COVID-19 Vaccination Practice of Children with Rheumatic Disease: A Survey-based Study

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ABSTRACT

Objective: This cross-sectional study was carried out to investigate the vaccination status of children with rheumatic disease and the reasons why children were not vaccinated.

Methods: In November 2021, a web-based questionnaire was shared with the families of patients who were over 12 years. The families were asked about the socio-demographic features and the reasons for not vaccinating.

Results: A total of 160 patients (90 females) were eligible for the study. The median age was 14.9 (12-17.9) years. The study group comprised 94 patients with autoinflammatory diseases, 43 patients with juvenile idiopathic arthritis, 18 patients with connective tissue diseases, and 5 patients with vasculitis. The parent-reported vaccination rate was 75% in our patient group. The median children age, the median parental age and parental vaccination rates were lower in unvaccinated patients (for all p-value <0.05). In this study, the most common reasons for not vaccinating children with rheumatic disease were fear of vaccine side effects, not-decided-yet, and concerns related to underlying rheumatic disease and medications used. There was no difference between the groups according to patient gender, diagnosis, and medications they were on. Similarly, education levels of the parents and employment status were comparable between the groups (for all p-value >0.05).

Conclusion: These results, together with the results of previous studies, may provide clues to governments and health authorities to understand the drivers of vaccine hesitancy and help increase the coverage of vaccination programs.

Keywords: Vaccine, COVID-19, hesitancy, rheumatic, children

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INTRODUCTION

A novel infectious disease named coronavirus disease-2019 (COVID-19) was defined in late 2019, after the isolation of a new coronavirus variant of severe acute respiratory syndrome coronavirus-2, from the patients who had contact with the same animal market and subsequently developed lower respiratory tract infection (1,2). The disease spread all over the world in a short time and became a pandemic. According to the World Health Organization (WHO) coronavirus dashboard, it caused 5,446,753 deaths world-wide by 5th January 2022 (3). Apart from its effects on public health, the disease has massively affected nearly all aspects of social and economic activities globally since the first case was reported, and its negative effects on daily life are still ongoing.

Although more than 2 years have passed since the identification of the disease, an effective treatment could not be developed for COVID-19. Therefore, social distance, face masks, personal hygiene, and vaccination are still of vital importance for preventing the disease. According to the report of WHO, currently, 331 vaccine products (194 are in the pre-clinical phase and 137 are in clinical trials) are under development (4). Studies regarding the efficacy and safety of COVID-19 vaccines in children and adolescents are increasing day by day, and early results show that many vaccines are effective and safe. In the light of current information, the American Academy of Pediatrics recommends that children and adolescents aged 5 years and older, who have no contraindications for COVID-19 vaccination, should be vaccinated with a vaccine approved for their age (5-9). Even though many studies have shown that the mortality and morbidity of COVID-19 in children is lower than in adults, vaccination of children is of great importance in order to control the pandemic as they may cause the spread of the disease (10,11). Therefore, many countries have included children of various age groups in their COVID-19 immunization programs. In Turkey, children older than 12 with chronic medical conditions have been being vaccinated since August 2021.

Although great progress has been made worldwide with COVID-19 vaccine programs, vaccine hesitancy, which is defined by WHO as a delay in the acceptance of the vaccine or the refusal to be vaccinated despite the possibility of accessing the vaccine, is increasing all over the world and has reached dimensions that may threaten public health and WHO listed vaccine hesitancy among the top 10 global health threats in 2019 (12-14). Therefore, it is essential to investigate the vaccination rates of the patients and the attitude of the parents against the vaccine to expand the scope of the vaccination programs.

This cross-sectional study was carried out to investigate the vaccination status of children with rheumatic disease followed in our center, and the reasons why children are not vaccinated for non-vaccinated ones.

METHODS

Study Group

In November 2021, a web-based questionnaire was prepared in Google Forms platform and shared with the families of patients

who had been followed up at İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine Department of Pediatric Rheumatology. In this form, the families were asked about the socio-demographic features (parental education, employment status, monthly income, COVID-19 vaccination status, household size), the children's diagnosis, medication history, follow-up duration and vaccination status. Additional questions to the families of unvaccinated children were asked about the reasons for not vaccinating.

In our country, children under the age of 12 years with chronic medical conditions were started to be vaccinated in August 2021 and the children with rheumatologic disease have been vaccinated since then. Currently, there is no vaccination program against COVID-19 for children under the age of 12 years in Turkey. Therefore, children with rheumatological diseases aged between 12 and 18 years and whose families volunteered to participate in the study were included in the study. An informed consent was obtained from the patients in the questionnaire, and patients who did not want to participate were excluded from the study.

Statistical Analysis

All of the statistical analyses were done by using IBM SPSS 21.0 program (SPSS Inc., Chicago, IL, USA).

Categorical variables were presented as numbers (percentages) and continuous variables as mean \pm standard deviation or median (minimum-maximum) depending on their distribution. The distribution of the continuous data was checked by the Kolmogorov-Smirnov test and/or Shapiro-Wilk tests. The comparison of the categorical variables was performed with the chi-square test. While continuous variables with normal distribution were compared with the Student's t-test, those without normal distribution were compared by using the Mann-Whitney U test. The p-value <0.05 was considered significant.

Ethics

The study and its protocol were reviewed and approved by İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine Institutional Review Board (decision no: 179227, date: 10.09.2021).

RESULTS

Baseline Characteristics and Demographic Features

After the survey was circulated, 402 participants fulfilled the survey. After the exclusion of duplicate entries (n=16), entries of the patients who were younger than 12 years of age (n=152) and were older than 18 years of age (n=71), and those who improperly filled entries (n=3); a total of 160 patients (90 females) were eligible for the study.

The median age was 14.9 (12-17.9) years, and the median followup duration was 8 (0.7-17) years. The study group comprised of 94 patients with autoinflammatory diseases [Familial Mediterranean fever (FMF): 91, hyperimmunoglobulin D syndrome (HIDS): 2, cryopyrin associated periodic syndrome: 1], 43 patients with juvenile idiopathic arthritis (JIA), 18 patients with connective tissue diseases [systemic lupus erythematosus (SLE): 13, dermatomyositis: 4, scleroderma: 1), and 5 patients with vasculitis (deficiency of adenosine deaminase-2 (DADA-2): 2, Behçet's disease (BD): 1, granulomatous polyangiitis: 1, Kawasaki disease (KD): 1].

Of 160 patients, 90 (56.3%) were using colchicine. While 33 patients were on conventional disease modifying anti-rheumatic drugs (cDMARDs) (methotrexate: 17, hydroxychloroquine: 8, mycophenolate mofetil: 8, cyclosporin A: 4, azathioprine: 3, sulfasalazine: 2, leflunomide: 1), 35 patients were under biologic disease modifying anti-rheumatic drugs (bDMARDs) (etanercept: 11, canakinumab: 11, adalimumab: 8, tocilizumab: 4, anakinra: 2). Baseline characteristics of the study group are presented in Table 1.

COVID-19 Vaccination Status of the Patients

The Ministry of Health of the Republic of Turkey started to vaccinate children over the age of 12 years with chronic diseases against COVID-19 in August 2021. Since then, all of our patients over the age of 12 years with rheumatological disease can be vaccinated. As the patients under 12 years of age were excluded from the study, all of the participants were within the scope of the COVID-19 vaccination program.

The overall parent-reported COVID-19 vaccination rate in our patient group was 75% and 40 patients with rheumatologic conditions (FMF: 24, JIA: 10, SLE: 2, HIDS: 1, BD: 1, KD: 1, DADA-2: 1) had not been vaccinated. Maternal and paternal COVID-19 vaccination rate among our patient group was 86.9% and 90.6%, respectively (Table 1).

Reasons Why Children are not Vaccinated

As it is presented in Table 2, the most common reason for children not being vaccinated was the fear of side effect, which was pointed out by 20 (50%) of the subjects. Of these parents, only 9 (22.5%) stated that they knew/heard someone around them had experienced side effects after COVID-19 vaccination. Other main reasons mentioned by parents were their children's having rheumatic disease (25%) and using immunosuppressive drugs (25%). A total of 8 (25%) of subjects specified the vaccine being produced abroad as a reason. When these subjects were asked if a kind of COVID-19 vaccine would be produced in Turkey, whether they would vaccinate their children; only 1 (12.5%) parent answered as "yes", 1 (12.5%) answered as "no", and 6 (75%) answered as "not sure". Disbelief in efficacy of the vaccine and disbelief in existence of coronavirus were pointed out as reasons by 5 (12.5%) and 1 (2.5%) of the parents. In addition, 5 (12.5%) mentioned that they were trying to protect their children naturally (herbal medicine, etc.) instead of vaccination. Ten (%25) parents stated that they had not decided yet.

Comparison of the Baseline Characteristics According to Vaccination Status

While the median age [15 (12-17.9) years vs. 14.6 (12-17.7) years; p-value: 0.02], maternal age [41 (32-57) years vs. 39 (33-50) years; p-value: 0.004] and paternal age [45 (33-71) years vs. 42 (36-56)

 Table 1. Socio-demographic characteristics of the study group

group	
	n (%) or median (minimum- maximum)
Number of patients	160 (100)
Gender (females, %)	90 (56.3)
Age (years)	14.9 (12-17.9)
Diagnosis n (%)	
Autoinflammatory diseases	94 (58.8)
Familial Mediterranean fever	91(56.9)
Hyperimmunoglobulin D syndrome	2 (1.3)
Cryopyrin associated periodic syndrome	1 (0.6)
Juvenile idiopathic arthritis	43 (26.9)
Connective tissue diseases	18 (11.3)
Systemic Lupus Erythematosus	13 (8.1)
Dermatomyositis	4 (2.5)
Scleroderma	1 (0.6)
Vasculitis	5 (3.1)
Deficiency of adenosine deaminase 2	2 (1.3)
Behçet's disease	1 (0.6)
Granulomatous polyangiitis	1 (0.6)
Kawasaki disease	1 (0.6)
Median follow-up duration (years)	8 (0.7-17)
Medications n (%)	
Colchicine	90 (56.3)
Methotrexate	17 (10.6)
Canakinumab	11 (6.9)
Etanercept	11 (6.9)
Hydroxychloroquine	8 (5)
Adalimumab	8 (5)
Tocilizumab	4 (2.5)
Mycophenolate mofetil	4 (2.5)
Cyclosporin A	4 (2.5)
Acetylsalicylic acid	4 (2.5)
Azathioprine	3 (1.9)
Sulfasalazine	2 (1.3)
Anakinra	2 (1.3)
Leflunomide	1 (0.6)
Maternal characteristics	
Median age (years)	41 (32-57)
Education Less than high school High school More than high school	59 (36.9) 63 (39.4) 38 (23.8)
Employment status Unemployed Employed	113 (70.7) 47 (29.3)

COVID-19 vaccination status Vaccinated Not vaccinated	139 (86.9) 21 (13.1)
Paternal characteristics	
Median age (years)	44 (33-71)
Education Less than high school High school More than high school	64 (40) 49 (30.6) 47 (29.4)
Employment status Unemployed Employed	32 (20) 128 (80)
COVID-19 vaccination status Vaccinated Not vaccinated Household	145 (90.6) 15 (9.4) 4 (2-7)
Family monthly income	
r anny meene	
<500\$	75 (46.9)
	75 (46.9) 55 (34.4)
<500\$. ,
<500\$ 500-1,000\$	55 (34.4)
<500\$ 500-1,000\$ 1,000-2,000\$	55 (34.4) 23 (14.4)
<500\$ 500-1,000\$ 1,000-2,000\$ 2,000-3,000\$	55 (34.4) 23 (14.4) 4 (2.5)
<500\$ 500-1,000\$ 1,000-2,000\$ 2,000-3,000\$ >3,000\$	55 (34.4) 23 (14.4) 4 (2.5)
<500\$ 500-1,000\$ 1,000-2,000\$ 2,000-3,000\$ >3,000\$ Patient's childhood vaccination status	55 (34.4) 23 (14.4) 4 (2.5) 3 (1.9)
<500\$ 500-1,000\$ 1,000-2,000\$ 2,000-3,000\$ >3,000\$ Patient's childhood vaccination status Vaccinated	55 (34.4) 23 (14.4) 4 (2.5) 3 (1.9) 154 (96.3)
<500\$ 500-1,000\$ 1,000-2,000\$ 2,000-3,000\$ >3,000\$ Patient's childhood vaccination status Vaccinated Not vaccinated	55 (34.4) 23 (14.4) 4 (2.5) 3 (1.9) 154 (96.3)
<500\$ 500-1,000\$ 1,000-2,000\$ 2,000-3,000\$ >3,000\$ Patient's childhood vaccination status Vaccinated Not vaccinated Patient's COVID-19 vaccination status	55 (34.4) 23 (14.4) 4 (2.5) 3 (1.9) 154 (96.3) 6 (3.8)
<500\$ 500-1,000\$ 1,000-2,000\$ 2,000-3,000\$ >3,000\$ Patient's childhood vaccination status Vaccinated Not vaccinated Patient's COVID-19 vaccination status Vaccinated	55 (34.4) 23 (14.4) 4 (2.5) 3 (1.9) 154 (96.3) 6 (3.8) 120 (75)

	n (%)
I am afraid of the side effects.	20 (50)
I have not decided yet.	10 (25)
My child is on immunosuppressive drug.	8 (20)
My child has a rheumatologic disease.	8 (20)
The vaccine was produced abroad.	8 (20)
I do not believe in the efficacy of the vaccine.	5 (12.5)
l am trying to protect my children naturally (herbal medicine, etc.).	5 (12.5)
I do not believe in coronavirus.	1 (2.5)

years; p-value: 0.004] were higher in the vaccinated patient group, the median follow-up duration [7 (0.7-17) years vs. 10 (3-15) years; p-value: 0.015] was lower than in non-vaccinated ones.

A total of 98.3% of COVID-19 vaccinated subjects and 90% of non-vaccinated children were vaccinated appropriately according to national immunization program (p-value =0.01). Similarly, among vaccinated ones, maternal (95% vs. 62.5%) and paternal COVID-19 vaccination rates (95% vs. 77.5%) were higher than in the non-vaccinated group (both p-value <0.001).

The rate of the patients with a family income lower than 500\$ was lower in the vaccinated patient group [48 (40%) vs. 27 (67.5%)] and the rate of the patients with a family income between 500\$ and 1,000\$ was higher in the vaccinated patient group than in the non-vaccinated patient group [48 (40%) vs. 7 (17.5%); p-value: 0.02].

While family history of COVID-19 among the first-degree relatives of the patients was lower in the vaccinated patient group than in the non-vaccinated patient group [52 (43.3%) vs. 25 (62.5%); p-value: 0.03], there was no difference between the groups according to COVID-19 related deaths among the first-degree relatives of the patients (p-value: 0.56).

There was no difference between the groups in terms of patient gender, diagnosis, and medications they were on. Similarly, education levels of the parents and employment status were comparable between the groups (for all p-value >0.05). All of the comparisons were represented in Table 3 and Figure 1.

DISCUSSION

In this cross-sectional study, we presented a parent-reported 75% vaccination rate in children with rheumatic disease over 12 years of age and a lower median age, lower parental age, and lower parental COVID-19 vaccination rate in unvaccinated patients. In addition, the most common reasons for not vaccinating children with rheumatic disease in this study were the fear of vaccine side effects, having not decided yet, and concerns related to underlying rheumatic disease and medications used.

In our study group, the parent-reported vaccination rate among children with rheumatic disease over 12 years of age was 75%. As of 7th January 2022, according to the European Centre for Disease Prevention and Control, the median cumulative uptake of at least one vaccine dose in the member states of the European Union was 32% for children between the ages of 10 and 14 years and 71.6% for children between the ages of 15 and 17 years (15). On the report of Ministry of Social Affairs and Health of France, it was stated that 82% of children between the ages of 12 and 17 years received at least one dose of COVID-19 vaccine and it was given as 60.8 % by the Federal Ministry of Health of Germany for children in the same age group (16,17).

To our knowledge, there are no exact data for Turkey and any other country on COVID-19 vaccine coverage among children with rheumatological diseases. There are only a few studies in the literature on the acceptance of a potential COVID-19 vaccine among adult patients with rheumatic diseases, which were usually conducted before or shortly after massive vaccination programs had launched. In these studies, conflicting reports were reported regarding the attitudes of rheumatology patients towards potential vaccines. While some studies reported a lower rate of acceptance of a potential COVID-19 vaccine among patients with rheumatic diseases than control groups, other studies reported a similar rate of intention to be vaccinated against COVID-19 in patients with rheumatic diseases and control groups (18-21). It has been shown that vaccine acceptance rates can change over

Table 3. Comparison of vaccination status of the patients according to demographic features

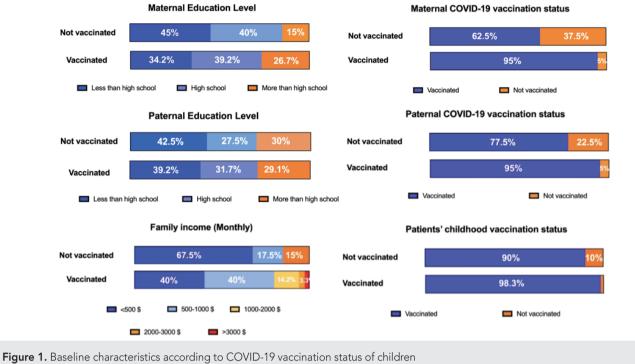
according to demographic	leatures		
	Vaccinated (n=120)	Not vaccinated (n=40)	p-value
Gender (females, %)	69 (57.5)	21 (52.5)	0.58
Age (years)	15 (12- 17.9)	14.6 (12- 17.7)	0.02
Diagnosis n (%)			
Autoinflammatory diseases	69 (57.5)	25 (62.5)	
Juvenile idiopathic arthritis	33 (27.5)	10 (25)	0.15
Connective tissue diseases	16 (13.3)	2 (5)	
Vasculitis	2 (1.7)	3 (7.5)	
Follow-up duration (years)	7 (0.7-17)	10 (3-15)	0.015
Medications n (%)			
Colchicine	65 (54.2)	25 (62.5)	0.35
Methotrexate	15 (12.5)	2 (5)	0.18
Canakinumab	9 (7.5)	2 (5)	0.58
Adalimumab	7 (5.8)	1 (2.5)	0.40
Hydroxychloroquine	6 (5)	2 (5)	1.00
Etanercept	6 (5)	5 (12.5)	0.10
Tocilizumab	2 (1.7)	2 (5)	0.24
Mycophenolate mofetil	3 (2.5)	1 (2.5)	1.00
Cyclosporin A	4 (3.3)	0 (0)	0.24
Acetylsalicylic acid	3 (2.5)	1 (2.5)	1.00
Azathioprine	3 (2.5)	0 (0)	0.31
Sulfasalazine	2 (1.7)	0 (0)	0.41
Anakinra	2 (1.7)	0 (0)	0.41
Leflunomide	1 (0.8)	0 (0)	0.56
Maternal characteristics			
Median age (years)	41 (32-57)	39 (33-50)	0.004
Education Less than high school High school More than high school	41 (34.2) 47 (39.2) 32 (26.7)	18 (45) 16 (40) 6 (15)	0.26
Employment status Unemployed Employed	82 (67.5) 39 (32.5)	32 (80) 8 (20)	0.13
COVID-19 vaccination status Vaccinated Not vaccinated	114 (95) 6 (5)	25 (62.5) 15 (37.5)	<0.001
Paternal characteristics			
Median age (years)	45 (33-71)	42 (36-56)	0.004
Education Less than high school High school More than high school	47 (39.2) 38 (31.7) 35 (29.2)	17 (42.5) 11 (27.5) 12 (30)	0.87
Employment status Unemployed Employed	23 (19.2) 97 (80.8)	9 (22.5) 31 (77.5)	0.64

COVID-19 vaccination status Vaccinated Not vaccinated	114 (95) 6 (5)	31 (77.5) 9 (22.5)	0.001	
Household	4 (2-7)	4 (3-7)	0.06	
Family monthly income				
<500\$	48 (40)	27 (67.5)		
500-1,000\$	48 (40)	7 (17.5)		
1,000-2,000\$	17 (14.2)	6 (15)	0.02	
2,000-3,000\$	4 (3.3)	0 (0)		
>3,000 \$	3 (2.5)	0 (0)		
Patient's childhood vaccination	status			
Vaccinated	118 (98.3)	36 (90)	0.01	
Not vaccinated	2 (1.7)	4 (10)		
Has anyone in the family had COVID-19?				
No	68 (56.7)	15 (37.5)	0.03	
Yes	52 (43.3)	25 (62.5)		
Has anyone in the family died due to COVID-19?				
No	119 (99.2)	40 (100)	0.56	
Yes	1 (0.8)	0 (0)		
COVID-19: coronavirus disease-2019				

time and there are differences between the time periods of the mentioned studies (22). This makes it difficult to compare the rates reported in studies with each other. Therefore, it would be more plausible to focus on the reasons for vaccine hesitancy and the demographics of vaccine hesitant patient population rather than acceptance rates.

The comparisons between vaccinated and non-vaccinated patients showed that the median age of the non-vaccinated patients was lower than that of the vaccinated patients. In accordance with our results, Verger et al. (23), in their study conducted with French adult population to assess their attitudes toward COVID-19 vaccination acceptance for children and adolescents, found that the COVID-19 vaccine acceptance rate of the participants was highest for adolescents (62.7%) and lowest for children under the age of 6 years (31%). Similarly, Goldman et al. (24) reported that a higher intention to vaccinate children is related to children being older. Another significant finding of our study is the median parental age of vaccinated patients being higher than that of non-vaccinated patients. There are several studies on parents'/caregivers' intentions to vaccinate their children against COVID-19 in the literature and one of the most frequently reported factors influencing parental attitudes in these studies is parental age (5). In vast majority of these studies, similar to our findings, it was reported that older parents tended to have positive attitude towards COVID-19 vaccination for their children (24-29).

In our study group, maternal and paternal vaccination rates against COVID-19 were higher among vaccinated children than in the nonvaccinated group. These results support the findings of previous studies reporting that the parents who wanted to vaccinate



COVID-19: coronavirus disease-2019

themselves against COVID-19 were more likely to vaccine their children (27,30,31). In addition to these, not surprisingly, the rates of children who were vaccinated appropriately according to national childhood immunization program among COVID-19 vaccinated subjects were higher than those of the remaining children. It is shown in the previous studies that the parents who had got influenza vaccine in the previous season were more reluctant to vaccine themselves and their children against COVID-19 (24,26,32,33). In addition, Skiefte et al. (34) reported that one of the main predictors of the COVID-19 vaccine acceptance was confidence in childhood vaccination. These findings were further supported by other studies (35,36). Contrary to these reports, Yılmaz and Sahin (27) found no association between parental willingness to have their children vaccinated and routine vaccination. Yet, in the same study, the authors reported that the parents whose children had received paid-for vaccines were more reluctant to allow their children to receive COVID-19 vaccine (27). These findings suggest that the unwillingness of parents to vaccinate their children against COVID-19 is not only specific to COVID-19 vaccine, but also associated with general opposition to vaccination. On the other hand, 90% of the non-vaccinated children in our study were vaccinated appropriately according to national childhood immunization program. It is more likely that the parents of patients in this group did not allow their children to be vaccinated against COVID-19 because of COVID-19 vaccinespecific concerns rather than general vaccine refusal. Thus, it will be beneficial for health authorities to analyze these parental profiles in detail and to develop strategies specific to these profiles for increasing the success and coverage of the vaccination program.

In our study, the top reason for rejecting COVID-19 vaccination for children with rheumatic disease was the fear of vaccine side effects, which was also reported as the most common reason for unwillingness to vaccinate children in several studies (5,24,27,30,32,34,37). Other reasons mentioned by the parents were concerns related to underlying rheumatic disease and medications used. In addition to these, 12.5% of the parents whose children were not vaccinated mentioned disbelief in the efficacy of the vaccine as a reason. There is an increasing number of studies in the literature on the efficacy and safety of COVID-19 vaccines in healthy children and in those with rheumatological diseases (6,38,39). Sharing the results of these current studies with parents by health authorities and health professionals can help for overcoming the most common reasons for vaccine hesitancy reported in several studies.

Study Limitations

The main limitation of our study is its being survey-based and the data collected were patient-reported. In addition, since it is a single-center study, our results may not reflect the entire Turkish society. Therefore, further studies with larger populations are needed to confirm our results.

CONCLUSION

We report a parent-reported 75% vaccination rate in children with rheumatic disease over 12 years of age and a lower median age, lower parental age, and lower parental COVID-19 vaccination rate in unvaccinated patients. In addition, the most common reasons for not vaccinating children with rheumatic disease in this study were the fear of vaccine side effects and concerns related

to underlying rheumatic disease and medications used. These results, together with the results of previous studies, may provide clues to governments and health authorities to understand the drivers of vaccine hesitancy and help increase the coverage of vaccination programs.

Ethics Committee Approval: The study and its protocol were reviewed and approved by Istanbul University-Cerrahpaşa Cerrahpaşa, Faculty of Medicine Institutional Review Board (decision no: 179227, date: 10.09.2021)

Informed Consent: An informed consent was obtained from the patients in the questionnaire, and patients who did not want to participate were excluded from the study.

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