMARDS used in paediatric rheumatology are

Table 1 Overarching principles for vaccination in paediatric patients with AIIRD

		Level of agreement (%)
1	The vaccination status, indications for vaccinations in addition to the National Immunisation Programme (NIP), and indications for withholding NIP vaccinations must be assessed yearly by the treating specialist in paediatric patients with AIIRD.	100%
2	Vaccinations should preferably be administered during quiescent disease.	100%
3	If possible, vaccinations should be administered 2–4 weeks prior to commencement of immunosuppression (especially B-cell depleting therapies), but necessary treatment should never be postponed.	81%
4	Adhere to the NIPs and to general rules applying to travels' vaccinations, except for live-attenuated vaccines in all immunosuppressed* patients	100%
5	Non-live vaccines can be administered to paediatric AIIRD patients on glucocorticosteroid or DMARD therapy.	100%
6	Live-attenuated vaccines should be avoided in immunosuppressed* paediatric patients with AIIRD, except for the MMR booster and varicella vaccination under specific conditions.	100%

*Immunosuppressed is further defined in Definitions in the Methods section.
AIIRD, autoimmune/inflammatory rheumatic disease; DMARD, disease-modifying antirheumatic drug; MMR, mumps measles rubella.

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immunosuppressive. Some drugs are 'immunomodulatory', while others are 'immunosuppressive' (eg, glucocorticoids and MMF).[20] We; therefore, clearly defined 'immunosuppressive' drugs, in line the previous 2011 recommendations and the 2019 update of EULAR recommendations for vaccination in adult patients.

In the principles, we often use the term 'immunosuppressed' patients. We defined 'immunosuppressed' according to the following definitions, mainly based on expert opinion: In adults, prednisolone in a dose ≥2 mg/kg or a total of ≥20 mg/day during ≥2 weeks is considered a high-dose of glucocorticoids.[6] In the 2011 paediatric version of the recommendations, it was already noted that in children a prednisolone dose of 20 mg/day is often equivalent to dosages below 2 mg/kg per day.[9] Therefore, in the current updated recommendations, prednisolone is considered 'immunosuppressive' in children in a dose of ≥0.5 mg/kg/day for ≥2 weeks. The experts further defined patients as immunosuppressed when using csDMARDS in the following dosages: cyclosporine >2.5 mg/kg/day, azathioprine ≥3 mg/kg/day, cyclophosphamide orally >2.0 mg/kg/day, leflunomide ≥0.5 mg/kg/day, mycophenolate mofetil ≥30 mg/kg/day or >1000 mg/day, MTX ≥15 mg/m^2/week or ≥25 mg/week, tacrolimus >1.5 mg/day). All patients were considered immunosuppressed when using bDMARDS or tsDMARDS. Finally, patients were considered immunosuppressed when using a combination of the above-mentioned drugs, at any dose.

RESULTS

Differences with the 2011 version of the recommendations

New in these recommendations are the overarching principles that serve as the basis of this update. These principles are generic and concern essential aspects of vaccination of pedAIIRD patients, such as timing of vaccination, relation with immunosuppressive treatment, relation with NIPs and responsibilities. The overarching principles are separated from individual recommendations on specific vaccinations, patient groups or medications. Six overarching principles were formulated (table 1).

Also, in the previous version, the separate recommendations were grouped based on use of immunosuppressive drugs, non-live vaccines and live-attenuated vaccines. As this gave considerable overlap between the individual recommendations, some of the recommendations regarding immunosuppressive drugs were combined with the recommendations on specific vaccines (tetanus toxoid, TT) and others were shifted toward the overarching principles (table 2).

Finally, the grade of recommendation could be increased based on new data on safety (MMR and VZV vaccine) and immunogenicity (pneumococcal conjugate vaccine (PCV) and HPV vaccine). The Delphi voting procedure showed high levels of agreement; none of the recommendations had a level of agreement below 7.5.

Table 2 Recommendations per vaccine in paediatric patients with AIIRD

Recommendations	Changes to 2011	Level of evidence			Grade of recommendation	Level of agreement: average/range 0–10 (% ≥8)
		Eff	Imm	Saf		
1. Non-live seasonal influenza vaccination should be strongly considered for paediatric patients with AIIRD treated with glucocorticosteroids or DMARDs.	'Strongly' has been added to this recommendation	4	2b	4	C	8.5 (93%)
2. Pneumococcal vaccination with PCV10 or PCV13 is recommended in all non-vaccinated paediatric patients with AIIRD.	PCV 10/13 is now 'recommended' instead of 'should be considered' in *all* non-vaccinated pedAIIRD patients	4	2b	4	C	8.8 (73%)
3. Tetanus vaccination should be administered in accordance with recommendations for the general population. In case of an indication for tetanus toxoid vaccination, passive immunisation is recommended for patients receiving B-cell depleting therapy in the past 6 months.	Recommendation on B-cell depleting therapy is new	4	2b	4	C	9.0 (80%)
4. Human papilloma virus vaccination should be strongly considered in non-vaccinated JSLE patients	'Should be advised' has been replaced for 'should be strongly considered'	NA	2b	4	C	9.5 (93%)
5.a) MMR booster vaccination can be administered to patients on MTX	MMR Boosters vaccination can be 'administered' instead of 'considered' in patients on MTX	NA	1	1	A	9.6 (100%)
b) MMR booster can be considered in patients treated with low-dose glucocorticosteroids TNFi, anti-IL1 and anti-IL6 therapy.	TNFi, anti-IL1 and anti-IL6 therapy has been added to this recommendation	NA	4	4	C	9.1 (93%)
6.a) VZV vaccination should be strongly considered in varicella vaccination/infection naive patients on MTX	This recommendation is now specified per treatment. In patients on MTX, 'strongly' is added to the recommendation.	NA	2b	4	C	9.1 (93%)
b) VZV vaccination can be considered in varicella vaccination/infection naïve patients on low-dose glucocorticosteroids, TNFi, anti-IL1 and anti-IL6 therapy.	Therapies have been specified in which VZV vaccination can be considered	NA	4	4	D	9.1 (100%)
7. Yellow fever vaccination should be avoided in all immunosuppressed* patients.	This recommendation has been changed in 'avoid in all immunosuppressed patients' instead of 'can be considered in patients on MTX <15 mg/m^2/week or low-dose glucocorticosteroids'	NA	NA	NA	D	9 (93%)

*Immunosuppressed is further defined in Definitions in the Methods section.
AIIRD, autoimmune/inflammatory rheumatic disease; DMARD, disease-modifying anti-rheumatic drug; Eff, efficacy; IL, interleukin; Imm, immunogenicity; jSLE, juvenile systemic lupus erythematosus; MMR, mumps measles rubella; MTX, methotrexate; NA, not analyzed; PCV, pneumococcal conjugate vaccine; Saf, safety; TNFi, tumour necrosis factor inhibitor; VZV, varicella zoster virus.

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Overarching principles

Principle 1: the vaccination status, indications for vaccinations in addition to the NIP, and indications for withholding NIP vaccinations should be assessed yearly by the treating specialist in pedAIIRD

This new principle has been given a prominent place within the recommendation. Optimal vaccination of pedAIIRD patients cannot be guaranteed when it is unclear who is responsible, as is shown by the low vaccination rate in pedAIIRD patients.[21 22] As the treating physician or nurse specialists have extensive expertise on the entire disease spectrum and its treatment, the committee considers it crucial that the treating physician is in charge. PedAIIRD patients are generally vaccinated according to the NIPs, which differ between countries as these programmes take into account local epidemiology, programmatic issues, resources and policies. However, some vaccines within the NIP may be contraindicated due to immunosuppressive treatments, whereas additional (booster) vaccinations may be required in specific patient groups. As the disease activity and its treatment changes over time, the vaccination status should be assessed regularly and at least yearly. The specialist should inform patients and their parents about the risk of infections, the indications for vaccinations and the possible adverse events (AEs) of vaccines to enable shared decision making between patients, their parents and their specialist.

Principle 2: vaccinations should preferably be administered during quiescent disease

The timing of vaccination in pedAIIRD patients in relation to disease activity was not discussed in the previous recommendation, but it is an important uncertainty in daily clinical practice and is therefore included as one of the main principles of these recommendations. The effect of disease activity on the safety and efficacy of vaccines has not been studied in detail. Most studies assessed the effect of immunosuppressive drugs on the safety and immunogenicity of vaccines rather than the effect of disease activity. Also, patients with high disease activity are often excluded from vaccination studies. Only two studies primarily assessed the effect of disease activity on vaccination-induced immunological responses. One prospective study in 110 patients with juvenile onset systemic lupus erythematosus (jSLE) showed that an SLE Disease Activity Index (SLEDAI) >8 was associated with lower seroconversion rates after H1N1 vaccination.[23] Also, in 30 jSLE patients vaccinated with the 23-valent pneumococcal polysaccharide vaccine (PPSV-23), those with higher SLEDAI scores responded less to vaccination, although there was no correction for the use of immunosuppressive drugs in this study.[24] In contrast, in 340 adult patients with rheumatoid arthritis (RA), higher disease activity did not impair H1N1 vaccination responses.[25] In conclusion, it is still largely unknown whether patients with high disease activity might be effectively and safely vaccinated. It is therefore the experts' opinion to vaccinate during quiescent disease whenever possible, but there is no absolute contraindication to vaccinate during high disease activity.

Principle 3: if possible, vaccinations should be administered 2–4 weeks prior to commencement of immunosuppression (especially B-cell depleting therapies), but necessary treatment should never be postponed

In the previous recommendations, the timing of vaccination against pneumococci and influenza in relation to B-cell depleting therapy was discussed, as well as the timing of the live-attenuated varicella zoster virus (VZV) vaccine in relation to planned immune suppression. However, the importance of timing of vaccination is not restricted to these three vaccines or B-cell depleting therapy: it is essential for all vaccines administered via NIPs and for all DMARDs. Therefore, this overarching principle was formulated, including the statement that necessary treatment should never be postponed for the planning of vaccination.

With regard to glucocorticosteroids, most patients included in the studies used low dosages of prednisolone (≤0.5 mg/kg/day or <20 mg/day). In such dosages, glucocorticosteroids had no detrimental effect on immunogenicity of vaccines or established antibody concentrations. In contrast, in pedAIIRD patients on dosages>20 mg/day, lower humoral responses were detected.[26 27] This was in line with data from adult AIIRD patients. From cDMARDS, MTX has most frequently been studied. In adult AIIRD, patients on MTX had reduced seroprotective antibodies after influenza vaccination, and an increased response was observed after 2 weeks withholding MTX[28] In children, MTX did not reduce antibody levels after influenza vaccination.[23 26 27 29–35] More recently, also the COVID-19 vaccination serological response appeared to be diminished by MTX in adult patients.[36 37]

Regarding bDMARDs, clear evidence is available for B-cell depleting therapies. Numerous studies in adult AIIRD patients showed lower to absent vaccine-induced humoral responses (PPSV-23, influenza vaccine, H1N1 vaccine) until 6 months after treatment.[4] In contrast, data on cellular immune response after rituximab (RTX), which might be more important for some infectious diseases, is scarce. In children, studies on B-cell depleting therapies are still limited. In a study on jSLE, nine patients received the PCV vaccination while on RTX. Of seven patients who received RTX within a window of 6 months prevaccination, six reached no protective antibody titers.[38] In another study, four jSLE patients on RTX were able to generate an adequate humoral immune responses on PPSV-23 vaccination, but the date of the last dose of RTX was not reported.[24] Based on these paediatric studies and more importantly the results in adult patients, the Task Force was convinced of the hampering effect of B-cell depleting therapies on humoral vaccine responses. Of other bDMARDS, TNFi were most frequently studied in children. Although these studies often showed that antibody titers were lower in patients on TNFi (in Meningococcal C,[39] influenza[33 34] and TT[40]), the majority of pedAIIRD patients on TNFi reached protective antibody concentrations.[29 41–45] This is in line with results from studies in adult patients. A meta-analysis of 12 studies in patients with RA showed that TNFi did not impair the seroprotection rates to influenza (308 patients) and pneumococcal vaccines (258 patients).[46] Anti-interleukin 6 (IL6) treatment did not reduce humoral responses to influenza vaccination in 27 JIA patients[47] and to VZV vaccination in 2 JIA patients.[48] This was also shown for influenza, pneumococcal, and tetanus vaccines in adult patients with RA.[49–52] PPSV-23 titres in four paediatric patients on canakinumab were protective and IL-1 blockade did not seem to hamper seroprotection in seven patients after HAV vaccination.[53 54] The diphtheria and tetanus vaccination response of children on abatacept was adequate as well.[55] For other bDMARDS data are lacking in pedAIRD patients.

A study with 155 patients with Kawasaki disease showed lower seroprotection rates and antibody titers in patients vaccinated with MMR within 9 months after intravenous immunoglobulin administration compared with controls.[56] This was unrelated to the amount of intravenous immunoglobulin doses. Patients who received the vaccination prior to intravenous immunoglobulin had equal titers compared with healthy controls.[56] It may

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therefore be considered to administer the MMR vaccination prior to (if clinically possible) or at least 9 months after intravenous immunoglobulins.

In conclusion, the Task Force recommends that vaccines should be ideally administered before planned immunosuppression or immune modulating therapies to obtain optimal vaccination responses, especially B cell-depleting therapy. However, necessary immunosuppressive treatment should never be postponed due to vaccination. When in doubt, serological immune responses should be measured after vaccination and patients can be boostered accordingly.

Principle 4: adhere to the NIPs and to general rules applying to travels' vaccinations, except for live-attenuated vaccines in immunosuppressed (as detailed in Definitions) patients

Throughout the previous recommendations it was recommended to adhere to NIPs, but this was indicated per vaccine and/or immunosuppressive drug. For clarity reasons the separate recommendations were combined into one overarching principle stating to adhere to NIP and travellers' vaccinations advice, except for live-attenuated vaccines in immunosuppressed patients. This overarching principle was also formulated to emphasise the importance of following the NIP in order to improve vaccination coverage. Vaccination coverage is still very low in pedAIIRD patients, although these patients are at increased risk of contracting infections that can be prevented by vaccinations.[21 57] In 200 JIA patients complete vaccination according to schedule was identified in only 52% of patients at 2.5 years and 68% at 10.5 years of age.[21] This was largely caused by low MMR vaccine coverage at 2.5 years (58%). Another study reported a coverage rate for children on bDMARDs of only 46% compared with 65% for patients on csDMARDs and 84% for patients who never received immunosuppressive therapy.[58] For patients with autoinflammatory disease coverage numbers were even lower: complete immunisation according to the French vaccination programme was reached in only 32% of patients at 2 years, 28% at 7 years, 6% at 15 years.[57] In addition, coverage of vaccines indicated specifically for risk groups, such as the pneumococcal and influenza vaccine for patients with SLE is low. In American jSLE patients, who have an indication for pneumococcal vaccination, the uptake of the 13-valent PCV was 6.7% and PPSV-23 8.9%.[59]

Finally, this principle was formulated to highlight that specific considerations apply to live-attenuated vaccines in immunosuppressed patients. This is further explained in overarching principle 6 and the vaccine-specific recommendations.

Principle 5: non-live vaccines can be administered to paediatric AIIRD patients on glucocorticosteroids or DMARD therapy

This principle was modified from the initial version in 2011 and upgraded to the overarching principles based on the increasing amount of evidence of the overall safety and immunogenicity of vaccination during the use of glucocorticoids and/or csDMARD, bDMARD and tsDMARDs in a variety of paediatric rheumatic diseases. Vaccines against HPV, hepatitis A and B, meningococci C, pneumococci (PPSV-23 and PCV7, PCV10 or PCV13), seasonal influenza, tetanus and diphtheria have been studied in pedAIIRD patients.[23 24 26 27 29–35 38 41–44 47 53–55 60–77] These vaccines did not aggravate the underlying disease or cause severe AEs. The majority of studies showed acceptable immunogenicity of these vaccines in patients using glucocorticosteroids or DMARDS.[26 27]

Again, it should be kept in mind that most studies included patients with quiescent disease on relatively low-dose immunosuppressive drugs; the immunogenicity of non-live vaccines in high-dose immunosuppressive drugs may be hampered. Also, none of the studies was powered to study infection rates, the primary goal of vaccination. Nevertheless, for most vaccines humoral immune responses can be considered good surrogate markers for protection against infection. The consistency of the various studies on varying vaccines supports the recommendation that pedAIIRD patients on glucocorticosteroids and DMARDS can be safely vaccinated with non-live vaccines with a generally protective immune response.

Principle 6: live-attenuated vaccines should be avoided in immunosuppressed pedAIIRD, except for the MMR booster and varicella vaccination under specific conditions

Live-attenuated vaccines should be avoided in immunosuppressed patients because of the risk of infections with the attenuated pathogen. For example, a case report described a 3-month old infant born to a mother with Crohn's disease using infliximab who had a lethal vaccination-induced mycobacterial infection after BCG vaccination.[78] Another patient using infliximab who was inadvertently vaccinated with the primary yellow fever (YF) vaccine developed fever and myalgia 1 week after vaccination, with a slight increase in transaminases and detectable viraemia.[79]

Exceptions to this principle are the live-attenuated MMR booster and varicella vaccination in patients treated with MTX and bDMARDs. This is further discussed in recommendation 5 and 6.

Recommendations for non-live vaccines

Recommendation 1: non-live seasonal influenza vaccination should be strongly considered for pedAIIRD on immunosuppressive therapies

According to the previous recommendations, seasonal influenza vaccination should be considered in all pedAIIRD patients. Currently, the seasonal non-live influenza vaccination should be strongly considered in pedAIIRD patients treated on immunosuppressive therapies. These modifications are explained below.

The seasonal influenza vaccination is not incorporated in the NIP and, therefore, only indicated for patients at risk for (complicated) influenza infections. Whether pedAIIRD patients are to be considered at risk is poorly studied, but the Task Force considers pedAIIRD patients using glucocorticosteroids or (b/ts) DMARDs at risk based on new data in line with previous results. In the 2011 version of the recommendations, data from adult AIIRD patients were extrapolated to paediatric patients.[9] Two retrospective studies in adult AIIRD showed an increased risk of admission for pneumonia or influenza (4.5%–7% vs 0.8%, OR 1.6) and for death by influenza (OR 2.7).[80 81] For the updated recommendation, a large retrospective cohort study in 46 030 adult RA patients showed an increased risk of influenza compared with matched healthy controls (1.33-fold higher risk), with a 2.75-fold increase in the incidence of complications in RA.[82] In addition, a study in 61 JIA patients which was performed during the months of peak occurrence of influenza infections in two consecutive years in Brazil, showed an incidence rate of 3.9–7.6 acute respiratory infections per 1000 child-days. Of these episodes, 26.6% were characterised as influenza-like illness, defined as fever plus at least one respiratory symptom and one constitutional symptom (headache, malaise, myalgia, sweat or chills, or fatigue). Disease was generally mild; only one patient developed a pneumonia. Unfortunately, no healthy controls were

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included and it is not mentioned in the study whether patients had to be admitted to the hospital.[31] Mainly based on the adult data, the experts consider (ped)AIIRD patients at risk of (severe) influenza infections. The Task Force added the restriction that this increased risk applies to patients treated with glucocorticosteroids or (b/ts)DMARDS, as no studies are performed in children with pedAIIRD without treatment. Also, studies on other infectious diseases, such as pneumococcal disease, show that this risk is more pronounced in patients on glucocorticosteroids or DMARDs.[6 83 84]

The word 'strongly' was added to this recommendation based on accumulating data on the safety and immunogenicity of the vaccine, as well as its efficacy in preventing influenza infections. The vaccine is well tolerated and induces a serological response that is associated with protection against infections. In patients with pedAIIRD, seroprotection rates were generally equal to healthy controls, except for patients using high-dose glucocorticoids[27 74] and for patients with jSLE,[23] especially those with high disease activity.[23 26 27 29–35 41 47 69 75] Likewise in patients on bDMARDs (TNFi and anti-IL6) seroprotection rates are equal compared with healthy controls, although in patients treated with TNFi, antibody titers tend to be lower and show a more rapid decline.[31 33 34 47]

The occurrence of influenza infection after vaccination (in other words, the efficacy of the vaccine) has been studied poorly in pedAIIRD patients. Only two studies reported on influenza infections after vaccination since 2011. In the first study with JIA patients, 1 out of 31 immunised JIA patients and 2 out of 14 non-immunised controls had influenza infection in the observational 6-month period postvaccination.[32] In the second previously mentioned study performed in 61 JIA patients in Brazil, influenza-like episodes were significantly more common in unvaccinated patients compared with vaccinated patients.[31] In addition, no positive influenza samples (out of 33 collected samples) were found during an influenza-like episode in immunised patients. In the current recommendation concerning adult patients, two large studies were added showing the effectiveness of seasonal influenza vaccination in SLE patients with a HR for hospitalisation of 0.82 (95% CI 0.73 to 0.92) and of 0.41 (95% CI 0.27 to 0.61) for death,[85] and in RA with a relative risk of influenza infection of 0.83 (95% CI 0.71 to 0.95).[86]

In conclusion, pedAIIRD patients on immunosuppression seem to be at risk of influenza infections and vaccination is safe and immunogenic, while it has been shown to be effective in preventing infections in adult AIIRD patients. This evidence led to the adjusted recommendation to strongly consider non-live seasonal influenza vaccination for pedAIIRD on immunosuppressive therapies. Live-attenuated influenza vaccine should be avoided in immunocompromised children.

Recommendation 2: pneumococcal vaccination with PCV10 or PCV13 is recommended in all non-vaccinated pedAIIRD

Streptococcus pneumoniae is a leading human pathogen with relatively high incidence affecting all age groups, and due to a high mortality, morbidity and expensive treatment, prevention against pneumococcal infections is WHO priority.[87–89] In the previous recommendations, it was stated that the pneumococcal vaccination can be considered in patients on high-dose immunosuppressive drugs or biological agents before therapy. This recommendation has now been modified, as the conjugated pneumococcal vaccine is included in the NIP in the majority of countries. The inclusion of PCV in the NIP is based on the high rates of invasive pneumococcal disease (IPD, ie, bacteraemia, meningitis or other infection of a normally sterile site) among young children, and the proven efficacy of the different PCV vaccines to prevent pneumococcal infections.[90] PCV proved to be effective in immunocompromised patients including AIIRD patients. After the introduction of PCV7 for all children, IPD caused by the seven serotypes had decreased by 90% (95% CI 77% to 96%) in immunocompromised persons of all ages, including AIIRD patients[91] and in an observational cohort of 497 adult RA and spondyloarthropathy patients, PCV7 reduced the risk of severe bacterial infection with approximately 45%.[92] The immunogenicity and safety of PCVs has also been shown in pedAIIRD patients, including patients on MTX and glucocorticosteroids. In addition, in the past 10 years accumulating data on bDMARDS have become available. Children using TNFi had equal seroprotection compared with controls,[43] but had lower antibody concentrations in one study.[10] The adequate safety and immunogenicity in pedAIIRD and the proven efficacy for all children has led to the recommendation to vaccinate all pedAIIRD patients with PCV10/13, if possible according to the NIP.

The question remains whether pedAIIRD patients should additionally receive a booster vaccination with the PPSV-23 in addition to the PCV10/13 vaccination via the NIP. This vaccine includes capsular polysaccharides of 23 serotypes, is T-cell independent and induces poor or absent antibody responses in children <2 years of age. The indication for PPSV-23 is dependent on the risk of (severe) pneumococcal infections in pedAIIRD patients not captured by PCV10/13. It has been shown in Canada, that 27% of isolates causing IPD in immunocompromised persons were serotypes not covered by PCV13 that could be prevented by PPSV-23.[91] Unfortunately, no studies are yet available in pedAIIRD patients on the incidence of IPD. One study reported a higher risk of hospitalisation for bacterial infections in JIA (especially when using high-dose glucocorticosteroids), but this study was not limited to *S. pneumoniae*.[93] In addition there are no studies on the efficacy of the PPSV-23 in addition to PCV10/13 in pedAIIRD to prevent IPD. The PPSV-23 vaccine has been shown to be safe in pedAIIRD by studies including 27 JIA and 30 jSLE patients.[24 42] Immunogenicity was moderate: in one study adequate seroconversion for all serotypes was only obtained in 53% and 30% of the patients on MTX versus MTX and TNFi respectively, although 77% of the patients vs 86% of the healthy controls had seroprotective levels in another study in jSLE.[24 42] Two vaccinated patients, however, experienced respectively pneumonia (while on RTX) and pneumococcal invasive disease (while on TNFi), but unfortunately the subtype of the pneumococcal bacteria was not mentioned in the studies and therefore a vaccination failure cannot be stated nor ruled out.[38 42]

In contrast, in adults, two studies have shown an increased risk of (invasive) pneumococcal infections in AIIRD patients. One demonstrated that RA and SLE patients had higher rates of pneumococcal disease (rate ratio 4.4 (95% CI 3.8 to 5.2)) and IPD (rate ratio 7.1 (95% CI 4.9 to 10.1)), as well as patients on glucocorticosteroids or immunosuppressive drugs.[83] The second study compared the incidence of IPD in 20.427 patients with systemic autoimmune disorders with 3 973 048 immunocompetent controls. An increased risk in AIIRD patients was shown with an incidence rate ratio (IRR) of 4.1 (95% CI 1.5 to 11).[91] Patients using immunosuppressive treatment had an IRR of 3.9 (95% CI 2.1 to 7.3). Several studies assessed the risk of pneumococcal infections in specifically SLE patients.[94–98] The incidence of IPD in SLE patients was 16/100 000 person-years, which was 13 times higher compared with the regular Dutch population.[98] Besides the higher frequency of pneumococcal infections, these infections tend to be more severe in

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immunocompromised patients.[99] The efficacy of the PPSV-23 vaccine to prevent IPD has been proven in healthy adults,[100] as well as in immunocompromised patients including AIIRD patients in a population-based study. IPD incidence declined significantly after PPSV-23 programme implementation (IRR 0.57, 95% CI 0.40 to 0.82).[91]

Due to this lack of data in children both on the occurrence of IPD and on the ability of the PPSV-23 vaccine to prevent pneumococcal disease in addition to PCV10/13, the Task Force decided after an intense discussion, that adding the PPSV-23-vaccinations to PCV10/13 cannot be recommended (yet) as standard care in all pedAIIRD. However, PPSV-23 can be considered in immunosuppressed patients or in SLE patients, as it is safe and immunogenic. It is then advised to administer the PPSV-23 vaccination every 5 years, in concordance with adult guidelines, in addition to PCV10/13.

Importantly, there seems to be a safety issue of pneumococcal vaccination in patients with cryopyrin associated periodic syndrome (CAPS).[53] A case series of 18 paediatric and 50 adult CAPS patients, in which all but one was treated with canakinumab, showed severe reactions after PPSV-23 vaccination. Vaccine reactions occurred in 80% after PPSV-23 vaccination (compared with 0% after PCV10/13), including severe local reactions at time of vaccination, fever (50%) and CAPS flares (n=2). In this study, only in four patients PPSV-23 antibody levels were measured, and those were all protective. We, therefore, recommend to avoid PPSV-23 in CAPS.

As in the 2011 version of the recommendations, PCV10/13 and PPSV-23 vaccination is recommended for patients with primary complement deficiencies and patients with functional asplenia as these patients have high risk of sepsis caused by pneumococci.[9]

In summary, PCV10/13 is recommended for all children including patients with pedAIIRD and, if PCV10/13 is included in the NIP, this programme can be followed. A 5-yearly PPSV-23 is not recommended as standard of care but can be considered in immunosuppressed patients and SLE patients. The taskforce recommends to avoid the PPSV-23 in CAPS due to safety reasons.

Recommendation 3: tetanus vaccination should be administered in accordance with recommendations for the general population. In case of an indication for TT vaccination, passive immunisation is recommended for patients receiving B-cell depleting therapy in the past 6 months

This recommendation is broadly similar to the 2011 version, but is modified in terms of the B-cell depleting therapy. Since 2011, four new studies on the seroprevalence of TT antibodies in pedAIIRD have been published (475 JIA patients, 30 jSLE patients).[40 55 61 101] Three studies showed lower to non-protective TT antibody concentrations in pedAIIRD patients several years after vaccination. Since the correlation between antibody concentrations and protection against tetanus infection is good in healthy children, these findings show that pedAIIRD may become unprotected against tetanus over time.[102] It is thus of utmost importance that booster TT vaccinations are administered to these patients when indicated. The TT vaccine is safe: no vaccine-related AEs were observed after DT vaccination.[55]

As it is also known from adult studies that humoral responses towards the TT vaccine with B-cell depleting therapy are severely hampered until 6 months after treatment, passive immunisation is recommended in these patients in case of indication for TT vaccination.[103 104] In the previous recommendations, passive immunisation was suggested, but given the evidence for lower antibody concentrations in pedAIIRD patients, this was rephrased into recommended.

Recommendation 4: HPV vaccination should be strongly considered in non-vaccinated jSLE patients

The HPV vaccine is administered to young adolescent girls via the NIP in most countries and it is an overarching principle to follow the NIP. Nevertheless, the experts opted for a specific recommendation on the HPV vaccine, to highlight the importance of this vaccine in SLE patients, like in the 2011 version of the recommendations. SLE patients have a higher risk of persistent (high-risk) HPV infections than healthy subjects, with a higher risk of squamous intraepithelial lesions and cervical cancer, as has been shown consistently by various groups in the world.[4] Therefore, protection against HPV infection is especially important in these patients. The HPV vaccine is 98%–100% effective against cervical intraepithelial neoplasia (CIN) caused by HPV16/18 in healthy women.[105]

No efficacy data are available from pedAIIRD patients, and a correlate of protection is still lacking.[18] However, all healthy vaccinated women protected against CIN had higher HPV16/18 antibody levels than those who had an infection, and therefore, antibody levels can be used as a surrogate marker.[18] Since 2011, four articles assessing the immunogenicity and safety of the HPV-vaccine in pedAIIRD have been published.[69–71 106] Antibody responses in JIA and IBD patients were broadly comparable to healthy controls. After the bivalent and quadrivalent HPV vaccine all but two out of 28 jSLE patients seroconverted, although 6 jSLE patients reported lower antibody concentrations compared with healthy controls.[69 70] The latter was also reported in a study in 39 adult SLE patients.[106] Another study including 34 adult SLE patients showed antibody concentrations comparable to a historical cohort of healthy controls.[107] The vaccine was generally well tolerated in children/adolescents, although one study in 22 jSLE patients reported 9 disease flares; unfortunately no unvaccinated control group was included in this study.[70] In contrast, an adult study reported no differences in disease activity between 50 vaccinated adult SLE patients and 50 SLE controls.[106] Importantly, population based studies have shown that the quadrivalent HPV vaccine was not associated with increased incidence of new-onset autoimmune disease in girls and women with other pre-existing autoimmune disease.[108 109] Based on the increased risk of persistent high-risk HPV infections and premalignant lesions in SLE patients, the good seroprotection rate after vaccination, the acceptable safety profile of the vaccine, despite the lack of efficacy data, HPV vaccination should be strongly considered in non-vaccinated jSLE patients.

Recommendations for live-attenuated vaccines

In line with the overarching principles, patients on (b-)DMARDs are considered immunosuppressed as defined in Definitions in the Methods section, and live-attenuated vaccines should be avoided in these patients. However, as stated in the previous recommendations, live-attenuated vaccines can be considered in patients using (b-)DMARDS on an individual base weighing the risk of infections versus the hypothetical risk of inducing infections by vaccination. For clarity, it is now indicated per vaccine whether deviations from the overarching principle can be considered. These recommendations only refer to systemic live-attenuated vaccines that are injected intramuscularly or subcutaneously and not to mucosal vaccines such as the live-attenuated influenza vaccine and rotavirus vaccine. Studies on the safety of

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these mucosal vaccines in immunosuppressed children are still lacking.

Recommendation 5: (a) MMR booster vaccination can be administered to patients on MTX; (b) MMR booster can be considered in patients treated with low-dose glucocorticosteroids TNFi, anti-IL1 and anti-IL6 therapy

The first part of the recommendation, MMR booster vaccination can be administered to patients on MTX is stronger compared with the recommendations in 2011 as the grade of recommendation increased from C to A. This is based on a randomised controlled trial on the safety of MMR-booster vaccination in 137 JIA patients including 60 using MTX (median dose 11 mg/m^2/week) and 15 on TNFi.[110] MMR booster vaccination did not induce disease flares, and no infections with the attenuated viruses were noted. All patients showed a significant increase in antibody concentrations. As the correlation between measles and rubella-specific antibody concentrations and protection against infection is good, these patients are considered to be seroprotected.[111]

Also in other studies in pedAIIRD patients, the immunogenicity of the MMR vaccines was generally good and comparable to patients without (b-)DMARDs.[40 101 110] However, the persistence of these antibodies may be shorter in pedAIIRD patients, as was shown for mumps,[40 63 101 112–114] rubella[101 112] and in one study in SLE patients for measles,[115] although other studies could not confirm the accelerated decline in antibodies for measles.[40 61 101]

For the second part of the recommendation, MMR booster can be considered in patients treated with low-dose glucocorticosteroids TNFi, anti-IL1 and anti-IL6 therapy, the LoE and grade of recommendation are much lower (LoE 4, grade C). In the past 10 years, several studies reporting on MMR vaccine-related AEs included patients vaccinated while on these bDMARDs, most often TNFi (n=123) and a smaller number on anti-IL1 (n=26) and anti-IL6 (n=6).[110 116–118] In a large multinational study (n=234 patients) focusing on safety of the MMR booster vaccine in pedAIIRD patients on bDMARDs, no vaccine-induced infections were observed and 13 mild AE were reported, consisting of local skin reaction, influenza-like symptoms, fever and pain, and none had moderate or severe AE.[117] Also in the other studies no vaccine-induced infections or severe AEs were documented indicating that these vaccines may be safely administered, although the LoE is too low for definite conclusions regarding safety.

Recommendation 6: (a) VZV vaccination should be strongly considered in varicella vaccination/infection naïve patients on MTX (b) VZV vaccination can be considered in varicella vaccination/infection naïve patients on low-dose glucocorticosteroids, TNFi, anti-IL1 and anti-IL6 therapy

The VZV is a highly contagious virus that causes varicella (chickenpox); a mild, self-limiting illness characterised by fever and a generalised vesicular rash. Complications are rare, but immunocompromised individuals have a higher risk of complications, consisting of bacterial superinfection of the skin lesions, pneumonia, encephalitis, hepatitis or haemorrhagic complications.[119–121] Following primary infection, the virus remains latent in the dorsal root ganglia and can reactivate later in life, causing shingles (herpes zoster). The incorporation of the (optional or mandatory) VZV vaccine in NIPs differs considerably between countries. In countries without routine VZV vaccination, the majority of the children get chickenpox early in childhood.

In VZV (vaccination and infection) naive pedAIIRD patients, there is always the threat of chickenpox. Exposures must be avoided, causing children to miss school and playgroups, immunosuppressive treatment may be interrupted with potentially negative consequences on disease, and there is a risk of severe disseminated disease.[120 121] Case reports exist of severe disseminated or even lethal varicella infections in pedAIIRD patients.[122 123] Since 2011, several studies on VZV infection rates and course in pedAIIRD patients were published. In a large retrospective case–control study, an increased risk for varicella-related admissions was found in patients with IBD.[124] In this study, 8 828 712 paediatric hospitalisations in the USA including 4434 varicella and 4488 herpes zoster-related hospitalisations were analysed. Compared with the general population, there was an increased risk for varicella-related hospitalisations in patients with Crohn's disease (OR 12.8 (95% CI 8.3 to 19.6)) and ulcerative colitis (OR 4.3 (95% CI 2.0 to 9.1)).[124] Four mild to severe VZV infections were described in 185 JIA patients on etanercept.[125] The incidence and severity of VZV infections in 156 JIA patients was similar in patients with etanercept compared with patients on MTX.[126] In comparison to the general population, the risk of VZV-related infections was increased in AIIRD patients on TNFi therapy in a large national database analysis with an estimated incidence rate for VZV-related hospitalisations of 1.9/100 000 PY in the general population versus 26/100 000 PY in AIIRD patients on anti-TNFα treatment.[127]

Data on the efficacy of the varicella vaccine in preventing VZV infections are currently insufficient in VZV naïve pedAIIRD patients. None of the available studies was significantly powered to assess the outcome on infection rates. Data on the efficacy of the vaccine come from studies performed in the late 1970s in children with underlying leukaemia. In the largest trial, more than 500 children with leukaemia in remission were vaccinated against chickenpox. The efficacy was 85% in preventing chickenpox and breakthrough cases were mild.[128 129] Subsequently, the efficacy and cost-effectiveness of the vaccine was shown in healthy children.[130–132] As vaccine failures do occur in considerable rates, a two-dose schedule is more effective against all VZV cases.[133] The immunogenicity of the VZV vaccine has been studied in pedAIIRD patients. VZV-specific antibody responses are critical in the control of acute infection and VZV-specific T-cell responses are essential for both recovery and maintenance of the latent phase of VZV.[134 135] In pedAIIRD patients, a humoral response was induced in the majority of patients and VZV-specific T-cell responses were comparable between pedAIIIRD patients and healthy controls.[136 137] However, it should be kept in mind that the correlation between humoral and cellular immunity and protection against VZV infection is uncertain.

Finally, the safety of this live-attenuated vaccine is of the upmost importance in VZV naïve patients. In the past decade, a total of 78 pedAIIRD varicella naïve patients receiving VZV vaccination were described/recruited in various studies, including patients on low-dose glucocorticosteroids (n=20), MTX (n=60) and bDMARDs (TNFi (n=8) anti-IL6 (n=5) anti-IL1 (n=5). Since the vaccination in these patients was a primary immunisation, it constitutes a higher risk of vaccine-induced infection with the attenuated virus than booster vaccines. There were no complicated or disseminated varicella infections and only three patients developed a vaccine-induced mild and transient VZV-like rash, of which one patient was admitted for i.v. acyclovir treatment for safety reasons.[136] No worsening in disease activity or disease flares were reported.[136 137] One study investigated a prevaccination check lists for patients; all patients met the prevaccination

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criteria and no AEs were observed.[138] Although these studies were small, the evidence for the safety of this vaccine in situations of immunosuppression has been broadened.

The VZV vaccine was extensively discussed by the Task Force. Knowing that the risk of (severe) infections is increased and based on the safety data in a small number of pedAIIRD patients it is the experts' opinion that in VZV naïve patients it is preferable to immunise in a controlled manner, rather than waiting for inevitable exposure to the wild type virus which endorses the risk of severe disseminated disease. Therefore, VZV vaccination should be strongly considered in VZV naïve patients on MTX. The Task Force does not recommend a treatment pause because of the risk of disease worsening or flares. Although we recommend to preferably vaccinate when patients are on MTX monotherapy, the VZV vaccine can be considered as well in patients treated with TNFi, anti-IL1, anti-IL6 and low-dose glucocorticosteroids, carefully weighing the risk of infections against the risk of inducing infections by vaccination, knowing that vaccine-induced infections with the attenuated virus are generally mild and can be treated with acyclovir.

Recommendation 7: YF vaccination should be avoided in all immunosuppressed patients

A single dose of YF vaccine is sufficient to confer sustained immunity and lifelong protection against YF disease and booster doses are no longer required.[139] No data exist on the safety of the primary YF vaccine in immunosuppressed pedAIIRD patients. One adult patient with Crohn's disease treated with MTX and infliximab, who inadvertently received YF vaccination, developed high fever, severe headache, general weakness and transiently elevated transaminase levels probably due to YF viraemia since the YF PCR became positive 6 days after vaccination,[79] whereas another patient on adalimumab showed no AEs on inadvertent YF vaccination.[140] Both patients were seroprotected after vaccination. We recommend measuring serum antibodies in patients previously vaccinated for YF and travelling into endemic areas. In case immunosuppressive drugs can be interrupted (according to existing guidelines[141]), YF vaccination can be safely administered if necessary.[142]

DISCUSSION

This 2021 update of the EULAR recommendations for vaccinations in pedAIIRD is based on a systematic literature review of published studies between 2009 and 2021 and is a combined effort of a taskforce consisting of 20 international experts including paediatric and adult rheumatologists, immunologists and a patient representative. The 15 recommendations from the 2011 EULAR paper have now been replaced, upgraded or adjusted and were subdivided into six overarching principles and seven recommendations. These overarching principles are the basis of the update covering essential aspects of vaccination in pedAIIRD.

Infectious diseases are still a great burden and risk for immunosuppressed children. Therefore, adherence to the Natural Immunisation Programme (NIP) is essential, thereby protecting the patients for vaccine-preventable infections. Still, the adherence to the NIP is low for pedAIIRD patients, as parents seem reluctant for vaccinations due to insufficient information provision and fear for AEs, hence special attention is needed from the treating physician.[21] The first overarching principle, therefore, states to assess the patient's NIP status and indications for vaccinations on a yearly base. As in adults, vaccinations are preferably administered in quiescent disease. If possible, vaccinations should be given 2–4 weeks before the start of immune suppression, especially RTX, but necessary treatment should never be postponed.

Since 2011 several new studies have been published, which especially increased the evidence on the safety of live-attenuated vaccines in immunosuppressed children. Still the overarching principle remains that live-attenuated vaccines should be avoided in all immunosuppressed pedAIIRD. The risk of a live vaccine in immunosuppressed children was shown by a case report on a newborn whose mother used infliximab during pregnancy, and who died from vaccine-induced tuberculosis after BCG vaccination.[78] However, the overarching principle includes an exception for the vaccination of MMR booster and varicella vaccination under specific conditions. The strength of the recommendation considering the MMR booster vaccination increased significantly; it is therefore now recommended that this booster can be safely administered to patients on MTX. This was mainly based on an RCT on the MMR booster vaccine showing no worsening of disease activity and no infections with the attenuated viruses.[110] Also, patients showed a significant increase in antibody concentrations and were considered to be protected against infection. LoE on administrating the MMR booster while treated with low-dose glucocorticosteroids and bDMARDs is much lower (LoE 3, grade of recommendation D), but these non-randomised cohort studies suggest it is safe with in general seroprotection levels comparable to healthy controls.[40 56 101 110 112 113 115–117 143]

There were no complicated or disseminated vaccine-induced varicella infections in VZV naive patients receiving VZV vaccination; only mild vesicular rashes occurred in a few patients.[58 118 136 138] Therefore, the recommendation on VZV was adjusted; this vaccination should now be strongly considered in varicella vaccination/infection naïve patients on MTX. In addition, VZV vaccination can be considered in varicella naïve patients treated with low-dose glucocorticosteroids, TNFi, anti-IL1 and anti-IL6 therapy. In VZV-naïve patients, the immunogenicity of the vaccine was equal in immunosuppressed children compared with healthy controls.[136] In the future, larger cohorts on primary VZV vaccination are needed, especially cohorts including patients on bDMARDs, to confirm these data on safety, immunogenicity and eventually efficacy. In addition, studies are warranted on the non-live VZV vaccine for VZV naïve patients, as this vaccine might further improve the safety profile of VZV vaccination in pedAIIRD patients.

In adults, several studies demonstrate that the pneumococcal infection rate is higher in AIIRD patients.[83 91] Specifically in SLE patients, these infections tend to be more severe, especially in those on (high-dose) immunosuppression. Therefore, pneumococcal vaccination with PCV10 or PCV13 is recommended in all non-vaccinated pedAIIRD, and in most countries, this vaccination is included in the NIP. Although additional PPSV-23 is recommended in immunosuppressed adult patients, we cannot recommend PPSV-23 as standard care in children; there are no data on the efficacy of the PPSV-23 in addition to the PCV vaccine to prevent pneumococcal disease in pedAIIRD. However, PPSV-23 can be considered every 5 years in immunosuppressed patients or in SLE patients, as it is safe and moderately immunogenic.[24 42] Of note, physicians should be aware of the high risk of adverse events including flares after PPSV-23 vaccination in CAPS patients.[53]

In 2011, no data were available on HPV vaccination in pedAIIRD.[9] Thanks to new studies the recommendation on HPV vaccination could be enforced; HPV vaccination should now be strongly considered in non-vaccinated JSLE patients. Although HPV is included in most NIP, this specific recommendation is

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made because the HPV vaccination is of utmost importance in SLE patients, since these patients have an increased risk to develop cervical cancer. Although efficacy trials are lacking, four new trials including patients with jSLE have proved good immunogenicity of the vaccine, and no severe adverse events.[69–71]

Seasonal influenza vaccination is not routinely included in the NIP. In the current recommendations it is now strongly suggested to consider annual inactivated or subunit influenza vaccination in all patients on glucocorticoids or (b/ts) DMARDs. Adding strongly to the recommendation is mainly based on adult data showing an increased risk for influenza infection in patients with AIIRD[82] and on accumulating data in pedAIIRD showing a good immunogenicity of the vaccine.[23 27 29–34 41 47 74 75] Efficacy is not well studied in children but small studies report a significant decrease in influenza-like illness after vaccination.[31 32]

Overall, studies performed in the past decade corroborate the results from previous trials that immunogenicity of the vaccines is sufficient in pedAIIRD patients using immunosuppressive drugs with the exceptions of high-dose glucocorticoids and intravenous immunoglobulin.[29 56] New in the current recommendations is the data on patients using bDMARDs. In general, patients vaccinated while treated with bDMARDs reached seroprotection. B-cell depleting therapy within the last 6 months is an exception.[38] Patients vaccinated while on TNFi are usually seroprotected but antibody titers, especially after influenza vaccination, are lower compared with other patients on DMARDS and the titers show a more rapid decline.[31 33 34] One study on tocilizumab showed similar seroprotection and antibody levels in patients on anti-IL6 compared with healthy controls.[47] It is important to realise that most data on bDMARDs are limited to immunogenicity and not efficacy. In order to increase the strength of these recommendations in the future and to obtain more knowledge on efficacy of vaccinations in patients on bDMARDs, larger cohort studies and ideally RCTs should be performed.

The past months (after these recommendations were completed) the first studies became available on the BNT162b2 mRNA COVID-19 vaccine.[144–147] These first reports show good short-term immunogenicity (97%–100% seropositivity in patients 1–3 months postvaccination) and only mild AE, including children on TNFi.[145 146] Flares after vaccination were reported, but no case control studies have been performed yet.[147] Future recommendations will include the COVID-19 vaccination.

In general, the NIP should be followed for all patients with pedAIIRD as in healthy children. Several vaccines within the NIPs require specific attention: the (10 or 13-valent) PCV vaccine is recommended in all non-vaccinated pedAIIRD patients and the vaccination against HPV is advocated in non-vaccinated jSLE patients. Also, the MMR booster can be administered safely in patients on MTX and can even be considered in patients on glucocorticoids and specified bDMARDS (TNFi, anti-IL1 and anti-IL6 therapy). Thus, postponing the MMR booster vaccination is often not required. Finally, additional vaccinations not included in the NIP may be considered in pedAIIRD patients: The yearly influenza vaccination should be strongly considered in all pedAIIRD patients. Physicians should be aware of the varicella status of their patients and strongly consider the VZV vaccination in varicella naive patients, also while on MTX. They also should consider this vaccination in naive patients on low-dose glucocorticosteroids, TNFi, anti-IL1 and anti-IL6 therapy.

In conclusion, studies from the past decade yielded significant new data on vaccinations in paediatric AIIRD. Specifically, information on the safety of life-attenuated vaccines, the safety and immunogenicity of vaccinations in patients treated with bDMARDs and the experience with the HPV vaccination have been increased and led to the adjustment and upgrade of the recommendations on vaccinations in pedAIIRD. No recommendations on COVID-19 vaccines in pedAIIRD are yet included in these recommendations, as studies were still ongoing by the time of the search.

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