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COVID-19 Vaccination Outcomes and Antibiotic Crisis and Overuse During the COVID-19 Pandemic in Bosnia and Herzegovina

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ABSTRACT

Background: COVID-19 has different presentations from mild flu like symptoms such as anosmia, dysgeusia, fever, sore throat, cough, dyspnea, headache, abdominal pain and diarrhoea to severe COVID-19 with the development of acute respiratory syndrome (ARDS), septic shock, metabolic acidosis, coagulation dysfunction, multiorgan failure or even death. **Objective:** The aim of this research project was to present and highlight the outcomes of the vaccination against COVID-19 and the widespread use of antibiotics during the initial admission and treatment of COVID-19 patients in out-of-hospital settings. **Methods.** This observational cross-sectional study was conducted between September 1st and September 24th 2021, during the fourth wave of COVID-19 outbreak in Bosnia and Herzegovina, among the patients admitted to the primary health care COVID-19 centre of Canton Sarajevo in Bosnia and Herzegovina.**Results.** Patients were mostly female 213 (53.3%), with a mean age of 48.8 ±18.6, with hypertension 129 (32.3%) or diabetes mellitus 35 (8.7%) as comorbidities and being COVID-19 unvaccinated 236 (59.0%) COVID-19 unvaccinated patients expressed more fever (X^2=9.93, p<0.05), had typical COVID-19 chest X ray presentation (X^2=6.08, p<0.05) and abnormal lung auscultation sounds (X^2=5.43, p<0.05). Out of all patients, 312 (78.0%) have received antibiotics and 3 (0.75%) antivirotics such as favipiravir as therapy for the treatment of COVID-19. The mean duration of the antibiotic regime was 10.2 ± 7.5 days with a minimum of 3 days and maximum of 62 days. The minimum CRP value when antibiotics were prescribed was 0.1 (ref. value <5mg/l). The most prescribed antibiotic was doxycycline 172 (43.0%), followed by ceftriaxone 139 (34.7%) and azithromycin 108 (27.0%). **Conclusion.** Our study showed that vaccination acts protective for the development of severe COVID-19 forms, as well as that antibiotics were overused among COVID-19 infected. The outcome of such malpractice could lead to antimicrobial resistance which will be seen in further years. Governmental agencies should advise physicians to change these trends.

Keywords: COVID-19, antibiotics overuse, vaccination outcomes.

1. BACKGROUND

Coronavirus disease 2019 (COVID-19) caused by the novel coronavirus SARS-CoV-2 which was identified in December 2019 in Wuhan City, China, has resulted in a global pandemic with over 400 million cases worldwide (1). COVID-19 has different presentations from mild flu like symptoms such as anosmia, dysgeusia, fever, sore throat, cough, dyspnea, headache, abdominal pain and diarrhoea to severe COVID-19 with the development of acute respiratory syndrome (ARDS), septic shock, metabolic acidosis, coagulation dysfunction, multiorgan failure or even death.

Apart from the pressure the virus has placed on global health systems, there has been rising concerns about an increase in antimicrobial resistance (AMR) as a result of increased antibiotic prescriptions for COVID-19 patients (2). Multiple Chinese studies have shown that the percentage of bacterial co-infection during active COVID 19 disease is fairly low and despite these data studies show that more than 71%,

in some (3) as high as 95%,of patients hospitalised due to COVID 19 had received antibiotics despite the co-infection rate of 1% (4). According to other research, 3.2 percent of blood cultures were positive within the first five days after hospitalisation, and the prevalence rose to 6.1% after that, indicating a low level of co-infection in COVID-19 patients (5). The percentages mentioned above relate to patients hospitalised due to COVID-19 pneumonia, while data on bacterial coinfections and secondary infections in outpatient settings is much poorly reported. One such study from the Netherlands reported that among 281 COVID-19 patients, bacterial co-infection was classified as unlikely in 233 patients (82.9%), possible in 35 patients (12.4%) and probable in 3 patients (1.1%). Despite this, within 72 h of hospital admission, 81% of the total study population and 78% of patients classified as unlikely bacterial co-infection received antibiotics (6).

AMR is a growing and pressing public health problem which costs US 2.8 million antibiotic-resistant infections each year with more than 35 000 deaths (7) and due to COVID-19 pandemic could be further amplified. It has been estimated that by 2050, AMR will be responsible for the death of 10 million people and will cost as much as US$ 100 trillion (8).

Estimating the extent of AMR in low income countries is hampered by limited data, and Bosnia and Herzegovina is no exception. Since the start of the COVID-19 pandemic Bosnia and Herzegovina has had 360 thousand cases and 15 thousand fatalities, making it the country with the third highest mortality rates in the world (9). This study is timely because it is the first in BIH to explore the usage of antibiotics in COVID-19 treatment, and because of the ever-raising concern about the AMR.

2. OBJECTIVE

The aims of this research project were multiple: a) to present and highlight the outcomes of the vaccination against COVID-19; b) to show the widespread use of antibiotics during the initial admission and treatment of COVID-19 patients in out-of-hospital settings; c) to appeal to the healthcare system and government agencies to prevent such patterns in order to prevent an AMR crisis in our country.

3. PATIENTS AND METHODS

This observational cross-sectional study was conducted between September 1st and September 24th 2021, during the fourth wave of COVID-19 outbreak in Bosnia and Herzegovina, among the patients admitted to the primary health care COVID-19 centre of Canton Sarajevo in Bosnia and Herzegovina.

Procedure and ethical considerations

The study was validated and approved in advance by the Bioethical Committee of Dom Zdravlja Kantona Sarajevo (01-06-12167-3/21). For the population of Canton Sarajevo, the minimum sample size estimated using the Cochran formula was 384 participants (z=384, 95%ci, E=5%). Patients were informed about their participation in the study, study goals, anonymity of the data given in the study. Exclusion criteria were (i) being younger than 18 years and (ii) not being a citizen of Canton Sarajevo.

The study included all data that were documented in COVID-19 patient center electronic system such as: (i) demographic characteristics (age, sex), (ii) previous medical comorbidities and therapies for them, (iii) COVID-19 diagnosis (severity of the disease, laboratory analysis, oxygen saturation, X-ray examination), (iv) COVID-19 treatment and outcome (specific medications used in the treatment) and (v) COVID-19 vaccination status.

Statistical analysis

The data was analysed using IBM Statistics v26.0's Statistical Package for Social Sciences (SPSS) and provided as simple frequencies and cross tabulations of demographic factors. COVID-19 immunisation status, treatment, and antibiotic use. Data that were normally distributed were

		COVID-19 vaccinated (164)	COVID-19 unvaccinated (236)
Sex	Male	77 (47.0%)	110 (46.6%)
	Female	87 (53.0%)	126 (53.4%)
Age	Mean ± SD	53.8 ± 16.8	45.4 ± 19.1
Comorbidities	Hypertension	64 (39.0%)	65 (27.5%)
	Diabetes mellitus	21 (12.8%)	14 (5.9%)
	Dyslipidemia	12 (7.3%)	16 (6.8%)
	COPD	3 (1.8%)	3 (1.3%)
	Ischemic heart disease	14 (8.5%)	17 (7.2%)
Medications used	ACE inhibitors	64 (39.0%)	65 (27.5%)
	Ca antagonists	63 (38.4%)	54 (22.9%)
	Beta blockers	51 (31.1%)	62 (26.3%)
	Diuretics	61 (37.2%)	60 (25.4%)
	Statins	12 (7.3%)	16 (6.7%)
	Nitroglycerin	14 (8.5%)	17 (7.2%)
	Acetylsalicylic acid	73 (44.5%)	93 (39.4%)
	Beta agonists	2 (1.2%)	1 (0.4%)
	Metformin	10 (6.1%)	12 (5.1%)
	Benzodiazepines	82 (50.0%)	93 (39.4%)
COVID-19 symptoms	Fever	119 (72.6%)	210 (89.0%)
	Coughing	128 (78.0%)	183 (77.5%)
	Sore throat	32 (19.5%)	39 (16.5%)
	Fatigue	53 (32.3%)	74 (31.4%)
	Osteomuscular pain	64 (39.0%)	94 (39.8%)
	Diarrhoea and vomiting	5 (3.0%)	17 (7.2%)
	Loss of smell and taste	5 (3.0%)	10 (4.2%)
COVID-19 test	Positive	155 (94.5%)	224 (94.9%)
	Negative	9 (5.5%)	12 (5.1%)

Table 1. Demographic characteristics, comorbidities, medications used in their recommended therapy, COVID-19 symptoms and COVID-19 test results among patients compared between COVID-19 vaccinated and unvaccinated cases

presented as mean ± standard deviation (SD) and by median (25^{th},75^{th} percentile) if not normally distributed. Chi square test was used to investigate significant.

4. RESULTS

After excluding 26 cases because of the exclusion criteria, a total of 400 patients who were admitted to COVID-19 centres of the primary health care service were included in the study. Patients were mostly female 213 (53.3%), with a mean age of 48.8 ±18.6, with hypertension 129 (32.3%) or diabetes mellitus 35 (8.7%) as comorbidities, using ACE inhibitors 129 (32.3%), acetylsalicylic acid 166 (41.5%) and benzodiazepines 175 (43.7%) in their recommended therapy and being COVID-19 unvaccinated 236 (59.0%). Being COVID-19 vaccinated was significantly more associated with older age (M=53.8±16.8 vs 45.4±19.1, (t)=4.494, p<0.001). All other demographic characteristics, comorbidities, medications used in their recommended therapy compared between COVID-19 vaccinated and unvaccinated are presented in Table 1.

PATIENTS COVID-19 SYMPTOMATOLOGY, PHYSICAL EXAM AND DIAGNOSTIC RESULTS

Patients admitted to the primary health care COVID-19 center of Canton Sarajevo predominately presented with fever 329 (82.3%), coughing 311 (77.7%), fatigue 127 (31.7%) and some form of osteomuscular pain 158 (39.5%), were COVID-19 positive 379 (94.7%) and unvaccinated against COVID-19 236 (59.0%). All other COVID-19 symptoms and COVID-19 test results presented in comparison between COVID-19 vaccinated and unvaccinated are presented in Table 1. Patients typically were respiratory sufficient (Sp02>95%) 342 (85.5%), with a normal heart rate (60-100 bpm) 340 (85.0%), normal blood pressure (120-139 systolic mmHg and 80-89 diastolic mmHg) 280 (70.0%), afebrile 367 (91.7%). Only a small proportion of patients presented with low oxygen saturation levels at the time od admission 58 (14.5%) out of which the majority was COVID-19 unvaccinated 39 (16.5%). Lung auscultation showed normal vesicular breath sound 323 (80.7%), while X ray showed typical COVID-19 pneumonia manifestation among 347 (86.7%) patients. Laboratory findings of patients found median leukocyte count of 4.8 (4.3, 8.2), CRP 12.4 (3.7, 36.1) and D-dimer levels 2783 (2156, 4341). COVID-19 unvaccinated patients were significantly more expressed fever (X^2=9.93, p<0.05), had typical COVID-19 chest X ray presentation (X^2=6.08, p<0.05) and abnormal lung auscultation sounds (X^2=5.43, p<0.05) Only 28 (7.0%) patients have needed hospitalisation for further treatment of the COVID-19 infection.). All other physical exam, laboratory, chest X ray findings and treatment modalities among patients compared between COVID-19 vaccinated and unvaccinated are presented in Table 2.

		COVID-19 vaccinated (164)	COVID-19 Unvaccinated (236)
Sp02	<94%	19 (11.6%)	39 (16.5%)
	>95%	145 (88.4%)	197 (83.5%)
Heart frequency	<60	2 (1.2%)	3 (1.3%)
	60-100	148 (90.3%)	192 (81.4%)
	>100	14 (8.5%)	41 (17.3%)
Blood pressure	<120/80	20 (12.2%)	38 (16.1%)
	120-139;80-89	123 (75.0%)	157 (66.5%)
	>140/90	21 (12.8%)	41 (17.4%)
Body temperature	<37.2	159 (97.0%)	208 (88.1%)*
	>37.2	5 (3.0%)	28 (11.9%)
Lung auscultation	Normal vesicular breath sound	142 (86.6%)	181 (76.7%)*
	Diminished breath sound	9 (5.5%)	16 (6.8%)
	Tubular breath sound	6 (3.7%)	23 (9.7%)
	Inspiratory crackles	5 (3.0%)	13 (5.5%)
	Wheezing	2 (1.2%)	3 (1.3%)
X Ray manifestation	Yes	129 (78.7%)	218 (92.4%)*
	No	25 (15.2%)	9 (3.8%)
	n/a	10 (6.1%)	9 (3.8%)
Laboratory			
Leukocytes	4,5-11 x 10^9/l	4.7 (4.2, 7.4)	5,2 (4.7, 8.3) x 10^9
CRP	<5 mg/l	12.6 (4.0, 26.2)	12.3 (3.0, 42.1)
D dimer	<500 ng/ml	2473 (2220, 2654)	3245 (1250, 5121)
Treatment			
Usage of antibiotics		130 (79.2%)	182 (77.1%)
Usage of antiviral medicine		1 (0.6%)	2 (0.8%)
Duration of therapy		7.0 (6.0, 13.0)	10.0 (6.0, 17.0)

Table 2. Physical exam, laboratory, chest X ray findings and treatment modalities among patients compared between COVID-19 vaccinated and unvaccinated cases

ANTIBIOTIC TREATMENT AMONG COVID-19 PATIENTS

Out of all patients admitted to the primary health care COVID-19 centre of Canton Sarajevo, 312 (78.0%) have received antibiotics and 3 (0.75%) antivirotics such as favipiravir as therapy for the treatment of COVID-19. Alongside antimicrobial agents, 62 (15.5%) patients received dexamethasone, low molecular heparin 41 (10.3%), rivaroxaban 6 (1.5%) and only 3 (0.75%) pantoprazole. Supportive treatment with vitamins, antipyretics, rest, nutrition was reported among 88 (22.0%) patients.

Even though COVID 19 is a viral infection and constant warnings that it does not react to antibiotics, results in this study showed a devastatingly high percentage of antibiotic use in positive patients. The mean duration of the antibiotic regime was 10.2 ± 7.5 days with a minimum of 3 days and

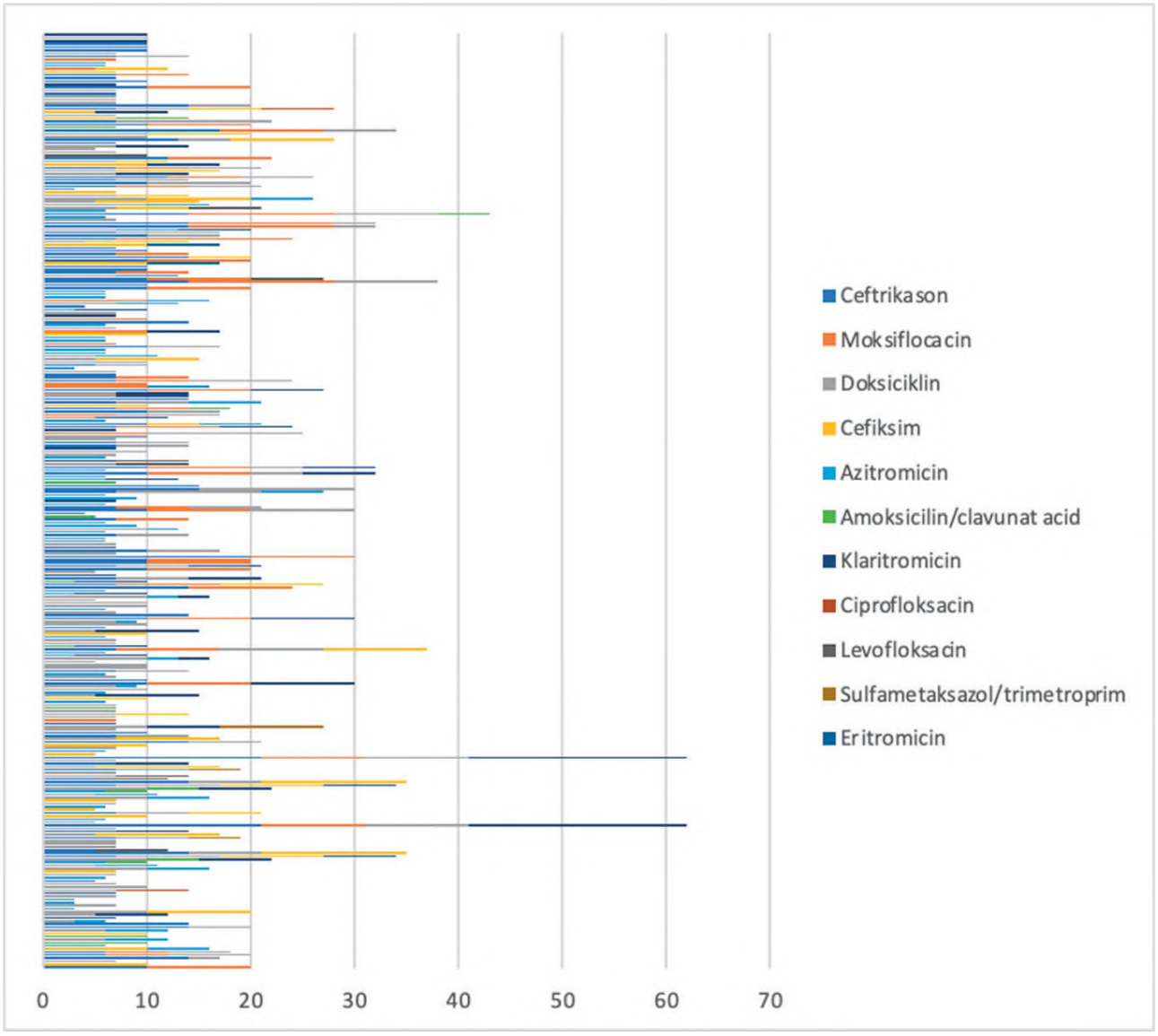

Chart 1. Duration of the antibiotic regime, and specific combination of the antibiotic used during the COVID-19 treatment period

maximum of 62 days. The minimum CRP value when antibiotics were prescribed was 0.1 (ref. value <5mg/l). The most prescribed antibiotic was doxycycline 172 (43.0%), followed by ceftriaxone 139 (34.7%) and azithromycin 108 (27.0%). Other antibiotics that were prescribed include moxifloxacin 93 (23.2%), clarithromycin 75 (18.7%), cefixime 79 (19.7%), amoxicillin-clavulanate 57 (14.2%), cephalexin 31 (7.7%), sulfamethoxazole-trimethoprim 16 (4.0%), levofloxacin 41 (10.2%), erythromycin 53 (13.2%) and ciprofloxacin 27 (6.7%). The most common regimes for COVID-19 infections that were observed included azithromycin 500mg per os for 6 days 61 (15.2%), ceftriaxone i.v. 2g for 10 days 40 (10.0%) or doxycycline 2x100mg per os for 7 days 92 (23.0%) which were further combined with other antibiotics. The duration of the antibiotic regime, and specific combination of the antibiotic used during the COVID-19 treatment period are displayed in Chart 1.

5. DISCUSSION

Out of 400 patients that met the inclusion criteria, 59% of them were unvaccinated, once more confirming the efficacy and protective effect of the vaccination. Percentage of confirmed cases was almost equally distributed between sexes, which is in accordance with earlier studies on COVID-19 that showed an equal distribution between sexes (10,11). Higher mean age in the vaccinated group probably reflects the scepticism of the younger population towards COVID-19 vaccination, and it is well documented that global vaccine hesitancy among younger people is an impediment to achieving targeted herd immunity (12-15). In both groups hypertension was the most prevalent chronic disease (64 and 65 patients respectively).

Among the patients with symptomatic COVID-19 infection, fever, cough and osteomuscular pain were most frequent symptoms reported both in the vaccinated and unvaccinated group. Biggest difference in reported symptoms between two groups was observed in fever prevalence, while other symptoms were almost equally reported in the vaccinated and unvaccinated group. Other studies on COVID-19 have reported a similar range of clinical findings (16,17, 18-21). In one study fever was present in almost all of the cases, similar to the unvaccinated group observed

in this study, but almost 20% had a low grade fever (<38°C) (16). In another study of 1099 patients from Wuhan, fever was present in only 44 percent on admission but was ultimately noted in 89 percent during the hospitalisation (22). Findings that higher percentage of patients that required oxygen supplementation in the unvaccinated group along with X-ray findings of higher percentage of pathological changes in unvaccinated patients were also found in one study from the USA aimed to determine the frequency of pneumonia at chest CT according to vaccination status, and clinical course of vaccinated and unvaccinated patients (23). Results showed pneumonia was present in 78% of non-vaccinated patients, but only 41% of vaccinated patients. Beyond the lower rates of pneumonia on CT, the clinical course of patients paralleled the chest CT findings: vaccinated patients were much less likely to require supplemental oxygen (odds ratios, .24, p=.005).

Similar to our results, one review study that analysed 19 studies on antibiotics use found that 74% of patients hospitalised for COVID-19 received antibiotics, despite only a minority of patients (17.6% among 4 studies) who received antibiotics had proven secondary or co- bacterial infection, indicating a major empiric use of antibiotics. A number of different studies have reported and reiterated about low secondary and co-infection rates with bacteria in COVID-19. Eight studies (24-31) recorded the occurrence of secondary infections and 2 (32, 33) reported co-infection rates. Pooled secondary and co-infection rate was 7.6% (123 out of 1614 patients). 4 studies reported frequency of use of different types of antibiotics (34-37). In contrast to our study where doxycycline was the most used antibiotic, it was not mentioned in the aforementioned studies, where fluoroquinolones were the most used, with 56.8% of patients (213 out of 375). Similarly to our results, ceftriaxone in 39.5% of patients (148 out of 375) and azithromycin in 29,1% of patients (109 out of 375) were 2nd and 3rd in frequency, respectively. In regards to the duration of antibiotic use, 3 other studies reported this data, but none had closely similar results to our study. Chen et al. (29) reported that it ranged between 3 and 17 days, with a median of 5 days. Borba et al. (34) reported a duration of 7 days (for Ceftriaxone) and 5 days (for Azithromycin). Pedersen et al. (28) reported that clarithromycin was discontinued if cultures for atypical bacteria were negative, whereas duration of treatment for meropenem and piperacillin-tazobactam was at least eight days. This once more confirms that antibiotics during covid 19 pandemic in BiH were used almost routinely. Xu et al. (38) noted that antibiotic use rate was higher (48% vs 41%) when duration of symptoms exceeded 10 days. They also reported that antibiotics were administered if fever lasted for more than seven days. Furthemore they noted that antibiotics were administered when C-reactive protein levels were 30 mg/L or more (normal range 0–8 mg/L), whereas in our study the lowest value of CRP when antibiotics were prescribed was 0,1. Four studies (31, 33, 39, 40) comparing survivors and non-survivors found no significant difference regarding antibiotic use.

Certain limitations of this study warrant consideration. First limitation of this study is reflected in a relatively small sample size compared to some other similar profile studies. Secondly the data was collected only from the institutions in the Canton of Sarajevo, and further studies need to be done to illuminate the trends present in the whole country.. Additionally we did not correct the data for the number of COVID-19 vaccines received, and some of the patients that were classified as "vaccinated", received only one dose of COVID-19 vaccine.. Correcting for this would probably account for even bigger differences in outcome results between the groups.

6. CONCLUSION

This cross-sectional study presented data regarding the antibiotic usage among 400 patients admitted in the outpatient COVID-19 primary care centre. As much as 78% of patients received antibiotic treatment during the course of the disease (79,2% of vaccinated and 77,1% of unvaccinated). Mean duration of treatment was 10,2 days, with the longest usage being astonishing 62 days. Furthermore, no clear criteria for antibiotic use could be found, because patients with leukocyte count as low as 4,5 x 10^9 and CRP levels of 0,1 mg/l were prescribed antibiotics. All of this indicates that antibiotics were clearly targeted at treating COVID-19 and not treating bacterial secondary or co-infections, which is against current world and local treatment recommendations. In addition to this our study showed that vaccination acts protective for the development of severe COVID-19 forms as a smaller percentage of vaccinated patients needed oxygen supplementation and X-rays showed smaller percentage of pathological changes in comparison to the unvaccinated group. Taking into consideration the raised concerns about increasing AMR that existed even before pandemics, it is crucial for governmental agencies to prevent such practices in order to prevent an AMR crisis in our society.

- **Author's contribution:** V. D and A. S gave substantial contributions to the conception or design of the work in acquisition, analysis, or interpretation of data for the work. V. D, A.S, and T. A-D.. had a part in article preparing for drafting or revising it critically for important intellectual content. A. A and A. M made their contribution in data acquisition and logistic support. All authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
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