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VACCINATION OF CHILDREN WITH RHEUMATIC DISEASES AGAINST COVID-19 AND INFLUENZA

CIJEPLJENJE DJECE S REUMATSKIM BOLESTIMA PROTIV COVID-19 I INFLUENCE

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Abstract

After the declaration of the pandemic of the disease caused by the coronavirus 19 (COVID-19), an increase in the hospitalization rate of sick children was recorded. Although the majority of children with rheumatic diseases did not have a severe form of COVID-19, with the exception of multisystem inflammatory syndrome in children (MIS-C), those who had other rheumatic diseases besides juvenile idiopathic arthritis were more likely to have serious outcomes. Therefore, the American College of Rheumatology (ACR) COVID-19 Vaccine Guidance Task Force and the Paediatric Rheumatology European Society (PReS) recommend vaccination against COVID-19 for children with autoimmune inflammatory rheumatic diseases. Studies have shown a good safety profile of the vaccine, with minimal or no side effects in most patients, and the most recent research has documented the high efficacy of the vaccine. Children and adolescents with rheumatic diseases have a high risk of serious complications due to influenza infection. Therefore, the European League Against Rheumatism (EULAR) and PReS strongly recommend the vaccination of children with inflammatory rheumatic diseases using the seasonal inactivated influenza vaccine, which is also safe and immunogenic.

Key words: vaccination, COVID-19, influenza, children, rheumatic diseases

Sažetak

Nakon proglašenja pandemije bolesti izazvane koronavirusom 19 (COVID-19) bilježi se povećanje stope hospitalizacije oboljele djece. Iako u većine djece s reumatskim bolestima nije bilo teškog oblika COVID-19, izuzevši multisistemski upalni sindrom kod djece (MIS-C), u onih koji su imali druge reumatološke bolesti osim juvenilnoga idiopatskog artritisa zabilježena je veća vjerojatnost ozbiljnih ishoda. Stoga Radna skupina za cijepljenje Američkoga reumatološkog društva (ACR) i Europsko pedijatrijsko reumatološko društvo (PReS) preporučuju cijepljenje protiv COVID-19 za djecu oboljelu od autoimunosnih upalnih reumatskih bolesti. Istraživanja su pokazala dobar sigurnosni profil cjepiva, s minimalnim nuspojavama ili bez njih u većine bolesnika, a najnovije istraživanje dokumentiralo je

visoku učinkovitost cjepiva. Djeca i adolescenti s reumatskim bolestima imaju velik rizik od ozbiljnih komplikacija uslijed infekcije gripom. Stoga Europska liga za borbu protiv reumatizma (EULAR) i PReS snažno preporučuju cijepljenje djece s upalnim reumatskim bolestima primjenom sezonskoga neživog cjepiva protiv gripe, a cjepivo je sigurno i imunogenično.

Ključne riječi: cijepljenje, COVID-19, influenca, djeca, reumatske bolesti

COVID-19

Introduction to COVID-19 in children

In November 2019, the first news about a severe respiratory infection caused by the new coronavirus (severe acute respiratory syndrome coronavirus-2, SARS-CoV-2) started to arrive from the Chinese city of Wuhan, and in March 2020, a pandemic of the disease caused by coronavirus 19 was declared. (COVID-19) (1). In the early stages of the pandemic, it seemed that the number of infected children was small, and children represented less than 2% of the total number of reported cases of the disease (2). Taking into account all factors, it is evident that such numbers were the result of a significant percentage of asymptomatic children and a low rate of testing in the pediatric population (3). With the progression of the pandemic, and especially with the appearance of the Omicron variant of SARS-CoV-2, the number of pediatric cases increased significantly, all the way up to 25% according to statistics from the United States of America (4).

Compared to adults, COVID-19 in the pediatric population is associated with milder symptoms and a lower risk of hospitalization and fatal outcome, and a large number of children are asymptomatic (5).

In April 2020, in Bergamo, Italy and England, a significant increase in the frequency and severity of Kawasaki disease was observed, i.e. the appearance of a hyperinflammatory syndrome similar to Kawasaki disease with features of toxic shock syndrome, associated with the COVID-19 disease (6). As the number of patients increased, the disease was soon named the Multisystem Inflammatory Syndrome in Children (MIS-C) (7). Table 1 contains the definitions of MIS-C (8).

The hospitalization rate of children with COVID-19 increased from 0.7% to 3.8% as the pandemic progressed, and the fatal outcome was recorded in about 0.01% of cases (4). Risk factors for severe disease in children younger than 2 years were chronic lung disease, neurological disorders, cardiovascular disease, preterm birth and airway anomalies, while in older children risk factors were nasogastric tube dependence, diabetes and obesity (9). The highest rates of hospitalization and severe illness were recorded in infants.

Characteristics of COVID-19 in children with rheumatic diseases

Research in the adult population of patients with rheumatic diseases showed an increased risk of hospi-

COVID-19

Uvod u COVID-19 u dječjoj dobi

U studenom 2019. godine iz kineskog su grada Wuhana počele pristizati prve vijesti o teškoj respiratornoj infekciji uzrokovanoj novim koronavirusom (engl. *severe acute respiratory syndrome coronavirus-2*, SARS-CoV-2), a u ožujku 2020. proglašena je pandemija bolesti izazvane koronavirusom 19 (COVID-19) (1). U ranim fazama pandemije činilo se da je broj inficirane djece bio malen te su djeca u ukupnom broju prijavljenih slučajeva bolesti bila zastupljena s manje od 2% (2). Po svemu sudeći takvi su brojevi bili posljedica znatnog postotka asimptomatske djece i niske stope testiranja u pedijatrijskoj populaciji (3). S napredovanjem pandemije, a osobito s pojavom varijante Omikron, broj pedijatrijskih slučajeva značajno je porastao, sve do 25% prema statističkim podatcima iz Sjedinjenih Američkih Država (4).

U usporedbi s odraslima, COVID-19 u dječjoj populaciji povezan je s blažim simptomima i manjim rizikom za hospitalizaciju i smrtni ishod, a velik je broj djece asimptomatski (5).

U travnju 2020. u Bergamu u Italiji i Engleskoj zamijećen je značajan porast učestalosti i težine Kawasakijeve bolesti odnosno pojava hiperinflamatornog sindroma sličnog Kawasakijevoj bolesti sa značajkama toksičnog šok sindroma, povezanog s bolesti COVID-19 (6). Kako se broj oboljelih povećavao, uskoro je bolest nazvana multisistemski upalni sindrom kod djece (engl. *multisystem inflammatory syndrome in children*, MIS-C) (7). U tablici 1 prikazane su definicije MIS-C-a (8).

Stopa hospitalizacije djece s COVID-19 porasla je s 0,7% do 3,8% s odmicanjem pandemije, a smrtni je ishod zabilježen u oko 0,01% (4). Čimbenici rizika za tešku bolest u djece mlađe od dvije godine bili su kronična bolest pluća, neurološki poremećaji, kardiovaskularne bolesti, nedonošenost i anomalije dišnih putova, dok su kod starije djece rizični čimbenici bili ovisnost o nazogastričnoj sondi, šećerna bolest i pretilost (9). Najviše stope hospitalizacije i teške bolesti zabilježene su u dojenčadi.

Obilježja COVID-19 u djece oboljele od reumatskih bolesti

Istraživanja u odrasloj populaciji oboljelih od reumatskih bolesti pokazala su povećani rizik za hospitalizaciju (46%) i smrtni ishod (9%) u oboljelih od

Table 1 Definition of multisystem infalammatory syndrome in children, MIS-C (modified according to reference no. 8)
Tablica 1. Definicija multisistemskog upalnog sindroma kod djece, MIS-C-a (prilagođeno prema referenciji 8)

Criteria / Kriteriji	RCPCH*	CDC	WHO**
Age / Dob	All children (regardless of age) / Sva djeca (bez obzira na dob)	<21 years / <21 godine	0–19 years / 0 – 19 godina
Fever /Vrućica	Persistent fever (38.5 °C or higher) / Perzistentna vrućica (38,5 °C ili viša)	Fever of 38.0 °C or more lasting for at least 24 hours *or* a subjective feeling of fever lasting for at least 24 hours / Vrućica 38,0°C ili više u trajanju od najmanje 24 sata *ili* subjektivni osjećaj vrućice u trajanju od najmanje 24 sata	Fever lasting at least 3 days / Vrućica u trajanju od najmanje 3 dana
Clinical symptoms / Klinički simptomi	Both criteria: 1. Dysfunction of one or more organs *and* 2. additional symptoms / Oba kriterija: 1. Poremećaj funkcije jednog ili više organa *i* 2. dodatni simptomi	Both criteria: 1. serious illness requiring hospital treatment *and* 2. involvement of 2 or more organ systems / Oba kriterija: 1. teška bolest koja zahtijeva bolničko liječenje *i* 2. zahvaćenost 2 ili više organskih sustava	At least 2 of the following: 1. rash, conjunctivitis and signs of inflammation of the skin and mucous membranes ; 2. hypotension and shock; 3. heart involvement; 4. coagulopathy; 5. acute gastrointestinal symptoms / Barem 2 od navedenog: 1. osip, konjunktivitis i znakovi upale kože i sluznica; 2. hipotenzija i šok; 3. zahvaćenost srca; 4. koagulopatija; 5. akutni gastrointestinalni simptomi
Markers of inflammation / Pokazatelji upale	All 3 listed: 1. neutrophilia *and* 2. elevated CRP *and* 3. lymphopenia / Sva 3 navedena: 1. neutrofilija *i* 2. povišen CRP *i* 3. limfopenija	Laboratory evidence of inflammation, including at least 1 of the following indicators: 1. elevated CRP; 2. accelerated ESR; 3. elevated fibrinogen; 4. elevated procalcitonin; 5. elevated D-dimers; 6. elevated ferritin; 7. elevated LDH; 8. elevated IL-6; 9. neutrophilia; 10. lymphopenia; 11. hypoalbuminemia / Laboratorijski dokaz upale, uključujući barem 1 od navedenih pokazatelja: 1. povišen CRP; 2. ubrzana SE; 3. povišen fibrinogen; 4. povišen prokalcitonin; 5. povišeni D-dimeri; 6. povišen feritin; 7. povišen LDH; 8. povišen IL-6; 9. neutrofilija; 10. limfopenija; 11. hipoalbuminemija	Elevated levels of inflammatory markers including any of the following: 1. ESR 2. CRP 3. procalcitonin / Povišene vrijednosti pokazatelja upale, uključujući bilo koji od navedenih: 1. SE 2. CRP 3. prokalcitonin
Association with SARS-CoV-2 / Povezanost sa SARS-CoV-2	Positive or negative PCR result / Pozitivan ili negativan nalaz PCR	Current or previous finding: 1. positive PCR test; 2. positive serology test; 3. positive antigen test *or* 4. contact with a person suffering from COVID-19 within the previous 4 weeks / Aktualni ili prethodni nalaz: 1. pozitivan PCR; 2. pozitivna serologija; 3. pozitivan antigenski test *ili* 4. kontakt s osobom oboljelom od COVID-19 unutar prethodna 4 tjedna	Evidence of COVID-19 in any of the following ways: 1. positive PCR test; 2. positive antigen test; 3. positive serology test *or;* 4. probable contact with a person suffering from COVID-19 / Dokaz COVID-19 na bilo koji od navedenih načina: 1. pozitivan PCR; 2. pozitivan antigenski test; 3. pozitivna serologija *ili* 4. vjerojatni kontakt s oboljelim od COVID-19
Exclusion criteria / Isključni kriteriji	Other infections / Druge infekcije	Confirmation of an alternative diagnosis / Potvrda alternativne dijagnoze	A clearly confirmed second microbiological cause of the disease / Jasno potvrđen drugi mikrobiološki uzročnik bolesti

MIS-C – Multisystem inflammatory syndrome in children / multisistemski upalni sindrom; RCPCH – Royal College of Paediatrics and Child Health / Kraljevski koledž za pedijatriju i zdravlje djece; CDC – Centers for Disease Control and Prevention / Centar za kontrolu i prevenciju bolesti; WHO – Word Health Organization / Svjetska zdravstvena organizacija; CRP – C-reactive protein / C-reaktivni protein; ESR/SE – erythrocyte sedimentation rate / sedimentacija eritrocita; LDH – lactate dehydrogenase / laktat dehidrogenaza; IL-6 – interleukin-6; PCR – polymerase chain reaction / lančana reakcija polimeraze; COVID-19 – Coronavirus disease 2019 / koronavirusna bolest 2019.
** In the definition of MIS-C according to the RCPHC, additional symptoms can be: abdominal pain, confusion, conjunctivitis, cough, diarrhea, headache, lymphadenopathy, mucosal changes, neck swelling, rash, breathing difficulties, sore throat, swelling of the hands and feet, syncope and vomiting. / U definiciji MIS-C-a prema RCPHC-u dodatni simptomi mogu biti: bol u trbuhu, smetenost, konjunktivitis, kašalj, proljev, glavobolja, limfadenopatija, promjene sluznica, oteklina vrata, osip, dišne tegobe, grlobolja, oteklina šaka i stopala, sinkopa i povraćanje.*
*** In the WHO definition, cardiac involvement is defined as myocardial dysfunction, pericarditis, valvulitis, or coronary artery disorders (including cardiac ultrasound findings or elevated troponin and/or N-terminal pro-B-type natriuretic peptide). / U definiciji prema SZO-u zahvaćenost srca definira se kao disfunkcija miokarda, perikarditis, valvulitis ili poremećaji koronarnih krvnih žila (uključujući nalaze ultrazvučnog pregleda srca ili povišene vrijednosti troponina i/ili N-terminalnog pro-B-tipa natriuretskog peptida).*

talization (46%) and fatal outcome (9%) in patients with systemic lupus erythematosus (SLE) and vasculitis (10–12). The main risk factors for hospitalization were a family history of cardiovascular disease, African American, Hispanic, or Asian descent, and a prednisone dose greater than 10 mg/day, while tumor necrosis factor alpha (TNF-alpha) inhibitors and/or synthetic disease-modifying drugs (disease-modifying antirheumatic drugs, DMARDs) had a protective effect.

According to data from three registries that included 607 pediatric patients and young patients (under 19 years of age) with rheumatic diseases from 25 countries who contracted COVID-19, the majority of patients, 62% of them, had juvenile idiopathic arthritis (JIA) (13). The data showed that the majority of patients with rheumatic diseases did not have a severe form of COVID-19, with the exception of patients with MIS-C. In the case of patients with MIS-C who contracted COVID-19, one in every 15 children and young people was hospitalized. However, patients who suffered from rheumatic diseases other than JIA (SLE, mixed connective tissue disease, vasculitis, or autoinflammatory diseases) were more likely to have severe outcomes, which was expected given the involvement of more organ systems and the need for more aggressive immunosuppressive therapy than the therapy administered to most patients with JIA. Obesity was proven to be a risk factor for the more severe form of COVID-19. Treatment with biological drugs, such as TNF-alpha inhibitors, was not proven to be associated with a more severe form of COVID-19 in children and young people with rheumatic diseases.

Vaccination of children against COVID-19

When it comes to the available vaccines against COVID-19 in children, the only one based on the messenger RNA (mRNA) that contains the coding sequence for a spike glycoprotein of the SARS-CoV-2 virus has been approved (4). It has been shown that this vaccine has a favorable safety profile, immunogenicity and short-term effectiveness in the prevention of COVID-19 in healthy individuals over 16 years of age (14) and in healthy adolescents aged 12 to 15 (15). On the basis of the aforementioned facts, the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have approved the use of vaccines for these age groups (16). Recently, the FDA (17) and the Centers for Disease Control and Prevention (18) have issued an authorization expanding the use of this vaccine in children aged 5 to 11 years.

Primary vaccination includes two doses in an interval of 21 days, although there is opinion that an interval of 8 weeks may be optimal for children 12 years of age and older, especially for males, because the small risk of myocarditis associated with the mRNA vaccine may be

sistemskog eritemskog lupusa (SLE) i vaskulitisa (10–12). Glavni rizični čimbenici za hospitalizaciju bili su anamneza kardiovaskularne bolesti, afro-američko, hispansko ili azijsko podrijetlo i doza prednizona veća od 10 mg/dan dok su inhibitori čimbenika tumorske nekroze alfa (TNF-alfa) i/ili sintetski lijekovi koji modificiraju tijek bolesti (engl. *disease-modifying antirheumatic drugs*, DMARD) imali protektivni učinak.

Prema podatcima iz triju registara koji su obuhvatili 607 pedijatrijskih bolesnika i mladih (mlađih od 19 godina) s reumatskim bolestima iz 25 zemalja koji su oboljeli od COVID-19, glavnina je bolesnika imala juvenilni idiopatski artritis (JIA), njih 62% (13). Podatci su pokazali kako u većine bolesnika s reumatskim bolestima nije bilo teškog oblika COVID-19 izuzevši MIS-C, pri čemu je hospitalizirano jedno na svakih 15 djece i mladih. Međutim, oni koji su imali druge reumatske bolesti osim JIA-e (SLE, mješovita bolest vezivnog tkiva, vaskulitis ili autoinflamatorne bolesti) imali su veću vjerojatnost ozbiljnih ishoda, što je bilo očekivano s obzirom na zahvaćenost većeg broja organskih sustava i potrebu za agresivnijom imunosupresivnom terapijom od većine bolesnika s JIA-om. Pretilost se pokazala kao rizični čimbenik za teži oblik COVID-19. Liječenje biološkim lijekovima, kao što su inhibitori TNF-alfa, nije se pokazalo povezanim s težim oblikom bolesti COVID-19 kod djece i mladih s reumatskim bolestima.

Cijepljenje djece protiv COVID-19

Od dostupnih cjepiva protiv COVID-19 u djece je odobreno jedino ono koje se osniva na glasničkoj RNA (mRNA) koja kodira za glikoprotein šiljka virusa SARS-CoV-2 (4). Pokazalo se da ovo cjepivo ima povoljan sigurnosni profil, imunogenost i kratkoročnu učinkovitost u prevenciji COVID-19 kod zdravih osoba starijih od 16 godina (14) i kod zdravih adolescenata u dobi od 12 do 15 godina (15), na temelju čega su Agencija za hranu i lijekove Sjedinjenih Američkih Država (engl. *United States Food and Drug Administration*, FDA) i Europska agencije za lijekove (engl. *European Medicines Agency*, EMA) odobrili primjenu cjepiva za ove dobne skupine (16). Nedavno su FDA (17) i Centar za kontrolu i prevenciju bolesti (engl. *Centers for Disease Control and Prevention*) (18) izdali prošireno odobrenje za primjenu u djece od 5 do 11 godina.

Primarno cijepljenje obuhvaća dvije doze odvojene 21 dan, premda postoje mišljenja kako bi interval od 8 tjedana mogao biti optimalan za djecu od 12 godina i stariju, posebno za osobe muškog spola, jer se mali rizik od miokarditisa povezan s mRNA cjepivom može smanjiti, a vršni odgovor protutijela i učinkovitost cjepiva mogu se povećati s intervalom duljim od četiri tjedna (4, 19). Imunokompromitirana djeca trebaju dobiti treću dozu 28 dana nakon druge doze (20).

reduced and the spike antibody response and vaccine efficacy may increase with an interval longer than 4 weeks (4, 19). Immunocompromised children should receive the third dose 28 days after the second dose (20). It is recommended that the booster dose is administered 5 months after the primary vaccination (21).

Overall, in children aged 5 to 11, the effectiveness of the vaccine was 90.7%, in those aged 12 to 15 it was over 95%, and in those aged 16 and older it was 95% (22–24).

Vaccine side effects are generally mild and most often consist of transient pain at the injection site, fever, fatigue, chills, and headache (14, 15, 22). Rare cases of myocarditis have been reported as a complication after vaccination. Myocarditis was more common in male adolescents and young adults, more often after the second dose of the vaccine at a median of 2 days after vaccination (23, 24). In most patients, 95% of them, the symptoms were mild and resolved quickly. Based on data from the Vaccine Adverse Event Reporting System (VAERS), the estimated rates of myocarditis were 70.7 per million doses for children aged 12 to 15, 105.9 per million doses for children aged 16 to 17, 52.43 per million doses for males aged 18, and 6.35 per million doses for females aged12 to 15, 10.98 per million doses for children aged 16 to 17 and 6.87 per million doses for children aged 18 (23) while the data for younger children is not known.

Vaccination against COVID-19 in children with rheumatic diseases

The American College of Rheumatology (ACR) COVID-19 Vaccine Guidance Task Force and the Paediatric Rheumatology European Society (PReS) recommended vaccination against COVID-19 for children with autoimmune inflammatory rheumatic diseases (25, 26). In adults suffering from rheumatic diseases who received the mRNA vaccine, seroconversion was achieved in 86% of cases, and side effects were mostly mild and transient (27), while no significant association was recorded between the vaccine against COVID-19 and the exacerbation of rheumatoid arthritis (28). However, the titer of antibodies to spike protein S1/S2 was significantly lower compared to healthy controls (27, 29).

A prospective, multicenter, international study of the safety and immunogenicity of mRNA vaccines in adolescents with rheumatic diseases, which included 91 patients, showed a good safety profile of the vaccine, with minimal or no side effects in 96.7% of patients (30). No negative impact of the vaccine on disease activity was observed, which remained stable after the second dose of vaccine. Seroconversion was achieved in 97.3% of cases, but, similar to adults, antibody titers to spike protein S1/S2 were significantly lower com-

Docjepljivanje se preporučuje pet mjeseci nakon završetka primarnog cijepljenja (21).

Sveukupno uzevši, u djece u dobi od 5 do 11 godina učinkovitost cjepiva iznosila je 90,7%, u onih u dobi od 12 do 15 godina iznosila je preko 95%, a u onih od 16 godina i starijih 95% (22–24).

Nuspojave cjepiva općenito su blage i najčešće se sastoje od prolazne boli na mjestu injekcije, vrućice, umora, zimice i glavobolje (14, 15, 22). Zabilježeni su rijetki slučajevi miokarditisa kao komplikacija nakon cijepljenja. Miokarditis je bio češći u muških adolescenata i mlađih odraslih, češće nakon druge doze s medijanom od dva dana nakon cijepljenja (23, 24). U većine bolesnika, njih 95%, simptomi su bili blagi i brzo su se povukli. Na temelju podataka iz sustava za prijavljivanje nuspojava cjepiva procijenjene stope miokarditisa iznosile su 70,7 na milijun doza za djecu od 12 do 15 godina, 105,9 na milijun doza u dobi od 16 do 17 godina, 52,43 na milijun doza u dobi od 18 godina za osobe muškog spola, a u osoba ženskog spola 6,35 na milijun doza u dobi od 12–15 godina, 10,98 na milijun doza u dobi od 16–17 godina te 6,87 na milijun doza u dobi od 18 godina (23), dok za mlađu djecu podatci nisu poznati.

Cijepljenje protiv COVID-19 u djece s reumatskim bolestima

Radna skupina za cijepljenje Američkoga reumatološkog društva (engl. *American College of Rheumatology*, ACR) i Europsko pedijatrijsko reumatološko društvo (engl. *Paediatric Rheumatology European Society*, PReS) preporučili su cijepljenje protiv COVID-19 za djecu oboljelu od autoimunosnih upalnih reumatskih bolesti (25, 26). U odraslih oboljelih od reumatskih bolesti koji su primili mRNA cjepivo serokonverzija je postignuta u 86%, a nuspojave su bile uglavnom blage i prolazne (27) pri čemu nije zabilježena značajna povezanost između cjepiva protiv COVID-19 i pogoršanja reumatoidnog artritisa (28). Međutim, visina titra protutijela na protein šiljka S1/S2 bila je značajno niža u usporedbi sa zdravim kontrolama (27, 29).

Prospektivno, multicentrično, međunarodno istraživanje sigurnosti i imunogeničnosti mRNA cjepiva u adolescenata s reumatskim bolestima, koje je obuhvatilo 91 bolesnika, pokazalo je dobar sigurnosni profil cjepiva, s minimalnim nuspojavama ili bez njih u 96,7% bolesnika (30). Nije primijećen negativan utjecaj cjepiva na aktivnost bolesti, koja je ostala stabilna nakon druge doze. Serokonverzija je postignuta u 97,3% slučajeva, ali su, slično kao i u odraslih, titrovi protutijela na protein šiljka S1/S2 bili značajno niži u usporedbi sa zdravim kontrolama. Međutim, još uvijek nije poznato na koji način titar protutijela na protein šiljka korelira s učinkovitosti cjepiva (31). Titrovi su bili najviši u bolesnika liječenih hidroksiklorokinom i

pared to healthy controls. However, it is still not known how the spike protein antibody titer correlates with vaccine efficacy (31). The titers were highest in patients treated with hydroxychloroquine and DMARDs in monotherapy, and lowest in those treated with mycophenolate mofetil.

The most recent study from Israel, which included 1639 children suffering from rheumatic diseases aged 12 to 18, who were vaccinated against COVID-19, documented the effectiveness of the vaccine at 95% after two doses, i.e., above 99% after the third dose (32). Treatment with immunomodulatory drugs did not affect the effectiveness of the vaccine. No COVID-19 infections were reported in adolescents treated with DMARDs or biological drugs who received two or three doses of the vaccine. Efficacy was 100% in patients treated with mycophenolate mofetil after two doses. The same study also showed that adolescents with rheumatic diseases have an increased risk of COVID-19 infection.

Vaccination against COVID-19 and multisystem inflammatory syndrome in children (MIS-C)

It is not known whether vaccination can induce or prevent MIS-C and whether natural infection that precedes vaccination or occurs at the time of vaccination plays a role in this (33). Studies have identified high levels of receptor-binding protein (RBD) antibodies in children with severe MIS-C. Both natural infection and vaccination with an mRNA vaccine have been shown to induce the formation of these antibodies (34).

Some studies have shown that vaccination against COVID-19 is associated with a reduced incidence of MIS-C, especially if 2 doses are administered. Thus, a study conducted in France from September to October 2021 revealed a significantly lower risk of MIS-C among vaccinated adolescents compared to non-vaccinated ones (35). In the study conducted by Zambrano et al., it was found that the protective effect of vaccination with two doses of mRNA vaccine on MIS-C was 91% (36). Despite reports of MIS-C occurring after vaccination, vaccination clearly reduces the overall number of MIS-C cases, possibly by preventing infection. These studies also indicate that vaccination is unlikely to cause the development of MIS-C.

INFLUENZA

Introduction to influenza in children

Flu (influenza) is an acute respiratory illness caused by the influenza A or B viruses, and less commonly by the influenza C viruses. The infection rate in children varies from year to year, ranging between 10 and 40 percent during a typical flu season (37). Influenza virus infections in children are associated with increased

DMARD-ovima u monoterapiji, a najniži u onih liječenih mikofenolat mofetilom.

Najnovije istraživanje iz Izraela koje je uključilo 1.639 djece oboljelih od reumatskih bolesti u dobi od 12 do 18 godina, a koji su cijepljeni protiv COVID-19, dokumentiralo je učinkovitost cjepiva od 95% nakon dvije doze odnosno iznad 99% nakon treće doze (32). Liječenje imunomodulatornim lijekovima nije utjecalo na učinkovitost cjepiva. Nisu zabilježene infekcije COVID-19 u adolescenata liječenih DMARD-ovim ili biološkim lijekovima koji su primili dvije ili tri doze cjepiva. Učinkovitost je iznosila 100% u bolesnika liječenih s mikofenolat mofetilom nakon dviju doza. Isto je istraživanje također pokazalo kako adolescenti s reumatskim bolestima imaju povećan rizik od infekcije COVID-19.

Cijepljenje protiv COVID-19 i multisistemski upalni sindrom kod djece (MIS-C)

Nije poznato može li cijepljenje potaknuti ili spriječiti MIS-C i ima li pritom ulogu prirodna infekcija koja prethodi cijepljenju ili se javlja u vrijeme cijepljenja (33). Istraživanja su identificirala visoke razine protutijela na protein koji veže receptor (RBD) u djece s teškim MIS-C-om. Pokazalo se da i prirodna infekcija i cijepljenje mRNA cjepivom izazivaju stvaranje tih protutijela (34).

Neka su istraživanja pokazala da je cijepljenje protiv COVID-19 povezano sa smanjenom učestalošću MIS-C-a, osobito ako se daju dvije doze. Tako je istraživanje provedeno u Francuskoj od rujna do listopada 2021. otkrilo značajno manji rizik od MIS-C-a među cijepljenim adolescentima u usporedbi s necijepljenima (35). Zambrano i suradnici našli su da zaštitni učinak cijepljenja dvjema dozama mRNA cjepiva na MIS-C iznosi 91% (36). Unatoč izvješćima o MIS-C nakon cijepljenja, cijepljenje jasno smanjuje ukupni broj slučajeva MIS-C,-a vjerojatno sprječavanjem infekcije. Ova istraživanja također ukazuju na malu vjerojatnost da će cijepljenje izazvati razvoj MIS-C-a.

INFLUENCA

Uvod u influencu u dječjoj dobi

Gripa je akutna respiratorna bolest koju uzrokuju virusi influence A ili B, a rjeđe virusi influence C. Stopa infekcije u djece varira iz godine u godinu, u rasponu između 10 i 40% tijekom tipične sezone influence (37). Infekcije virusom influence u djece povezane su s povećanom učestalošću posjeta liječniku, hospitalizacijama, korištenjem antibiotika, izostancima iz škole te s posla za roditelje. Mala djeca i ona s određenim zdravstvenim stanjima imaju povećan rizik od teške infekcije ili komplikacija te hospitalizacije. Stopa hospitalizacije zbog gripe veća je u djece mlađe od pet godina

frequency of visits to the doctor, hospitalizations, use of antibiotics, and absences from school (for children) and work (for parents). Small children and those with certain medical conditions have an increased risk of severe infection or complications and hospitalization. The rate of hospitalization due to influenza is higher in children under 5 than in older children. During the 2015–2016 to 2019–2020 flu season, hospitalization rates ranged from 41 to 93 per 100,000 population in children under 5 years of age and from 10 to 24 per 100,000 population in older children (38). Common complications of influenza include middle ear infection (otitis media), pneumonia, and exacerbation of chronic lung disease (eg, asthma). Secondary bacterial infection (pneumonia or bacteremia), most often caused by pneumococcus or staphylococcus, can occur in children with or without high-risk conditions.

Influenza in children with rheumatic diseases

Children and adolescents with rheumatic diseases, especially those receiving immunosuppressive drugs, have a high risk of serious complications due to influenza infection (39, 40), which is shown in more detail in Table 2 (41). Complications of infection in the upper respiratory tract often occur, and the use of TNF-alpha inhibitors increases the risk of infection (39, 40). According to research, pneumonia as a complication of influenza in patients with childhood-onset SLE caused one in 11 deaths in a 15-year study conducted in a pediatric intensive care unit (42).

Vaccination against influenza in children with rheumatic diseases

Vaccination is considered an effective preventive measure in reducing the risk of contracting influenza. Annual vaccination against influenza is recommended for all children from 6 months to 18 years and all patients with chronic diseases (43). The vaccine against influenza has been found to be safe and effective in healthy children. One dose of the vaccine is highly immunogenic in children aged 9 years and older, while two doses are required for the production of a protective antibody titer in younger children during the first vaccination (44).

The European Alliance of Associations for Rheumatology (EULAR) and PReS strongly recommend the vaccination of children with inflammatory rheumatic diseases using a seasonal inactivated influenza vaccine (45). The vaccine is well-tolerated and elicits a serological response associated with protection against infection. In children with autoimmune inflammatory rheumatic diseases, seroconversion rates were equal to healthy controls except in patients treated with high doses of glucocorticoids and patients with childhood-onset SLE (46). In patients treated with biological

nego u starije djece. Tijekom sezone gripe od 2015. – 2016. do 2019. – 2020. stope hospitalizacija kretale su se od 41 do 93 na 100.000 u djece mlađe od pet godina i od 10 do 24 na 100.000 u starije djece (38). Uobičajene komplikacije gripe uključuju upalu srednjeg uha, upalu pluća i egzacerbaciju kronične plućne bolesti (npr. astme). Sekundarna bakterijska infekcija (pneumonija ili bakterijemija), najčešće uzrokovana pneumokokom ili stafilokokom, može se pojaviti u djece s ili bez visokorizičnih stanja.

Influenca u djece s reumatskim bolestima

Djeca i adolescenti s reumatskim bolestima, osobito oni koji primaju imunosupresivne lijekove, imaju velik rizik od ozbiljnih komplikacija uslijed infekcije gripom (39, 40), što je podrobnije prikazano u tablici 2 (41). Često se javljaju komplikacije infekcije na gornjim dišnim putovima, a primjena inhibitora TNF-alfa povećava rizik od infekcije (39, 40). Pneumonija kao komplikacija influence u bolesnika sa SLE-om s početkom u dječjoj dobi uzrokovala je jedan na jedanaest smrtnih slučajeva u petnaestogodišnjem istraživanju u pedijatrijskoj jedinici intenzivnog liječenja (42).

Cijepljenje protiv influence u djece s reumatskim bolestima

Cijepljenje se smatra učinkovitom preventivnom mjerom u smanjenju rizika od obolijevanja od influence. Godišnje cijepljenje protiv gripe preporučuje se svoj djeci od šest mjeseci do osamnaest godina te svim bolesnicima s kroničnim bolestima (43). Utvrđeno je da je cjepivo protiv gripe sigurno i učinkovito u zdrave djece. Jedna doza cjepiva visoko je imunogena u djece u dobi od devet godina i starije, dok su za produkciju zaštitnog titra protutijela potrebne dvije doze u mlađe djece prilikom prvog cijepljenja (44).

Europska liga za borbu protiv reumatizma (engl. *European Alliance of Associations for Rheumatology*, EULAR) i PReS snažno preporučuju cijepljenje djece s upalnim reumatskim bolestima primjenom sezonskoga neživog cjepiva protiv gripe (45). Cjepivo se dobro podnosi i izaziva serološki odgovor koji je povezan sa zaštitom od infekcije. U djece s autoimunosnim upalnim reumatskim bolestima stope serokonverzije bile su jednake zdravim kontrolama osim u bolesnika koji su liječeni visokim dozama glukokortikoida i bolesnika sa SLE-om koji započinje u dječjoj dobi (46). U bolesnika liječenih biološkim lijekovima (inhibitorima TNF-alfa i interleukina (6) stope serokonverzije bile su usporedive sa zdravim kontrolama iako su u bolesnika liječenih inhibitorima TNF-alfa titrovi protutijela obično bili niži uz brži pad (47).

Učinkovitost cjepiva protiv influence u djece s reumatskim bolestima nije dovoljno istražena te su za

Table 2 Risk groups for the development of influenza complications (modified according to reference no. 41)
Tablica 2. Rizične skupine za razvoj komplikacija influence (prilagođeno prema referenciji 41)

Children under 5 years old, especially under 2 years old / Djeca mlađa od 5 godina, a posebno mlađa od 2 godine
Adults older than 65 years / Odrasli stariji od 65 godina
Pregnant women and postpartum women up to 2 weeks after delivery / Trudnice i babinjače do 2 tjedna nakon poroda
Residents of retirement homes and long-term care facilities / Štićenici domova za starije osobe i ustanova za dugotrajnu njegu
Black people, Latinos, American Indians, and Alaska Natives / Osobe crne rase, Latinoamerikanci, američki Indijanci i starosjedioci Aljaske
People with underlying diseases: • asthma • neurological and neurodevelopmental diseases (including disorders of the brain, spinal cord and peripheral nerves and muscle such as cerebral palsy, epilepsy, stroke, intellectual disability, moderate to severe developmental delay, muscular dystrophy and spinal cord injury) • chronic lung disease (e.g. chronic obstructive pulmonary disease, cystic fibrosis) • heart diseases (e.g. congenital heart defects, congestive heart failure, coronary artery disease) • hematological disorders (e.g. sickle cell anemia) • endocrinological disorders (e.g. diabetes) • kidney diseases • liver diseases • metabolic disorders (e.g. hereditary metabolic diseases and mitochondrial disorders) • weakened immune system due to diseases (e.g. HIV, AIDS, cancer) or drugs (e.g. chemotherapy or radiation therapy, chronic use of glucocorticoids) • children younger than 19 years who receive long-term therapy with acetylsalicylic acid • obese people (body mass index ≥40) / Osobe s podležećim bolestima: • astma • neurološke i neurorazvojne bolesti (uključujući poremećaje mozga, leđne moždine i perifernih živaca i mišića kao što su cerebralna paraliza, epilepsija, moždani udar, intelektualna onesposobljenost, umjereno do teško zaostajanje u razvoju, mišićna distrofija i ozljeda leđne moždine) • kronična bolest pluća (npr. kronična opstruktivna bolest pluća, cistična fibroza) • bolesti srca (npr. prirođene srčane greške, kongestivno zatajenje srca, bolest koronarnih arterija) • hematološki poremećaji (npr. srpasta anemija) • endokrinološki poremećaji (npr. šećerna bolest) • bubrežne bolesti • bolesti jetre • metabolički poremećaji (npr. nasljedne metaboličke bolesti i mitohondrijski poremećaji) • oslabljen imunološki sustav zbog bolesti (npr. HIV, AIDS, rak) ili lijekova (npr. kemoterapija ili terapija zračenjem, kronična primjena glukokortikoida) • djeca mlađa od 19 godina koja primaju dugotrajnu terapiju acetilsalicilnom kiselinom • pretile osobe (indeks tjelesne mase ≥40)

drugs (TNF-alpha and interleukin-6 inhibitors), seroconversion rates were comparable to healthy controls, although in patients treated with TNF-alpha inhibitors, antibody titers were usually lower with a faster decline (47).

The effectiveness of the influenza vaccine in children with rheumatic diseases has not been sufficiently investigated, and so far, only two studies have been conducted, according to which influenza was more common in the unvaccinated patients compared to the vaccinated patients (48).

The most common side effect of the vaccine is a local reaction with pain at the injection site, and fever may also occur, while serious side effects are rare (49).

Children with rheumatic diseases have a higher risk of influenza infection, and the vaccine is safe and immunogenic.

A multicenter cross-sectional study conducted in 9 countries (50), in which the Referral Center for Paedi-

sada provedena samo dva istraživanja prema kojima je influenca bila češća u necijepljenih u odnosu na cijepljene (48).

Najčešća nuspojava cjepiva jest lokalna reakcija s bolom na mjestu injekcije, a može se pojaviti i vrućica, dok su ozbiljne nuspojave rijetke (49).

Djeca s reumatskim bolestima imaju veći rizik od infekcije gripom, a cjepivo je sigurno i imunogenično.

Multicentrično presječno istraživanje u devet zemalja (50), u kojima je sudjelovao i Referentni centar za pedijatrijsku i adolescentnu reumatologiju Republike Hrvatske, o procjeni stope cijepljenja protiv gripe u djece s JIA-om i o utjecaju pandemije COVID-19 na odluku roditelja/skrbnika o cijepljenju djece protiv gripe pokazalo je kako je najveća stopa procijepljenosti protiv gripe u Grčkoj (79,3%), a najmanja u Turskoj (1,1%). Roditelji/skrbnici koji su zaposleni i koji imaju fakultetsko obrazovanje češće će cijepiti djecu protiv gripe u odnosu na nezaposlene i one sa završenom

Table 3 Comparison of European, American and Australian recommendations for the vaccination of children with rheumatic diseases against COVID-19 and influenza (according to reference no. 26, 51 and 52)

Tablica 3. Usporedba europskih, američkih i australskih preporuka za cijepljenje djece s reumatološkim bolestima protiv COVID-19 i influence (sastavljeno prema referencijama 26, 51 i 52)

Parameter / Parametar	Recommendations of the PReS / Preporuke PReS-a	CDC guidelines / Smjernice CDC-a	ATAGI recommendations / Preporuke ATAGI-ja
Specifying the disease category / Specificiranje kategorije bolesti	All children with rheumatic diseases who have low disease activity or are in remission, and who are treated with methotrexate and biological drugs / Sva djeca s reumatološkim bolestima koja imaju nisku aktivnost bolest ili su u remisiji, a koja se liječe metotreksatom i biološkim lijekovima	Immunocompromised (including those treated with glucocorticoids and drugs that can suppress the immune system) / Imunokompromitirani (uključujući one koji se liječe glukokortikoidima i lijekovima koji mogu suprimirati imunološki sustav)	Immunocompromised / Imunokompromitirani
Age group / Dobna skupina	from the age of 5 / od navršenih 5 godina	from the age of 6 months / od navršenih 6 mjeseci	from the age of 6 months / od navršenih 6 mjeseci
Vaccine specification / Specificiranje cjepiva	a vaccine based on messenger RNA / cjepivo koje se osniva na glasničkoj RNA	for children aged 6 months to 11 years: Moderna monovalent vaccine for children aged 12 to 17: Moderna monovalent vaccine, and as a booster dose use Pfizer-BioNTech bivalent vaccine OR for children aged 6 months to 12 years: Pfizer-BioNTech monovalent vaccine for children aged 12 to 17: Pfizer-BioNTech monovalent or bivalent vaccine OR for children 12 years and older: Novavax monovalent vaccine / za djecu od navršenih 6 mjeseci do 11 godina: monovalentno cjepivo Moderna za djecu od navršenih 12 godina do 17 godina: monovalentno cjepivo Moderna, a kao booster doza koristiti Pfizer-BioNTech dvovalentno cjepivo *ili* za djecu od navršenih 6 mjeseci do 12 godina: monovalentno cjepivo Pfizer-BioNTech za djecu od navršenih 12 godina do 17 godina: monovalentno ili dvovalentno cjepivo Pfizer-BioNTech *ili* za djecu od 12 godina i stariju: monovalentno cjepivo Novavax	pediatric formulation of the Moderna (Spikevax) vaccine for children aged 6 months to 4 years for children over 5 years of age, the Pfizer or Moderna vaccine / pedijatrijska formulacija cjepiva Moderna (Spikevax) za djecu od navršenih 6 mjeseci do 4 godine za djecu od navršenih 5 godina cjepivo Pfizer ili Moderna
Number of doses / Broj doza	it is recommended to receive 3 doses of the vaccine / preporučuje se primiti 3 doze cjepiva	it is recommended to receive 3 doses of the Moderna monovalent vaccine at the age of 6 months to 11 years, and for older people 3 doses of the Moderna vaccine and after that one booster dose of the Pfizer-BioNTech bivalent vaccine it is recommended to receive 3 doses of the Pfizer-BioNTech vaccine at the age of 6 months to 4 years, and for older people 3 doses of the Pfizer-BioNTech vaccine and then one booster dose / preporučuje se primiti 3 doze monovalentnog cjepiva Moderna u dobi od 6 mjeseci do 11 godina, a za starije 3 doze cjepiva Moderna i nakon toga jednu booster dozu Pfizer-BioNTech dvovalentnog cjepiva preporučuje se primiti 3 doze cjepiva Pfizer-BioNTech u dobi od 6 mjeseci do 4 godine, a za starije 3 doze cjepiva Pfizer-BioNTech i nakon toga jednu booster dozu	it is recommended to receive 2 doses, and those who are severely immunocompromised should receive 3 doses / preporučuje se primiti 2 doze, a oni koji su teško imunokompromitirani 3 doze

▶

Table 3 Continued
Tablica 3. Nastavak

Parameter / Parametar	Recommendations of the PReS / Preporuke PReS-a	CDC guidelines / Smjernice CDC-a	ATAGI recommendations / Preporuke ATAGI-ja
Recommendations in relation to MIS-C / Preporuke vezane uz MIS-C	after MIS-C, vaccination is recommended in the duration of 6 months after complete clinical recovery and with normal heart function, and in children who developed MIS-C after vaccination against COVID-19, it is recommended to stop further vaccination / nakon MIS-C-a preporučuje se cijepljenje 6 mjeseci nakon potpunog kliničkog oporavka i uz normalnu funkciju srca, a u djece koja su razvila MIS-C nakon cijepljenja protiv COVID-19 preporučuje se obustaviti daljnje cijepljenje	not specified / nije specificirano	not specified / nije specificirano
Recommendations in relation to influenza vaccination / Preporuke vezane uz cijepljenje protiv gripe	it is recommended to get vaccinated against influenza once a year, but not to do it at the same time as vaccination against COVID-19 (there should be a break in the duration of at least 2 weeks between vaccinations) / preporučuje se cijepljenje protiv gripe jednom godišnje ali ne u isto vrijeme kada i cijepljenje protiv COVID-19 (cjepiva trebaju biti odvojena najmanje 2 tjedna)	for children aged 6 months to 4 years, other vaccines should be administered with an interval of 7–14 days, and children aged 5 years and older can receive other vaccines at the same time as the vaccine against COVID-19 / za djecu od navršenih 6 mjeseci do 4 godine druga cjepiva trebaju biti primijenjena s razmakom od 7–14 dana, u djece od 5 godina i starije moguće je primiti ostala cjepiva istovremeno s cjepivom protiv COVID-19	it is possible to receive the influenza vaccine at the same time as the COVID-19 vaccine / moguće je primiti cjepivo protiv gripe u isto vrijeme kada i cjepivo protiv COVID-19

PReS – Paediatric Rheumatology European Society / Europsko pedijatrijsko reumatološko društvo; CDC – Centers for Disease Control and Prevention / Centar za kontrolu i prevenciju bolesti; ATAGI – Australian Technical Advisory Group on Immunisation; COVID-19 – Coronavirus disease 2019 / koronavirusna bolest 2019; MIS-C – Multisystem inflammatory syndrome in children / multisistemski upalni sindrom.

atric and Adolescent Rheumatology of the Republic of Croatia also participated, which presented the assessment of the influenza vaccination rate in children with JIA and the impact of the COVID-19 pandemic on the decision of parents/caregivers to vaccinate of children against influenza showed that the highest rate of vaccination against influenza was in Greece (79.3%), and the lowest rate was recorded in Turkey (1.1%). Parents/caregivers who are employed and who have completed tertiary education are more likely to vaccinate their children against influenza compared to the unemployed and those who have only completed primary school education. When it comes to the parents who decided against vaccination, 52% of them did not have the opportunity to discuss their decision with the doctor. In addition to that, the main reasons for them deciding against vaccination were the unawareness of the need for vaccination (36%), and 13% of subjects stated that the doctor advised them not to vaccinate the child against influenza. The majority of parents (67%) believe that getting information before vaccination could

samo osnovnom školom. Među roditeljima koji se nisu odlučili za cijepljenje njih 52% nije imalo mogućnost prodiskutirati o svojoj odluci s liječnikom, a glavni razlozi za necijepljenje bili su neznanje o postojanju potrebe za cijepljenjem (36%), dok je 13% ispitanika izjavilo da im je liječnik savjetovao da ne cijepe dijete protiv gripe. Najveći broj roditelja (67%) smatra da bi informacije prije cijepljenja mogle poboljšati procijepljenost. Oni koji su cijepili svoju djecu protiv gripe češće bi se odlučili cijepiti djecu protiv COVID-19.

ZAKLJUČNE PREPORUKE VEZANE UZ CIJEPLJENJE DJECE S REUMATOLOŠKIM BOLESTIMA PROTIV COVID-19 I INFLUENCE

U tablici 3 navedene su europske, američke i australske preporuke za cijepljenje djece s reumatološkim bolestima protiv COVID-19 i influence (26, 51, 52). Može se vidjeti kako se preporuke razlikuju ovisno o dobi u kojoj se savjetuje cijepljenje, vrsti cjepiva i broju doza. Cjepivo protiv COVID-19 preporučuje se imunokom-

improve the vaccination uptake. Those who vaccinated their children against influenza were more likely to choose to vaccinate their children against COVID-19.

FINAL RECOMMENDATIONS IN RELATION TO THE VACCINATION OF CHILDREN WITH RHEUMATIC DISEASES AGAINST COVID-19 AND INFLUENZA

Table 3 lists European, American and Australian recommendations for vaccination of children with rheumatic diseases against COVID-19 and influenza (26, 51, 52). It is evident that the recommendations differ depending on the age at which vaccination is recommended, the type of vaccine and the number of doses. The vaccine against COVID-19 is recommended for immunocompromised children and children with rheumatic diseases (depending on the recommendations) from the age of 6 months or later, and the influenza vaccination is recommended for all children after 6 months of age, especially those suffering from chronic diseases.

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promitiranoj djeci i djeci s reumatološkim bolestima, ovisno o preporukama, od navršenih šest mjeseci života ili kasnije, a cijepljenje protiv gripe svoj djeci nakon šest mjeseci života, a osobito onoj oboljeloj od kroničnih bolesti.

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