

Severity of COVID-19 Symptoms among University of Belgrade Students during the July–September 2021 Pandemic Wave: Implications for Vaccination

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Highlights of the Study

- A majority of students (59.3%) had moderate clinical symptoms of COVID-19.
- Only 21.8% of students were fully vaccinated with 2 doses.
- Vaccinated students were 78% less likely to develop moderately severe symptoms of COVID-19.
- Vaccinated students were 96% less likely to develop severe symptoms of COVID-19.

Keywords

COVID-19 · University students · Vaccination

Abstract

Objective: The aim of this study was to identify the intensity of COVID-19 symptoms during the pandemic wave during July–September 2021 and to identify factors associated with having moderate and severe symptoms of COVID-19 among affected students in the University of Belgrade. **Material and Methods:** This study was carried out at the Institute for Students' Health (ISH) in Belgrade, Serbia. The ISH is the referral institution for health care delivery at primary and secondary levels. This analysis includes students who presented from July 1 until September 30, 2021, when the latest pandemic wave of COVID-19 was observed among university students. Data were extracted from students' electronic medical re-

ords. Three levels of COVID-19 symptom intensity were defined: mild, moderate, and severe. **Results:** Of students seeking medical care at the ISH who were diagnosed with COVID-19, 27.3% had mild disease and the majority, 59.3%, had moderate disease, and 13.4% had severe symptoms. Of all students, 124 (21.8%) were fully vaccinated with 2 doses of Sinopharm (81, 60.9%), Pfizer-BioNTech (38, 28.6%), Sputnik V (7, 5.3%), or the Oxford-AstraZeneca vaccine (7, 5.3%). The multiple multinomial regression model suggests that students who were vaccinated against COVID-19 were 78% less likely to develop moderate symptoms and 96% less likely to develop severe symptoms of COVID-19. **Conclusion:** Students who are vaccinated against COVID-19 are at lower risk of developing moderate and severe symptoms of the disease.

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Introduction

The lockdown as a result of the COVID-19 pandemic in Serbia lasted from March to May 2020 [1]. During the lockdown, all activities at universities in Serbia were suspended, and student dormitories were closed. Due to these control measures, very few university students were affected by COVID-19. After reopening in May 2020, an increasing number of students from the University of Belgrade, the largest university in Serbia, began presenting at the Institute for Students' Health (ISH), the referral center for health care delivery for this population group. Since that period, the dynamic of the COVID-19 pandemic among university students could be charted in several distinctive waves: June–August 2020, October–December 2020, January–April 2021, and July–September 2021, the last of which is ongoing at the time of preparation of this manuscript. The vaccination against COVID-19 among students began in March 2021, and immunization activities in this population group was the most intense over March, April, and May 2021 [2].

University students in Serbia, generally aged 19–26 years, represent a healthy young adult population in which severe symptoms of COVID-19 and hospitalizations are not expected. In fact, about 1 in 5 students may be asymptomatic [3]. Typical clinical symptoms among college students included weakness; nasal congestion; thoracic pain; loss of smell, taste, and appetite as well as sleeping problems [4]. However, despite lower risk, some students do develop severe clinical presentation of COVID-19 and require additional management of their health status.

In the university setting, close contact between students on-campus and in dormitories as well as participation in various activities, such as sports tournaments, or social events facilitates the viral spread [5–7]. Immunization helps to prevent the severe outcomes of the disease, and inadequate vaccination coverage may require mass testing of asymptomatic individuals to identify potential reservoirs in order to control the COVID-19 pandemic among university students [8]. Additionally, travel and semester breaks may facilitate the exposure to the novel coronavirus in this population group [3, 9]. This may increase the risk of catching the new SARS-CoV-2 variants, to which previous immunization may have limited effectiveness [10, 11]. As students may be exposed to the novel coronavirus more often through various school-related activities and close contacts with each other which favor high viral concentration, they may develop various clinical symptoms of COVID-19. Thus far, data on the preva-

lence of moderate and severe clinical presentation of COVID-19 among university students are lacking. Information about potential risk factors for severe symptoms of COVID-19 could help university health facilities improve and adapt their approach to prevention and treatment in this population group. The purpose of this study is to identify the severity of COVID-19 symptoms during the ongoing pandemic wave (July–September 2021) and explore factors associated with having moderate and severe symptoms of COVID-19 in the population of affected students in the University of Belgrade, Serbia.

Methods

Setting and Participants

This study was carried out at the ISH in Belgrade, Serbia. The ISH is the referral institution for health care delivery at primary and secondary levels for students who are enrolled at institutions of higher education in Belgrade (approximately 100,000 students). The health care system in Serbia is supported by mandatory contributions to health insurance, and students do not incur any cost for using services of the ISH.

Students who present the symptoms of COVID-19 come to the ISH, in the COVID-19 outpatient unit, set up at the beginning of the pandemic in spring 2020, for physical examination, collection of blood samples, chest X-ray, and to receive therapy. The samples are tested using rapid antigen test and polymerase chain reaction test. A systematic surveillance of COVID-19 through the ISH system began in June 2020. Mass vaccination against COVID-19 in the student population in ISH began in March 2021 with 3 vaccines (Sinopharm, Pfizer-BioNTech, and Oxford-AstraZeneca). This analysis includes the students who presented at the ISH from July 1 until September 30, 2021, when the latest pandemic wave of COVID-19 was observed among university students in Belgrade.

Data Collection

All students who tested positive for SARS-CoV-2 were interviewed to collect sociodemographic characteristics (age, gender, type of faculty [medical sciences/social science and humanities/natural science and mathematics/technology and engineering science], and living in student dormitory [yes vs. no]), complaints related to their illness which included a detailed history (COVID-19 vaccination status [having received at least 1 dose of the vaccine vs. not vaccinated], previous COVID-19 infection [yes vs. no], and perception of the location where students were exposed to COVID-19 [does not know/contact with familiar person(s)/travel/at work/at sports activities/social events]), and physical examination. All data were entered into students' electronic medical records. Additionally, an address where students would spend the following 2 weeks was noted. Each positive student was contacted by an epidemiologist via telephone over the following days when the assessment of the clinical symptoms of COVID-19 was performed. When needed, students who had severe symptoms and longer course of the disease were contacted several times.

The COVID-19 symptom intensity was defined as mild, moderate, and severe. The definitions and classification of the inten-

Table 1. Criteria for definition and classification of COVID-19 symptoms intensity among Belgrade University students

Grading and duration of COVID-19 symptoms	Fever	Other symptoms	Laboratory findings
Mild symptoms lasting for 1–3 days	No fever or fever $\leq 37.5^{\circ}\text{C}$ lasting up to 3 days or fever $> 37.5^{\circ}\text{C}$ lasting for 1 or 2 days	Nasal congestion, nasal discharge, and mild sore throat (having none, 1 or 2 out of 3 complaints)	Laboratory parameters are normal or deviate from reference values up to 5%
Moderate symptoms lasting for 4–7 days	Fever $37.6\text{--}38.5^{\circ}\text{C}$ lasting 4–7 days and at least 2 symptoms/complaints listed in column "other symptoms"	Intense sore throat, loss of smell and taste, diarrhea, intense muscle aches, weakness, cough, and headache	Laboratory parameters deviate from reference values from 6% to 20%
Severe symptoms lasting for 8 days or longer	Fever $\geq 38.6^{\circ}\text{C}$ and at least 3 symptoms/complaints listed in the column "other symptoms"	Chills and shivering, profuse sweating, intense and persistent headache, chest pain, persistent cough, breathing difficulties, nausea and vomiting, complete loss of smell and taste, and extreme exhaustion	Laboratory parameters deviate from reference values more than 20%

sity of COVID-19 symptoms are presented in Table 1. The key difference between COVID-19 symptoms was their duration.

Of all students who presented severe symptoms of COVID-19, the majority were treated at home, while an epidemiologist from the ISH was in telephonic contact with all of them. Only a few patients (8 in total) were hospitalized at the ISH. The presentation of clinical symptoms and their duration did not materially differ between students with severe symptoms who were hospitalized and who were treated at home. The main reason behind hospitalization instead of discharge was to prevent viral spread to susceptible dormitory residents or family members. Additionally, because of the lack of statistical power, students who were hospitalized were analyzed together with students with severe symptoms but were treated at home.

Data Analysis

To describe the study sample, percentage and median were used. Students were classified according to clinical symptoms of COVID-19 into 3 groups: mild, moderate and severe symptoms. Categorical variables were tested using the χ^2 test (gender, type of faculty, living in student dormitory and vaccination status) and Fisher's exact test (had COVID-19 before and location of the exposure to COVID-19). Continuous variable (age) was tested using the Kruskal-Wallis test.

To examine factors associated with having moderate and severe COVID-19 symptoms, multiple multinomial regression was applied. In the model, the dependent variable was the intensity of COVID-19 symptoms (1-mild/2-moderate/3-severe, where the subgroup of students with mild COVID-19 symptoms was used as the reference category). Independent variables in the model were demographic (gender, age, and type of faculty) and epidemiological characteristics (having been vaccinated against COVID-19, having had COVID-19 previously, location of COVID-19 exposure, and living in dormitory). The effect measure is odds ratio with corresponding 95% confidence intervals. The significance level of probability was set at $p < 0.05$. All analyses were performed in R version 4.0.5. Visualizations were created with Power BI.

Results

The study sample comprised a total of 568 University students. The topographic distribution of students' origin is presented in Figure 1. The majority of the affected students were residing in the capital city of Belgrade (Fig. 1a). However, students who reside across Serbia were represented in the study sample. A small proportion of students were from Bosnia and Herzegovina and Montenegro as well as from other continents (Fig. 1b). Cumulative chronological distribution of the confirmed COVID-19 cases is presented in Figure 2. The resurgence of COVID-19 among students began in mid-August and continued to rapidly increase throughout September.

Clinical Symptoms of COVID-19

Of students seeking medical care at the ISH who were diagnosed with COVID-19, 27.3% had mild disease, and the majority, 59.3%, had moderate disease, and 13.4% had severe symptoms. Eight out of 76 (10.5%) students with severe symptoms were hospitalized. Demographic and epidemiological characteristics of the students according to the intensity of symptoms of COVID-19 are presented in Table 2.

Overall, the affected students were similar with regards to gender, age, field of study, living in dormitory, having had COVID-19 previously, and location of COVID-19 exposure. However, the students differed according to vaccination status. Specifically, students who had mild symptoms were more frequently vaccinated compared to students who had moderate and severe symptoms of COVID-19 (Table 2).

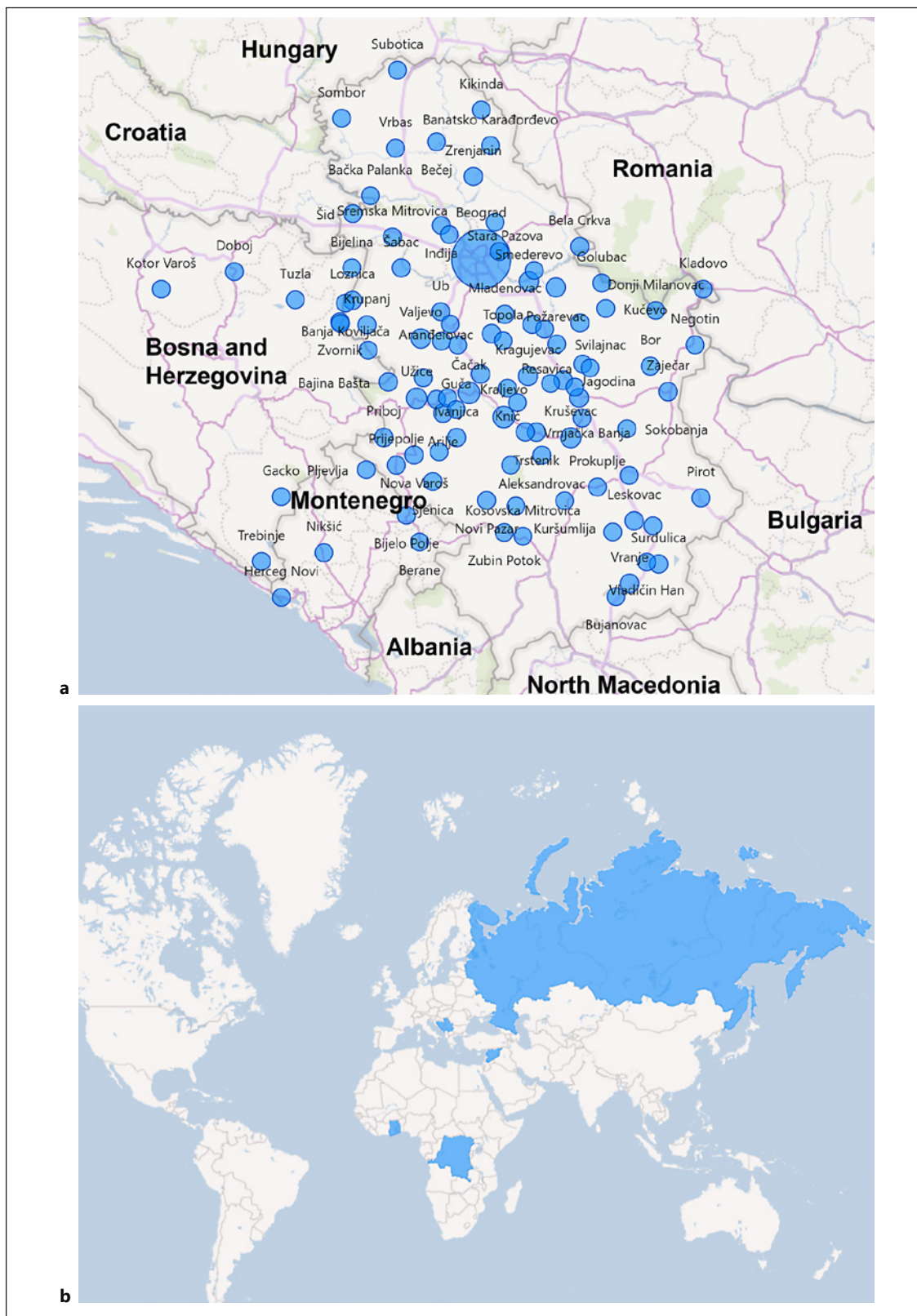


Fig. 1. Topographic distribution of the origins of COVID-19-positive students in the period July-September 2021 in Serbia and neighboring countries (a) and worldwide (b).

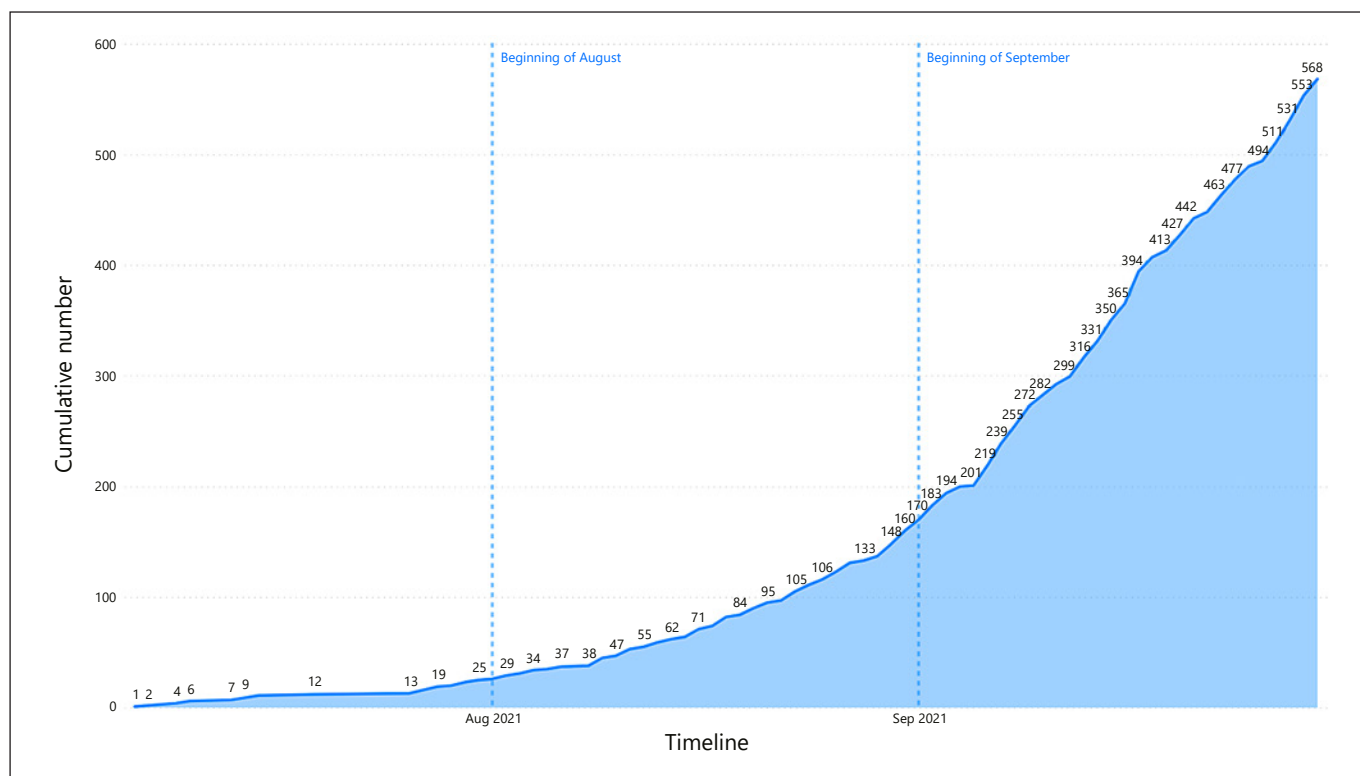


Fig. 2. Cumulative number of COVID-19-positive students from July to the end of September 2021 at the University of Belgrade.

COVID-19 Vaccination among Students

A total of 124 students (21.8%) in the study sample were fully vaccinated (i.e., with 2 doses). Another 9 students (1.5%) received 1 dose of the vaccine. With regards to the types of vaccines, the largest proportion of the vaccinated students received Sinopharm vaccine (81, 60.9%). Other students received Pfizer-BioNTech (38, 28.6%), Sputnik V (7, 5.3%), and Oxford-AstraZeneca (7, 5.3%). No differences in the type of vaccine between students with different clinical presentations of COVID-19 were observed ($p = 0.8464$).

Factors Associated with Moderate and Severe COVID-19 Symptoms

The multiple multinomial regression model suggests that vaccination against COVID-19 is associated with lower likelihood of developing moderate and severe symptoms. Specifically, students who were vaccinated against COVID-19 were 78% less likely to develop moderately severe symptoms and 96% less likely to develop severe symptoms of COVID-19 (Table 3).

Discussion

This study sought to elucidate factors associated with the onset of more severe symptoms of COVID-19 among university students. To the best of our knowledge, this study is the first to describe the intensity of clinical symptoms of COVID-19 and the association of factors specific to a university student population. The results of this study suggest that vaccination against SARS-CoV-2 is a single independent factor associated with lower likelihood of developing moderate to severe symptoms of COVID-19 in a sample of university students. In this set of students, demographic and other epidemiological characteristics did not seem to increase the chance of having more severe symptoms.

The interest in vaccination among university students in Belgrade was the highest from March to May 2021. In June 2021, the interest in vaccination was remarkably lower, and this corresponded to the lower frequency of newly diagnosed people with COVID-19 in the general population in Serbia. With the resurgence of new cases in August and September 2021, the interest in vaccination

Table 2. Sociodemographic characteristics according to the severity of the clinical symptoms of COVID-19

Variable	Clinical symptoms of COVID-19			p value
	mild (N = 155)	moderate (N = 337)	severe (N = 76)	
Gender, n (%)				
Male	58 (27.1)	123 (57.5)	33 (15.4)	0.5194
Female	97 (27.4)	214 (60.4)	43 (12.2)	
Median age (IQR)	23.0 (3.75)	23.0 (3.0)	23.0 (3.0)	0.289
Type of faculty, n (%)				
Medical sciences	18 (33.3)	33 (61.1)	3 (5.6)	0.1989
Social science and humanities	51 (27.7)	114 (62.0)	19 (10.3)	
Natural science and mathematics	41 (4.3)	19 (67.9)	5 (17.9)	
Technology and engineering sciences	46 (27.7)	92 (54.4)	31 (18.3)	
Other*	36 (27.1)	79 (59.4)	18 (13.5)	
Living in student dormitory, n (%)				
Yes	19 (30.2)	35 (55.5)	9 (14.3)	0.801
No	136 (29.9)	302 (59.8)	67 (13.3)	
Having had COVID-19 before, n (%)				
Yes	8 (25.0)	22 (68.7)	2 (6.3)	0.4574
No	147 (27.4)	315 (58.8)	74 (13.8)	
Vaccination status, n (%)				
Not vaccinated	81 (18.4)	281 (64.7)	73 (16.9)	<0.001
Received as least 1 dose	74 (55.6)	56 (42.1)	3 (2.3)	
Location of the exposure to COVID-19, n (%)				
Does not know	48 (25.7)	116 (62.0)	23 (12.3)	0.4628
Contact with familiar person(s) [†]	58 (32.0)	104 (57.5)	19 (10.5)	
Travel/tourism	16 (22.9)	40 (57.1)	14 (20.0)	
At work [‡]	8 (18.2)	29 (65.9)	7 (15.9)	
At sport activities	1 (25.0)	2 (50.0)	1 (25.0)	
Parties/meet-ups/social outings	24 (30.0)	46 (56.1)	12 (14.6)	

IQR, interquartile range; p, probability. * Other type of faculties: college, private universities, art schools, and police academy. [†] Either family members or friends/acquaintances/partners. [‡] Those students who do paid work while studying; Fisher's exact test was used to test variables having had COVID-19 before and the location of the exposure to COVID-19; all other variables were tested using the χ^2 test.

against COVID-19 remained low. This is in line with COVID-19 vaccine hesitancy observed worldwide [12–14]. Overall, according to ISH records, of students who received the vaccines until October 2021, 68.4% (8,706 students) were immunized with Pfizer-BioNTech, 30% (3,826 students) with Sinopharm, and 1.6% (210) with Oxford-AstraZeneca. Although Sputnik V was available to the general population in Serbia, this vaccine was not administered at the ISH because of the storage requirements. However, this vaccine was available at vaccination sites throughout the city. Students were free to choose the vaccine of their choice. The distribution of the administered vaccines in the student population was different from the general population in Serbia, where most people received Sinopharm [15]. Potential reasons for such a distribution could be related to the tendency of the Western

European countries to recognize the mRNA vaccines as the most appropriate way of protection in the pandemic circumstances. However, the size of the sample in this study did not allow for a more detailed analysis of the association between the type of vaccine and likelihood of having diverse intensity of COVID-19 symptoms.

Bearing in mind that university students and young people in general are the most mobile population group, the location of exposure to SARS-CoV-2 should be meticulously explored in the field to understand the patterns of transmission [16]. In this study, none of the places of exposure were singled out as factors associated with a more severe clinical presentation. However, it is worthwhile to consider them. In our set of students, different places of exposure were reported. Depending on the month of observation, these reports had the tendency to

Table 3. Factors associated with developing moderate and severe COVID-19 symptoms (referent group: students with mild symptoms): results of the multiple multinomial regression model

Variables	Moderate versus mild symptoms			Severe versus mild symptoms		
	OR	95% confidence interval	<i>p</i> value	OR	95% confidence interval	<i>p</i> value
Gender						
Male	Ref	–	–	Ref	–	–
Female	0.98	0.63, 1.52	>0.9	0.72	0.38, 1.35	0.3
Age	0.94	0.85, 1.04	0.2	0.95	0.82, 1.09	0.5
Type of faculty						
Medical sciences	Ref	–	–	Ref	–	–
Social science and humanities	1.01	0.49, 2.07	>0.9	0.67	0.17, 2.70	0.6
Natural science and mathematics	1.04	0.60, 1.82	0.9	1.36	0.58, 3.19	0.5
Technology and engineering sciences	2.32	0.69, 7.76	0.2	4.05	0.88, 18.5	0.072
Other	0.88	0.51, 1.51	0.6	1.79	0.82, 3.92	0.14
Living in student dormitory						
Yes	Ref	–	–	Ref	–	–
No	1.40	0.72, 2.70	0.3	1.23	0.47, 3.21	0.7
Having had COVID-19 before						
Yes	0.82	0.34, 1.98	0.7	2.38	0.46, 12.3	0.3
No	Ref	–	–	Ref	–	–
Vaccination status						
Not vaccinated	Ref	–	–	Ref	–	–
Received as least 1 dose	0.22	0.14, 0.34	<0.001	0.04	0.01, 0.15	<0.001
Location of the exposure to COVID-19						
Does not know	Ref	–	–	Ref	–	–
Contact with familiar person(s)	1.32	0.79, 2.19	0.3	1.25	0.57, 2.74	0.6
Travel/tourism	1.90	0.76, 4.74	0.2	2.91	0.84, 10.1	0.092
At work	1.51	0.74, 3.06	0.3	2.48	0.93, 6.62	0.069
At sport activities	1.48	0.12, 18.5	0.8	5.47	0.24, 122	0.3
Parties/meet-ups/social outings	0.92	0.49, 1.73	0.8	1.40	0.55, 3.55	0.5

OR, odds ratio.

form clusters, rather than be continuously reported during the study period.

Specifically, over the summer months, during school break, the ISH records showed few students with symptoms indicative of COVID-19. Nevertheless, from mid-July to mid-August 2021, a higher rate of exposure during travel was reported. The increased occurrence of COVID-19 during holidays has been previously reported [17, 18]. Holiday destinations for summer vacation among youth in Serbia are commonly the seaside in Montenegro, Greece, Turkey, and Egypt. Additionally, some countries in the Balkan region did not require specific COVID-19 testing or proof of COVID-19 vaccination to cross the border. For this reason, many students preferred visiting those places.

Another noteworthy feature in this population group is the fact that some students did paid work during sum-

mer holidays. In our study, doing paid work could be considered as marginally associated with having severe symptoms of COVID-19 (odds ratio 2.48, 95% confidence interval 0.93, 6.62; *p* = 0.06). The university students reported to have worked in the summer months in bars and cafes, shopping malls, bookstores, and ticket booths (selling bus tickets or event tickets). It is likely that longer exposure and high viral concentration during working hours could be underlying factors in the development of more severe COVID-19 symptoms. In fact, it has been reported that preventive measures against COVID-19 were less strict during 2021 compared to those in 2020 [19] as well as that wearing only face masks at the workplace might not be sufficient to be fully protected [20], which could be applicable in places where the students were employed in the past summer.

Toward the end of the summer break, fewer students reported holiday travel. Instead, they reported visiting social events, parties, and weddings. At the beginning of September, students reported having household members with COVID-19, which suggested a shift in the mode of transmission with the focus on domestic setting (nuclear family, flat sharing, and room sharing). Recent studies have shown that the level of transmission of COVID-19 is the highest in social interaction with household members [21, 22] as it may be challenging for some to entirely distance in smaller households and rooms in student dormitories.

Bearing in mind that the ISH is the main institution for health care of university students, the results of this study are likely generalizable to the university student population in Belgrade. However, it should be mentioned that in this study, it was not possible to include more variables, such as having chronic diseases and higher body mass index of the participants, which may predispose individuals to having more severe symptoms of COVID-19 and introduce unmeasured confounding. On the other hand, student populations are generally healthy and high prevalence of chronic diseases is not expected. Also, the intensity of COVID-19 symptoms is not expected to be severe. This study only included students who presented the symptoms of COVID-19 and visited the ISH seeking medical help. It is quite likely that many vaccinated students became infected yet developed such mild symptoms that they did not seek medical help. Therefore, the effect estimates observed in this analysis related to the real-world protective efficacy may be much greater than the 78% and 96% reported for moderate and severe COVID-19 symptoms. The associations in this study only propose a potential causal relationship. Ideally, a prospective cohort study of vaccinated and nonvaccinated students would allow for the estimation of absolute and relative risks for COVID-19.

Conclusion

In conclusion, this study showed that university students who were vaccinated against COVID-19 are at lower risk of developing moderate and severe symptoms of the disease. Vaccination coverage in the university student population in Belgrade is suboptimal. Because of their mobility, social contacts in and out of school, and higher likelihood of exposure to SARS-CoV-2, it is of paramount importance to increase vaccination coverage to achieve a high level of herd immunity.

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Statement of Ethics

This research complies with the guidelines for human studies and should include evidence that the research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. This study protocol was reviewed and approved by the Ethics Committee of the ISH (Approval No. 2527/2). The data from the records of the ISH were analyzed, and no additional information except those collected at examination was collected from the participants. For this reason, consent for participation in this study received a waiver from the Ethics Committee.

Conflict of Interest Statement

The authors declare that they have no conflicts of interest.

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None.

Author Contributions

M.P.: study design, data collection, data entry, data analysis, and interpretation and drafted the manuscript; S.F. and M.N.: study design, data analysis, interpretation, and provided critical review of the manuscript; A.P., M.P., M.T., M.O., Z.Z., V.L., and M.M.: study design, data collection, data entry, data analysis, and provided critical review of the manuscript; T.G.: study design, data analysis, interpretation, and drafted the manuscript. All the authors approved the final version of the manuscript before submission.

Data Availability Statement

The dataset underlying this study is available on a reasonable request to the corresponding author.

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