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Vaccination in Paediatric Rheumatology

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Abstract As awareness of the risk of vaccine-preventable diseases for children with rheumatic diseases has increased, vaccination has become an important clinical consideration and focus of research in paediatric rheumatology. Conflicting reports in the literature and differing advice from national bodies regarding the safety of different vaccines for this patient population have led to confusion in the minds of many rheumatologists as to what is appropriate. This article will provide an overview of crucial aspects of the recently published European League Against Rheumatism recommendations regarding vaccination of paediatric patients with rheumatic disease, and will review advances in this field since their publication.

Keywords Paediatric rheumatic diseases · PRDs · Vaccine-preventable diseases · Immunosuppression · European League Against Rheumatism · EULAR · Non-live vaccines · Live vaccines · MMR booster · Pandemic influenza vaccination · Human papillomavirus vaccine · HPV · Corticosteroid · DMARD

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Introduction

Over the last 15 years there has been a substantial increase in interest within the rheumatology community regarding vaccination of patients with paediatric rheumatic diseases (PRDs). This interest has arisen in the context of greater awareness of the increased risk of vaccine-preventable diseases for this patient group, the increasing use of more substantial immunosuppression (e.g. biological agents) for managing PRDs, and the introduction of several new vaccines into many national immunisation programs (e.g. human papillomavirus (HPV) and varicella zoster vaccines). There are three main concerns regarding the administration of vaccines to patients with PRDs:

1. the risk of precipitating flares of rheumatic illness;
2. uncertainty regarding induction of adequate immunity, including long-term protection; and
3. the risk of disseminated infection with vaccine-strain pathogens after administration of live vaccines to immunosuppressed patients.

Inconsistencies in published recommendations and conflicting reports regarding safety have led to substantial differences in practice in this area by rheumatologists.

Widespread variation in approach to vaccinations for children with PRDs was raised as a concern in a report from Britain over a decade ago [1]. One of the factors identified as contributing to this variation was a lack of consistency in published guidelines, particularly with respect to vaccine use for patients on immunosuppressive therapy, and the lack of any guidelines specific to PRD patients. A recent report examining 21 national guidelines for vaccination of adult

patients with rheumatic disease suggests that such lack of consistency continues to exist [2].

Another important concern identified in this area is the suboptimum rate of vaccination among children with PRD, with almost 40 % of patients having incomplete vaccination for age at their most recent clinic visit in a study at a Canadian tertiary children's hospital [3]. Uncertainty of parents and/or rheumatologists regarding the safety of some vaccinations for patients with PRD and the possible failure of rheumatologists to monitor the immunisation status of patients who do not have a primary care physician were advanced as possible reasons for this finding. That rheumatologists do not necessarily see themselves as responsible for such monitoring was clearly revealed in a study of adult rheumatologists in Ireland, of whom only 5 % believed the rheumatology clinic to be the best setting for ensuring appropriate vaccination of patients with rheumatic disease [4].

In this context, two expert subcommittees of the European League Against Rheumatism (EULAR) have published separate recommendations regarding vaccination of children and adults with rheumatic disease, which address immunosuppressive therapy and the safety and efficacy of live and non-live vaccines for patients with paediatric and adult rheumatic diseases [5••, 6•]. This article will provide a précis of key aspects of the paediatric recommendations and review advances in this field since their publication.

EULAR Recommendations

The EULAR recommendations for vaccination of children with PRDs were based on the consensus opinion of experts in rheumatology, immunology, vaccine evaluation, public health, and epidemiology after a systematic literature review of citations in the MEDLINE and EMBASE databases [7••, 8]. Fifteen recommendations were produced: ten covering the use of live-attenuated and non-live vaccines, and five related to managing immunization in the setting of immunosuppressive therapy.

Non-live Vaccines

Table 1 lists the non-live vaccines for which it is recommended to adhere to national vaccination guidelines for children with PRDs. It is noted that non-live vaccines may be administered in the setting of glucocorticoids, disease-modifying antirheumatic drugs (DMARDS), and/or anti-tumour-necrosis-factor (TNF) therapy, but that serological response should be determined for those on high-dose glucocorticoids (defined as ≥2 mg kg^{-1} or 20 mg day^{-1} for ≥2 weeks) or rituximab and considered for those on anti-TNF therapy. The same recommendation is made for patients on methotrexate who are given 23-valent pneumococcal vaccine. Given the substantial effect of rituximab therapy on circulating B-cells, it is recommended that patients requiring pneumococcal or influenza immunisation be administered these vaccines before starting rituximab therapy, and that tetanus immunoglobulin rather than booster immunisation should be given to these patients if they sustain a tetanus-prone wound. Where vaccination against encapsulated organisms (i.e. haemophilus influenzae type B, pneumococcus, and meningococcus) is not part of a national immunisation program, it is suggested that these vaccines be given to PRD patients with hypocomplementaemia or functional asplenia and considered for all patients before commencement of biological agents or high-dose immunosuppression. Seasonal influenza vaccination was recommended for all patients with PRDs.

Table 1 Non-live vaccines suitable for administration to children with rheumatic diseases according to the EULAR recommendations regarding vaccines for patients with PRDs

Cholera
Diphtheria[a]
Haemophilus influenzae type B
Hepatitis A
Hepatitis B
Human papillomavirus
Japanese encephalitis
Meningococcus
Pertussis
Pneumococcus
Inactivated Polio virus (IPV)
Rabies
Tetanus
Tickborne encephalitis
Typhoid Fever

[a] Vaccines in bold are those included in the current WHO list of vaccines recommended for all populations (February 2014) [9]

Live Vaccines

Administration of live-attenuated vaccines to children with rheumatic disease has been of particular concern, given the theoretical possibility that even attenuated infection may cause flares of underlying rheumatic illness or may evolve to follow a more severe course in those with altered immunity. Despite these concerns, descriptions of the former are rare [10, 11], and the latter have been reported only in immunocompromised patients with non-rheumatic disease or those with immunodeficiency [1, 12–14]. With respect to live-attenuated vaccines, the EULAR recommendations suggest that national vaccination guidelines be followed except for patients on high-dose DMARD therapy, high-dose glucocorticoids, or biological agents, for whom it was suggested that these vaccines be avoided (Table 2). These therapies, however, were not regarded as an absolute contra-indication to administration

Table 2 Consensus definitions of "high-dose" corticosteroid and disease-modifying antirheumatic drug (DMARD) therapy in the EULAR recommendations regarding vaccines for patients with PRDs

Drug	Dose
Glucocorticoids	≥2 mg kg^{-1} or 20 mg day^{-1} for ≥2 weeks or intravenous "pulse" therapy
Methotrexate	>15 mg m^{-2} $week^{-1}$
Cyclosporin	>2.5 mg kg^{-1} day^{-1}
Sulphasalazine	>40 mg kg^{-1} day^{-1} or 2.0 g day^{-1}
Azathioprine	>3 mg kg^{-1} day^{-1}
6-Mercaptopurine	>1.5 mg kg^{-1} day^{-1}
Leflunomide	>0.5 mg kg^{-1} day^{-1}
Cyclophosphamide (Oral)	>2.0 mg kg^{-1} day^{-1}

of live-attenuated vaccines: it is suggested that vaccination may be considered on a case-by-case basis if the probable benefits outweigh the "hypothetical risk" of vaccine-strain infection. It is suggested that "booster" doses of varicella zoster vaccine (VZV), measles, mumps, and rubella (MMR) vaccine, and yellow fever vaccine (YFV) may be given to patients on low-dose methotrexate (<15 mg m^{-2} $week^{-1}$) or low-dose corticosteroids, and that screening for varicella zoster immunity be performed for all patients and VZV be administered to those found to be non-immune before commencing immunosuppressive therapy. Where such vaccination is appropriate it is suggested that BCG be administered before commencing immunosuppressive therapy and that it not be used in the setting of active Kawasaki disease.

Recent Progress

MMR Booster

The safety and/or efficacy of the MMR booster vaccine for children with JIA has been the subject of several recent studies. Primary vaccination with MMR has not been studied because it is typically given before the age of onset of most PRDs. In 2007 a retrospective study of 207 JIA patients, including 49 on low-dose methotrexate (median dose 11 mg m^{-2}), found MMR revaccination was not associated with flares of disease or vaccine-strain viral infection in the six months after immunisation [15]. In 2009, low-dose methotrexate (10 mg m^{-2} $week^{-1}$) with or without concurrent etanercept (0.4 mg kg^{-1} twice weekly) was reported not to significantly interfere with humoral or cell-mediated immunity to MMR viral strains, nor to cause vaccine failure or overt vaccine-strain viral infection in the six months after administration, in a smaller prospective case-control study of 15 children with JIA and 22 healthy controls [16]. These findings have recently been confirmed in a prospective randomised trial of 137 JIA patients, in which booster MMR vaccination was immunogenic—with seroprotection rates of 97–100 %—and did not result in increased incidence of disease flares in the 12 months after administration [17••]. The intervention group in this study included 29 patients on low-dose methotrexate (median 10.6 mg m^{-2} $week^{-1}$) and nine patients on anti-TNF or anti-IL-1 therapy, which were briefly withheld at the time of immunisation; none of the patients developed overt vaccine-strain viral infection.

Although collectively these results are encouraging, a recent retrospective study of 400 PRD patients, examining the long-term persistence of antibodies to MMR, diphtheria, and tetanus vaccinations, suggests that the immunity acquired may not be sustained [18••]. In this study, geometric mean concentrations of antibodies to mumps, rubella, diphtheria, and tetanus among PRD patients were lower than those for a group of 2,176 healthy controls. This was particularly apparent for those whose immunisation was longer ago, 18.9 % of whom lacked protective antibody concentrations to mumps and rubella, compared with 5.2 and 1.2 %, respectively, of healthy controls. Patients with systemic JIA had the lowest prevalence of seroprotection to MMR and, with those with polyarticular JIA, were more likely to be on immunosuppressive medications; however, neither corticosteroid nor methotrexate use was found to affect antibody titres.

Pandemic Influenza Vaccination

The safety and immunogenicity of seasonal influenza vaccination for patients with PRDs is well established, and annual immunisation for all children with PRDs is recommended [5••, 19]. Until recently, little was known about the response to pandemic influenza A H1N1/2009 vaccine in this patient population. Because H1N1/2009 is one of the major disease-causing influenza A strains internationally, administration of the relevant vaccine may still have public health value for high-risk patients in countries where seasonal influenza vaccination is not available [20]. The response to monovalent adjuvant-free pandemic influenza A H1N1/2009 vaccine was evaluated in a prospective study of 237 patients with a variety of rheumatic diseases, including 99 with SLE and 93 with JIA, and 91 age-matched controls [21•]. Although seroconversion rates were lower in the rheumatic-disease group (74.3 %, compared with 95.6 % in the control group), the rate of post-vaccination seroprotection was significantly less than that of controls only for participants with SLE. Despite these findings, all patient groups had adequate vaccine response according to criteria set by the European Medicines Agency (EMEA) and by the Food and Drug Administration (FDA) in the United States. Glucocorticoid use was identified as having the only significant negative effect on the rate of seroconversion in a multivariate analysis that included disease type,

lymphopenia, steroid use, and combination therapy with steroid and a DMARD. Itching at the site of vaccination and arthralgia were more common in the patient group, but there were no other significant differences in adverse events. Effect on stability of disease was not examined. This latter aspect, and concern that confounding by indication resulting from the inclusion of heterogeneous diagnoses may have affected the analysis of the effect of therapy on vaccine response, prompted the same research group to further investigate the JIA, jSLE, and JDM patient groups separately.

In the JIA study, the response of 95 patients to inactivated adjuvant-free influenza A H1N1/2009 vaccine was compared with that of 91 age-matched controls. Subjects underwent clinical and laboratory evaluation on the day of vaccination and 21 days later [22•]. Although JIA patients had adequate vaccine response according to EMEA and FDA criteria, their rate of seroconversion was lower than that of controls, and for the polyarticular-onset subtype this was statistically significant (80 % vs. 95.6 %, $p=0.0098$). Contrary to the findings of the earlier study [21•], treatment with steroids was not found to affect vaccine response. This was true also for other immunosuppressive therapy (conventional DMARDs and biologicals). Patients experienced mild self-limited arthralgia after immunisation more frequently than controls, but otherwise the two groups did not differ in adverse-event rate or type. No flares of disease were noted, although the follow-up period was brief.

In the jSLE study, the response of 118 jSLE patients to inactivated adjuvant-free pandemic influenza A H1N1/2009 vaccine was compared with that of 102 healthy controls of similar age [23•]. Serological response was measured 21 days after administration, and surveillance for effects on disease activity continued for four months post vaccination. Seroconversion (63.6 vs. 91.2 %, $p<0.001$) and seroprotection (73.7 vs. 95.1 %, $p<0.001$) rates and GMT fold-change in antibody titres (8.1 vs. 19.9, $p<0.001$) were all significantly lower for jSLE patients, although still meeting EMEA and FDA criteria for adequate vaccine response. In univariate analysis the dose of corticosteroids was found to be significantly higher among non-seroconverters; however, in multivariate analysis only disease activity as measured by the SLEDAI-2 K was found to have a significant negative affect on seroconversion rate. No deleterious effect on disease activity was noted. As in the JIA study, reports of itch at the vaccination site and arthralgia were significantly more frequent in the patient group, but otherwise adverse-event rate and type did not differ between the groups.

The JDM study examined responses to the H1N1/09 vaccine of 30 JDM patients compared with 81 age-matched controls [24•]. Serological assessment of vaccine response was again conducted 21 days after administration, as were clinical and laboratory assessments of JDM activity. Compared with controls, patients had lower rates of seroconversion (86.7 vs. 97.5 %, $p=0.044$) but similar rates of seroprotection and factor increase in antibody titres. As in the JIA and jSLE studies, despite the observed differences from the control-group responses, the patient-group responses met EMEA and FDA criteria for adequate vaccine response. Factors associated with a lower seroconversion rate in univariate analyses included chronic disease course and immunosuppression with high-dose steroids (>20 mg day^{-1}) or combination therapy with steroids, methotrexate, and cyclosporin. No effects on disease activity were noted and adverse events were regarded as mild and occurred with equal frequency in the patient and control groups.

Taken together, these recent studies suggest that monovalent pandemic adjuvant-free influenza A H1N1/2009 immunisation for children with JIA, jSLE, or JDM, on a range of immunosuppressive agents, is effective and does not seem to cause instability of the underlying disease. Consideration might be given to the use of two doses of vaccine for children at risk of lower response rates, for example those with polyarticular JIA, active jSLE, or JDM who have chronically active disease or are on high-dose steroids or combination immunosuppressive therapy. It is a routine recommendation in many countries that all children <9 years of age should have two doses of seasonal influenza vaccine (>28 days apart) in the first year of administration [25]. The use of two doses of non-adjuvanted influenza A H1N1/2009 for children aged >9 years with PRD has recently been revealed to be safe and immunogenic [26].

Human Papillomavirus Vaccine

Data regarding the safety and efficacy of HPV vaccination for patients with PRD are currently scarce [19]. Interim safety data from use of the quadrivalent HPV vaccine (HPV types 6, 11, 16, and 18) for 22 females aged 9–26 years indicated an acceptable safety profile; however, immunogenicity data was not reported [27]. Bivalent HPV vaccine (HPV types 16 and 18) was safe, immunogenic, and not associated with disease flares for 68 girls with JIA up to 12 months after completion of vaccination [28••]. A smaller study, from the same group, of the bivalent HPV vaccine for six patients with JDM and six with pSLE also suggested overall good immunogenicity [29••]. In both studies, trends toward lower antibody responses were observed in the patient groups compared with healthy controls.

We conducted a study at our centre in which in the post-vaccination serostatus of girls with a variety of PRDs, who had been administered the quadrivalent HPV vaccine as part of a national HPV vaccination program, was compared with historical data from healthy controls. Samples for serological assay were obtained opportunistically at the time of blood collection for monitoring of the participants' underlying

Table 3 Diagnoses and degree of immunosuppression of 38 girls with paediatric rheumatic diseases in whom serostatus after HPV vaccination was assessed (RCH, Melbourne)

Diagnosis	No.	Immunosuppression level[a] (no.)		
		0	1	2
Juvenile idiopathic arthritis (JIA)	28	3	10	15
Systemic lupus erythematosus	6	0	5	1
Juvenile dermatomyositis	2	0	0	2
Scleroderma	1	0	1	0
Sjogren's disease	1	0	1	0
TOTAL	38	3	17	18

[a] Level 0, no therapy or NSAIDs only; level 1, single DMARDs or low-dose corticosteroids; level 2, high dose corticosteroids (>2.0 mg kg^{-1} day^{-1}) or biological agents or combination of DMARD and corticosteroid or combination of DMARDs

disease or its therapy, with all participants >1 month post their final 4vHPV vaccine dose.

Thirty-eight females with a median age of 14.5 years (range 11.8–24.7 years) were enrolled. The most common diagnosis was JIA (Table 3). Therapy at the time of vaccination was graded according to the probable level of suppression of immune response (Table 3). Samples were collected at a median of 1.4 months (0.9–23.1 months) after the third dose of HPV vaccine. Although there was a trend for antibody levels to be lower in patients compared with historical controls, the differences were not statistically significant (Fig. 1). When post-immunisation antibody titres of the four vaccine serotypes were examined by therapy level, there was a trend toward reduced titres in the most immunosuppressed group (Level 2) for three of the four serotypes (6, 11, and 16). However, between-group differences were not significant.

Regarding vaccine safety in our study, one of the 38 subjects reported a disease flare in association with immunisation. This was a 15-year-old patient with polyarticular JIA being treated with etanercept and methotrexate, who had active arthritis at the time of the immunisation course. Two days after the final dose of vaccine she experienced a significant flare of arthritis in her left hip. This lasted for six weeks and improved with physiotherapy without changes to her medication regimen. No other significant adverse events were reported by the subjects, their treating rheumatologists, or their parents.

Our data suggest that the quadrivalent HPV vaccine is associated with high rates of post-immunisation seroprotective antibodies in children with PRDs on a range of immunosuppressive therapy, and has an acceptable safety profile. More detailed studies, with larger numbers of patients and both baseline and post-immunisation antibody assays, will be required to definitively determine the effect of immunosuppression on serological response to quadrivalent HPV immunisation and fold-changes in HPV serotype antibodies after HPV immunisation for this patient group. Because there is currently no recognized seroprotective cut-off for the HPV vaccine antibody response, long-term surveillance for clinical disease will be required to determine efficacy for this population.

Conclusions

Increasing awareness of the importance of vaccination for children with PRDs has motivated a concerted effort in recent years to collate what is known about the safety and efficacy of vaccines for this patient group, and has given impetus to ongoing research in this field. Available data are reassuring with regard to concerns surrounding administration of vaccines to this population; both non-live and live-attenuated vaccines are safe and have good short-term immunogenicity for patients with PRD, including those on standard-dose non-biological immunosuppressive therapy. More data is required

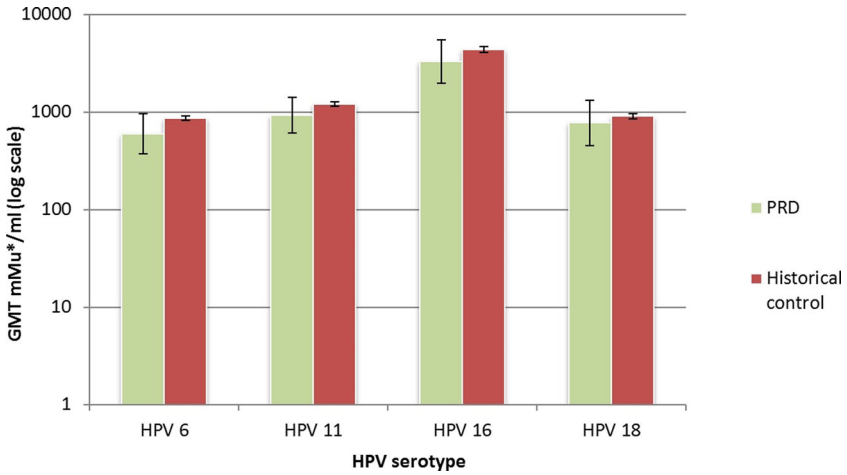

Fig. 1 Post-immunisation antibody titres to HPV vaccine serotypes of 38 girls with paediatric rheumatic disease (PRD) compared with historical healthy controls. *GMT mMU*, geometric mean titre milli Merck units

regarding new (e.g. HPV) and travel vaccines. However, the consistent finding of lower antibody responses to vaccine antigens for PRD patients compared with healthy controls, across a range of PRDs and for different vaccines, and recent findings suggesting reduced longevity of vaccine-induced immunity may have implications regarding the need to monitor immunity to vaccine-preventable disease and the administration of booster vaccine doses to PRD patients.

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Compliance with Ethics Guidelines

Conflict of Interest Dr Akikusa has no conflicts of interest to declare. Dr Crawford reports non-financial support from Merck during the conduct of the HPV study; grants from BioCSL, other from Pfizer, outside the submitted work.

Human and Animal Rights and Informed Consent This article contains information from a study involving humans performed by the authors which was approved by the local human research ethics committee. This article does not contain any studies with animal subjects performed by any of the authors.

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