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Coronavirus Pandemic

Immediate and long-term effects of COVID-19 on antibiotic dispensing: increasing use of Watch antibiotics

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Abstract
Introduction: The coronavirus disease 2019 (COVID-19) pandemic affected antibiotic usage worldwide. However, there is limited data from Serbia. Dispensing of oral antibiotics in Serbian pharmacies was analyzed to calculate monthly and yearly changes between 2018-2021, and to explore immediate and long-term effects of COVID-19 on antibiotic dispensing during this period.
Methodology: The number of antibiotic packages dispensed from pharmacies during the study period was analyzed with a Chi-square test to assess the average change in annual dispensing, and an interrupted time-series analysis was used to evaluate the impact of the pandemic on antibiotic dispensing. The data from 2018-2021 were retrieved from the database of a large community pharmacy chain in Serbia.
Results: The average number of antibiotic packages dispensed per day and per pharmacy was higher in 2021 compared to 2018 by one package. However, the dispensing of macrolides increased significantly; 17.7% (2018) vs. 22.5% (2021) ($p < 0.05$). In general, an increase in antibiotic dispensing was detected during COVID-19 for total antibiotics (16.4%), Watch antibiotics (44.8%), third-generation cephalosporins (80.4%), macrolides (45.5%) and azithromycin (83.7%). However, the immediate effect of COVID-19 was a decrease in the dispensing of Watch antibiotics, penicillin, and third-generation cephalosporins ($p < 0.05$); and a notable long-term COVID-19 effect was an increase in the dispensing of azithromycin ($p < 0.05$).
Conclusions: In spite of a relatively stable trend of total antibiotic dispensing before and during COVID-19 pandemic, the use of Watch antibiotics, third-generation cephalosporins, and macrolides (particularly azithromycin) showed an increasing trend in dispensing that should be optimized.

Key words: antibiotic; drug dispensing; COVID-19; bacterial resistance; Serbia.

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Introduction
Antimicrobial resistance (AMR) has been identified by the World Health Organization (WHO) as one of the top ten global public health threats [1]. Unnecessary and improper use of antibiotics leads to the development of AMR [2], and the coronavirus disease 2019 (COVID-19) pandemic has further aggravated the situation [3,4]. While most healthcare professionals were engaged in treating COVID-19, disruption to healthcare services for other patients changed medicine use patterns, leading to increased risk of AMR [5].

In the last decade (2010-2019), total antibiotic utilization in Serbia was well above the European average, even though Serbian health institutions have taken significant steps to strengthen the prudent use of antibiotics [6]. In 2019, Serbia ranked third in Europe with total antibiotic utilization of 28.65 defined daily doses (DDDs) per 1000 inhabitants per day (DID) [6]. Cyprus (30.1 DID) and Greece (34.1 DID) reported higher consumption [7]. On the other hand, the average total consumption of antibiotics for systematic use in 30 countries in Europe was 19.4 DID [7]. Therefore, the high antibiotic utilization in Europe, particularly in Southeast Europe, calls for concerted efforts to reduce AMR.

Since November 2015, the Serbian Ministry of Health has joined the global effort to combat AMR and to ensure the prudent use of antibiotics. In 2018, the national guideline for rational antibiotic use was published to raise awareness among the population and healthcare providers about the serious risks associated with irrational antibiotic use [8]. However, much more has to be done to address the increasing trend of irrational antibiotic use in Serbia [6], and in particular to raise awareness regarding the risks of self-medication with antibiotics [9,10].

During the COVID-19 pandemic, antibiotic utilization patterns may have altered and added to the development of AMR [3]. A review and meta-analysis indicated that among COVID-19 patients (n = 2010), the overall proportion of bacterial co-infection was low, less than 10%, but antibiotic usage was high and more than 70% of COVID-19 patients received antibiotics, including broad-spectrum antibiotics, even when not clinically indicated [11]. In Serbia, more than half of COVID-19 patients in the tertiary hospitals took antibiotics prior to admission, of which a third took more than one antibiotic, while 72.2% of the patients were prescribed antibiotics upon admission despite a very low number of coinfections and no evidence of clinical benefit [12]. Excessive use of antibiotics during the COVID-19 pandemic has been reported in low- and middle-income countries including Bangladesh [13]. Therefore, the pandemic changed the landscape of AMR by compromising many of the actions implemented in recent years [14]. WHO discourages the use of antibiotics for mild and moderate COVID-19 cases unless there is clinical suspicion of a bacterial infection and recommends antibiotics use for severe COVID-19 cases where there is increased risk of secondary bacterial infections and death [15].

In Serbia, the treatment of COVID-19 cases followed the guidelines for clinical management of COVID-19 that were recommended by health institutions around the world. According to the Serbian guidelines for treating COVID-19, use of antibiotics was not advised unless there was a clear indication (likely or proven bacterial infection and stage 3 of the disease (positive nasopharyngeal swab, moderate clinical presentation, severe hypoxia and cytokine storm) [12].

Analysis of antibiotic dispensing data and potential changes due to the impact of the pandemic, can help guide additional measures to prevent AMR. Given the high level of AMR in Serbia [8], it was important to identify the change in antibiotic use in Serbia during the two years of the COVID-19 pandemic compared to the pre-pandemic period, as well as to identify the specific antibiotics that need to be monitored. The issue of AMR extends beyond the national framework due to the easy and rapid spread of infections, and data from all areas are equally important. Since a national and publicly available database of antibiotics that are prescribed and dispensed is not available in Serbia, results from this study based on community pharmacies can give an insight into the actual consumption patterns of this group of drugs.

The present study aimed to analyze the trend of dispensing antibiotics by community pharmacies in Serbia over four years, from 2018 to 2021, and to explore the immediate and long-term effects of the COVID-19 pandemic on antibiotic dispensing during the observed period.

Methodology

Study design

This is a longitudinal study on the dispensing of oral antibiotics in Serbia from January 2018 to December 2021. The data was obtained from the database of a private pharmacy chain. The number of pharmacies associated with this pharmacy chain in Serbia increased over the years (Table 1), indicating preparedness to address the demand for their services in the market. Data from all pharmacies associated with the pharmacy chain were included in the study. The share of individual antibiotics and antibiotic subclasses in the overall numbers of antibiotics dispensed in the study period were calculated. The interrupted time-series (ITS) analysis was based on monthly antibiotic dispensing data from the 78 pharmacies that were part of the pharmacy chain from 2018 to 2021. This was done to ensure that the increasing number of pharmacies over the years did not lead to a false impression of increasing drug dispensing. The data source pharmacy chain had extensive geographical coverage which ensured a good representation of drug dispensing from around the country.

Table 1. Antibiotic dispensing in pharmacies, Serbia, 2018-2021.

Year	Pharmacies (N)	Dispensed packages (N)	Packages/pharmacy/day (avg. N)	Packages/pharmacy/week (avg. N)	Patients (N)	% of patients who were dispensed antibiotics, %*
2018	78	129418	5.3	32	2582576	5
2019	81	161916	6.4	38.4	3352399	4.8
2020	103	184349	5.7	33.8	3841233	4.8
2021	140	265576	6.1	36.5	4741377	5.6

N: total number; avg. N: average number; *$p < 0.05$.

Monthly dispensing data over four years (2018–2021) were used to assess average monthly and annual dispensing, and to conduct an ITS analysis to evaluate the impact of the COVID-19 pandemic on antibiotic dispensing. A state of emergency due to COVID-19 was declared in Serbia on 18 March 2020. Accordingly, the period until March 2020 was considered the pre-COVID-19 period, and from April 2020 to December 2021 as the COVID-19 period.

The data were expressed as the number of antibiotic packages per international nonproprietary name (INN). This unit has also been used in other studies [16,17]. We applied the anatomical therapeutic chemical (ATC) classification system to analyze the dispensing of antibiotics [18]. The medicines classified in the ATC classification J01 group (antibacterials for systemic use) were considered in this analysis. Analyzed oral forms of the antibiotic subgroups are presented in Table 2. Additionally, antibiotic subcategories were also analyzed depending on the risk of resistance development associated with specific antibiotic classes and the level of prescribing during the years (Table 2). The Watch group from WHO's AWaRe (Access, Watch, Reserve) classification was analyzed since it includes antibiotic classes with higher resistance potential [19]. Sixteen antibiotics in our database belonged to this group (Table 2).

In addition, the monthly dispensing data of the most used antibiotic groups before and during the COVID-19 pandemic period were also extracted (Table 2). Moreover, commonly used antibiotics, amoxicillin and azithromycin [6], were included in our analysis.

Data analysis

The following calculations were used to analyze the changes in dispensing practice during the study period:

- Proportion of patients who were dispensed antibiotics in each year (calculated as the total number of all dispensed antibiotic packages divided by the total number of receipts representing the number of patients at the annual level in all pharmacies of the pharmacy chain).
- Average number of antibiotic packages dispensed per pharmacy per day in a year (calculated as the total number of dispensed antibiotics divided by the total number of pharmacies and by the total number of days in the corresponding year, excluding Sunday. Sunday is a nonworking day in more than 90% of the pharmacies in the pharmacy chain).
- Average number of antibiotic packages dispensed per pharmacy per week in each year (calculated as the total number of dispensed antibiotics divided by the total number of pharmacies in the corresponding year and by the total number of weeks in the year).
- Proportion of certain antibiotics and antibiotic subclasses in the total number of antibiotics dispensed in a year (calculated as a proportion of each INN and each antibiotic group in the total number of antibiotics dispensed per year).
- Change in percentage of the yearly mean of dispensed antibiotics.

Statistical analysis

The trend of overall antibiotics dispensed over the years was analyzed using the Chi-square test. A comparative analysis of antibiotics dispensed in the pre-COVID-19 and during-COVID-19 periods was also performed. The antibiotics dispensed were expressed as the mean number of total dispensed antibiotics packages, before and during the COVID-19 pandemic. The change in the mean number of packages was used to express the difference in dispensing before and during the pandemic for each observed antibiotic subclass defined in Table 2.

An ITS analysis was conducted to investigate changes in the monthly antibiotic dispensing trends associated with the COVID-19 outbreak. ITS, the strongest, quasi-experimental approach for evaluating longitudinal effects of interventions, is used to estimate the size of the effect at different time points, as well as changes in the trend of the effect over time [20]. The number of dispensed antibiotic packages was the dependent variable, while time in months was the

Table 2. Antibiotics included in the analysis.

Antibiotics total	J01AA tetracyclines, J01CA penicillin with extended spectrum, J01CR combinations of penicillin including beta-lactamase inhibitors, J01DB first-generation cephalosporins, J01DC second-generation cephalosporins, J01DD third-generation cephalosporins, J01EE combinations of sulphonamides with trimethoprim including derivatives, J01FA macrolides, J01FF lincosamides, J01MA fluoroquinolones, J01XE nitrofuran derivatives, J01XX other antibacterials
Watch antibiotics	J01DC second-generation cephalosporins, J01DD third-generation cephalosporins, J01FA macrolides, J01MA fluoroquinolones, J01XX other antibacterials
Antibiotics with the highest usage in Serbia	J01FA macrolides, J01DD third-generation cephalosporins, J01CA penicillins, J01CA04 amoxicillin, J01FA10 azithromycin

independent variable. Separate ITS models were run with the time variable to reveal immediate effect (January 2018 - March 2020: time value = 0; April 2020 – December 2021: time value = 1), or long-term effect (January 2018 - March 2020: time value = 0; April 2020 – December 2021: time values were 1, 2, 3, …, 21). The ITS analysis included autoregressive integrated moving average (ARIMA) models and took into consideration the existence of seasonality. Statistical significance was set at 0.05. The analysis was performed using the Statistical Package for Social Sciences software (SPSS 28.0 for Windows, SPSS Inc., Chicago, IL, USA).

Results

The share of patients in the pharmacy chain who were dispensed antibiotics varied across the observed period: 5% (2018), 4.8% (2019), 4.8% (2020), and 5.6% (2021) ($p < 0.05$, Table 1). The average number of antibiotic packages dispensed per day, per pharmacy, and per year increased in 2021 compared to 2018 (n = 5.3 (2018), n = 6.1 (2021)) (Table 1).

The highest trend in dispensing was detected for macrolides whose share in total antibiotic dispensing yearly increased from 17.7% in 2018 to 22.5% in 2021 ($p < 0.05$) (Supplementary Table 1). Among macrolides, azithromycin was the most dispensed drug, and its share in the total number of antibiotics dispensed increased by more than 10% between 2018 and 2020 (11.2 vs. 20.4%, respectively; $p < 0.05$; Supplementary Table 1). Cephalosporins were the second most dispensed group. The dispensing of third-generation cephalosporins almost doubled from 2018 to 2021 (5.8 vs. 10.4%, respectively; $p < 0.05$; Supplementary Table 1). On the contrary, a decrease in penicillin dispensing was observed in 2020 compared to 2018 (17 vs. 13%, respectively; $p < 0.05$; Supplementary Table 1). Finally, the most dispensed antibiotic in 2018 and 2019 was amoxicillin with a share of 15.6 and 14.9%, respectively, while azithromycin dominated in 2020 and 2021 with a share of 20.4% and 16.9%, of total antibiotic packages dispensed (Supplementary Table 1).

Comparison of antibiotic dispensing before and after the emergence of COVID-19

A great increase in the mean number of dispensed antibiotic packages was detected during the COVID-19 period compared to the pre-COVID-19 period, particularly for Watch antibiotics (44.8%), third-generation cephalosporins (80.4%), macrolides (45.5%) and azithromycin (83.7%) (Table 3). On the other hand, a marked decrease in penicillin and amoxicillin dispensing was identified during the COVID-19 period compared to the pre-COVID-19 period; 6.8 and 5.1%, respectively (Table 3). Figure 1 shows changes in antibiotic monthly dispensing across the observed period, and additional details are available in Supplementary Table 2. The highest decrease in penicillin and amoxicillin dispensing was observed in April 2020 (50.6% and 50.8%, respectively) and May 2020 (49.1% and 49.3%, respectively), compared to the mean monthly dispensing in 2018/2019 (Figure 1, Supplementary Table 2). The trend of antibiotic dispensing is presented in Figure 2. Watch antibiotics showed a trend that was very similar to the total antibiotic dispensing, but at a lower level. On the other hand, penicillin, third-generation cephalosporins, and macrolides showed a similar trend, where macrolides were the most frequently dispensed class through the entire observed period. Changes in trend and extent of antibiotic dispensing after the COVID-19 outbreak are obvious.

ITS analysis showed that the immediate effect of the COVID-19 outbreak was a significant decrease in the extent of dispensing of some antibiotics such as the Watch antibiotics, penicillin, and third-generation cephalosporins ($p < 0.05$) (Table 4). A significant long-term effect and an increase in dispensing were recorded for azithromycin ($p < 0.05$). The impact of the COVID-19 outbreak on the total antibiotic consumption was

Table 3. Comparison of antibiotic dispensing before and after the emergence of the COVID-19.

	Pre-COVID-19 period, January 2018-March 2020 (mean N)	COVID-19 period, April 2020 -December 2021 (mean N)	Mean change, pre-COVID-19 vs. COVID-19 period (N)	% change, pre-COVID-19 vs. COVID-19 period
Antibiotics total	12417.2	14451.6	2034.4	16.4
Watch antibiotics	4889.3	7081.8	2192.5	44.8
Penicillins	2010	1872.6	-137.4	-6.8
Third-generation cephalosporins	749.6	1352.2	602.6	80.4
Macrolides	2328.2	3388.5	1060.3	45.5
Amoxicillin	1867.1	1771.5	-95.5	-5.1
Azithromycin	1457.6	2677.8	1220.2	83.7

mean N: mean number of dispensed packages; N: number of dispensed packages.

Figure 1. Changes in the monthly dispensing of antibiotics before and after the emergence of COVID-19 (March 2020). **A:** total antibiotics; **B:** penicillins; **C:** Watch antibiotics; **D:** third-generation cephalosporins; and **E:** macrolides.

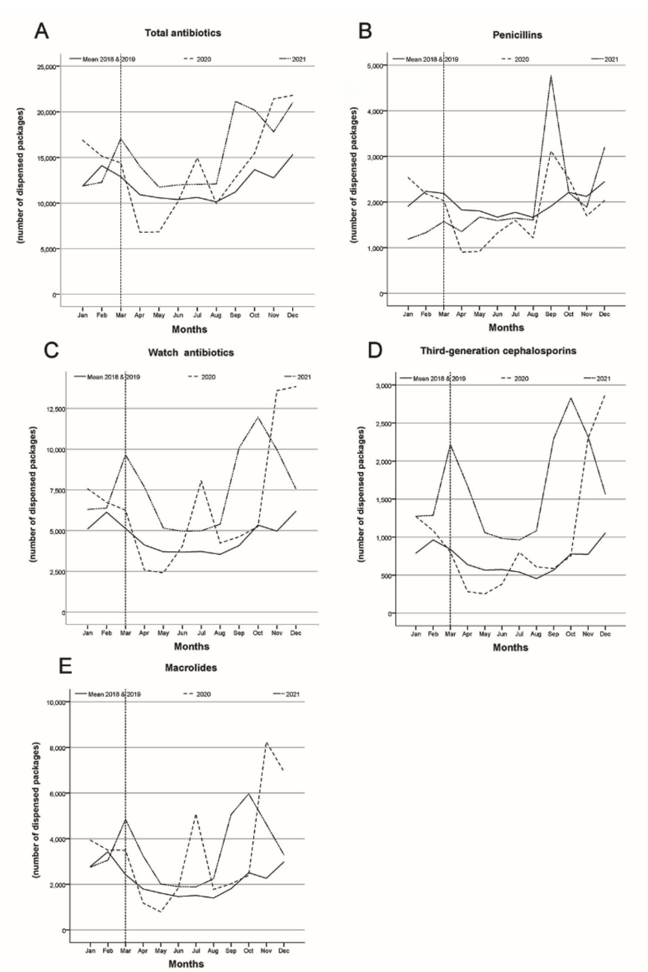
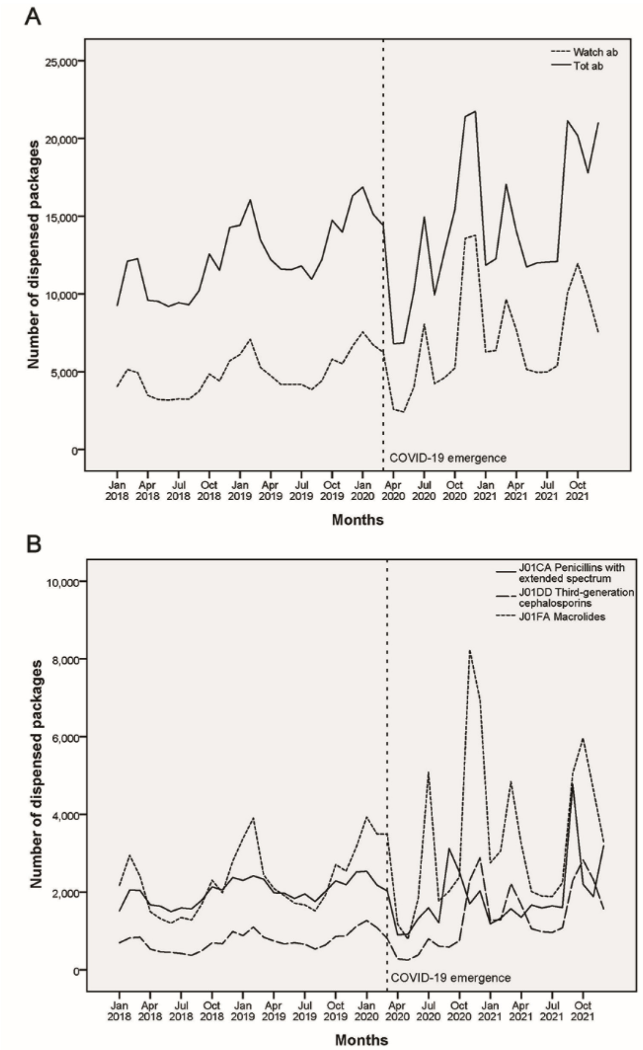


Figure 2. Trend of antibiotic dispensing between January 2018 and December 2021. **A:** total antibiotics and Watch antibiotics; **B:** penicillins, third-generation cephalosporins and macrolides.



close to significant, for both immediate effect and decreased dispensing, and long-term effect and increased dispensing, $p = 0.05$ (Table 4).

Discussion

To the best of our knowledge, this is the first study exploring antibiotic dispensing before and during the COVID-19 pandemic in Serbia. This study showed an increase in the dispensing of certain antibiotics (azithromycin, levofloxacin, second- and third-generation cephalosporins, nitrofurantoin and fosfomycin) in 2020 and 2021 compared to 2018 and 2019. Our results agree with another study performed in Serbia during the COVID-19 pandemic [12]. However, ITS analysis showed that the significant long-term effect of the COVID-19 outbreak in increased dispensing was observed only in the case of azithromycin. In contrast, a decrease in dispensing was noted across all other antibiotic subcategories, and ITS confirmed significant immediate effect of the COVID-19 outbreak in decreasing dispensing of the Watch antibiotics, penicillin, third-generation cephalosporins and amoxicillin during the period of the study (2018-2021). However, the long-term effect of the COVID-19 outbreak in increasing dispensing of total antibiotics should be assessed in future studies to determine if the trend has become an established antibiotic dispensing practice to guide further AMR stewardship programs.

The average number of antibiotics dispensed per day per pharmacy was 5.3 (2018), 6.4 (2019), 5.7 (2020) and 6.1 (2021). The increase from 2018 to 2019 reflects the traditional growing trend of antibiotic consumption in Serbia, which is in line with the results of the study that showed an increase from 23.91 DID in 2018 to 28.65 DID in 2019, at the national level [6]. Considering the Global Burden of Disease Study data,

Table 4. Interrupted time-series analysis of antibiotic dispensing calculated as the number of antibiotic packages, Serbia, January 2018-December 2021.

	Model Component	Estimate (number of packages)	t value
Antibiotics total	Immediate Effect	-2313.2	-2.01* (p = 0.05)
	Long Term Effect	163.4	2.05 *(p = 0.05)
Watch antibiotics	Immediate Effect	-3189.4	-2.27** (p = 0.03)
	Long Term Effect	1714.3	1.91 (p = 0.06)
Penicillins	Immediate Effect	-918.5	-2.19** (p = 0.04)
	Long Term Effect	16.6	0.04 (p = 0.97)
Third-generation cephalosporins	Immediate Effect	-768.2	-4.13** (p = 0.00)
	Long Term Effect	-211.1	-0.63 (p = 0.53)
Macrolides	Immediate Effect	-1648.8	-1.51 (p = 0.14)
	Long Term Effect	857.3	1.56 (p = 0.13)
Amoxicillin	Immediate Effect	-846.9	-2.07* (p = 0.05)
	Long Term Effect	16.1	0.04 (p = 0.97)
Azithromycin	Immediate Effect	-1307.9	-1.29 (p = 0.21)
	Long Term Effect	1068.7	2.28** (p = 0.03)

*p = 0.05, **p < 0.05, two-tailed.

where the prevalence rate for communicable, including maternal, neonatal and nutritional diseases in Serbia declined during the 2010–2019 period (from 41,882 in 2010 to 38,054 in 2019) [21], the reasons for this increase in antibiotic consumption need to be determined.

According to another Serbian study, amoxicillin was the most used antibiotic in Serbia in 2008 [22], and this study showed similar results for 2018-2019. Use of amoxicillin represented 38% of all antibiotics used in Serbia in 2019 [6]. Additionally, it is the most used antibiotic in self-medication and is used in the case of common cold, cough, pharyngitis and toothache [10]. On the other hand, the proportion of azithromycin use in Serbia in 2019 was around 10% of all antibiotics [6]. In a recent study in Serbia, over-prescribing of antibiotics (mostly macrolides and beta-lactams) by physicians for a diagnosis of acute bronchitis (78.5%) was shown, which is not aligned with the recommendations in the guidelines for appropriate antibiotic use [23]. The fall in the dispensing of most antibiotics, including amoxicillin during the COVID-19 period, suggests a potential decrease in the occurrence of respiratory tract infections as a result of social distancing and other protective measures implemented during the COVID 19 period. On the other hand, azithromycin was intensively used in the treatment of COVID-19 patients which resulted in the increase in dispensing in 2020 and 2021 [24]. Similarly, a decrease in dispensed antibiotic prescriptions was recorded in Sweden (17%, 2020 vs. 2019) due to the general decrease in the incidence of respiratory infections attributable to the recommendations and restrictions implemented to mitigate the COVID-19 pandemic [25].

Macrolides are bacteriostatic antibiotics and possess anti-inflammatory and immunomodulatory actions extending beyond their antibacterial activity [26]. For this reason, macrolides were proposed as an option for viral respiratory infections, including COVID-19, that present an inflammatory basis [27]. Azithromycin did not result in a superior clinical improvement of COVID-19 patients [28]. Despite the reported beneficial effect of co-treatment of hydroxychloroquine with azithromycin [29], many clinical trials using this combination therapy did not give encouraging results in COVID-19 therapy, primarily because of its treatment inefficiency and substantial cardiovascular adverse effects [8,30,31]. According to a review of studies between June 2020 and March 2021 on the global use of antibiotics in COVID-19 patients, the seven most frequently prescribed antibiotics were all Watch antibiotics [32]. These findings are consistent with a recently published study investigating the changes in hospital antimicrobial usage before and during the COVID-19 pandemic [33]. Our results also suggested an increase in dispensing the same group of antibiotics during COVID-19. A statistically significant increasing trend in the use of Watch antibiotics was also observed in Serbia during the 10 year period 2010-2019 [6]. These results suggest the need for more prudent prescription of antibiotics by clinicians to limit further development of AMR.

The antibiotic dispensing pattern during the COVID-19 pandemic seems to be different in Serbia compared to the UK where the initial months of the pandemic were associated with high levels of total antibiotic prescription, which rapidly fell below expected levels during the national lockdown, and it was suggested that this decline was indicative of reduced primary care attendance [34]. According to one recent European cross-national comparison of drugs prescribed before and during the COVID-19 pandemic, there was a substantial decrease in dispensed volumes of antibiotics for systemic use in all studied countries/regions (Czechia, Germany, Romagna (Italy), Lithuania, Slovenia, Catalonia (Spain), Sweden, and Scotland (United Kingdom)) [35]. In Japan, a reduction in antimicrobial use in 2020 during the COVID-19 pandemic, compared to preceding years was also detected, similar to the results of this study [36].

Finally, the results of this study suggest a significant change in antibiotic dispensing practice in Serbia before and during the COVID-19 pandemic. However, other circumstances were also analyzed to observe the entire burden of disease in Serbia, with particular focus on communicable diseases as potential factors that impact the antibiotic dispensing practice. The national health statistical reports list the number of communicable diseases cases in the corresponding period: (i) 2018, 11.960; (ii) 2019, 46.081 (methodological change compared to 2018, influenza diagnosis included, and represented 89.13% of total number of cases); (iii) 2020, 268.998 (78.93% COVID-19 cases); (iv) 2021, 687.257 (99.57% COVID-19 cases) [37-40]. These data show significant differences in the communicable diseases burden in 2018/19 and 2020/21, when COVID-19 cases dominated. Moreover, the burden of other communicable diseases decreased in 2021 in comparison to previous years, probably due to social distance recommendations issued during the pandemic.

Strengths and weaknesses

The most important strength of this study is the methodology used. The ITS, known as the strongest, quasi-experimental approach for evaluating longitudinal effects of interventions [20], was used to estimate the overall impact of the COVID-19 pandemic (immediate and long-term COVID-19 effects) on the trend of antibiotic dispensing in community pharmacies. Our results reflect the antibiotic dispensing practice in the entire country since the data source pharmacy chain had good geographical coverage and included numerous pharmacies located all around the country. Additionally, we were able to estimate the seasonal variation since there was data on dispensing per month, which is of interest to analyze, especially during the COVID-19 period.

A limitation of the study was that it was conducted using only the number of antibiotic packages per INN data without any patient-level clinical information. Therefore, the search for factors related to antibiotic use was limited to descriptive analyses. There was a possibility that one receipt prescribed two packages of antibiotics, and in such a situation we counted two patients instead of one, and this gave us a false positive result. However, this type of error was present in all analyzed years, and therefore, the change in the share of patients with dispensed antibiotics from year to year reflected relevant changes in dispensing practice.

Conclusions

Our study highlighted the significant impact of the COVID-19 pandemic on antibiotic dispensing trends in Serbia. We observed a change in the pattern of antibiotic consumption due to COVID-19. The antibiotics that should be used in practice with caution are Watch antibiotics, third-generation cephalosporins, macrolides, and particularly azithromycin, because we observed a long-term increasing trend in the use of these. Further studies are needed, including information on patients, indications, and clinical outcomes to assess the extent to which antibiotic prescribing is consistent with local guidelines to help optimize their use further and to limit AMR.

Ethical approval

Ethical approval for the study was obtained by the Ethical Committee of the pharmacy chain which provided antibiotic dispensing data for the analysis (February 1, 2022).

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Authors’ contributions

Tanja Tomic and Marina Odalovic: study conception and design; data collection and analysis and interpretation of data; drafting and revising the manuscript; Martin Henman and Milena Santric Milicevic: study conception and design; Ivana Tadic, Jelena Antic Stankovic, Zoran Bukumiric and Dragana Lakic: analysis and interpretation of data; Martin Henman, Ivana Tadic, Jelena Antic Stankovic, Milena Santric Milicevic Zoran Bukumiric and Dragana Lakic: revision of the manuscript. All authors read, reviewed and approved the final version of the manuscript.

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Annex – Supplementary Items

Supplementary Table 1. Proportion of antibiotics dispensed yearly in Serbia, 2018-2021.

Antibiotics (ATC code, INN)	Dispensed packages, n (%)			
	2018	2019	2020	2021
J01A tetracyclines*	14460 (11.2)	16719 (10.3)	18493 (10.0)	22411 (8.4)
• J01AA tetracyclines				
J01AA02 doxycycline*	14396 (11.1)	16662 (10.3)	18437 (10)	22331 (8.4)
J01AA07 tetracycline	64 (0.1)	57 (0.0)	56 (0.0)	80 (0.0)
J01C beta-lactam antibacterials, penicillins*	21950 (17)	25903 (16)	23957 (13)	34906 (13.1)
• J01CA penicillins with extended spectrum				
J01CA01 ampicillin*	1732 (1.3)	1756 (1.1)	1621 (0.9)	1947 (0.7)
J01CA04 amoxicillin*	20218 (15.6)	24147 (14.9)	22336 (12.1)	32960 (12.4)
J01C beta-lactam antibacterials, penicillins*	17662 (13.7)	23335 (14.4)	19151 (10.4)	33642 (12.7)
• J01CR combinations of penicillins, including beta-lactamase inhibitors				
J01D other beta-lactam antibacterials*	18000 (13.9)	21986 (13.6)	22322 (12.1)	28810 (10.9)
• J01DB first-generation cephalosporins				
J01DB01 cefalexin*	17026 (13.2)	20836 (12.9)	21712 (11.8)	27837 (10.5)
J01DB05 cefadroxil*	974 (0.8)	1150 (0.7)	610 (0.3)	973 (0.4)
J01D other beta-lactam antibacterials*	1488 (1.2)	2699 (1.7)	2343 (1.3)	4213 (1.6)
• J01DC second-generation cephalosporins				
J01DC02 cefuroxime*	449 (0.4)	1292 (0.8)	1430 (0.8)	1883 (0.7)
J01DC04 cefaclor*	235 (0.2)	181 (0.1)	59 (0.0)	34 (0.0)
J01DC10 cefprozil*	804 (0.6)	1226 (0.8)	854 (0.5)	2296 (0.9)
J01D other beta-lactam antibacterials*	7451 (5.8)	9810 (6.1)	13546 (7.4)	27579 (10.4)
• J01DD third-generation cephalosporins				
J01DD08 cefixime*	6504 (5.0)	8182 (5.1)	12171 (6.6)	24658 (9.3)
J01DD13 cefpodoxime*	947 (0.7)	1628 (1.0)	1375 (0.8)	2921 (1.1)
J01EE, combinations of sulphonamides with trimethoprim, including derivatives	4848 (3.8)	6336 (3.9)	6867 (3.7)	9127 (3.4)
• J01EE01 sulfamethoxazole and trimethoprim				
J01F macrolides, lincosamides and streptogramins*	22954 (17.7)	29495 (18.2)	46564 (25.3)	59802 (22.5)
• J01FA Macrolides				
J01FA01 erythromycin*	1783 (1.4)	2292 (1.4)	1589 (0.9)	2233 (0.8)
J01FA03 midecamycin*	68 (0.1)	133 (0.1)	58 (0.0)	37 (0.0)
J01FA06 roxithromycin*	980 (0.8)	1214 (0.8)	1311 (0,7)	2498 (0.9)
J01FA09 clarithromycin*	5678 (4.4)	7885 (4.9)	6093 (3.3)	10060 (3.8)
J01FA10 azithromycin*	14445 (11.2)	17971 (11.1)	37513 (20.4)	44974 (16.9)
J01F macrolides, lincosamides and streptogramins	2639 (2.0)	3290 (2.0)	3747 (2.0)	5329 (2.0)
• J01FF lincosamides				
• J01FF01 clindamycin				
J01M quinolone antibacterials*	14905 (11.5)	17262 (10.7)	22323 (12.1)	32156 (12.1)
• J01MA fluoroquinolones				
J01MA01 ofloxacin	39 (0.03)	/	/	/
J01MA02 ciprofloxacin*	10405 (8.0)	11920 (7.4)	12931 (7.0)	18644 (7.0)
J01MA06 norfloxacin*	1140 (0.9)	1365 (0.8)	1289 (0.7)	1485 (0.6)
J01MA12 levofloxacin*	3172 (2.5)	3857 (2.4)	7907 (4.3)	11634 (4.4)
J01MA14 moxifloxacin*	149 (0.1)	120 (0.1)	196 (0.1)	393 (0.2)
J01XE nitrofuran derivatives*	210 (0.2)	767 (0.5)	551 (0.3)	915 (0.3)
J01XE01 nitrofurantoin*	210 (0.2)	767 (0.5)	551 (0.3)	915 (0.3)
J01XX other antibacterials*	2852 (2.2)	4314 (2.7)	4487 (2.4)	6687 (2.5)
J01XX01 fosfomycin*	2553 (2)	3892 (2.4)	4146 (2.3)	6594 (2.5)
J01XX07 nitroxoline*	298 (0.2)	420 (0.3)	341 (0.2)	88 (0.0)
J01XX08 linezolid	1 (0.00)	2 (0.00)	/	5 (0.00)

ATC: anatomical therapeutic chemical; INN: international nonproprietary names; / = no data available. *$p < 0.05$.

Supplementary Table 2. Comparison of monthly antibiotic dispensing, expressed as the number of packages, in Serbia; before and after COVID-19; 2018-2021.

	Months	2018	2019	2020	Mean number of packages (2018-March 2020)	2020	Change in % (Mean 2018-March 2020 vs. April-December 2020)	2021	Change in % (Mean 2018-March 2020 vs. 2021)
Antibiotics total	January	9285	14430	16890	13535	/	/	11881	-12.2
	February	12123	16072	15145	14446.7	/	/	12273	-15.0
	March	12293	13476	14401	13390	/	/	17052	27.3
	April	9607	12218	/	10912.5	6797	-37.7	14030	28.6
	May	9540	11608	/	10574	6853	-35.2	11737	11.0
	June	9201	11566	/	10383.5	10206	-1.7	11995	15.5
	July	9439	11807	/	10623	14961	40.8	12054	13.5
	August	9312	10954	/	10133	9946	-1.8	12092	19.3
	September	10220	12219	/	11219.5	12775	13.9	21142	88.4
	October	12576	14747	/	13661.5	15448	13.1	20190	47.8
	November	11535	13987	/	12761	21416	67.8	17810	39.6
	December	14288	16325	/	15306.5	21806	42.5	21019	37.3
Watch antibiotics	January	4087	6123	5105	5105	/	/	6302	23.4
	February	5164	7104	6134	6134	/	/	6385	4.1
	March	4974	5286	5130	5130	/	/	9651	88.1
	April	3488	4750	/	4119	2579	-37.4	7675	86.3
	May	3227	4181	/	3704	2408	-35.0	5155	39.2
	June	3177	4184	/	3680.5	4040	9.8	4962	34.8
	July	3254	4188	/	3721	8058	116.6	4989	34.1
	August	3229	3860	/	3544.5	4237	19.5	5395	52.2
	September	3745	4425	/	4085	4624	13.2	10084	146.9
	October	4866	5816	/	5341	5256	-1.6	11957	123.9
	November	4417	5528	/	4972.5	13591	173.3	9965	100.4
	December	5723	6654	/	6188.5	13836	123.6	7568	22.3
Penicillins with extended spectrum	January	1517	2302	2537	2118.7	/	/	1186	-44.0
	February	2054	2418	2180	2217.3	/	/	1329	-40.1
	March	2045	2332	2031	2136.0	/	/	1573	-26.4
	April	1673	1982	/	1827.5	902	-50.6	1353	-26.0
	May	1638	1972	/	1805	918	-49.1	1670	-7.5
	June	1499	1837	/	1668	1320	-20.9	1593	-4.5
	July	1595	1954	/	1774.5	1597	-10.0	1647	-7.2
	August	1569	1758	/	1663.5	1216	-26.9	1604	-3.6
	September	1795	2020	/	1907.5	3121	63.6	4769	150.0
	October	2135	2290	/	2212.5	2513	13.6	2202	-0.5
	November	2055	2190	/	2122.5	1699	-20.0	1887	-11.1
	December	2375	2517	/	2446	2031	-17.0	3195	30.6
Third-generation cephalosporins	January	697	881	1271	949.7	/	/	1275	34.3
	February	823	1103	1086	1004.0	/	/	1285	28.0
	March	841	841	806	829.3	/	/	2217	167.3
	April	534	743	/	638.5	283	-55.7	1674	162.2
	May	464	668	/	566	253	-55.3	1060	87.3
	June	450	697	/	573.5	381	-33.6	983	71.4
	July	422	659	/	540.5	800	48.0	963	78.2
	August	373	535	/	454	608	33.9	1083	138.5
	September	493	640	/	566.5	587	3.6	2292	304.6
	October	696	862	/	779	752	-3.5	2830	263.3
	November	672	875	/	773.5	2300	197.3	2321	200.1
	December	986	1122	/	1054	2882	173.4	1568	48.8

Supplementary Table 2 (continued). Comparison of monthly antibiotic dispensing, expressed as the number of packages, in Serbia; before and after COVID-19; 2018-2021.

	Months	2018	2019	2020	Mean number of packages (2018-March 2020)	2020	Change in % (Mean 2018-March 2020 vs. April-December 2020)	2021	Change in % (Mean 2018-March 2020 vs. 2021)
Macrolides	January	2175	3385	3933	3164.3	/	/	2753	-13.0
	February	2948	3905	3497	3450.0	/	/	3060	-11.3
	March	2403	2444	3493	2780.0	/	/	4843	74.2
	April	1495	2092	/	1793.5	1178	-34.3	3244	80.9
	May	1317	1912	/	1614.5	790	-51.1	2013	24.7
	June	1202	1717	/	1459.5	1836	25.8	1900	30.2
	July	1349	1672	/	1510.5	5087	236.8	1887	24.9
	August	1283	1517	/	1400	1773	26.6	2241	60.1
	September	1696	1924	/	1810	2022	11.7	5060	179.6
	October	2306	2709	/	2507.5	2389	-4.7	5966	137.9
	November	1984	2541	/	2262.5	8242	264.3	4637	105.0
	December	2796	3166	/	2981	6943	132.9	3295	10.5
Amoxicillin	January	1311	2098	2391	1933.3	/	/	1099	-43.2
	February	1883	2270	2060	2071.0	/	/	1254	-39.4
	March	1877	2171	1892	1980.0	/	/	1469	-25.8
	April	1562	1838	/	1700	837	-50.8	1263	-25.7
	May	1522	1841	/	1681.5	852	-49.3	1582	-5.9
	June	1392	1723	/	1557.5	1223	-21.5	1509	-3.1
	July	1474	1821	/	1647.5	1480	-10.2	1554	-5.7
	August	1445	1645	/	1545	1122	-27.4	1519	-1.7
	September	1661	1889	/	1775	3006	69.4	4633	161.0
	October	1986	2157	/	2071.5	2389	15.3	2091	0.9
	November	1908	2035	/	1971.5	1585	-19.6	1772	-10.1
	December	2197	2363	/	2280	1900	-16.7	3063	34.3
Azithromycin	January	1533	2100	2391	2008.0	/	/	1099	-45.3
	February	1904	2376	2060	2113.3	/	/	1254	-40.7
	March	1455	1497	1892	1614.7	/	/	1469	-9.0
	April	865	1239	/	1052	837	-20.4	1263	20.1
	May	784	1156	/	970	852	-12.2	1582	63.1
	June	748	1044	/	896	1223	36.5	1509	68.4
	July	810	1055	/	932.5	1480	58.7	1554	66.6
	August	833	879	/	856	1122	31.1	1519	77.5
	September	1106	1169	/	1137.5	3006	164.3	4633	307.3
	October	1434	1696	/	1565	2389	52.7	2091	33.6
	November	1238	1487	/	1362.5	1585	16.3	1772	30.1
	December	1735	1893	/	1814	1900	4.7	3063	68.9

/ = not applicable.