Vaccination coverage in children with rheumatic diseases

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Abstract

Objective

To assess vaccination status in a cohort of children with rheumatic diseases followed at the University Children's Hospital Ljubljana and to evaluate the most common reasons for vaccination dropout.

Methods

Patients with rheumatic diseases who were evaluated at the rheumatology outpatient clinic between January 2015 and January 2017 received a questionnaire about their vaccination status and reasons for potential vaccination dropout. Vaccination coverage for individual vaccines was determined at 5, 10, 18 years and at the time of their last clinic visit.

Results

Data were received from 187 out of 424 enrolled patients (44.1%). Majority of included patients had juvenile idiopathic arthritis (n=165), followed by childhood-onset systemic lupus erythematosus (n=6), juvenile dermatomyositis (n=5), mixed connective tissue disease (n=3), chronic recurrent multifocal osteomyelitis, juvenile systemic sclerosis, Takayasu's arteritis (n=2 each), granulomatous polyangiitis and fibromyalgia (n=1 each). Vaccination coverage was complete in 91.9%, 70.3%, 66.7% and 64.7% of patients at 5, 10, 18 years and at their last clinic visit, respectively. Most commonly omitted vaccines were hepatitis B and second dose of measles, mumps and rubella vaccine. Most common additional vaccine was against rotavirus. Most common reason for vaccination dropout was suggestion of the treating rheumatologist.

Conclusion

Thirty-five percent of our patients remain incompletely vaccinated and thus susceptible to vaccine-preventable diseases. Physicians play a crucial role in the decision to vaccinate.

Key words

vaccination, paediatric rheumatic diseases, immunocompromised

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Introduction

Infections remain among the leading causes of morbidity and mortality in children with paediatric rheumatic diseases (PRD) despite significant progress in diagnosis and treatment that has reduced complications and improved survival in these patients (1). Children with PRD are at increased risk for more frequent and severe infections due to immune dysfunction associated with immune-modulating therapy as well as underlying inflammatory and autoimmune disease process (1-4). The rate of serious bacterial infections in children with juvenile idiopathic arthritis (JIA), the most common rheumatic disease in childhood, has been estimated to be two-fold higher than in children without JIA, independent of immunosuppressive therapy (5). Furthermore, children with JIA were found to have an increased rate of opportunistic infections (6). Many of these infections are vaccine-preventable so vaccinations are even more important in these patients compared to healthy population, to achieve the highest possible protection.

Despite growing evidence for vaccine safety and efficacy in children with PRD some questions and concerns remain, especially regarding vaccination with live-attenuated vaccines in immunocompromised patients. Fear of infection with live-attenuated virus is the major concern, so currently vaccination with live-attenuated vaccines in patients treated with high-dose immunosuppressive therapy is not recommended. Immune response after vaccinations with non-live and live-attenuated vaccines may be diminished and at this point long term protection after vaccination in these patients is in question. Furthermore, there is a theoretical possibility of disease exacerbation after vaccination as well as concern of triggering autoimmune reactions in patients with established autoimmune diseases (3, 4). This might cause delay or refusal of vaccines by parents and physicians.

Few data are available on actual vaccination coverage in children with PRD. Two studies published so far reported suboptimal immunisation rates in these patients (7, 8).

The aim of this study was to determine the percentage of patients with PRD with a full vaccination status according to the Slovenian National Immunisation Programme, assess coverage rates for individual mandatory and recommended vaccines and evaluate the most common reasons for vaccination dropout.

Materials and methods

The study design was a retrospective cohort study. All patients with rheumatic diseases who visited outpatient rheumatology department at University Children's Hospital (UCH) Ljubljana between 1st January 2015 and 15th January 2017 were invited to participate in the study. Patients with the following diagnoses according to the published classification criteria were invited: JIA, childhood-onset systemic lupus erythematosus (cSLE), juvenile dermatomyositis (JDM), juvenile systemic sclerosis (jScl), mixed connective tissue disease (MCTD), chronic recurrent multifocal osteomyelitis (CRMO), fibromyalgia and primary systemic vasculitis (excluding Kawasaki disease and IgA vasculitis due to their mostly self-limiting course).

Potential candidates were identified by reviewing electronic medical records at UCH Ljubljana, using the applicable International Classification of Disease, Tenth Revision (ICD-10) codes. A written invitation to participate in the study was sent to the identified candidates. Parents or guardians were asked to provide the vaccination records in form of the vaccination booklet and to complete a semi-structured questionnaire about reasons for potential vaccination dropout.

Patients' demographic data, ICD-10 diagnosis, International League of Associations for Rheumatology (ILAR) disease subtype and type of therapy were obtained from the hospital electronic medical records.

Vaccination schedules for mandatory and recommended vaccines for each birth cohort were obtained from applicable versions of the national immunisation programme. In Slovenia, mandatory vaccinations include tetanus, diphtheria, polio (inactivated polio

Table I. Patient characteristics.

Variable		Value
Total number of patients		187
Number of females (%)		128 (68.5)
Median age (range) in years		12.1 (1.5–22.9)
Median age at diagnosis (range) in years		6 (0.7–16.9)
Therapy (%)	NSAIDs	87.6
	corticosteroids – intraarticular	61.3
	corticosteroids – systemic*	52.2
	methotrexate	57.5
	other non-biological DMARDs ¥	19.4
	biological therapy	32.6

NSAIDs: non-steroidal anti-inflammatory drugs; DMARDs: disease-modifying anti-rheumatic drugs. *Including bridging therapy. ¥Including azathioprine, cyclophosphamide, cyclosporine, hydroxychloroquine, mycophenolate mofetil, leflunomide, sulfasalazine and tacrolimus.

vaccine, IPV), pertussis, Haemophilus influenzae type b (Hib), measles, mumps, rubella (MMR) and hepatitis B vaccines. Vaccination against tick-borne encephalitis (TBE), which is an endemic disease in Slovenia, is mandatory for pupils and students who are exposed to infection with TBE virus during training and recommended for all other persons over 1 year of age who reside or plan activities in endemic areas. All other vaccinations including human papilloma virus, influenza, pneumococcus, rotavirus and varicella vaccination are recommended. Vaccination coverage against tuberculosis, which had been mandatory in Slovenia for all new-borns until 2004, was not evaluated in our study (9). We created cohorts of included patients aged 5, 10 and 18 years regardless of their date of birth. Descriptive statistics were used to analyse the proportion of patients with complete vaccination status for mandatory vaccines at 5, 10, 18 years and at the time of their last clinic visit and to determine coverage rates for individual mandatory and recommended vaccines at these times.

Univariate analyses for complete vaccination coverage with mandatory vaccines were performed for gender, age at diagnosis and type of therapy (non-steroidal anti-inflammatory drugs (NSAIDs) and/or intraarticular corticosteroids, methotrexate and/or other non-biological disease-modifying anti-rheumatic drugs (DMARDs), biological therapy) for all included patients and for disease subtype for patients with JIA. Qualitative variables were evaluated using a two-tailed Pearson's chi-square test or a two-tailed Fisher's exact test as appropriate and quantitative variables using a two-tailed Mann-Whitney U-test. Analyses were conducted using SPSS for Windows (v. 22.0, SPSS Inc., Chicago, IL, USA). Level of significance was set at $p<0.05$. The study was approved by the Slovenian National Medical Ethics Committee. Patients whose parents or guardians provided their complete vaccination records and signed the informed consent form were included in the study.

Results

Data were received from 187 out of 424 invited patients (44.1%). Patient characteristics are presented in Table I. Majority of included patients had JIA (n=165, 88.2%). The most common JIA subtype was oligoarticular JIA (n=97, 58.8% of JIA), followed by polyarticular JIA (n=35, 21.2%), systemic onset JIA (n=12, 7.3%), enthesitis-related arthritis (n=10, 6.1%), psoriatic arthritis (n=8, 4.8%) and undifferentiated arthritis (n=3, 1.8%). Other diagnoses included cSLE (n=6), JDM (n=5), MCTD (n=3), CRMO, jScl, Takayasu's arteritis (n=2 each), granulomatous polyangiitis (GPA) and fibromyalgia (n=1 each).

Vaccination status was complete in 91.9%, 70.3%, 66.7% and 64.7% of patients at 5, 10, 18 years and at the time of their last clinic visit, respectively. Coverage rates for individual mandatory and recommended vaccines are presented in Table II. The most commonly omitted vaccine was the third dose of hepatitis B vaccine in 40 out of 162 eligible patients (24.7%), followed by the second dose of MMR vaccine in 34 out of 164 eligible patients (20.7%). One hundred and eighty-four (98.4%) patients received the first dose of MMR vaccine and 130 out of 164 eligible patients (79.3%) received the first dose of hepatitis B vaccine.

Patients with complete vaccination status were older at the time of diagnosis than patients with incomplete vaccination status (median = 7.8 years and median = 4.1 years, respectively; $p=0.001$). Patients who were at least 6 years old at the time of diagnosis were 2.75 times [1.47–5.12] more likely to be up to date with mandatory vaccinations than patients who were diagnosed younger. Patients who never received systemic immunosuppressive therapy were 2.97 times [1.2–7.07] more likely to be up to date with their mandatory vaccinations than patients who were receiving methotrexate and/or other non-biological DMARDs at any time and 6.24 times [2.58–15.33] more likely compared to patients who were receiving biological therapy at any time. Among patients receiving non-biological DMARDs, addition of systemic corticosteroid therapy did not significantly impact the vaccination status ($p=0.313$). Vaccination coverage was complete in 48 of 57 (84.2%) children who never received systemic immunosuppressive therapy, in 44 of 68 (64.7%) children who were receiving non-biological DMARDs and in 28 of 61 (45.9%) children who were receiving biological therapy at any time. Vaccination coverage for mandatory vaccines by type of therapy is presented in Table III. Gender and JIA subtype were not found to be significant factors for having a complete vaccination status ($p=0.146$ and $p=0.382$, respectively). Vaccination coverage for mandatory vaccines by diagnosis is presented in Table IV. Coverage rates for children with CRMO, jScl, Takayasu's arteritis, GPA and fibromyalgia were 100%.

Reasons for vaccination dropout were provided by 39 (20.9 %) patients or patients' families. The most common reason was suggestion of the treating rheumatologist (n=21), followed by an active disease (n=14), suggestion of the

Table II. Coverage rates for individual vaccines.

	At 5 years		At 10 years		At 18 years		Last clinic visit	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Polio	172	163 (94.8)	121	119 (98.3)	30	29 (96.7)	187	177 (94.7)
Haemophilus influenzae type b	169‖	160 (94.7)	118	116 (98.3)	27	26 (96.3)	184	174 (94.6)
Diphtheria	172	163 (94.8)	121	102 (84.3)	30	25 (83.3)	187	158 (84.5)
Tetanus	172	163 (94.8)	121	102 (84.3)	30	24 (80)	187	157 (84)
Pertussis	172	162 (94.2)	121	101 (83.5)	30	24 (80)	187	157 (84)
Measles, Mumps, Rubella	172	169 (98.3)	121	106 (87.6)	30	25 (83.3)	187	151 (80.7)
Hepatitis B	-		121	99 (81.8)	30	24 (80)	164	122 (74.4)
Rotavirus*	62¶	14 (22.6)	-		-		62	21 (33.9)
Human papillomavirus*	-		-		15	5 (33.3)	64·	20 (31.3)
Tick-borne encephalitis*	-		-		-		187	46 (24.6)¥
Varicella*	-		-		-		187	25 (13.4)¥
Influenza*	-		-		-		187	19 (10.2)¥
Pneumococcus*	-		-		-		187	8 (4.3)¥
Complete vaccination status	172	158 (91.9)	121	85 (70.3)	30	20 (66.7)	187	121 (64.7)

N: number of eligible children; n: number of vaccinated children.
*Recommended vaccines are not included in the complete vaccination status. ¥Received at least one dose of the vaccine. ·Includes only females who were over 11 years old when the vaccine became available and thus eligible for vaccination. ‖Children born after 1995 when Hib vaccine became part of the immunisation programme. ¶Children born after 2008 when the vaccine became available in Slovenia. Three children were also vaccinated against Hepatitis A virus and 1 child against meningococcus, rabies and S. typhi.

Table III. Vaccination coverage by type of therapy.

	NSAIDs and/or intraarticular CS only		MTX and/or other non-biological DMARDs		Biological therapy	
	N	n (%)	N	n (%)	N	n (%)
Polio	57	56 (98.2)	68	62 (91,2)	61	58 (95.1)
Haemophilus influenzae type b	57	56 (98.2)	67	60 (89.6)	59	57 (96.6)
Diphtheria	57	53 (93)	68	59 (86.8)	61	45 (73.8)
Tetanus	57	52 (91.2)	68	59 (86.8)	61	45 (73.8)
Pertussis	57	53 (93)	68	58 (85.3)	61	45 (73.8)
MMR 1st dose	57	57 (100)	68	66 (97.1)	61	60 (98.4)
2nd dose	50	48 (96)	58	48 (82.8)	56	34 (60.7)
Hepatitis B	50	47 (94)	58	42 (72.4)	56	33 (58.9)
Complete vaccination status	57	48 (84.2)	68	44 (64.7)	61	28 (45.9)

N: number of eligible children; n: number of vaccinated children; CS: corticosteroids; NSAIDs: non-steroidal anti-inflammatory drugs; DMARDs: disease-modifying anti-rheumatic drugs; MMR: measles, mumps, rubella vaccine. 1 patient was receiving only systemic CS and was excluded from this evaluation.

primary paediatrician (n=11), fear of inducing flare of the disease (n=9), side effects after previous vaccinations and fear of side effects after vaccination (n=6 each). Other common reasons included frequent colds (n=3) and other concomitant illnesses (n=2).

Discussion

Vaccinations in patients with rheumatic diseases are of crucial importance, as they are more prone to infections than healthy population because of disease and immunosuppressive therapy. Some infections, such as measles or varicella, can be life threatening in immunocompromised patients.

Despite growing evidence for vaccine safety and efficacy in children with PRD the few published studies found suboptimal vaccination coverage in these patients. A Canadian study on 200 children with JIA reported complete vaccination status in 52%, 68% and 61% of patients at 2.5 years, 10.5 years and their last clinic visit, respectively (7). In a German study on 715 children with JIA one third of patients were incompletely vaccinated, most commonly per physicians' suggestion. Vaccination coverage was comparable to the general population in preschool children and lower in older children (24–79% for tetanus and diphtheria and 60–75% for MMR). MMR vaccination rate was lower in patients with systemic or polyarticular JIA compared to oligoarticular JIA and in patients on immunosuppressive therapy compared to patients without immunosuppressive therapy (8). At least one immunisation was withheld in 38% of 82 children with PRD from Canada, most commonly for active disease, followed by recommendation by healthcare provider (10). Vaccination coverage was incomplete in 43.5% of 207 children with PRD from Brazil, most commonly because of family or patient fear, followed by contraindication by the physician (11). Suboptimal vaccination rates have also been found in adults with rheumatoid arthritis (RA) (12).

Among our patients, more than one third remain incompletely vaccinated. Vaccination coverage for mandatory vaccines is comparable to the general

Table IV. Vaccination coverage by diagnosis.

Diagnosis		N	Complete vaccination coverage for mandatory vaccines n (%)
JIA	All subtypes	165	102 (61.8)
	Oligoarticular	97	62 (63.9)
	Polyarticuar	35	19 (54.3)
	Systemic onset	12	5 (41.7)
	Enthesitis-related	10	6 (60.0)
	Psoriatic	8	7 (87.5)
	Undifferentiated	3	3 (100.0)
cSLE		6	5 (83.3)
JDM		5	3 (60)
MCTD		3	3 (100)

JIA: juvenile idiopathic arthritis; cSLE: childhood onset systemic lupus erythematosus; JDM: juvenile dermatomyositis; MCTD: mixed connective tissue disease.

population at the age of 5 years but lower than in general population thereafter. Regarding the most commonly omitted vaccines, vaccination rates are lower than in general population for all three doses of hepatitis B vaccine, whereas coverage rate for MMR vaccine compares favourably with the general population for the first dose, but it is much lower for the second dose. The number of children with complete vaccination status in Slovenia is not known, data are available only for individual vaccines. In 2017, vaccination coverage for diphtheria, tetanus, pertussis, Hib and IPV was above 91% in all age groups. Ninety-three percent of children received the first dose of MMR vaccine at 12 months and 94.3% received the second dose at 5–6 years. For hepatitis B, 87.2% of children received all three doses at 5–7 years (13).

The most common recommended vaccine in our cohort is against rotavirus, which is given before the age of 6 months and thus before the onset of most PRD (14). Slovenia does not have varicella vaccination in the mandatory programme and there is high incidence of varicella infection, especially among preschool children (13, 15). Varicella vaccination coverage in our cohort is low, but with 13.4 % still higher than in general population. Only 10.2% of our cohort were vaccinated against influenza at least once and only 4.3% against pneumococcus despite recommendations, which include all children with immunosuppression (16, 17). Other studies reported varying, but higher vaccination rates – 24% and 60% for influenza and 15% and 86% for pneumococcal vaccine (7, 10, 11).

More than 20% decline in complete vaccination status between 5- and 10-year-olds in our cohort and both most commonly omitted vaccines, hepatitis B and second dose of MMR, scheduled at 5–7 years appear to correlate with median age at diagnosis, 6 years. Furthermore, children who are older at the time of diagnosis are more likely to be up to date with their vaccinations. It seems that most children receive scheduled vaccinations before disease onset and later disease process and therapy affect decision to vaccinate. Children who are treated with any systemic immunosuppressive therapy are less likely to be completely vaccinated. This was especially seen in patients on biological therapy, of whom only 45.9% are completely vaccinated, compared to 84.2% of children without systemic immunosuppressive treatment. Concomitant systemic CS therapy does not significantly impact the vaccination status, which is probably due to CS only having been used as a bridging therapy in majority of our patients. We were surprised to see that the risk for vaccination omission in our cohort is the same for live-attenuated and non-live vaccines, with the most commonly omitted vaccine being hepatitis B. Parents as well as doctors might choose to omit this vaccination due to perceived low risk of hepatitis B virus (HBV) infection in Slovenian children. However, many patients with PRD require long-term immunomodulatory therapy which may continue into adulthood and which also presents a risk for HBV reactivation. It was recently reported that screening for HBV infection and vaccination against HBV in adult patients are suboptimal despite the international consensus guidelines (12, 18). This underlines the importance of hepatitis B vaccination in childhood. Regarding low vaccination coverage for second dose of MMR vaccine in our cohort, it was somehow expected since administration of live-attenuated vaccines to patients with immunosuppression is still controversial and may lead to rheumatologists' reluctance towards vaccination in certain cases.

According to current recommendations by the European League Against Rheumatism (EULAR) from 2011 there is no contraindication for non-live vaccines in patients with PRD and they should be administered following national vaccination guidelines. Live-attenuated vaccines can be administered to patients with PRD unless they are on high-dose glucocorticoids or DMARDs or biological therapy. In these cases, live-attenuated booster vaccines can be considered on a case-to-case basis, regarding level of disease activity, degree of immunosuppression and associated risks as well as benefits of the vaccination, but more precise guidelines are not yet available (3). Studies included in the recommendations and in a more recent review reported no increase in adverse effects or disease activity after vaccination and no vaccine-induced infections after MMR booster vaccination in JIA patients, including 14 patients on biological therapy, or after VZV vaccination in JIA and cSLE patients (3, 4, 19-22).

Three recent studies on VZV vaccination in children with PRD, including 18 patients on biological therapy, reported no serious adverse effects or disease flares and no varicella infection after vaccination. However, in some patients immunity decreased over time and few of them later developed varicella infection (23-25). On the other hand, a recent international survey on 17 patients with autoinflammatory diseases (among them 7 patients with sJIA), who had received live-attenuated vaccine while on therapy with IL-1 or IL-6 blocking agents, reported on 3 sJIA patients who

experienced adverse effects after vaccination – a VZV infection after booster VZV vaccination, a pneumonia after booster MMR vaccination and a diarrhoea after oral polio vaccination. Seven patients, including 3 patients with sJIA, experienced mild disease flares after vaccination, 4 of which were associated with discontinuation of IL-1 blockade before vaccination (26).

Our study has some limitations such as low response rate and vaccination recording. Possible reasons for low response rate include retrospective nature of the study, contacting eligible patients via regular mail instead of in person and increasing parents' vaccine hesitancy in general (27). Given the suboptimal vaccination coverage in our cohort of less than half of all invited patients it is possible that vaccination coverage among all PRD patients would be even lower. Another limitation could be use of vaccination booklet as a source of vaccination data. In the future, a wide implementation of the national electronic immunisation registry would improve similar studies as well as clinical work. The leading reason for vaccination dropout in our cohort is suggestion of the treating rheumatologist. In other studies, it was not specified whether it was a primary care physician or a paediatric rheumatologist who advised against vaccination, but there is evidence that healthcare providers' attitudes towards vaccination are among the most important influences on the decision to vaccinate (8, 10, 11, 28). What is more, lack of physician recommendation was the most common reason for low vaccination coverage in adult patients with RA (12). Knowledge on vaccination in paediatric rheumatology is still expanding, and regular education of all involved in the care of PRD patients is of great importance. For example, it was shown that simple interventions, such as presentations for healthcare providers, creation of vaccination algorithms and vaccination reminders to providers can significantly improve pneumococcal vaccination rates in paediatric rheumatology patients (29). Furthermore, active surveillance of patients' vaccinations and good communication between paediatric rheumatologists, primary paediatricians who perform vaccinations, patients and parents are essential. Vaccination coverage in our patients with PRD is suboptimal and this also appears to be a shared problem. Among the most problematic vaccines in our cohort is the second dose of MMR vaccine. Given the current measles outbreaks, a booster MMR vaccination should be considered before the start of immunosuppressive therapy. Patients who are older at the time of diagnosis are more likely to have received all mandatory vaccinations, so it might be feasible to move the booster dose to an earlier age in countries where it is scheduled later. Since this is not always possible, booster vaccination can also be considered in stable disease and on low dose immunosuppressive therapy (3, 4, 30). We found the same risk for vaccination omission for live and non-live vaccines, as the most commonly omitted vaccine is hepatitis B vaccine. Even more worrisome, we found very low vaccination rates for pneumococcus and influenza, which are recommended in all PRD patients. The importance of these vaccinations should be actively presented to eligible patients and their guardians. In general, greater vigilance on vaccination status of PRD patients is necessary. Vaccination schedules can be tailored to individual patients, including antibody titre sampling, catch-up and booster vaccinations when needed.

References

1. CASTILLO RD, DE LA PENA W, MARZAN KA: Diagnosis and management of infectious complications of childhood rheumatic diseases. *Curr Rheumatol Rep* 2013; 15: 322.
2. HURD A, BEUKELMAN T: Infectious Complications in Juvenile Idiopathic Arthritis. *Curr Rheumatol Rep* 2013; 15: 327.
3. HEIJSTEK MW, OTT DE BRUIN LM, BIJL M *et al*.: EULAR recommendations for vaccination in paediatric patients with rheumatic diseases. *Ann Rheum Dis* 2011; 70: 1704-12.
4. GROOT N., HEIJSTEK MW, WULFFRAAT NM: Vaccinations in Paediatric Rheumatology: an Update on Current Developments. *Curr Rheumatol Rep* 2015; 17: 46.
5. BEUKELMAN T, XIE F, CHEN L *et al*.: Rates of hospitalized bacterial infection associated with juvenile idiopathic arthritis and its treatment. *Arthritis Rheum* 2012; 64: 2773-80.
6. BEUKELMAN T, XIE F, BADDLEY JW *et al*.: Incidence of selected opportunistic infections among children with juvenile idiopathic arthritis. *Arthritis Rheum* 2013; 65: 1384-9.
7. MORIN MP, QUACH C, FORTIN E, CHÉDEVILLE G: Vaccination coverage in children with juvenile idiopathic arthritis followed at a paediatric tertiary care centre. *Rheumatology* 2012; 51: 2046-50.
8. MINDEN K, NIEWERTH M, BORTE M, SINGENDONK W, HAAS JP.: Immunization in children and adolescents with rheumatic diseases [Impfungen bei rheumatischen Erkrankungen des Kindes- und Jugendalters]. *Z Rheumatol* 2007; 66: 111-20.
9. The Slovenian immunization programme for 2017. [internet] 2017 [cited 10 October 2018]. Available from: http://www.nijz.si/sites/www.nijz.si/files/uploaded/program_2017.pdf .
10. VAZHAPPILLY S, VANDERKOOI O, BENSELER S *et al*.: Immunization Status and Barriers in Childhood Rheumatic Diseases (abstract). American College of Rheumatology/ Association of Rheumatology Health Professionals Annual Meeting, 2014.
11. LIMA MELO JM, PILEGGI GC, MARTINS DE CARVALHO L, LEME FERRIANI VP: Immunization status of children with rheumatic diseases: can the pediatric rheumatologist help to improve? (abstract) Pediatric Rheumatology European Society Congress, 2010.
12. MERONI PL, ZAVAGLIA D, GIRMENIA C: Vaccinations in adults with rheumatoid arthritis in an era of new disease-modifying antirheumatic drugs. *Clin Exp Rheumatol* 2018; 36: 317-28.
13. Analysis of immunizations in Slovenia in 2017. National Institute of Public Health of the Republic of Slovenia. Centre for Infectious Diseases. Ljubljana, 2019.
14. SULLIVAN DB, CASSIDY JT, PETTY RE: Pathogenic implications of age of onset in juvenile rheumatoid arthritis. *Arthritis and rheumatism* 1975; 18: 251-5.
15. SOČAN M, BERGINC N, LAJOVIC J: Varicella susceptibility and transmission dynamics in Slovenia. *BMC Public Health* 2010; 10: 360.
16. GROHSKOPF LA, SOKOLOW LZ, BRODER KR *et al*.: Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices – United States, 2017–18 influenza season. *MMWR Recomm Rep* 2017; 66: 1-20.
17. NUORTI JP, WHITNEY CG; CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC): Prevention of pneumococcal disease among infants and children - use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine - recommendations of the Advisory Committee on immunization Practices (ACIP). *MMWR Recomm Rep* 2010; 59: 1-18.
18. IHDAYHID D, EDELMAN J, KEEN HI: Vaccination for hepatitis B virus in an Australian pre-biologic population with rheumatoid arthritis. *Clin Exp Rheumatol* 2019; 37: 164.
19. BARBOSA CM, TERRERI MT, ROSARIO PO, DE MORAES-PINTO MI, SILVA CA, HILARIO MO: Immune response and tolerability of varicella vaccine in children and adolescents with systemic lupus erythematosus previously exposed to varicella-zoster virus. *Clin Exp Rheumatol* 2012; 30: 791-8.
20. HEIJSTEK MW, KAMPHUIS S, ARMBRUST W *et al*.: Effects of the live attenuated mea-

sles-mumps-rubella booster vaccination on disease activity in patients with juvenile idiopathic arthritis: a randomized trial. *JAMA* 2013; 309: 2449-56.
21. PILEGGI GC, DE SOUZA CB, FERRIANI VP: Safety and immunogenicity of varicella vaccine in patients with juvenile rheumatic diseases receiving methotrexate and corticosteroids. *Arthritis Care Res* 2010; 62: 1034-9.
22. BORTE S, LIEBERT UG, BORTE M, SACK U: Efficacy of measles, mumps and rubella revaccination in children with juvenile idiopathic arthritis treated with methotrexate and etanercept. *Rheumatology* 2009; 48: 144-8.
23. TOPLAK N, AVČIN T: Long-term safety and efficacy of varicella vaccination in children with juvenile idiopathic arthritis treated with biologic therapy. *Vaccine* 2015; 33: 4056-9.
24. GROOT N, PILEGGI G, SANDOVAL CB *et al*.: Varicella vaccination elicits a humoral and cellular response in children with rheumatic diseases using immune suppressive treatment. *Vaccine* 2017; 35: 2818-22.
25. SPETH F, HINZE CH, ANDEL S, MERTENS T, HAAS JP: Varicella-zoster-virus vaccination in immunosuppressed children with rheumatic diseases using a pre-vaccination check list. *Pediatr Rheumatol Online J* 2018; 16: 15.
26. JYARATANAM J, TER HAAR NM, LACHMANN HJ *et al*.: The safety of live-attenuated vaccines in patients using IL-1 or IL-6 blockade: an international survey. *Pediatr Rheumatol Online J* 2018; 16: 19.
27. MEDICAL ADVISORY COMMITTEE OF THE IMMUNE DEFICIENCY FOUNDATION, SHEARER WT, FLEISHER TA, BUCKLEY RH *et al*.: Recommendations for live viral and bacterial vaccines in immunodeficient patients and their close-contacts. *J Allergy Clin immunol* 2014; 133: 961-6.
28. DOHERTY M, SCHMIDT-OTT R, SANTOS JI *et al*.: Vaccination of special populations: Protecting the vulnerable. *Vaccine* 2016; 34: 6681-90.
29. HARRIS G, MALETTA KI, REN B, OLSON JC: Improving pneumococcal vaccination in pediatric rheumatology patients. *Pediatrics* 2015; 136: 681-6.
30. SOUSA S, DUARTE AC, CORDEIRO I *et al*.: Efficacy and safety of vaccination in pediatric patients with systemic inflammatory rheumatic diseases: a systematic review of the literature. *Acta Reumatol Port* 2017; 42: 8-16.