High incidence of multisystem inflammatory syndrome and other autoimmune diseases after SARS-CoV-2 infection compared to COVID-19 vaccination in children and adolescents in south central Europe

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Abstract

Objective

To estimate the incidence and describe the spectrum of inflammatory and autoimmune diseases linked to SARS-CoV-2 infection and COVID-19 vaccination in children from two neighbouring south central European countries.

Methods

We performed a multi-centre prospective cohort study of children under 18 years diagnosed with inflammatory/autoimmune diseases linked to SARS-CoV-2 infection or COVID-19 vaccination, who were admitted to the paediatric tertiary care hospitals in Slovenia and Friuli Venezia Giulia, Italy, from January 1, 2020, to December 31, 2021. Disease incidence was calculated based on laboratory-confirmed cases only.

Results

Inflammatory and autoimmune diseases linked to SARS-CoV-2 were diagnosed in 192 children (127 laboratory-confirmed), of whom 112 had multisystem inflammatory syndrome (MIS-C), followed by vasculitis, neurological and cardiac diseases. Calculated risk of MIS-C was 1 in 860 children after SARS-CoV-2 infection and cumulative incidence of MIS-C was 18.3/100,000 of all children. Fifteen children had severe COVID-19. Two patients with MIS-C and a patient with myositis presented after COVID-19 vaccination. All 3 had at presentation also a serologically proven recent SARS-CoV-2 infection. After MIS-C, nine patients were vaccinated against COVID-19 and 25 patients had a SARS-CoV-2 reinfection, without recurrence of MIS-C.

Conclusion

Autoimmune diseases following SARS-CoV-2 infection in children were 8.5 times as common as severe COVID-19. MIS-C was the most common manifestation and its incidence in this predominantly white population was higher than previously reported. MIS-C does not seem to recur after SARS-CoV-2 reinfection or COVID-19 vaccination. Autoimmune diseases were much more common after SARS-CoV-2 infection than after COVID-19 vaccination.

Key words

multisystem inflammatory syndrome in children, COVID-19, autoimmunity, epidemiology, vaccination

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes coronavirus disease-19 (COVID-19), which generally has a mild or even asymptomatic course in children (1-4). A subset of patients presents with a severe multisystem inflammation in the weeks following the acute SARS-CoV-2 infection, which has been termed multisystem inflammatory syndrome in children (MIS-C). MIS-C is characterised by fever, conjunctivitis, signs of muco-cutaneous inflammation, gastrointestinal symptoms, hypotension or shock, cardiac dysfunction, elevated inflammatory markers, and coagulopathy (4-6). While it shows a considerable clinical overlap with Kawasaki disease (KD), children with MIS-C are generally older, show a wider spectrum of symptoms and a different cardiac phenotype, with a predominant myocardial involvement in MIS-C, compared to coronary artery involvement in KD. Classic KD is more common in children of Asian descent and most cases of MIS-C have been reported from Europe and the USA, most commonly in children of African and Hispanic heritage (5, 7). For the diagnosis of MIS-C, evidence of present or recent SARS-CoV-2 infection or likely contact with a patient with COVID-19 is required (4). The estimated incidence varies from 0.2 to 11.4 per 100,000 persons younger than 21 years (8, 9).

Since the first cases of MIS-C were reported in Spring 2020, many other systemic and organ-specific inflammatory and autoimmune diseases have been increasingly recognised in patients following SARS-CoV-2 infection, with some resembling well-established autoimmune diseases and others presenting with a completely new phenotype that has not been observed before the COVID-19 pandemic (10-13). There is a complex interaction between SARS-CoV-2 and the immune system, which plays a dual role in COVID-19. It needs to contain the virus during the acute infection, but afterwards a dysregulated immune response with hyperinflammation, macrophage activation, breakage of immune tolerance and chronic inflammation and autoimmunity can occur (11). Some features tend to appear within the first two weeks of the acute SARS-CoV-2 infection and others in a late post-infectious stage and may develop even in patients with asymptomatic SARS-CoV-2 infection. The severity ranges from benign, self-limiting disorders such as chilblains, to systemic, life-threatening syndromes such as MIS-C, which require aggressive immunosuppressive and immunomodulatory treatment. The clinical phenotype seems to be influenced by age, sex, and ethnicity, with two of the more common manifestations, MIS-C and chilblains, predominantly affecting children and adolescents (10, 11).

COVID-19 vaccination has now become available to all persons 5 years of age and older. Current data show that COVID-19 vaccines are well-tolerated and safe (14). It has been postulated that SARS-CoV-2 can act as a trigger for autoimmunity and even though the pathophysiology of MIS-C and other autoimmune diseases following COVID-19 remains incompletely understood, it is thought to be a postinfectious complication associated with a dysregulated immune response to SARS-CoV-2 infection (15-17). Therefore, some questions and concerns remain about possible immune-related adverse events after exposure to any SARS-CoV-2-derived antigen (18).

Our understanding of SARS-CoV-2 and related manifestations is evolving. The aim of this study was to estimate the incidence and describe the spectrum of inflammatory and autoimmune diseases linked to SARS-CoV-2 infection and COVID-19 vaccination in children and adolescents from two neighbouring south central European countries and regions, Slovenia and Friuli Venezia Giulia (FVG), Italy.

Methods

We performed a multi-centre prospective cohort study of all children and adolescents (under 18 years) newly diagnosed with MIS-C or other inflammatory/autoimmune diseases linked to SARS-CoV-2 infection or with a serious adverse event (SAE) after COVID-19 vaccination, who were admitted to the paediatric tertiary care hospitals in Slovenia or FVG, Italy during the pe-

Table I. Epidemiological and patient data (n=192).

		Slovenia	FVG (Italy)	All
n of persons <18 years in the region*		374,210	171,822	546,032
n of confirmed COVID-19 cases in persons <18 years until December 31, 2021 (%)[¥]		65,438 (17)	20,573 (12)	86,011 (16)
n of inflammatory and autoimmune diseases	MIS-C	77	35	112
	Vasculitis	38	36	74
	Neurological	4	0	4
	Myocarditis/pericarditis	1	1	2
	All	120	72	192
Median (IQR) age at diagnosis in years	MIS-C	10 (6.3-14.4)	7.6 (4.6-11.1)	8.7 (5.5-13.9)
	Vasculitis	13.9 (11.2-16.3)	13.8 (12.3-14.8)	13.8 (11.7-15.6)
	Other	14.4 (10.0-5.3)	12.9	13.7 (10.7-15.1)
	All	11.0 (7.9-15.0)	11.7 (7.0-14.2)	11.9 (7.6-14.7)
Male (%)	MIS-C	40 (52)	18 (51)	58 (52)
	Vasculitis	12 (32)	7 (19)	19 (26)
	Other	3 (60)	1 (100)	4 (67)
	All	55 (46)	26 (36)	81 (42)

COVID-19: Coronavirus disease; FVG: Friuli Venezia Giulia region in Italy; IQR: interquartile range; MIS-C: multisystem inflammatory syndrome in children; n: number. *On Jan 1, 2021.

[¥]In FVG, Italy, confirmed COVID-19 cases were defined by positive SARS-CoV-2 PCR before January 14, 2021, and by positive SARS-CoV-2 PCR or SARS-CoV-2 rapid antigen test (RAT) thereafter. In Slovenia, confirmed COVID-19 cases were defined by positive SARS-CoV-2 PCR or SARS-CoV-2 RAT between December 21, 2020, and February 12, 2021, and by positive SARS-CoV-2 PCR at all other times.

riod from January 1, 2020, to December 31, 2021.

The participating centres included Children's Hospital, University Medical Centre Ljubljana (UMCL) and Division of Paediatrics, University Medical Centre Maribor (UMCM) from Slovenia, and Institute of Child and Maternal Health - IRCCS Burlo Garofolo, University of Trieste, Italy. These centres serve a combined population of around 3.3 million people, including 546,032 children and adolescents (Statistical Office of the Republic of Slovenia and Central Directorate for Health, Social Policies and Disabilities, FVG, Italy). Due to healthcare organisation in these regions, all children and adolescents with serious medical conditions after SARS-CoV-2 infection or COVID-19 vaccination were admitted at one of the participating centres.

All eligible patients were identified by the treating physicians and the data were prospectively entered in the hospital database. The numbers of children and adolescents with SARS-CoV-2 infection confirmed by PCR and/or rapid antigen testing (RAT), or after at least one dose of a COVID-19 vaccine until December 31, 2021, were obtained by the Slovenian National Institute of Public Health and the Central Directorate for Health, Social Policies and Disabilities, FVG, Italy.

MIS-C diagnosis was based on case definition by the United States Centres for Disease Control and Prevention (CDC) and the World Health Organisation (WHO). The case definition included individuals <18 years of age presenting with fever, laboratory evidence of inflammation with multisystem organ involvement and evidence of current or recent SARS-CoV-2 infection or likely exposure (3, 4). Other inflammatory and autoimmune diseases that have been described in association with SARS-CoV-2 infection were considered if there was no alternative more likely diagnosis. These included but were not limited to hemophagocytic syndromes, vasculitis, myositis, arthritis, chilblain lesions, erythema multiforme and other cutaneous manifestations, immune thrombocytopenic purpura, Guillain-Barré syndrome (GBS), autoimmune encephalitis, myocarditis, pericarditis, pancreatitis and long COVID (10, 19). Systemic or organ-specific inflammatory and autoimmune manifestations were reported as separate diseases if they did not develop as a part of clinical manifestations of MIS-C. Cases were classified as confirmed or probable based on the results of confirmatory viral and serological testing. Confirmed cases of diseases linked to SARS-CoV-2 infection were defined by laboratory evidence of present or recent SARS-CoV-2 infection, which included a positive PCR to SARS-CoV-2 within the 3 months prior to or at the time of clinical presentation, and/or positive IgA, IgM and/or IgG to SARS-CoV-2. Cases with a typical clinical presentation, but without laboratory evidence of SARS-CoV-2 infection (due to negative or unknown test results or lack of testing) were considered as probable. Only confirmed cases were considered for estimating the disease incidence. In patients who received COVID-19 vaccine before the onset of autoimmune manifestation, anti-nucleocapsid (anti-N) and anti-spike S1 receptor binding domain (anti-S) antibodies were evaluated. Anti-S antibodies are induced by SARS-CoV-2 infection or COVID-19 vaccination, whereas anti-N antibodies occur only after SARS-CoV-2 infection and are not induced by spike-based vaccines, which are currently the only type of COVID-19 vaccines available for clinical use (20-22). Therefore, all patients with anti-N positivity were considered to have had a recent SARS-CoV-2 infection in addition to COVID-19 vaccination.

Inflammatory and autoimmune diseases were considered early if they occurred within 2 weeks from the onset of COVID-19 symptoms and late if they occurred after that.

The European Medicines Agency definition of serious adverse events was used, which includes a requirement for inpatient hospitalisation or prolongation of existing hospitalisation (23). All medical events observed after COVID-19 vaccination which required a hospital admission were considered. Diagnosis of severe and critical COVID-19 was based on predefined criteria by the WHO (24).

Demographic and clinical data, information about the SARS-CoV-2 infection and COVID-19 vaccination before and/or after inflammatory or autoimmune disease, vaccine type, timing and number of doses were reviewed. Complete KD was defined based on the American Heart Association guidelines (25).

The study was approved by the Slovenian National Ethics Committee for Research in Medicine (approval no. 0120-536/2020/3) and by the Friuli Venezia Giulia Ethics Committee (approval no. CEUR-2021-Os-36). Informed consent was obtained by patients' parents or legal guardians.

This study was conducted as a part of the EU interregional Italy-Slovenia project CATTEDRA (Cross border cooperation for innovative diagnosis of rare diseases in paediatrics).

Results

Clinical spectrum of autoimmune diseases associated with SARS-CoV-2

During the study period from January 1, 2020, to December 31, 2021, 192 children and adolescents in Slovenia and FVG, Italy were diagnosed with inflammatory and autoimmune diseases linked to SARS-CoV-2.

Epidemiological and patient data are summarised in Table I. Median age at diagnosis was 11.9 years. The most common disease was MIS-C, which was diagnosed in 112 patients (UMCL 67, IRCCS 35, UMCM 10). Other diseases included vasculitis in 74 patients (UMCL 38, IRCCS 36), of whom the vast majority presented with chilblain-like lesions and one each with gastrointestinal and cutaneous vasculitis, recurrent urticaria, recurrent petechiae, exanthema of the face with periorbital swelling and necrotising stomatitis. The neurological cases included patients with a rare GBS variant with predominant cranial nerve involvement, peripheral facial palsy, autoimmune encephalitis and long COVID. One patient presented with acute myocarditis and one with acute pericarditis. Temporal distribution of inflammatory and autoimmune diseases linked to SARS-CoV-2 infection and COVID-19 vaccination is presented in Figure 1.

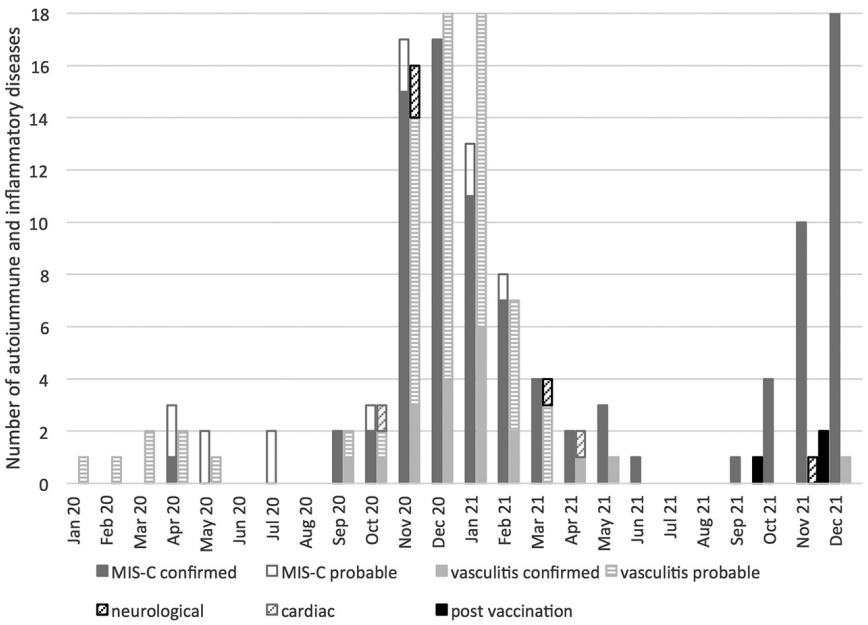

Fig. 1. Temporal distribution of inflammatory and autoimmune diseases linked to SARS-CoV-2 infection and COVID-19 vaccination by time of onset, Slovenia and Friuli Venezia Giulia, Italy, 2020-2021.
COVID-19: coronavirus disease; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; MIS-C: multisystem inflammatory syndrome in children.
Confirmed cases were defined by laboratory confirmed present or recent SARS-CoV-2 infection within 3 months prior to disease onset.

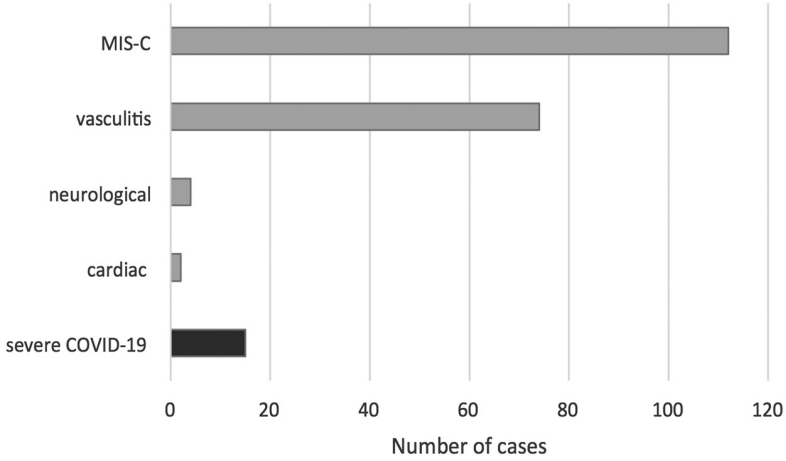

Fig. 2. Inflammatory and autoimmune diseases linked to SARS-CoV-2 and severe COVID-19 in children and adolescents, Slovenia and Friuli Venezia Giulia, Italy, 2020-2021.
COVID-19: coronavirus disease; MIS-C: multisystem inflammatory syndrome in children; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

Clinical and laboratory characteristics of patients with MIS-C are presented in Tables II and III. A complete KD phenotype was observed in 30% of patients with MIS-C, more commonly in children younger than 5 years of age.

At the time of diagnosis, patients with MIS-C were younger than patients with

Table II. Clinical characteristics of patients with MIS-C (n=112).

Days with fever, median (IQR)		5 (4–7)
Fulfilled criteria for Kawasaki disease (KD)*, n of KD/n (%)	<5 years of age	11/20 (55)
	≥5 years of age	23/92 (25)
n of organ systems involved, n (%)	2-3	24 (21)
	4-5	74 (66)
	≥6	14 (13)
Haematologic[¥], n (%)		109 (97)
Dermatologic and mucocutaneous•, n (%)		103 (92)
Gastrointestinal[‖], n (%)		97 (86)
Cardiovascular[¶], n (%)		84 (75)
Lymphadenopathy**, n (%)		58 (52)
Neurologic[$], n (%)		46 (41)
Respiratory[§], n (%)		37 (33)
Renal***, n (%)		7 (6)

MIS-C: multisystem inflammatory syndrome in children; n: number.
*Criteria for classic Kawasaki disease, according to the American Heart Association (25).
[¥] Haematologic: elevated D-dimer, thrombocytopenia, lymphopenia, hepato-/splenomegaly.
• Dermatologic and mucocutaneous: rash, conjunctival injection, mucocutaneous lesions.
[‖] Gastrointestinal: abdominal pain, vomiting, diarrhoea.
[¶] Cardiovascular: elevated troponin, myocarditis, cardiac dysfunction, coronary artery dilation or aneurysm, hypotension, pericardial effusion, mitral regurgitation.
** Lymphadenopathy: cervical lymphadenopathy >1.5 cm diameter, generalised lymphadenopathy, mesenterial lymphadenopathy.
[$] Neurologic: headache, encephalopathy.
[§] Respiratory: cough, dyspnoea, chest pain, pulmonary oedema, pneumonia, acute respiratory distress syndrome, pleural effusion.
***Renal: acute kidney injury.

Table III. Laboratory characteristics of patients with MIS-C (n=112).

Laboratory test	n	Median (IQR)
CRP, peak (mg/l)	112	167 (118-217)
D-dimer, peak (µg/l)	108	2585 (1507-5095)
Troponin, peak (ng/l)	99	89 (26-537)
BNP, peak (pg/ml)	102	2863 (1059-7216)
Ferritin, peak (µg/l)	104	435 (256-873)
Haemoglobin, nadir (g/dl)	112	10.9 (10.0-11.7)
Lymphocytes, nadir (cells/µl)	108	730 (475-1299)
Platelets, nadir (10^3 cells/µl)	112	155 (107-249)

IQR: interquartile range; MIS-C: multisystem inflammatory syndrome in children; n: number.

Table IV. Inflammatory and autoimmune manifestations linked to SARS-CoV-2 infection by age.

	0-6 years	6-12 years	12-18 years
MIS-C, n (%)	28 (25)	47 (42)	37 (33)
Vasculitis, n (%)	7 (10)	13 (17)	54 (73)
Neurologic, n (%)	0	1 (25)	3 (75)
Cardiac, n (%)	0	1 (50)	1 (50)

MIS-C: multisystem inflammatory syndrome in children; n: number; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

other inflammatory and autoimmune diseases. Age distribution of inflammatory and autoimmune diseases linked to SARS-CoV-2 infection is presented in Table IV. Half of the patients with MIS-C and 19 of 74 (26%) patients with vasculitis were male. All included patients were White.

Data required for estimation of time interval between SARS-CoV-2 infection and onset of inflammatory or autoimmune disease, including positive PCR test, documented close contact to a person with COVID-19 or COVID-like illness without laboratory confirmation, were available for 89 patients. Median (range) time from SARS-CoV-2 infection to onset of MIS-C was 31 days (IQR 26–39 days) and to onset of vasculitis 42 days (IQR 30–55 days). Early manifestations included two patients with MIS-C, a patient with autoimmune encephalitis and a patient with acute myocarditis.

A preceding symptomatic COVID-like illness within the 3 months prior to onset of inflammatory or autoimmune disease was present in 59 of 192 (31%) patients (38% of patients with MIS-C, 15% of patients with vasculitis and 83% of patients with neurological and cardiac manifestations). It was confirmed by PCR in 43 of 59 (73%) patients.

A positive molecular or antibody test for SARS-CoV-2 was found in 100 of 112 (89%) patients with MIS-C and 27 of 80 (34%) patients with other autoimmune diseases, including all neurological and cardiac manifestations. These 127 cases were considered confirmed. Sixty of 112 (54%) patients with MIS-C tested positive by serology only, 34 (30%) by both serology and PCR and 6 (5.4%) by PCR only, 3 had negative serology and were not tested by PCR and the remaining nine patients were not tested with either method. COVID-19 diagnostic testing is presented in Table V.

Epidemiology of autoimmune diseases associated with SARS-CoV-2

Until December 31, 2021, 86,011 cases of confirmed COVID-19 were documented among children and adolescents in Slovenia and FVG, Italy, which accounts for approximately 16% of the paediatric population. Among them, 192 (0.2%) were diagnosed with autoimmune diseases linked to SARS-CoV-2, of which 127 were considered confirmed. This suggests a risk of autoimmune diseases linked to SARS-CoV-2 of one in 677 children and adolescents after SARS-CoV-2 infection and one in 4300 of all children and adolescents. Calculated risk of MIS-C was one in 860 children and adolescents after SARS-CoV-2 infection and one in 5460 of all children and adolescents. Cumulative incidence of MIS-C since the start of the pandemic was 18.3/100,000 children and adolescents. In the same period, 15 children and

Table V. COVID-19 diagnostic testing.

		Slovenia	FVG (Italy)	All
Positive serology n/n tested (%)	MIS-C	74/76 (97)	20/23 (87)	94/99 (95)
	Vasculitis	19/37 (51)	1/1	20/38 (53)
	Neurological	3/4 (75)	-	3/4 (75)
	Cardiac	0/1 (0)	1/1	1/2 (50)
	All	96/118 (81)	22/25 (88)	118/143 (83)
Positive PCR* n/n tested (%)	MIS-C	31/77 (40)	9/9 (100)	40/86 (47)
	Vasculitis	5/20 (25)	2/21 (10)	7/41 (17)
	Neurological	3/4 (75)	-	3/4 (75)
	Cardiac	1/1 (100)	0/1 (0)	1/2 (50)
	All	39/101 (39)	11/21 (52)	50/133 (38)
Confirmed cases n (%)	MIS-C	77 (100)	23 (66)	100 (89)
	Other	23 (54)	4 (11)	27 (34)
	All	100 (83)	27 (38)	127 (66)

COVID-19: Coronavirus disease; FVG: Friuli Venezia Giulia region in Italy; MIS-C: multisystem inflammatory syndrome in children; n: number.
*Twelve patients with MIS-C had a positive PCR to SARS-CoV-2 at the disease onset, 8 of them had positive serology, 2 had negative serology and 2 were not tested. A patient with myocarditis and a patient with autoimmune encephalitis had a positive PCR to SARS-CoV-2 at the disease onset and negative serology. In all other cases, PCR test was positive during COVID-19 within 3 months prior to disease onset.

adolescents were hospitalised with severe COVID-19, three of whom had a critical illness. Thus, the calculated risk of severe COVID-19 was one in 5734 children and adolescents after SARS-CoV-2 infection and one in 36,402 of all children and adolescents (cumulative incidence 2.7/100,000 children and adolescents). Summary of all inflammatory and autoimmune diseases linked to SARS-CoV-2 and severe COVID-19 is presented in Figure 2.

Vaccination against COVID-19 and autoimmune diseases

Until December 31, 2021, 95,191 children and adolescents aged 5 to 18 years (46,733 in Slovenia and 48,458 in FVG, Italy) received at least one dose of COVID-19 vaccine, which accounts for 12%, 28% and 17% of children and adolescents in Slovenia, FVG and combined population from both regions, respectively.

Two 15-year-old boys received the second dose of Pfizer/BioNTech vaccine 6 and 27 days before MIS-C onset. They had no history of symptomatic COVID-19 illness or a positive PCR to SARS-CoV-2 prior to or at admission. A sixteen-year-old girl presented with acute myositis a few hours after the application of second dose of Pfizer/BioNTech vaccine. She had a history of COVID-19 11 months before symptom onset. All three patients had positive anti-N and anti-S antibodies, which confirms a prior subclinical SARS-CoV-2 infection in addition to serological response to COVID-19 vaccination. Nine patients were vaccinated against COVID-19 after MIS-C and one patient after peripheral facial palsy. One of them received one dose and all other received two doses of Pfizer/BioNTech vaccine, with a median (IQR) time from disease onset to vaccination of 8 months (range 6 to 16 months). None of them experienced a SAE or recurrent episode of inflammatory or autoimmune disease after vaccination.

Reinfection with SARS-CoV-2 and recurrence rate in patients with MIS-C

Twenty-five patients with MIS-C were reinfected with SARS-CoV-2 mean 8.8 months (range 1.2–16.5 months) after MIS-C. Twenty of them had a positive SARS-CoV-2 PCR test, 3 had a positive SARS-CoV-2 RAT and two had a documented increase in levels of SARS-CoV-2 antibodies. No patients had recurrence of clinical manifestations of MIS-C or other inflammatory/autoimmune diseases during the mean follow-up period of 6 months (range 2.3–9.7 months).

Discussion

We observed a high incidence of MIS-C and other autoimmune diseases linked to SARS-CoV-2 in children and adolescents from two neighbouring south central European countries and regions. From the onset of COVID-19 pandemic to December 31, 2021, 0.2% of children and adolescents with confirmed SARS-CoV-2 infection from Slovenia and FVG, Italy, presented with a diverse spectrum of inflammatory and autoimmune diseases linked to SARS-CoV-2. The most common was MIS-C with estimated risk of 1 in 860 children and adolescents after SARS-CoV-2 infection or cumulative incidence of 18.3/100,000 of all children and adolescents. None of our patients who have had MIS-C and were later vaccinated against COVID-19 or had a SARS-CoV-2 reinfection had a relapse of MIS-C.

Studies from the USA reported an incidence of MIS-C of 316/1,000,000 SARS-CoV-2 infections in persons under 21 years or 0.2–11.4/100,000 persons in the same age group, with disproportionately high numbers of affected children of non-White ethnicity (8, 9, 26, 27). A Danish study reported an incidence of MIS-C of 1/4100 SARS-CoV-2 infected persons under 18 years or 2/100,000 persons under 18 years, and an Italian study 10.3/100,000 persons under 19 years (28, 29). We found a comparatively higher incidence of MIS-C in predominantly white population of children and adolescents from south central Europe.

In contrast to adults, children are less likely to develop serious disease upon infection with SARS-CoV-2, but are at increased risk for inflammatory and autoimmune diseases linked to the virus (1, 20, 30). In our cohort, hospitalisations due to MIS-C were 6.5 times as common as hospitalisations due to severe COVID-19 and overall, autoimmune diseases following SARS-CoV-2 infection were 8.5 times as common as severe COVID-19.

Besides MIS-C, we observed a diverse spectrum of other autoimmune diseases linked to SARS-CoV-2, including vasculitis, neurological and cardiac diseases. The second most common was vasculitis, the majority of which was chilblains, but also included isolated cases of gastrointestinal and cutaneous vasculitis, recurrent urticaria, recurrent petechiae, exanthema of the face with

periorbital swelling and necrotising stomatitis (31). Interestingly, almost no cases of vasculitis were seen during or after the Delta wave of COVID-19 pandemic (32). Notably, the proportion of females with chilblains in our cohort was higher than previously reported (33, 34). Children with vasculitis were older than children with MIS-C, but a wide range of age at clinical presentation was observed in both groups. A higher proportion of confirmed cases and patients with symptomatic COVID-like illness in the preceding 3 months as well as shorter time interval from suspected COVID-19 to the onset of clinical symptoms were observed in patients with MIS-C, neurological and cardiac manifestations compared to patients with vasculitis.

Twenty-five patients with MIS-C from our cohort had a laboratory confirmed reinfection with SARS-CoV-2 and developed no signs of MIS-C afterwards. A further 9 patients who were vaccinated against COVID-19 after MIS-C and one patient who was vaccinated after peripheral facial palsy experienced no SAE or recurrence of inflammatory or autoimmune disease after vaccination. It is currently unknown whether MIS-C and other autoimmune diseases can recur after a reinfection with SARS-CoV-2 or re-exposure to viral antigens due to COVID-19 vaccination (35). MIS-C has a significant clinical overlap with KD and in our cohort a third of patients with MIS-C, including over a half of patients under 5 years of age, also fulfilled criteria for classic KD, which is similar to other published studies (7, 36). Both MIS-C and KD have temporal association with infectious diseases and are associated with immune system alteration, systemic inflammation and cytokine storm (7). An artificial intelligence guided gene signature has placed the two syndromes on the same host-immune response continuum, albeit MIS-C was placed further along the severity spectrum compared to KD. This suggests shared proximal pathways of immunopathogenesis (37). On the other hand, MIS-C also has some important differences, including specific differences in the immune cell response (5, 7, 10, 15, 16).

The recurrence of KD was reported to be rare with up to 4% in Asian countries and about 1.5% in North America, with most cases occurring within 2 years of the initial episode, but it is yet unclear whether the same will be true for patients with MIS-C (38). A case of reinfection with SARS-CoV-2 after MIS-C was reported, 13 months after the initial MIS-C diagnosis. The patient had no symptoms of MIS-C in the 2 months after reinfection (39). However, a patient with recurrent KD during acute SARS-CoV-2 infection and a patient with MIS-C who also fulfilled criteria for atypical KD were reported, 11 months and 6 years after the previous episode of KD (38, 40). Even though the exact cause of KD remains unknown, current understanding suggests an immune response to classic antigen, including T- and B-cell memory, that is protective against future exposure in most patients (25, 41). A robust memory T- and B-cell immune response has been demonstrated after SARS-CoV-2 infection, which may contribute to protection against recurrent episodes of MIS-C (42). It is yet unclear whether this immunologic memory will prevent recurrences of MIS-C after reinfection with new variant SARS-CoV-2 strains. Due to the rising rates of reinfection with SARS-CoV-2 as well as availability of COVID-19 vaccination to children, patients with MIS-C should have close outpatient follow-up (43). Current data are reassuring, and recurrence of MIS-C, like KD, seems to be unlikely.

Until December 31, 2021, 95,191 children and adolescents aged 5 to 18 years in Slovenia and FVG, Italy received at least one dose of COVID-19 vaccine. In the same period, three cases of serious inflammatory and autoimmune diseases following COVID-19 vaccination were diagnosed in this population, including two patients with MIS-C and a patient with myositis. Notably, all three vaccinated patients had a prior SARS-CoV-2 infection, which was confirmed by anti-N SARS-CoV-2 antibody positivity. All other patients with MIS-C and other autoimmune diseases were unvaccinated.

Multisystem inflammatory syndrome is rarely reported after vaccination and most cases were in adults (MIS-A). The majority of reported patients with MIS-A in temporal association with COVID-19 vaccination had evidence of prior SARS-CoV-2 infection (18, 44-46). Few cases of MIS-C following COVID-19 vaccination have been described so far. Two patients, who developed MIS-C 10 and 5 weeks after the second vaccination with mRNA COVID-19 vaccines, both had positive antibodies to SARS-CoV-2, but the anti-N antibodies were not determined (47, 48). Further two patients were diagnosed with MIS-C 5 and 27 days after the second and first dose of mRNA COVID-19 vaccine, respectively. Both had negative anti-N antibodies and high levels of anti-S antibodies, indicating a vaccine-induced rather than a SARS-CoV-2 infection-induced antibody response (49, 50).

There is some evidence that COVID-19 vaccination may be protective against MIS-C. None of the 107 French adolescents with MIS-C were fully vaccinated and 7 patients had received a single dose of COVID-19 mRNA vaccine (51). In a US report 97 of 102 hospitalised children with MIS-C were unvaccinated and none of the vaccinated MIS-C patients required respiratory or cardiovascular life support. Estimated vaccine effectiveness after 2 doses of Pfizer/BioNTech vaccine was 91% (95% CI 78–97%) (52).

Myositis has been described as a manifestation of acute COVID-19 and MIS-C, and few cases reported myositis following COVID-19 vaccination in adults (53-55). To the best of our knowledge, our patient with myositis is the first reported case of myositis following COVID-19 vaccination in children.

In agreement with the studies published so far, in our cohort, autoimmune diseases were much more frequent following SARS-CoV-2 infection compared to COVID-19 vaccination. While close monitoring for adverse events after vaccination is required, the three patients from our cohort together with other published cases underline the need to exclude prior SARS-CoV-2 infection in patients with suspected MIS-C or other inflammatory and autoimmune diseases after COVID-19 vaccination, to avoid unjustifiably contributing to the vaccine hesitancy (18, 47, 48).

This study has some limitations. Identification and reporting of patients with milder inflammatory and autoimmune diseases, such as chilblains, may not have been complete and even milder, self-limiting cases of MIS-C could have gone undiagnosed. Access to SARS-CoV-2 microbiological testing was variable among regions, especially during the early phases of the pandemic. The incidence of MIS-C was calculated based on PCR and/or RAT-positive cases of SARS-CoV-2 infection. It was shown that serology-based incidence of SARS-CoV-2 infection was more reliable than incidence based on positive PCR testing, which could be a more than twofold underestimation (28). However, no such data was available for our study population and the cumulative incidence of MIS-C per 100,000 persons younger than 18 years was high compared to other studies published so far.

In conclusion, we report a diverse spectrum of autoimmune diseases linked to SARS-CoV-2 in children and adolescents from two neighbouring south central European regions. MIS-C was the most common manifestation and its incidence in this predominantly white population was higher than previously reported. Based on our limited experience, MIS-C does not seem to recur after SARS-CoV-2 reinfection or COVID-19 vaccination, however long-term data are lacking. Autoimmune diseases were much more common after SARS-CoV-2 infection than after COVID-19 vaccination and were 8.5 times as frequent as severe COVID-19 in children. Results should be considered while advising COVID-19 pharmaceutical and non-pharmaceutical interventions aimed at children and adolescents. Additional research is needed to address the potential protection of COVID-19 vaccination against development of MIS-C in case of breakthrough infections.

References

1. MEHTA NS, MYTTON OT, MULLINS EWS *et al*.: SARS-CoV-2 (COVID-19): what do we know about children? A systematic review. *Clin Infect Dis* 2020; 71: 2469-79. https://doi.org/10.1093/cid/ciaa556
2. VINER RM, WARD JL, HUDSON LD *et al*.: Systematic review of reviews of symptoms and signs of COVID-19 in children and adolescents. *Arch Dis Child* 2021; 106: 802-7. http://dx.doi.org/10.1136/archdischild-2020-320972
3. Centers for Disease Control and Prevention Internet]. Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19) [updated 2020 Mar 27; cited 2021 Dec 31]. Available from: https://emergency. cdc.gov/han/2020/han00432.asp.
4. World Health Organization [Internet]. Multisystem inflammatory syndrome in children and adolescents temporally related to COVID-19 [updated 2020 May 15; cited 2021 Dec 31]. Available from: https://www.who.int/news-room/commentaries/ detail/multisystem-inflammatory-syndrome-in-children-and-adolescentswith- covid-19.
5. JIANG L, TANG K, LEVIN M *et al*.: COVID-19 and multisystem inflammatory syndrome in children and adolescents. *Lancet Infect Dis* 2020; 20: e276-88. https://doi.org/10.1016/S1473-3099(20)30651-4
6. GODFRED-CATO S, BRYANT B, LEUNG J *et al*.: COVID-19-Associated multisystem inflammatory syndrome in children-United States, March-July 2020. *MMWR Morb Mortal Wkly Rep* 2020; 69: 1074-80. http://dx.doi.org/10.15585/mmwr.mm6932e2
7. SHARMA C, GANIGARA M, GALEOTTI C *et al*.: Multisystem inflammatory syndrome in children and Kawasaki disease: a critical comparison. *Nat Rev Rheumatol* 2021; 17: 731-48. https://doi.org/10.1038/s41584-021-00709-9
8. BELAY ED, ABRAMS J, OSTER ME: Trends in geographic and temporal distribution of US children with multisystem inflammatory syndrome during the COVID-19 pandemic. *JAMA Pediatr* 2021; 175: 837-45. https://doi.org/10.1001/jamapediatrics.2021.0630
9. LEE EH, KEPLER KL, GEEVARUGHESE A *et al*.: Race/ethnicity among children with COVID-19-associated multisystem inflammatory syndrome. *JAMA Netw Open* 2020; 3: e2030280. https://doi.org/10.1001/jamanetworkopen.2020.30280
10. RAMOS-CASALS M, BRITO-ZERÓN P, MARIETTE X: Systemic and organ-specific immune-related manifestations of COVID-19. *Nat Rev Rheumatol* 2021; 17: 315-32. https://doi.org/10.1038/s41584-021-00608-z
11. NOVELLI L, MOTTA F, DE SANTIS M, ANSARI AA, GERSHWIN ME, SELMI C: The JANUS of chronic inflammatory and autoimmune diseases onset during COVID-19 – a systematic review of the literature. *J Autoimmun* 2021; 117: 102592. 117. https://doi.org/10.1016/j.jaut.2020.102592
12. LIU Y, SAWALHA AH, LU Q: COVID-19 and autoimmune diseases. *Curr Opin Rheumatol* 2021; 33: 155-62. https://doi.org/10.1097/BOR.0000000000000776
13. SAPKOTA HR, NUNE A: Long COVID from rheumatology perspective – a narrative review. *Clin Rheumatol* 2022; 41: 337-48. https://doi.org/10.1007/s10067-021-06001-1
14. CASTELLS MC, PHILLIPS EJ: Maintaining safety with SARS-CoV-2 vaccines. *N Engl J Med* 2021; 384: 643-9. https://doi.org/10.1056/NEJMra2035343
15. CONSIGLIO CR, COTUGNO N, SARDH F *et al*.: The immunology of multisystem inflammatory syndrome in children with COVID-19. *Cell* 2020; 183: 968-81.e7. https://doi.org/10.1016/j.cell.2020.09.016
16. ROWLEY AH: Understanding SARS-CoV-2-related multisystem inflammatory syndrome in children. *Nat Rev Immunol* 2020; 20: 453-4. https://doi.org/10.1038/s41577-020-0367-5
17. PUXEDDU I, FERRO F, BARTOLONI E *et al*.: COVID-19: the new challenge for rheumatologists. One year later. *Clin Exp Rheumatol* 2021; 39: 203-13.
18. BELAY ED, GODFRED CATO S, RAO AK *et al*.: Multisystem inflammatory syndrome in adults after severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) infection and Coronavirus disease 2019 (COVID-19) vaccination. *Clin Infect Dis* 2022; 75(1): e7411-8. https://doi.org/10.1093/cid/ciab936
19. LUDVIGSSON JF: Case report and systematic review suggest that children may experience similar long-term effects to adults after clinical COVID-19. *Acta Paediatr* 2021; 110: 914-21. https://doi.org/10.1111/apa.15673
20. WEISBERG SP, CONNORS TJ, ZHU Y *et al*.: Distinct antibody responses to SARS-CoV-2 in children and adults across the COVID-19 clinical spectrum. *Nat Immunol* 2021; 22: 25-31. https://doi.org/10.1038/s41590-020-00826-9
21. HEINZ FX, STIASNY K: Distinguishing features of current COVID-19 vaccines: knowns and unknowns of antigen presentation and modes of action. *NPJ Vaccines* 2021; 6: 104. https://doi.org/10.1038/s41541-021-00369-6
22. DÖRSCHUG A, FRICKMANN H, SCHWANBECK J *et al*.: Comparative assessment of sera from individuals after s-gene rna-based sars-cov-2 vaccination with spike-protein-based and nucleocapsid-based serological assays. *Diagnostics* (Basel) 2021; 11: 426. https://doi.org/10.3390/diagnostics11030426
23. ICH Topic E 2 A [Internet]. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting Step 5 note for guidance on clinical safety data management: definitions and standards for expedited reporting, [updated 2006; cited 2021 Dec 31]. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-use_en-15.pdf.
24. World Health Organization [Internet]. Clinical management of COVID-19: interim guidance, 27 May 2020 [updated 27 May 2020; cited 2021 Dec 31]. Available from: https://apps.who.int/iris/handle/10665/332196.
25. MCCRINDLE BW, ROWLEY AH, NEWBURGER JW *et al*.: Diagnosis, treatment, and long-term management of Kawasaki disease: A scientific statement for health professionals from the American Heart Association. *Circulation* 2017; 135: e927-99. https://doi.org/10.1161/CIR.0000000000000484
26. PAYNE AB, GILANI Z, GODFRED-CATO S *et al*.: Incidence of multisystem inflammatory syndrome in children among US persons infected with SARS-CoV-2. *JAMA Netw Open* 2021; 4: e2116420. https://doi.org/10.1001/jamanetworkopen.2021.16420
27. DUFORT EM, KOUMANS EH, CHOW EJ *et*

al.: Multisystem inflammatory syndrome in children in New York State. *New Engl J Med* 2020; 383: 347-58. https://doi.org/10.1056/NEJMoa2021756
28. HOLM M, HARTLING UB, SCHMIDT LS *et al*.: Multisystem inflammatory syndrome in children occurred in one of four thousand children with severe acute respiratory syndrome coronavirus 2. *Acta Paediatr* 2021; 110: 2581-3. https://doi.org/10.1111/apa.15985
29. CASTAGNOLA E, MARIANI M, STICCHI C *et al*.: Incidence rate of MIS-C in paediatrics: A good reason to vaccinate children against SARS-CoV-2. *Acta Paediatr* 2022; 111: 123-4. https://doi.org/10.1111/apa.16081
30. RAMASWAMY A, BRODSKY NN, SUMIDA TS *et al*.: Immune dysregulation and autoreactivity correlate with disease severity in SARS-CoV-2-associated multisystem inflammatory syndrome in children. *Immunity* 2021; 54: 1083-95.e7. https://doi.org/10.1016/j.immuni.2021.04.003
31. EMERŠIČ N, TOMAŽEVIČ T, TOČKOVA O *et al*.: Case report: Necrotizing stomatitis as a manifestation of COVID-19-associated vasculopathy. *Front Pediatr* 9 2021; 9: 800576. https://doi.org/10.3389/fped.2021.800576
32. SHIEHZADEGAN S, ALAGHEMAND N, FOX M, VENKETARAMAN V: Analysis of the Delta Variant B.1.617.2 COVID-19. *Clin Pract* 2021; 11: 778-84. https://doi.org/10.3390/clinpract11040093
33. MOLAEE H, EMADI SN, M'IMUNYA JMN, DAVOUDI-MONFARED E, MOHAMMED A, RAZAVI Z: Chilblain or perniosis-like skin lesions in children during the COVID-19 pandemic: a systematic review of articles. *Dermatol Ther* 2022; 35: e15298. https://doi.org/10.1111/dth.15298
34. MCCLESKEY PE, ZIMMERMAN B, LIEBERMAN A *et al*.: Epidemiologic analysis of chilblains cohorts before and during the COVID-19 Pandemic. *JAMA Dermatol* 2021; 157: 947-53. https://doi.org/10.1001/jamadermatol.2021.2120
35. EBINA-SHIBUYA R, NAMKOONG H, SHIBUYA Y, HORITA N: Multisystem Inflammatory Syndrome in Children (MIS-C) with COVID-19: Insights from simultaneous familial Kawasaki Disease cases. *Int J Infect Dis* 2020; 97: 371-3. https://doi.org/10.1016/j.ijid.2020.06.014
36. HENDERSON LA, CANNA SW, FRIEDMAN KG *et al*.: American College of Rheumatology Clinical Guidance for multisystem inflammatory syndrome in children associated with SARS-CoV-2 and hyperinflammation in pediatric COVID-19: Version 2. *Arthritis Rheumatol* 2021; 73: e13-e29. https://doi.org/10.1002/art.41616
37. GHOSH P, KATKAR GD, SHIMIZU C *et al*.: An Artificial Intelligence-guided signature reveals the shared host immune response in MIS-C and Kawasaki disease. *Nat Commun* 2022; 13: 2687. https://doi.org/10.1038/s41467-022-30357-w
38. MEDAGLIA AA, SIRACUSA L, GIOÈ C, GIORDANO S, CASCIO A, COLOMBA C: Kawasaki disease recurrence in the COVID-19 era: a systematic review of the literature. *Ital J Pediatr* 2021; 47: 95. https://doi.org/10.1186/s13052-021-01041-4
39. BUDDINGH EP, VOSSEN ACTM, LAMB HJ, VAN DER PALEN RLF, BRINKMAN DMC: Reinfection with severe acute respiratory syndrome coronavirus 2 without recurrence of multisystem inflammatory syndrome in children. *Pediatr Infect Dis* J 2021; 40: e491-2. https://doi.org/10.1097/INF.0000000000003280
40. RENGANATHAN A, GARG A, CHOWDHARY S, RAJ D: SARS-CoV-2 infection triggering recurrence of Kawasaki disease in a 10-year-old child. *BMJ Case Rep* 2021; 14: e240972. http://dx.doi.org/10.1136/bcr-2020-240972
41. FRANCO A, SHIMIZU C, TREMOULET AH, BURNS JC: Memory T-cells and characterization of peripheral T-cell clones in acute Kawasaki disease. *Autoimmunity* 2010; 43: 317-24. https://doi.org/10.3109/08916930903405891
42. CROMER D, JUNO JA, KHOURY D *et al*.: Prospects for durable immune control of SARS-CoV-2 and prevention of reinfection. *Nat Rev Immunol* 2021; 21: 395-404. https://doi.org/10.1038/s41577-021-00550-x
43. WANG J, KAPERAK C, SATO T, SAKURABA A: COVID-19 reinfection: A rapid systematic review of case reports and case series. *J Investig Med* 2021; 69: 1253-5. http://dx.doi.org/10.1136/jim-2021-001853
44. AL BISHAWI A, ALI M, AL-ZUBAIDI K, ABDELHADI H: Beware of the ambiguous enemy of multisystem inflammatory syndrome in adult (MIS-A) following Covid-19 infection or vaccination. *Clin Case Rep* 2021; 9: e05138. https://doi.org/10.1002/ccr3.5138
45. NUNE A, IYENGAR KP, GODDARD C, AHMED AE: Multisystem inflammatory syndrome in an adult following the SARS-CoV-2 vaccine (MIS-V). *BMJ Case Rep* 2021; 14: e243888. http://dx.doi.org/10.1136/bcr-2021-243888
46. STAPPERS S, CEULEERS B, VAN BRUSSELEN D, WILLEMS P, DE TAVERNIER B, VERLINDEN A: A case of multisystem inflammatory syndrome (MIS-A) in an adult woman 18 days after COVID-19 vaccination. *Acta Clin Belg* 2022; 77: 772-7. https://doi.org/10.1080/17843286.2021.1977899
47. BUCHHORN R, MEYER C, SCHULZE-FORSTER K, JUNKER J, HEIDECKE H: Autoantibody release in children after corona virus mrna vaccination: A risk factor of multisystem inflammatory syndrome? *Vaccines* (Basel) 2021; 9: 1353. https://doi.org/10.3390/vaccines9111353
48. ABDELGALIL AA, SAEEDI FA: Multisystem inflammatory syndrome in a 12-year-old boy after mrna-sars-cov-2 vaccination. *Pediatr Infect Dis J* 2022; 41: e93-4. https://doi.org/10.1097/INF.0000000000003442
49. CHAI Q, NYGAARD U, SCHMIDT RC, ZAREMBA T, MØLLER AM, THORVIG CM: Multisystem inflammatory syndrome in a male adolescent after his second Pfizer-BioNTech COVID-19 vaccine. *Acta Paediatr* 2022; 111: 125-7. https://doi.org/10.1111/apa.16141
50. YALÇINKAYA R, NUR ÖZ F, POLAT M *et al*.: A case of multisystem inflammatory syndrome in a 12-year-old male after COVID-19 mRNA vaccine. *Pediatr Infect Dis J* 2022; 41:e87-9. https://doi.org/10.1097/INF.0000000000003432
51. LEVY M, RECHER M, HUBERT H *et al*.: Multisystem inflammatory syndrome in children by COVID-19 vaccination status of adolescents in France. *JAMA* 2022; 327: 281-3. https://doi.org/10.1001/jama.2021.23262
52. ZAMBRANO LD, NEWHAMS MM, OLSON SM *et al*.: Effectiveness of BNT162b2 (Pfizer-BioNTech) mRNA vaccination against multisystem inflammatory syndrome in children among persons aged 12-18 Years – United States, July-December 2021. *MMWR Morb Mortal Wkly Rep* 2022; 71: 52-8. http://dx.doi.org/10.15585/mmwr.mm7102e1
53. SAUD A, NAVEEN R, AGGARWAL R, GUPTA L: COVID-19 and myositis: what we know so far. *Curr Rheumatol Rep* 2021; 23: 63. https://doi.org/10.1007/s11926-021-01023-9
54. MARAMATTOM BV, PHILIPS G, THOMAS J, SANTHAMMA SGN: Inflammatory myositis after ChAdOx1 vaccination. *Lancet Rheumatol* 2021; 3: e747-9. https://doi.org/10.1016/S2665-9913(21)00312-X
55. RAMALINGAM S, ARORA H, LEWIS S *et al*.: COVID-19 vaccine-induced cellulitis and myositis. *Cleve Clin J Med* 2021; 88: 648-50. https://doi.org/10.3949/ccjm.88a.21038