EULAR recommendations for vaccination in paediatric patients with rheumatic diseases

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ABSTRACT

Evidence-based recommendations for vaccination of paediatric patients with rheumatic diseases (PaedRD) were developed by following the EULAR standardised procedures for guideline development. The EULAR task force consisted of (paediatric) rheumatologists/immunologists, one expert in vaccine evaluation, one expert in public health and infectious disease control, and one epidemiologist. A systematic literature review was conducted in MEDLINE, EMBASE, and abstracts of the EULAR and American College of Rheumatology meetings of 2008/9. The level of evidence and strength of recommendation were based on customary scoring systems. Delphi voting was applied to assess the level of agreement between task force members.
107 papers and eight abstracts were used. The majority of papers considered seasonal influenza (41) or pneumococcal (23) vaccination. 26 studies were performed specifically in paediatric patients, and the majority in adult rheumatoid arthritis and systemic lupus erythematosus patients. Fifteen recommendations were developed with an overall agreement of 91.7%.
More research is needed on the safety and immunogenicity of (live-attenuated) vaccination in PaedRD, particularly in those using biologicals, and the effect of vaccination on prevention of infections.

Vaccination has greatly reduced the burden of childhood infections.[1] Paediatric patients with rheumatic diseases (PaedRD) are at increased risk of infections, due to the immunosuppressive effect of the disease or its treatment.[2–4] With current aggressive treatment strategies incorporating the early use of immunosuppressive drugs and biological agents, susceptibility to infections increases further.[5] In this context, safe vaccination and adequate serological responses to vaccinations are vital. The immunogenicity of vaccinations might be reduced as a result of the immunosuppressed status. In addition, the safety profile might differ from healthy subjects. Moreover, the potential effects of vaccination on the underlying disease must be considered. Generally, recommendations on the immunisation of children with rheumatological diseases follow the recommendations for immunosuppressed patients (patients with solid organ transplantation, haematological malignancy, immunodeficiency), in which live-attenuated vaccines are contraindicated when using high-dose immunosuppressive drugs.[6 7] However, to what extent antirheumatic treatment actually suppresses the immune system remains unclear.

Our aim was to develop recommendations for vaccinations in PaedRD based on available evidence in the literature.

METHODS

The recommendations were constructed using the European League Against Rheumatism (EULAR) standard operating procedures.[8] An expert committee was instituted, consisting of eight paediatric rheumatologists/immunologist (IK-P, AF, KM, AR, MA, GSP, MB, NMW), one adult rheumatologist/immunologist (MB), one expert in vaccine evaluation (RB), one expert in public health and infectious disease control (FvdK), one epidemiologist (KM) and two physicians/PhD students in charge of the systematic literature research (MWH, LMOdB).

First, the expert committee defined search terms for the systematic literature review (see supplementary tables 1–5, available online only), which was conducted in MEDLINE in December 2009, in MEDLINE and EMBASE in November 2010 and abstracts from EULAR and American College of Rheumatology meetings in 2008/9. Relevant papers, among others found by searching references from keynote papers, were added by experts. Exclusion criteria were: non-rheumatic autoimmune diseases, malignancies, immunodeficiencies, transplantations, atopic diseases, animal studies, infections rather than vaccinations, vaccine development, phase I–III trials, in-vitro studies, non-English papers. Papers concerning the potential role of vaccinations in inducing rheumatic diseases were excluded, because these recommendations focus on the effect of vaccination on established disease.[9–15]

Experts independently graded literature on methodological quality and level of evidence.[8] Each paper was evaluated by at least three experts. Abstracts were rated a level of evidence 3 or 4. Data were extracted using predefined criteria. Results of studies on adult patients with rheumatic diseases were extrapolated to juvenile patients. Critical appraisal results were debated, and subsequently the recommendations were formulated. The strength of each recommendation was based on the level of evidence.[8] Finally, a closed Delphi voting procedure was performed to determine the level of agreement with the recommendation ranging from 0 (no agreement) to 10 (maximal agreement). Recommendations on which the agreement was below 7.5 were removed.

RESULTS

Sixty papers were critically appraised on vaccination versus immunosuppressive drugs and 147 on vaccination versus rheumatic diseases after the first search (figure 1). In the second search (November

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2010), six of the included abstracts had come out as full text papers and three additional papers were found. Evidence on vaccinations versus immunosuppressive drugs (table 1) and versus rheumatic diseases (table 2) was summarised. The task force agreed on 15 recommendations, reaching a level of agreement of 7.9–9.8 (table 3).

Noteworthy was that antibody responses were taken as surrogate endpoints for efficacy in all studies; only three studies evaluated the occurrence of infections (pneumococcal, flu, varicella) after vaccination.[16–18] Most studies were powered for immunogenicity analysis, not safety. Results on safety should be interpreted with caution.

Medication use

When indicated according to national guidelines, non-live vaccines can be administered to PaedRD patients using glucocorticosteroids, disease-modifying antirheumatic drugs (DMARD) and/or anti-tumour necrosis factor alpha (TNFα) therapy.

Non-live composite vaccines administered to patients on glucocorticosteroids, DMARD or anti-TNFα treatment do not aggravate disease or cause serious adverse events in comparison with healthy subjects. For glucocorticosteroids this was shown for the hepatitis B virus (HBV) vaccine, flu and pneumococcal polysaccharide vaccine (PPV).[19–30] For methotrexate the safety of the flu and 23-valent PPV (PPV23) was shown in adult rheumatoid arthritis and systemic lupus erythematosus (SLE) patients.[21 25 26 30–32] Data on DMARD other than methotrexate were scarce.[19 21–23 25–27 30 33–37] Non-live vaccines were safe in those studies, with similar disease activity following flu and PPV vaccination and no serious adverse events.[21–23 25 27 30 33] Regarding biological agents, PPV23, the heptavalent pneumococcal conjugate vaccine (PCV7) and the flu vaccine were safe in patients on anti-TNFα treatment.[16 21 28 31 32 38] Data on other biological agents were too limited to make definite statements on safety.

In patients using rituximab, disease activity was similar before and after influenza vaccination and adverse events after flu, PPV23 and tetanus toxoid (TT) vaccination were comparable to healthy controls and patients without rituximab.[39–41] Influenza vaccination in patients on tocilizumab (anti-interleukin 6) did not induce disease flares.[36]

It is recommended to determine pathogen-specific antibody concentrations after vaccination in PaedRD patients on high-dose glucocorticosteroids (≥2 mg/kg or a total dose of ≥20 mg/day for 2 weeks or more) or on rituximab, and can be considered in patients on anti-TNFα treatment at the time of vaccination.

In contrast to the good serological responses while using low-dose glucocorticosteroids (in children <0.5–2.0 mg/kg per day[25 28] or <10 mg/day[20 21 23 24 26 27 29] in adults), three studies including adult patients on glucocorticosteroids greater than 10 mg/day showed reduced responses to influenza vaccination.[19 22 30]

Rituximab blunted the immune response to TT and flu vaccines when administered 1 month after treatment.[35 39–43] When these vaccinations were administered 6–10 months after rituximab, immune responses were adequate[39 40] to reduced.[44] Similarly, the immune response to PPV23 administered 6–7 months after rituximab treatment was reduced.[39–41 43 44]

Anti-TNFα treatment did not reduce the percentage of patients reaching protective antibody concentrations after TT, flu and pneumococcal vaccinnation,[16 21 24 28 31 37 38 43 45–50] although some studies found lower geometric mean antibody concentrations (GMC).[31 51 52] Thirty-one juvenile idiopathic arthritis (JIA) patients on anti-TNFα treatment had similar protection rates after PCV7 as patients without anti-TNFα. However, GMC to three serotypes were lower.[16] Reduced responses were also described in 10 spondylarthropathy patients on anti-TNFα therapy.[53] Measuring pathogen-specific antibodies can be considered in patients on anti-TNFα therapy.

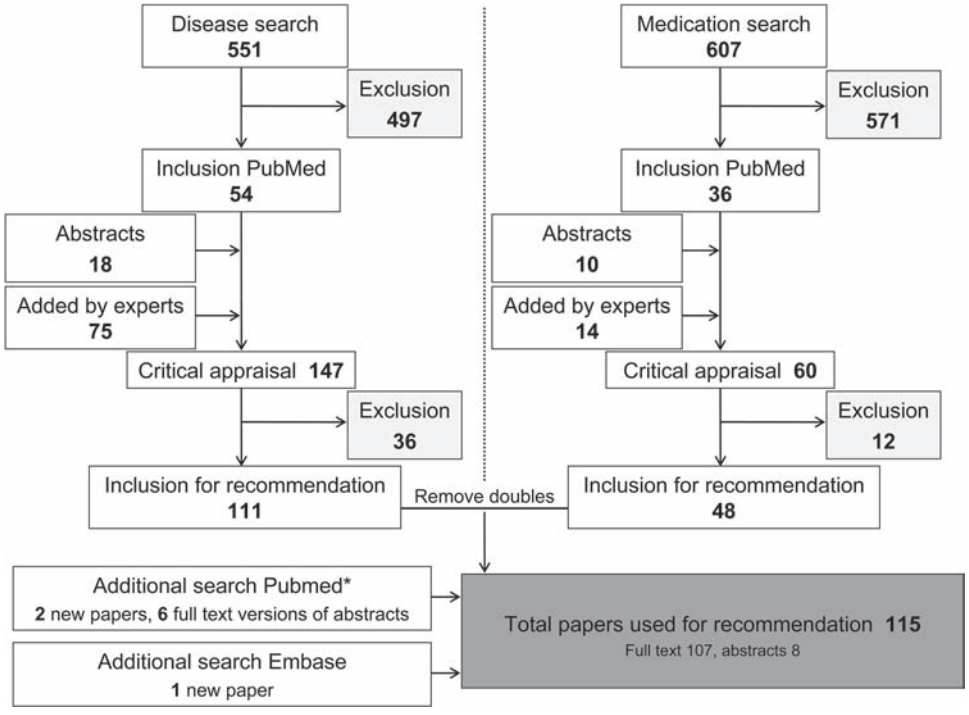

Figure 1 Search strategy for the systematic literature review. Two searches were performed, (A) one for vaccinations in combination with paediatric auto-inflammatory or rheumatic diseases and (B) one for vaccinations in combination with immunosuppressive drugs. *An additional search was performed in PubMed and EMBASE in November 2010 using the same search string to obtain additional recently published papers.

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Table 1 Immunosuppressive drugs vs immunogenicity and safety of vaccination

Medication	Studies (abstract)	Patients (juvenile)/ healthy controls	LoE	Immunogenicity (LoE)	Safety (LoE)
Corticosteroids*	14 (1)	1087 (147)/288	1B–4	Good immunogenicity HBV (2A), flu (2A), PPV (2B), VZV (3) on GC <10 mg/ day	Composite vaccines safe in 287 patients (1B)
				Lower response to flu on GC >10 mg/day (3), trend to lower response to VZV on GC <10 mg/day (+ other immunosuppressive drugs) (3)	Live vaccines (VZV, MMR booster, YFV booster) safe in 35 patients on GC <10 mg/day (3)
Methotrexate	18 (3)	1758 (230)/226	2A–4	Good immunogenicity HBV (2A), flu (2A), TT (4), MMR (3) with methotrexate <15 mg/m^2/week	Composite vaccines safe in 200 patients (2A)
				Lower response to PPV23 on methotrexate 13–25 mg/week (2A), trend to lower response to VZV on methotrexate 12–25 mg/m^2/week (3)	Live vaccines (VZV, MMR booster, YFV booster) safe in 135 patients on methotrexate <15 mg/m^2/week (3)
Other DMARD	10 (1)	627 (49)/231	1B–4	Good immunogenicity PPV on AZA and CFM (3)	Composite vaccines safe in 210 patients (1B)
				Lower response to flu on AZA, CFM and HCQ (2A)	YFV booster safe in 44 patients (4)
Anti-TNFα	23 (4)	2181 (186)/318	1B–4	Good immunogenicity flu (2A), PPV23 (1B), PCV (2B), MMR (3), TT (4)	Composite vaccines safe in 414 patients (2A)
				Lower response to PPV23 (2A), PCV7 (4), HBV (3), trend to lower response to YFV (3)	Live booster (MMR, YFV) vaccines safe in 28 patients (3)
Rituximab	6 (1)	313 (0)/70	1B–4	Good immunogenicity TT 6 months after rituximab (1B)	Composite vaccines safe in 133 patients (1B)
				Lower response to flu (2A), PPV23 (1B)	YFV booster vaccine safe in 3 patients (4)
Anti-IL-6	2 (2)	98 (31)/19	3	Good immunogenicity flu (3)	Composite vaccines safe in 31 patients (3)
Anti-CD11a	1 (0)	62 (0)/0	1B	Good immunogenicity PPV23 compared to placebo in 62 psoriasis patients (1B)	NA
				Lower TT-specific antibodies, but similar protection rate in 62 psoriasis patients (1B)	

*Only three papers studied paediatric patients, in these studies the maximum GC dose was 10 mg/day or dosages below 0.5–2 mg/kg per day.
AZA, azathioprine; CFM, cyclophosphamide; DMARD, disease-modifying antirheumatic drugs; GC, glucocorticosteroids; HBV, hepatitis B virus vaccine; HCQ, hydroxychloroquine; LoE, level of evidence; MMR, measles, mumps, rubella vaccine; NA, not applicable; PCV7, 7-valent pneumococcal conjugate vaccine; PPV23, 23-valent pneumococcal polysaccharide vaccine; TNF, tumour necrosis factor; TT, tetanus toxoid vaccine; YFV, yellow fever vaccine.

Data were too limited to construct recommendations on the measurement of antibody concentrations in patients on newer biological agents.[36 37 54 55]

In PaedRD patients with an indication for pneumococcal or influenza vaccination, it is recommended to vaccinate before rituximab use whenever possible.

Rituximab impairs the immune response until 6 months after treatment.[35 39–41 43 44] In eight rheumatoid arthritis patients receiving flu and PPV23 vaccination 6 days before initiating rituximab treatment, responses were comparable to patients without rituximab,[44] suggesting that immunisations should be given before rituximab treatment whenever possible.

In PaedRD patients with a contaminated wound, it is suggested to administer tetanus immunoglobulin to patients treated with rituximab in the past 6 months, because responses to TT vaccination can be reduced.

Responses to TT vaccination are reduced in the first month after rituximab treatment, whereas responses 6 months after rituximab treatment are adequate. The immune response in the period between the first and sixth month after rituximab treatment is currently unknown.[39 42] As responses to TT vaccination may be reduced, the committee suggests administering tetanus immunoglobulin in patients with a contaminated wound that have been treated with rituximab in the past 6 months.

It is recommended to determine pneumococcal serotype-specific antibody concentrations after PPV23 vaccination in PaedRD patients on methotrexate at the time of vaccination.

The immunogenicity of vaccines has predominantly been tested in adult patients on standard dose methotrexate of 15 mg/week. Responses to vaccines were sufficient in patients using methotrexate, except for the PPV23 vaccination, and possibly for other polysaccharide vaccines. Protection rates were comparable with patients without methotrexate or healthy controls after HBV (one study), flu (five studies) and TT vaccination (one study).[21 24–26 30 45 46] In contrast, in all seven studies including the T-cell-independent PPV, lower responses were found in patients treated with methotrexate 15 mg/week, or in a minority with 15–25 mg/week.[24 32 48 50 52 56 57] The effect of synthetic DMARD other than methotrexate on antibody responses is unknown, because results of studies were contradictory.[19 21–23 25 27 30 33 34] In those patients, determining pneumococcal serotype-specific antibody concentrations after PPV23 vaccination can be considered. If responses are insufficient, the conjugate vaccine can be considered, because this vaccine may be more immunogenic in immunocompromised patients.[58]

Live-attenuated vaccines

It is recommended to withhold live-attenuated vaccines in PaedRD patients on high-dose DMARD, high-dose glucocorticosteroids or biological agents. However, vaccination can be considered on a case-to-case basis weighing the risk of infections versus the hypothetical risks of vaccination.

According to the manufacturer's statement, live-attenuated vaccines should not be administered to immunosuppressed patients, given the risk of inducing infection by vaccination.

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Table 2 Immunogenicity and safety of vaccinations in PaedRD

Vaccine	Studies (abstract)	Patients (juvenile)/ healthy controls	LoE	Immunogenicity (LoE)	Safety (LoE)
BCG*	10 (0)	16124 (16063)/65	2B–4	Lower responses to PPD in 115 JIA patients and 20 SLE patients several years after BCG (2B)	Local inflammation at BCG site in 8169 Kawasaki disease patients (3)
HAV/HBV	9 (2)	432 (49)/56	2B–3	Good immunogenicity HAV in 10 patients (3) and HBV in 344 patients (2B)Lower responses HBV in 44 RA patients (3), and in 40 SpA patients on anti-TNFα (3)	HAV safe; no worsening of disease in 10 patients (3) HBV safe; similar disease activity as non-vaccinated patients in 44 patients (2B), no worsening of disease in 77 patients (3), no severe AE in 293 patients (3)
Hib	2 (0)	85 (0)/0	3	Good immunogenicity in 85 patients (3)	Safe; no worsening of disease in 85 patients (3)
HPV	1 (1)	22 (22)/0	4	NA	Safe; no serious AE in 22 patients (4)
Flu	41 (4)	2551 (131)/901	1B–3	Good immunogenicity in 1035 patients (1B–3)Good immunogenicity, but lower GMC or lower responses to 1 strain in 408 patients (1B–3)Lower responses on immunosuppressive drugs in 760 patients (1B–3)Lower responses in 206 patients (1B–2B)	Safe; similar disease activity as non-vaccinated patients in 429 patients (1B–2B), no worsening of disease in 871 patients (3), similar AE as HC in 177 patients (2B)
Meningococcal	1 (0)	234 (234)/0	3	Good immunogenicity in 234 patients (NeisVac-C), despite lower GMC in patients on immunosuppressive drugs (3)	Safe; no worsening of disease in 234 patients (NeisVac-C) (3)
MMR*	7 (0)	321 (229)/22	2B–3	Good immunogenicity in 98 patients (3)	Safe; no worsening of disease in 222 patients (3)Case reports of flares of JIA and ITP (4)
Pneumococcal	23 (1)	1889 (63)/142	1B–3	Good immunogenicity PPV in 557 patients (2A) and PCV7 in 63 JIA patients, including 31 on anti-TNFα (2B)Lower responses to PPV in 311 patients (2B), 20 patients on anti-TNFα (2A) and to PCV7 in 10 patients on anti-TNFα (3)	PPV safe; similar disease activity as non-vaccinated patients in 117 patients (1B), no worsening of disease in 157 patients (3), similar AE as HC in 131 patients (3), no serious AE in 40 patients (3)PCV safe; no worsening of disease, no severe AE in 63 JIA patients (3)
Polio*	1 (0)	115 (0)/0	3	NA	Four flares after IPV/OPV vaccination in 73 SLE patients vs no flares in 37 SLE controls (3)
TDaP/TD/TT	10 (1)	501 (138)/156	2B–3	Good immunogenicity TT in 316 patients, also 6 months after rituximab, and on anti-TNFα (2B)Good immunogenicity TD in 34 patients (3)Good immunogenicity TT, but lower GMC in 92 patients (3) and in 41 patients on anti-CD11a (2B)Poor responders to TT among 29 SLE patients (3)	TT safe; no worsening of disease in 113 patients, no severe AE in 103 patients (3)
Travellers' vaccines†	1 (0)	1 (0)/0	4	NA	Transverse myelitis reported 3 months after rabies vaccination (4)
VZV*	3 (1)	86 (30)/47	2B–3	Good immunogenicity to zoster in 55 patients (3)Responses within range of controls in 25 patients, but trend towards lower response (2B)Five of 6 IBD patients had positive immunity (4)	Safe; no worsening of disease in 86 patients (3–4), no serious AE in 31 patients (3–4), similar AE as HC in 55 patients (3)VZV-like rash in 20% of patients (4)
YFV*	2 (0)	91 (0)/15	2B–3	Trend to lower GMC, 1 non-responder of 17 patients on anti-TNFα and methotrexate (2B)	Safe; similar AE as HC in 91 patients (3)

*Live-attenuated vaccines, both non-live as live-attenuated OPV are available.
†Cholera, Japanese encephalitis, rabies, tickborne encephalitis (FSME), typhoid fever.
AE, adverse events; BCG, bacillus Calmette–Guérin; GMC, geometric mean antibody concentrations; HAV, hepatitis A virus vaccine; HBV, hepatitis B virus vaccine; HC, healthy controls; Hib, *Haemophilus influenzae* type B vaccine; HPV, human papillomavirus vaccine; IBD, inflammatory bowel disease; IPV, inactivated poliovirus; ITP, idiopathic thrombocytopenic purpura; JIA, juvenile idiopathic arthritis; LoE, level of evidence; MMR, measles, mumps, rubella vaccine; NA, not applicable; NeisVac-C, meningococcal serogroup C conjugate vaccine; OPV, oral poliovirus vaccines; PaedRD, paediatric patients with rheumatic diseases; PCV7, 7-valent pneumococcal conjugate vaccine; PPD, purified protein derivative of tuberculin; PPV, pneumococcal polysaccharide vaccine; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SpA, spondylarthropathy patients; TD, tetanus-diphtheria vaccine; TDaP, tetanus-diphtheria-acellular pertussis vaccines; TNF, tumour necrosis factor; TT, tetanus toxoid vaccine; VZV, varicella zoster virus vaccine; YFV, yellow fever virus vaccines.

The immunosuppressive effect of DMARD or glucocorticosteroids depends on the dosage and duration of use. Current cut-off values for high dosages differ and are predominantly based on consensus.[6 59] The committee has defined high DMARD dosages as intravenous pulse therapy or dosages higher than the standard dosages (methotrexate 15 mg/m^2 per week, cyclosporine 2.5 mg/kg per day, sulphasalazine 40 mg/kg per day up to 2 g/day, azathioprine 1–3 mg/kg, cyclophosphamide 0.5–2.0 mg/kg per day orally, leflunomide 0.25–0.5 mg/kg per day, 6-mercaptopurine 1.5 mg/kg per day).[60–62] For glucocorticosteroids, 2 mg/kg or greater or a total of 20 mg/day or more during 2 weeks or more is considered a high dose.[6 59] Noteworthy is that a chronically administered glucocorticosteroid dose of 20 mg/day is equivalent to dosages below 2 mg/kg per day in children. In these patients less than 2 mg/kg per day are also considered high dosages.

Available studies on live-attenuated vaccines usually include patients on low-dose DMARD or glucocorticosteroids, and the available evidence on safety is reassuring. The measles, mumps, rubella (MMR) booster and yellow fever virus (YFV) booster were safe in patients on methotrexate less than 15 mg/m^2 per

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Table 3 Recommendations with grade of recommendation and Delphi score on agreement among experts

RC		Grade	Delphi score (mean (SD))
	IMMUNOSUPPRESSIVE DRUGS		
1	When indicated according to national guidelines*, non-live vaccines can be administered to PaedRD using glucocorticosteroids, DMARDs and/or anti-TNFα therapy.	C	9.8 (0.4)
2	To assure adequate immune responses, it is recommended to determine pathogen-specific antibody concentrations after vaccination in all PaedRD on high-dose glucocorticosteroids† (≥2 mg/kg or ≥20 mg/day for ≥2 weeks) or on rituximab. Measuring pathogen-specific antibody concentrations can be considered in patients on anti-TNFα treatment.	C	8.4 (2.9)
3	In patients with an indication for pneumococcal or influenza vaccination, it is recommended to vaccinate prior to rituximab use whenever possible.	C	9.8 (0.6)
4	In PaedRD with a contaminated wound, it is suggested to administer tetanus immunoglobulin to those patients treated with rituximab in the past 6 months, since responses to TT vaccination can be reduced.	D	9.6 (0.9)
5	To assure adequate immune responses, it is recommended to determine pneumococcal strain-specific antibody concentrations after the PPV23 in PaedRD on methotrexate at time of vaccination.	C	7.9 (3.4)
	LIVE-ATTENUATED VACCINES		
6	Until more data are available, it is recommended to withhold live-attenuated vaccines in patients on high-dose DMARD,† high-dose glucocorticosteroids† or biological agents. However, vaccination can be considered on a case-to-case basis weighing the risk of infections vs the hypothetical risk of inducing infections by vaccination.	D	9.2 (0.9)
7	It is recommended to adhere to national vaccination guidelines for live-attenuated vaccines in PaedRD unless patients are on high-dose DMARD,† high-dose glucocorticosteroids† or biological agents. Boosters vaccinations against VZV, MMR and YFV can be considered in patients on methotrexate <15 mg/m^2/week or low-dose glucocorticosteroids.	C	8.9 (1.5)
8	It is recommended to withhold BCG vaccination during active Kawasaki disease.	C	9.5 (0.9)
9	It is recommended to assess VZV infection and vaccination history in PaedRD, especially in those patients anticipating high-dose immunosuppressive therapy† or biologicals. In case of a negative history for VZV infection or vaccination, VZV vaccine should be considered, ideally before initiation of immunosuppressive therapy.‡	D	9.2 (1.2)
	NON-LIVE VACCINES		
10	The TT vaccine should be administered to patients with juvenile SLE and JIA according to the national vaccination guidelines.	B	9.8 (0.6)
11	It is recommended to adhere to national vaccination guidelines* for vaccination against hepatitis B virus, tetanus, diphtheria, pertussis, Hib, pneumococci and meningococci in PaedRD.	C	9.8(0.6)
12	It is recommended to adhere to national vaccination guidelines* for vaccination against hepatitis A virus, poliovirus, Japanese encephalitis, typhoid fever, rabies, cholera or tickborne encephalitis in PaedRD.	D	8.9 (1.8)
13	Annual influenza vaccination should be considered in all PaedRD.	D	8.4 (2.2)
14	In the case vaccinations against Hib, pneumococci and meningococci are not included in the national vaccination programmes*, these vaccinations are recommended for PaedRD with low complement levels or functional asplenia. These vaccinations can be considered in patients on high-dose immunosuppressive drugs† or biological agents before therapy.‡	D	9.3 (1.6)
15	It is recommended to adhere to national vaccination guidelines* for vaccination against HPV in PaedRD. Given the higher risk of HPV infection in female SLE patients, these patients should be advised to be vaccinated in the adolescence. However, physicians should be vigilant on potential thromboembolic events.	D	9.2 (1.6)

*National vaccination guidelines worldwide can be found on http://apps.who.int/immunization_monitoring/en/globalsummary/scheduleselect.cfm.
†High-dose DMARD are defined as intravenous pulse therapy, cyclosporine >2.5 mg/kg per day, sulphasalazine >40 mg/kg per day or 2 g/day, azathioprine >3 mg/kg, cyclophosphamide orally >2.0 mg/kg per day, leflunomide >0.5 mg/kg per day, or 6-mercaptopurine >1.5 mg/kg per day. High-dose glucocorticosteroids are dosages ≥2 mg/kg or ≥20 mg/day for 2 weeks or more. In patients chronically treated with 20 mg/day glucocorticosteroids, dosages below 2 mg/kg per day are also considered high dosages.
‡Generally 2–4 weeks is recommended before immunosuppressive therapy is commenced.
BCG, bacillus Calmette–Guérin; DMARD, disease-modifying antirheumatic drugs; Hib, *Haemophilus influenzae* type B; HPV, human papillomavirus; JIA, juvenile idiopathic arthritis; MMR, measles, mumps, rubella; PaedRD, paediatric patients with rheumatic diseases; PPV23, 23-valent pneumococcal polysaccharide; RC, recommendation; SLE, systemic lupus erythematosus; TNF, tumour necrosis factor; TT, tetanus toxoid; VZV, varicella zoster virus; YFV, yellow fever virus.

week (n=118), various DMARD (sulphasalazine, leflunomide, cyclosporine, cyclophosphamide), anti-TNFα (n=28) and rituximab (n=3).[35 63–65] Similarly, primary varicella zoster virus (VZV) vaccination did not induce severe adverse events or disease flares in 25 PaedRD patients on glucocorticosteroids, methotrexate, and/or various DMARD.[17] Data on patients on high-dose glucocorticosteroids, high-dose DMARD or biological agents are scarce. Therefore, the committee considers it prudent to withhold these vaccines in such patients until more data are available.

It is recommended to adhere to national vaccination guidelines for live-attenuated vaccines in PaedRD patients unless patients are on high-dose DMARD, high-dose glucocorticosteroids or biological agents. Booster vaccinations against VZV, MMR and yellow fever can be considered in patients on methotrexate less than 15 mg/m/per week or low-dose glucocorticosteroids.

MMR and VZV vaccinations can be given safely and efficaciously when PaedRD patients are not immunosuppressed as a result of treatment. In addition, evidence supports the safety of VZV, MMR and YFV booster vaccines in patients on methotrexate less than 15 mg/m^2 per week or low-dose glucocorticosteroids.[17 63–65]

In contrast to one case report of a flare systemic JIA after rubella vaccination, larger studies failed to find this association.[66] In two studies including 15 and 207 JIA patients, respectively, MMR booster vaccination did not increase disease activity, not even when using regular methotrexate dosages and low-dose glucocorticosteroids.[63 64] MMR booster showed good immunogenicity in 10 JIA patients, irrespective of regular methotrexate dosages and etanercept.[63]

More studies are required before recommendations on primary vaccinations with live-attenuated vaccines can be made. The primary VZV vaccination was studied in 25 PaedRD patients, of whom all were on methotrexate treatment (mean dose 16.4 mg/m^2 per week) and 13 patients were on glucocorticosteroids (0.1–0.7 mg/kg per day). The response rate was 50% in patients versus 72% in 18 healthy controls. No severe adverse events, generalised varicella infection, herpes zoster or worsening of disease activity were reported.[17] Adequate immunogenicity was found in 28 patients with SLE and six with inflammatory bowel disease after VZV booster vaccination.[67 68]

No severe adverse events were seen after YFV booster in 91 adult patients with rheumatic disease on various amounts of immunosuppressive drugs, including 26 patients on biological

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agents.[35 65] Effects on disease activity are unknown. The immunogenicity of YFV booster vaccination was good, although responses were reduced in patients on TNFα blocking agents.[65]

The risk of contracting tuberculosis is increased in patients treated with immunosuppressive drugs, especially TNFα-blocking agents.[69–78] Bacillus Calmette–Guérin (BCG) vaccination should be administered before initiating immunosuppressive drugs.[79 80] The safety of BCG vaccination has not been studied. Regarding efficacy, reduced induration sizes to the tuberculin skin test were found in 115 JIA and 20 SLE patients on low-dose immunosuppressive drugs.[81 82]

It is recommended to withhold BCG vaccination during active Kawasaki disease.

This recommendation is supported by literature describing local inflammation at the BCG vaccination site in 37–50% of 15805 Kawasaki patients.[83–88]

It is recommended to assess VZV infection and vaccination history in PaedRD patients, especially in those patients anticipating high-dose immunosuppressive therapy or biological agents. In case of a negative history for VZV infection or vaccination, VZV vaccine should be considered, ideally beforethe initiation of immunosuppressive therapy.

Case reports exist of severe disseminated primary VZV infections or zoster infections in patients on anti-TNFα therapy or methotrexate.[89–91] VZV vaccination has been proved beneficial in immunocompromised juvenile leukaemia patients and HIV patients.[92 93] Based on the above, we suggest assessing VZV infection or vaccination status in all PaedRD patients, especially in those anticipating immunosuppressive treatment or biological agents. In case of a negative or inconclusive history for chickenpox or VZV vaccination, VZV vaccine should be considered, ideally before the initiation of immunosuppressive therapy or biological agents. Current consensus-based guidelines recommend to wait at least 2–4 weeks before starting treatment.[6 92]

Non-live composite vaccines

It is recommended to adhere to national vaccination guidelines for vaccination against cholera, diphtheria, Haemophilus influenzae type B (Hib), hepatitis A virus (HAV), HBV, Japanese encephalitis, pertussis, pneumococci, poliovirus and meningococci, rabies, tetanus, tickborne encephalitis and typhoid fever, in PaedRD patients.

Based on the evidence supporting the safety and immunogenicity of non-live composite vaccines, the committee recommends adhering to national vaccination programmes. Evidence strongly supported the safety and immunogenicity of TT vaccination in juvenile SLE and JIA patients, even when using immunosuppressive drugs.[45 94 95] Most studies supported the safety and immunogenicity of diphtheria,[95] Hib,[96 97] HAV,[98] HBV,[26 53 98–102] PPV,[27 51 52 54 103–106] pneumococcal conjugate[16 53] and meningococcal conjugate vaccines.[107] Four SLE flares were described after polio vaccination in a retrospective analysis.[10] Well-controlled prospective studies were not available. Data for vaccination against cholera, Japanese encephalitis, tickborne encephalitis and typhoid fever were lacking.[108]

Annual influenza vaccination should be considered in all PaedRD patients

General recommendations state that children that are 'immunosuppressed' should receive annual inactivated influenza vaccinations.[7] As 'immunosuppressed' is not further specified, the question arises as to whether PaedRD patients are at higher risk of (complications of) flu infection. Two large retrospective studies showed an increased risk of flu in older patients with rheumatic diseases and a beneficial effect of vaccination on admission for pneumonia/flu or death.[109 110]

Seasonal influenza vaccination was safe and immunogenic in adult and PaedRD patients.[19–25 28–31 33 34 36–38 40 41 47 111–121] Vaccination reduced the occurrence of viral respiratory and bacterial infections after vaccination.[18] Based on the possible increased risk of (complicated) flu infections and the safety and immunogenicity of non-live flu vaccines, annual influenza vaccination can be considered in all PaedRD patients.

If vaccinations against Hib, pneumococci and meningococci are not included in the national vaccination programmes, these vaccinations are recommended for PaedRD patients with low complement levels or functional asplenia. These vaccinations can be considered in patients on high-dose immunosuppressive drugs or biological agents before therapy.

Patients with complement deficiencies or functional asplenia, such as some SLE[122] and polyarticular JIA[123 124] patients, are at increased risk of acquiring Hib, meningococcal and pneumococcal infections.[122] Vaccinations against these pathogens are recommended when pathogen-specific antibody concentrations are insufficient.

It is recommended to adhere to national vaccination guidelines for vaccination against human papillomavirus (HPV) in PaedRD patients. Given the higher risk of HPV infection in female SLE patients, these patients should be advised to be vaccinated in adolescence. However, physicians should be vigilant for potential thromboembolic events.

Preliminary results showed no serious adverse events after HPV vaccination (gardasil) in 22 JIA and seronegative inflammatory arthritis patients.[125]

SLE patients may have a higher risk of persistent HPV infections than healthy subjects, with a higher risk of squamous intraepithelial lesions and cervical cancer.[126–128] These data underline the necessity of protection against HPV infection in juvenile SLE patients before they become sexually active. Noteworthy is that venous thromboembolic events were reported after Gardasil vaccination.[129] Although it is uncertain whether these thromboembolic events can be attributed to HPV vaccination, vigilance after HPV vaccination in SLE patients seems warranted.[130 131]

DISCUSSION

Safe and effective vaccination is crucial in PaedRD patients given the increased risks of infections.[2–5] The EULAR task force formulated 15 recommendations on vaccination in PaedRD patients. As evidence was lacking for numerous vaccines, diseases and immunosuppressive drugs, most recommendations have strength C or D.

The recommendations refer to national vaccination guidelines, as these take into consideration local epidemiology, programmatic issues, resources and policies. Worldwide, these guidelines differ considerably (http://apps.who.int/immunization_monitoring/en/globalsummary/scheduleselect.cfm). Vaccinations against Hib, pneumococci and meningococci, HPV and VZV are not uniformly included in national guidelines, but are considered important in the management of PaedRD patients. For these vaccines, specific recommendations were made.

Generally, the immunogenicity of vaccines is good in PaedRD patients. There are some exceptions, depending on the type and dose of immunosuppressive treatment and the type of vaccine. Methotrexate reduced responses to T-cell-independent PPV, whereas T-cell-dependent responses to conjugate and live-attenuated vaccines were good. Responses to various vaccines (flu, VZV) were reduced in patients on high-dose

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glucocorticosteroids or azathioprine. Anti-TNFα did not reduce the immunogenicity of vaccines according to most controlled studies. Rituximab reduced responses to both T-cell-independent and T-cell-dependent vaccines. Offering vaccination before immunosuppressive drugs or determining antibodies may be considered in these patients. Notably, the effect of immunosuppressive drugs or disease on the persistence of antibodies after vaccination is still unknown. In addition, the effect of vaccination on the infection rate should be assessed.

Regarding safety, both disease activity and adverse events were studied. Importantly, most studies were underpowered to assess safety. Sufficiently powered safety studies are warranted. Nonetheless, non-live vaccines seem to be safe while using glucocorticosteroids (2.5–40 mg/day), methotrexate 7–25 mg/week, other DMARD such as azathioprine, or biological agents. Limited data so far indicate that live-attenuated booster vaccines are safe in patients on regular methotrexate dosages, low-dose glucocorticosteroids and anti-TNFα therapy. Although it is sensible to withhold live-attenuated vaccines in patients on high-dose immunosuppressive drugs and biological agents, these vaccines, especially booster vaccinations, are not contraindicated as such. Primary vaccines are generally administered before the onset of rheumatic diseases, and booster vaccines may be administered when essential.

Finally, these recommendations need to be updated regularly, because new evidence will become available on vaccinating PaedRD patients on immunomodulating drugs.

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