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RESEARCH ARTICLE

Evaluation of Hospital Antibiotic Consumption during the COVID-19 Pandemic

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Abstract: ***Introduction*****:** Antimicrobial resistance (AMR) is a pressing global health issue exacerbated by the overuse of antibiotics during the COVID-19 pandemic. Despite WHO guidelines against antibiotics for mild-to-moderate COVID-19 cases without bacterial co-infection, significant misuse has been reported globally. This study aimed to evaluate antibiotic consumption during the COVID-19 pandemic at a hospital in North Macedonia and to analyze adherence to WHO guidelines, with a focus on antimicrobial stewardship, using the ATC and WHO AWaRe classification systems. To analyze antibiotic utilization trends from January 2020 to December 2021 and assess adherence to WHO guidelines, focusing on the potential impact on AMR.

Methods**:** This retrospective observational study measured antibiotic consumption in defined daily doses (DDD) per 100 occupied bed-days (DDD/100 OBD) using ATC and WHO AWaRe classifications. Data were obtained only from ICU inpatients treated at the Clinical Hospital in Shtip, North Macedonia. Trends in annual consumption were analyzed, including rate-of-change calculations for individual antibiotics between 2020 and 2021.

Results**:** Total antibiotic consumption decreased from 2902.6 DDD/100 OBD in 2020 to 2286.5 DDD/100 OBD in 2021. A third-generation cephalosporin, ceftriaxone, was the most consumed antibiotic, accounting for 57.62% of total consumption in 2020 and 48.55% in 2021. Tetracycline use slightly increased from 13.88% in 2020 to 15.83% in 2021. Fluoroquinolone use decreased significantly from 15.22% in 2020 to 6.5% in 2021. Carbapenem consumption rose sharply from 1.7% in 2020 to 14.37% in 2021, while azithromycin use declined threefold. Antibiotics in the Access group accounted for less than 20% of total usage, while those in the Watch group predominated.

Discussion**:** The study highlights a continued reliance on broad-spectrum antibiotics during the pandemic, diverging from WHO recommendations emphasizing Access to antibiotics. These trends suggest inadequate implementation of antimicrobial stewardship practices and raise concerns about their long-term impact on AMR. Limitations include the retrospective, single-center design, which may limit the generalizability of the findings.

Conclusion**:** The findings underscore the high dependency on Watch category antibiotics and a limited focus on Access antibiotics, contrary to WHO recommendations. This highlights the urgent need for robust antimicrobial stewardship programs to control inappropriate antibiotic use and combat AMR.

Keywords: Antibiotics, drug utilization, COVID-19, defined daily doses (DDD), aware classification, antimicrobial stewardship programs.

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1. INTRODUCTION

Antimicrobial resistance (AMR) is an urgent global health threat. An estimated 1.27 million individuals, including 214,000 newborns, lose their lives to resistant infections every year globally [1]. The abuse or misuse of antimicrobial drugs is related to an increased risk of AMR worldwide. Antibiotic consumption per capita related to overuse or inappropriate use in low- and middle-income countries (LMICs) is growing rapidly [2-4] .

Official data from the Centers for Disease Control and Prevention (CDC) show that 2.8 million infections and 35,000 deaths occur per year in the United States as a result of resistant infections, whereas in the European Union (EU)/European Economic Area, 670,000 infections and 33,000 deaths have been reported [5–7]. It is estimated that by 2050, the number of resistant infections worldwide will rise to $10 million per year, associated with costs of $100–$210 trillion or approximately 1% of the global gross domestic product due to loss of productivity [8-11]. Rational antibiotic utilization and monitoring of antimicrobial use are critical for control of AMR [12-14].

Inappropriate antibiotic utilization was also witnessed during the coronavirus disease 2019 (COVID-19) pandemic. Antibiotics were administered to hospitalized patients to prevent secondary bacterial infections [15-20]. About 80% of patients with COVID-19 demonstrated an asymptomatic or mild-to-moderate course of illness, while the remaining 20% developed a severe form of illness. Empirical treatment of suspected bacterial infections in COVID-19 patients was also observed in many tertiary care facilities. The World Health Organization (WHO) and other experts recommend against starting antibiotic treatment for COVID-19 cases that are suspected or confirmed to be mild. They also advise against prescribing antibiotics for moderate COVID-19 cases unless laboratory results confirm a bacterial infection, and in critically ill patients, unless there is a clear clinical indication [12].

Despite clear guidelines from the WHO recommending that antibiotics should be reserved for hospitalized COVID-19 patients with confirmed bacterial co-infections, there has been undue use of antibiotics among COVID-19 patients, particularly those with mild-to-moderate illness who do not show signs or symptoms of bacterial co-infection. Antibiotics may offer therapeutic advantages to COVID-19 patients who have bacterial co-infections, those who are immunocompromised, or individuals with extended hospital stays due to their increased risk of bacterial infections [21]. Studies have shown that in approximately 90% of COVID-19 patients where antibiotics were used systematically, the prescription was empirical, and this could exacerbate the already serious problem of antibiotic resistance [22–24].

Post-pandemic research has confirmed that up to 75% of COVID-19 patients were treated with antibiotics, although bacterial co-infection was not confirmed [12, 25]. The bacterial co-infection rate of COVID-19 patients was almost 28% in Europe, and patients with mild or medium symptoms were not reported for co-infection because these patients were not tested for infection [26]. A review found that in nearly all of the studies analyzed, fewer than 4% of hospitalized patients had a recorded bacterial co-infection. In contrast, another meta-analysis indicated that 7% of hospitalized COVID-19 patients had a bacterial co-infection, with the rate rising to 14% in studies focusing exclusively on intensive care patients [27, 28].

Many LMICs, including the Republic of North Macedonia, lack the implementation of a robust antimicrobial stewardship program (AMS), which was additionally worsened during the COVID-19 pandemic. Overprescribing and irrational antibiotic use in LMICs during the pandemic, after the return to normalcy in 2021 and 2022, may have been associated with a higher prevalence of non-COVID infections and increased use of antibiotics [29,30]. Studies conducted in several countries confirmed an increase in antimicrobial consumption in ICUs during the pandemic [31–34]. Frequent prescribing of antibiotics and empirical treatment was also witnessed in the Republic of North Macedonia. Therefore, antimicrobial monitoring, especially during the pandemic, was crucial to identify concerning signs of misuse or overuse. The pandemic has impacted the implementation of health awareness programs and preventive health care [35].

Our retrospective study aimed to examine the consumption of antibiotics in patients with COVID-19 admitted to intensive care units (ICU) in the Clinical Hospital in Shtip, the Republic of North Macedonia, from January 2020 to December 2021. In addition, to identify the trends of antibiotic use during the COVID-19 pandemic, when the hospital was transformed into a COVID-19 Center.

2. METHODS

A descriptive retrospective study was carried out at the Clinical Hospital in Shtip in order to evaluate antibiotic consumption over two years during the COVID-19 pandemic. The hospital had been allocated the necessary resources for the management of patients with COVID-19. Ethical approval of the study was obtained from the Research Ethics Committee of the Clinical Hospital Shtip. A total of 1069 and 1549 COVID-19 patients were admitted to this hospital in 2020 and 2021, respectively. The study included patients of all age groups, both male and female, with or without comorbidities, all within an inpatient setting. The datasets were anonymized, containing no patient identifiers or any identifiable patient information.

Data on the consumption of antibiotics during the period of January 2020 to December 2021 were collected and classified according to the Anatomical Therapeutic Chemical Classification System (ATC) code [36] and WHO AWaRe Classification Database of Antibiotics for evaluation and monitoring of use [37]. The WHO AWaRe Classification categorizes antibiotics into Access (first- and second-line treatments with lower resistance risk), Watch (broad-spectrum antibiotics with higher resistance risk, used carefully), and Reserve (last-line treatments for multi-drug-resistant infections).

Data were obtained from the ICU department, which had 35 beds during the evaluated period. It was one of the reference hospitals to care for critically ill patients affected by COVID-19 in the eastern and central part of the Republic of North Macedonia. The average occupancy rate of beds in the

intensive care units during the period was above 90%. The total number of hospital days (bed/day) BD, during the study period, and the index of occupancy of hospital beds were collected from the administration department of the Clinical Hospital, whereas the quantity of antibiotics with ATC code J01 dispensed during the studied period was obtained from the hospital pharmacy.

This data included the consumption of oral and intravenous antibiotics prescribed to inpatients, and antibiotics prescribed upon discharge were excluded from this calculation. The quantity of antibiotics was converted into several daily defined doses (DDD) per 100 occupied bed-days (DDDs/100 OBD) *via* the anatomical-therapeutic-chemical (ATC) and DDD drug classification, where DDD is the average maintenance dose per day for a drug used for its main indication in adults. DDD values for every antibiotic are calculated separately with the Antibiotic Consumption Calculator (ABC Cal Version 3.1 constructed by Monnet DL, Staten Serum Institute 2006). DDDs = Number of boxes x number of tablets in the box or number of vials x grams of active compound in tablet or vial/the DDD value of the antibiotic in grams. In this calculation method, the form used for in-bed patients is the ratio of the total DDD per 100 occupied-bed-days [38, 39]. Appropriate statistical analysis was applied in the evaluation of the obtained data.

The rate of change in antibiotic usage between 2021 and 2020 was calculated for each antibiotic. This was determined by the formula:

Rate of change = (DDD_{2021}/100 OBD –DDD_{2020}/100OBD) / (DDD_{2020}/100 OBD)

For those antibiotics not used in 2020, artificial values were assigned to highlight their absence. Specifically, J01CR05 piperacillin and enzyme inhibitor, J01MA14 moxifloxacin, and J01DH02 meropenem were assigned an artificial rate of change with a value of 6 (a significant positive change) to indicate their absence in 2020. A scatter plot was generated using Matplotlib to visualize the data. The x-axis represents the level of antibiotic use in 2021 (DDD per 100 OBD), while the y-axis shows the rate of change in antibiotic use (2021 *vs*. 2020). Points were plotted with varying colors and markers to differentiate between antibiotics.

3. RESULTS

Monitoring and optimizing antibiotic use are critical for preventing the development of AMR. The impact of AMR on the delivery of regular and urgent care units in hospitals has been widely recognized [12, 35]. In 2020, a total of 1069 (712 male and 357 female) COVID-19 patients and 1549 (1021 male and 528 female) COVID-19 patients in 2021were admitted to the Clinical Hospital in Shtip. Antibiotic consumption was calculated for all antibiotics used during the study period of two years (2020–2021). Total antibiotic consumption (intravenous and oral) in 2020 was 2902.6 DDD/100 OBD and decreased to 2286.5 DDD/100 OBD in 2021. Compared to intravenous consumption, oral consumption of antibiotics remained low during 2020 and 2021 in the Clinical Hospital in Shtip. When stratified by the route of administration, oral antibiotic use for 2020 and 2021 was 622.79 DDD/100 OBD or 21.46% and 380.07 DDD/100 OBD or 16.62%, respectively. In both evaluated years, more than 80% of the antibiotics were administered parenterally.

During the evaluated period, monthly antibiotic consumption varied, as illustrated in Fig. (**1**). This figure highlights evident fluctuations in usage patterns across different months. The average consumption per month in 2020 was 241.88 ± 132.31 DDD/100 OBD, and in 2021 it was 190.54±53.14. The increase in antibiotic use compared to January 2020 (62.3 DDD/100 OBD) and February 2020 (38.2DBD) was confirmed in March 2020 with 282.1 DDD/100 OBD, and rose to the highest value in April 2020 with 440.1 DDD/100 OBD, followed by 437.5 DDD/100 OBD in September 2020. During eleven months in 2021, the antibiotic consumption was above 145 DDD/100 OBD, except in August 2021, when the consumption decreased to 82.4 DDD/100 OBD.

Patients with COVID-19 at the Clinical Hospital in Shtip were prescribed antibiotics from nine different classes (Table **1**) without culture tests being conducted, with a particular emphasis on the frequent use of antibiotics from Watch category of the AWaRe classification by WHO. The results showed different antibiotic use patterns between 2020 and 2021 (Figs. **2a** and **b**, respectively). The obtained results confirmed that the most frequently used antibiotics in the evaluated period were third-generation cephalosporins, where ceftriaxone accounted for 1672.4 DDD/100 OBD or 57.62% of total antibiotic consumption in 2020 and 1110 DDD/100 OBD or 48.55% of total antibiotic consumption in 2021. Tetracyclines were represented with 402.8 DDD/100 OBD (13.88 %) in 2020 *vs*. 361.9 DDD/100 OBD (15.83%) in 2021, while the use of fluoroquinolones decreased from 441.9 DDD/100 OBD or 15.22% in 2020 to 148.5 DDD/100 OBD or 6.5%. In the two years, an increase in carbapenems utilization was observed, from 49.2 DDD/100 OBD in 2020 to 328.6 DDD/100 OBD in 2021. Consumption of macrolide antibiotic (azithromycin) in 2020 accounted for 6.1% of total antibiotic consumption or 177 DDD/100 OBD, and in 2021, there was a threefold decrease in consumption or 2.33% of total antibiotic utilization (53.2 DDD/100 OBD). During 2020, antibiotic classes presented with up to 2.5% (0.26-2.43%) utilization were carbapenems 49.2 DDD/100 OBD (1.7%), lincosamides 65.4 DDD/100 OBD (2.25%), glycopeptide antibacterials 20.7 DDD/100 OBD (0.71%), and imidazole derivative 62.2 DDD/100 OBD (2.43%). In 2021, the utilization of these antibiotic classes was as follows: carbapenems 328.6 DDD/100 OBD (14.37%), lincosamides 218.2 DDD/100 OBD (9.54%), glycopeptide antibiotics 26.7 DDD/100 OBD (1.17%), and imidazole derivative 6.0 DDD/100 OBD (0.26%).

The hospital's Access group antibiotic use for 2020 and 2021 was 18.10% and 19.76%, respectively. Comparative monthly utilization (Table **2**) of antibiotics from Access and Watch categories in the evaluated period of two years is presented in Fig. (**3**).

The most frequently used antibiotics that contributed to over 99% of total hospital antibiotic use in the evaluated period, as listed in Table **2**, are graphically presented in Fig. (**4**). Data demonstrated trends in antimicrobial utilization during the two-year study period. The most frequently used antibiotics were ceftriaxone, doxycycline, ciprofloxacin –

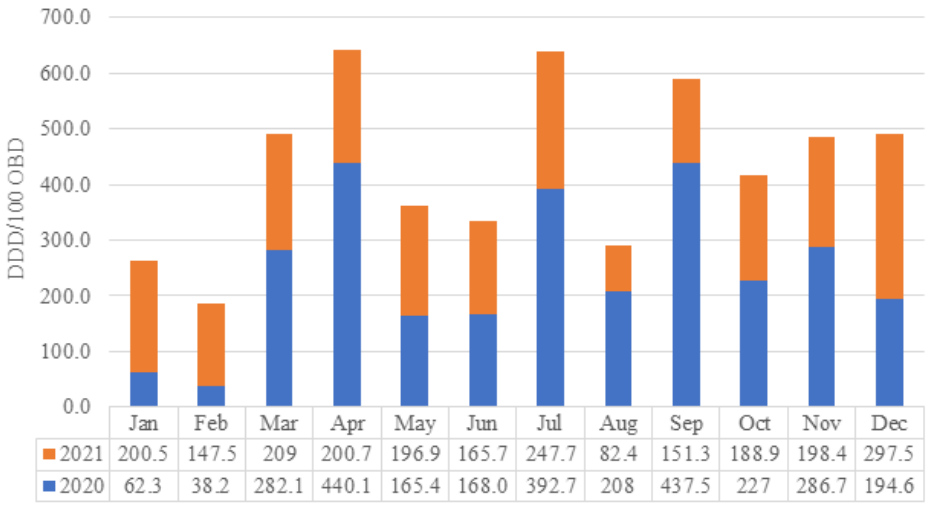

Fig. (1). Monthly antibiotic consumption in 2020 and 2021 presented with the number of DDD per 100 Bed Days (OBD). (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Table 1. Consumption of different classes of antibiotics presented as DDDs/100 OBD and percentage during 2020 and 2021 in the Clinical Hospital in Shtip.

ATC	2020 DDDs/100 OBD	% of Total Consumption in 2020	2021 DDDs/100 OBD	% of Total Consumption in 2021
J01A - Tetracyclines	402.8	13.88	361.9	15.83
J01C - Beta-lactam antibacterials, Penicillins	2.1	0.07	33.8	1.48
J01DD - Third-generation cephalosporins	1672.4	57.62	1110	48.55
J01DH - Carbapenems	49.2	1.70	328.6	14.37
J01FA - Macrolides	177	6.10	53.2	2.33
J01FF - Lincosamides	65.4	2.25	218.2	9.54
J01MA - Fluoroquinolones	441.9	15.22	148.5	6.49
J01XA - Glycopeptide antibacterials	20.7	0.71	26.7	1.17
J01XD - Imidazole derivatives	70.4	2.43	6	0.26
J01 - Antibacterials for systemic use (Total)	2902.6	100	2286.5	100

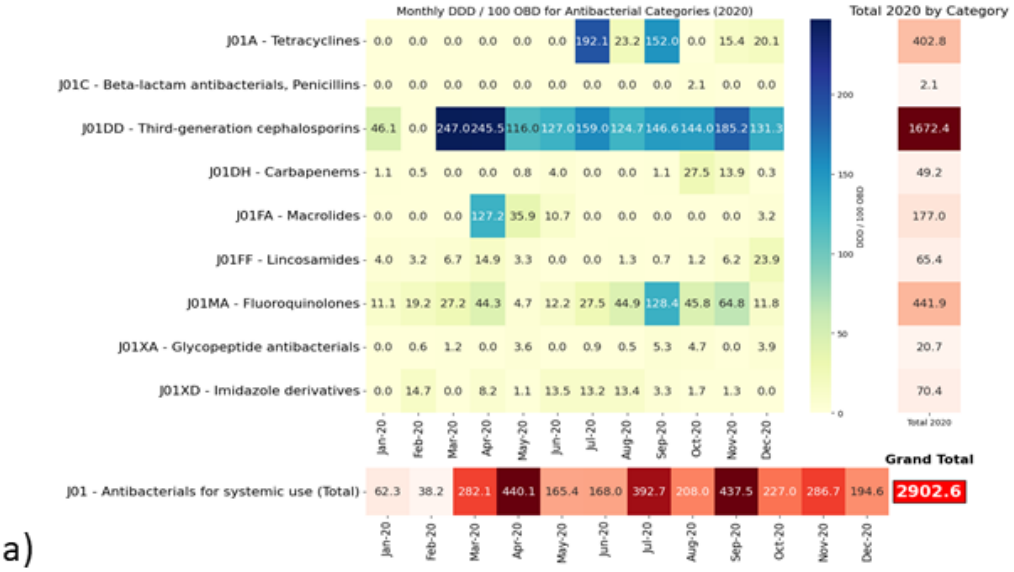

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Fig. (2). Contd…

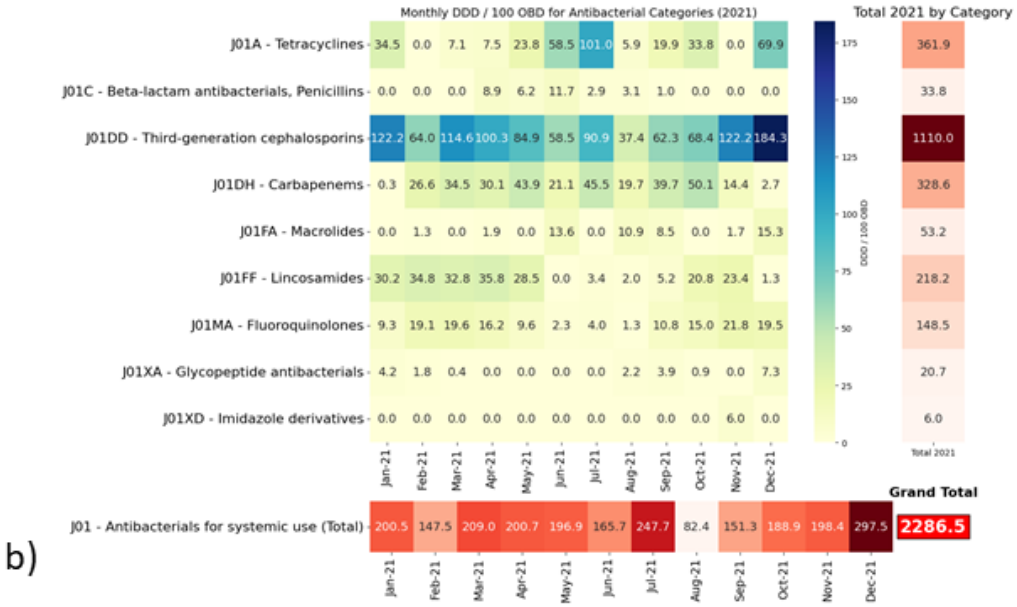

Fig. (2). Monthly antibiotic utilization during (**a**) 2020 and (**b**) 2021. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Table 2. Antibiotics utilized in clinical hospital shtip during january 2020-december 2021.

-	-	ATC	Route of Administration	WHO AWaRe Category	Generic Drug	2020 DDD/ 100 OBD	2021 DDD/ 100 OBD
J01A - Tetracyclines	J01AA - Tetracyclines	J01AA02	Oral	Access	Doxycycline	402.8	370.7
J01C- Beta-lactam antibacterial, Penicillins	Beta-lactam antibacterials, Penicillins	J01CA12	Parenteral	Watch	Piperacillin	2.1	0
	J01CR - Comb. of penicillins (incl. beta-lactamase inhibitors)	J01CR05	Parenteral	Watch	Piperacillin and enzyme inhibitor	0	33.8
J01D- Other beta-lactam antibacterials	J01DD - Third-generation cephalosporins	J01DD01	Parenteral	Watch	Cefotaxime	2.51	0.6
		J01DD04	Parenteral	Watch	Ceftriaxone	1672.0	1110.0
	J01DH - Carbapenems	J01DH02	Parenteral	Watch	Meropenem	0	39.9
		J01DH03	Parenteral	Watch	Ertapenem	9.98	26.8
		J01DH51	Parenteral	Watch	Imipenem and enzyme inhibitor	39.27	261.4
J01F - Macrolides, lincosamides and streptogramins	J01FA - Macrolides	J01FA10	Oral	Watch	Azithromycin	177.1	39.6
	J01FF - Lincosamides	J01FF01	Parenteral	Access	Clindamycin	33.96	115.9
		J01FF02	Parenteral	Watch	Lincomycin	31.4	115.9
J01M - Quinolones antibacterials	J01MA - Fluoroquinolones	J01MA02	Oral	Watch	Ciprofloxacin	42.89	4.4
		J01MA02	Parenteral	Watch	Ciprofloxacin	399.09	115.7
		J01MA14	Parenteral	Watch	Moxifloxacin	0	28.5
J01X - Other antibacterials	J01XA - Glycopeptide antibacterials	J01XA01	Parenteral	Watch	Vancomycin	20.70	26.7
	J01XD - Imidazole derivatives	J01XD01	Parenteral	Watch	Metronidazole	70.44	0

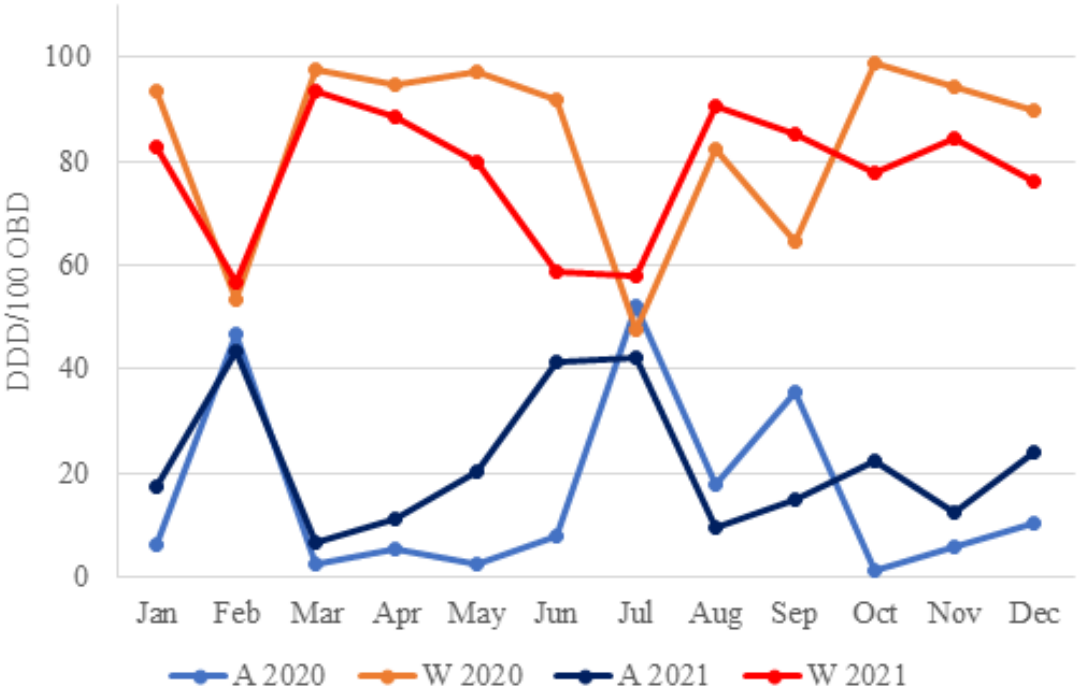

Fig. (3). Use of antibiotics from Access (A) and Watch (W) categories according to AWaRe classification is presented as the number of DDD /100 OBD categorized by months during 2020 and 2021. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

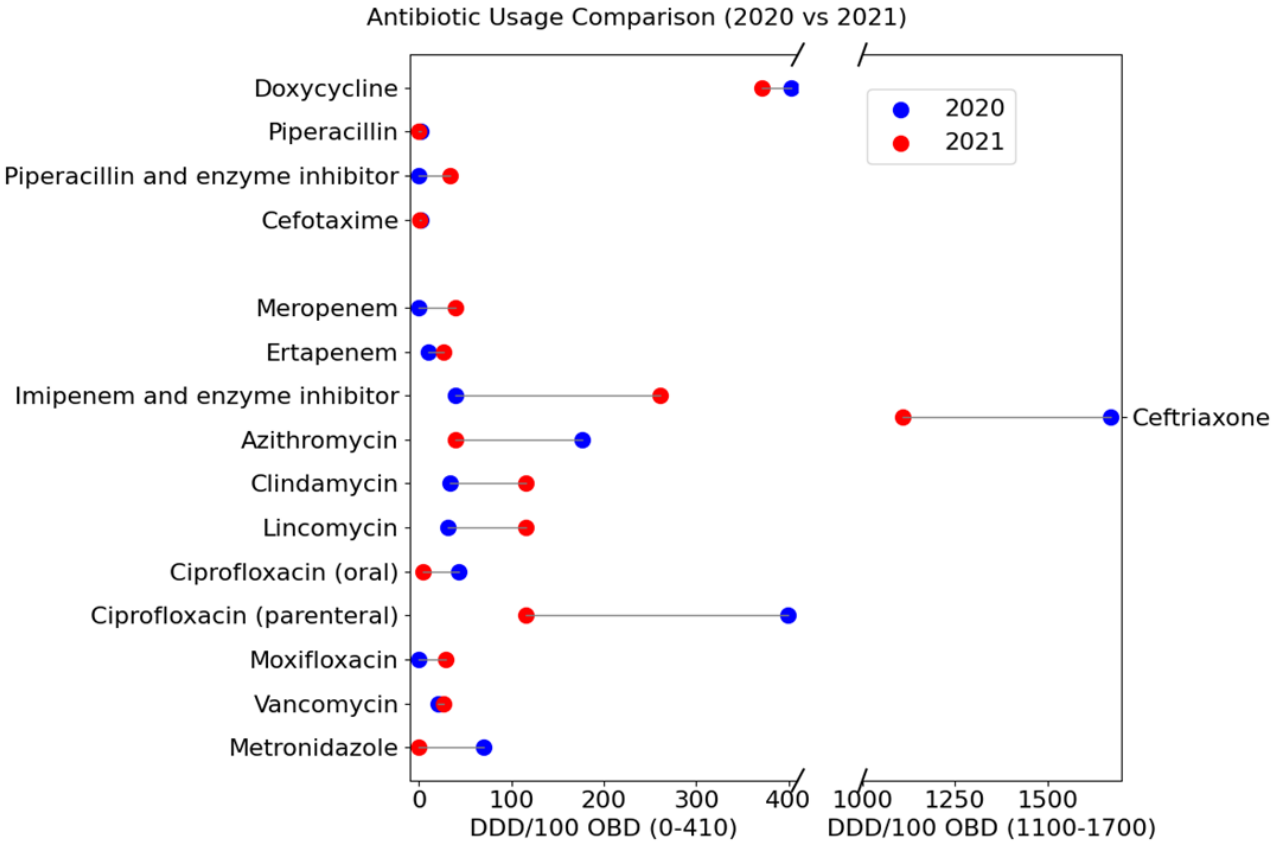

Fig. (4). Most frequently used antibiotics during 2020 and 2021 analyzed by ATC classification in Clinical Hospital Shtip. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

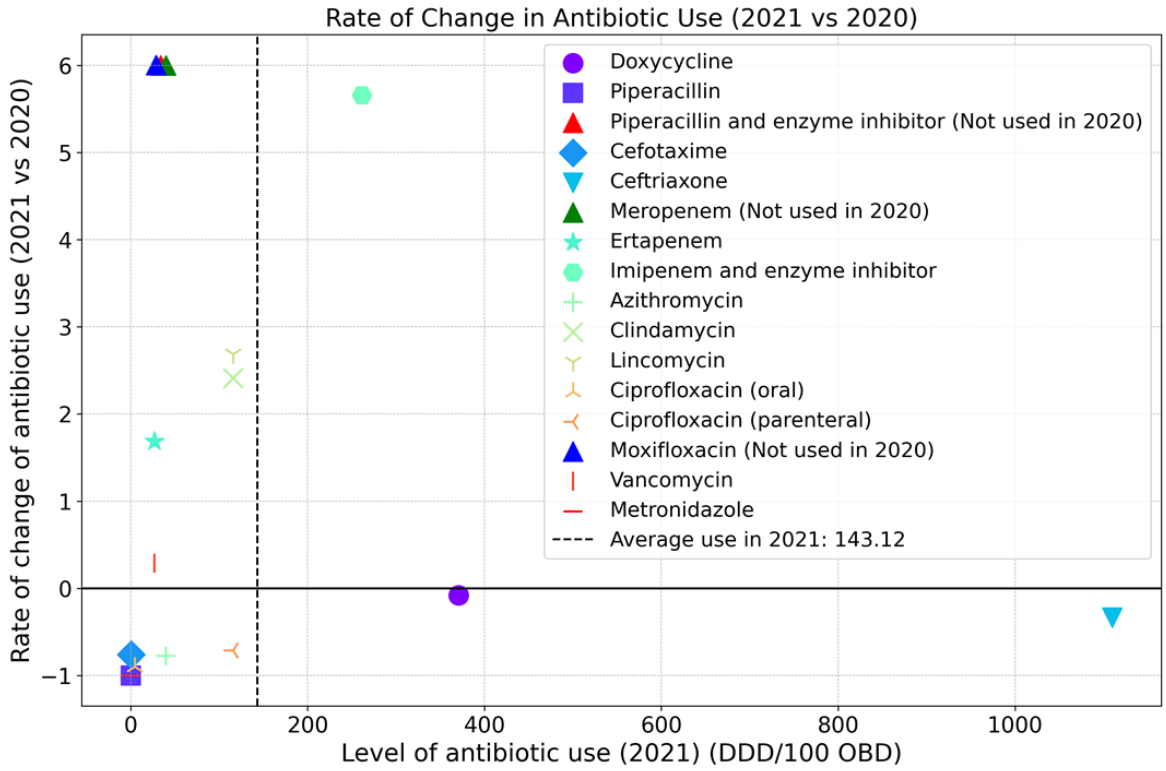

Fig. (5). Rate of change in antibiotic use between 2020 and 2021. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

both oral and parenteral, azithromycin, moxifloxacin, imipenem/cilastatin, clindamycin, and lincomycin. Interesting patterns were observed in the trends of utilization of different antibiotics during the COVID-19 pandemic (January 2020 - December 2021). Monthly analysis of the obtained data during 2020-2021 showed that ceftriaxone, a third-generation cephalosporin, accounted for more than 50% of antibiotic consumption during 14 months, especially in 2020 when the utilization of ceftriaxone accounted for more than 70% of monthly consumption in January, March, May, and June.

The group of fluoroquinolones (oral and parenteral ciprofloxacin and moxifloxacin) was the second group of most frequently utilized antibiotics. Ciprofloxacin utilization presented with 399.09 DDDs/100 OBD, as parenteral dosage form and 42.89 DDDs /100 OBD as oral dosage form in 2020, decreased to 115.9 DDDs /100 OBD, as parenteral dosage form and 4.4 DDDs/100 OBD as oral dosage form in 2021. Moxifloxacin was introduced in the treatment in March 2021 and accounted for 28.5 DDDs/100 OBD in 2021. Analyzed by month, ciprofloxacin accounted for between 9.6% and 29.4% of monthly antibiotic consumption during 2020 (from January to April and from August to November). Starting from December 2020 and during 2021, the utilization of this antibiotic declined, and accounted for approximately 10% of monthly consumption during this period.

From December 2020 to April 2021, an increase in lincomycin consumption was observed, accounting for between 10.2 and 23.6% of monthly antibiotic utilization. In 2020, lincosamides consumption was as follows: clindamycin 33.96 of DDD/100 OBD and lyncomicin 31.9 of DDDs/100 OBD, and in 2021, more than a threefold increase was observed for both antibiotics, reaching utilization of ~116 of DDD/100 OBD. A high increase in carbapenems consumption was observed in 2021 compared to 2020. In 2020, meropenem was not used in the treatment of COVID-19 patients, while its consumption reached 39.9 DDDs/100 OBD in 2021.

Ertapenem consumption rose from 9.98 of DDDs/100 OBD to 26.8 of DDDs/100 OBD, meropenem from zero up to 39.9 DDDs/100OBD in 2021, whereas consumption of imipenem/cilastatin increased 6.6-fold, from 39.27 of DDDs/100 OBD to 261.4 of DDDs/100 OBD in 2020 vs 2021, respectively.

The macrolide azithromycin was intensively used during April and May 2020, accounting for 28.9% and 11.7% of monthly consumption, respectively, and a total use of 177.10 DDDs/100 OBD during 2020. A more than fourfold decrease in azithromycin use was observed in 2021, with 39.6 DDDs/100 OBD. The glycopeptide antibacterial vancomycin showed utilization of only 20.70 DDDs/100 OBD in 2020 and 26.70 DDDs/100 OBD in 2021. The imidazole derivative metronidazole was used only during 2020, and total consumption of this antibiotic was 70.44 DDDs/100 OBD for that year.

Fig. (**5**) presents the rate of change in antibiotic usage between 2020 and 2021. Antibiotics positioned below the horizontal axis showed a decrease in consumption compared to the previous year, while those above it showed an increase. Piperacillin with enzyme inhibitor, meropenem, and moxifloxacin, marked with red triangles, were not used in 2020,

and their values in the chart are artificially assigned to indicate their significant usage in 2021. Conversely, the use of piperacillin and metronidazole was discontinued in 2021, while imipenem with an enzyme inhibitor exhibited a significant rate of change.

4. DISCUSSION

The findings from the results of antibiotic utilization at the Clinical Hospital in Shtip, the Republic of North Macedonia, during the COVID-19 pandemic in the period between January 2020 and December 2021, indicate that current antimicrobial stewardship programs (AMS) practices are either ineffective or not properly implemented to prevent indiscriminate antibiotic use. Therefore, it is essential to routinely investigate antimicrobial usage in tertiary care facilities and hospital pharmacies to enhance patient safety and improve clinical outcomes [40, 41].

Our results, in line with many other studies, confirmed an increase in antibacterial utilization during COVID-19. This consumption was higher in 2020, but it declined during 2021, although some specific trends in the use of antibiotic classes were noticed during the evaluated period. Several factors likely contributed to the rise in antimicrobial use during the COVID-19 pandemic, such as early confusion about treatment methods, hospital overcrowding, a shortage of doctors with the required expertise, reduced activity from antimicrobial stewardship teams, and the absence of initial therapeutic protocols. This highlights the crucial role of antimicrobial stewardship in ensuring the effective use of antibiotics in hospitals, particularly during emergencies [12, 31, 42].

The results of the study highlighted a notable decrease in the use of combinations of penicillins with beta-lactamase inhibitors during the COVID-19 outbreak in 2021 compared to 2021. These findings were also reported by other researchers, explaining it with reduced hospitalizations due to airway respiratory tract infections (ARTIs) during the COVID-19 pandemic, which led to the decrease in the consumption of this group of antibiotics [43-47].

Although using third-generation cephalosporins as first-line therapy is considered inappropriate, this choice was not due to a lack of availability or shortages of first-line antibiotics but rather a decision made by the prescribers [22]. A comparable trend was observed in several other countries of the world, such as China, India, Scandinavia, and other Southeast Asian countries [38, 48–53]. Ceftriaxone is typically prescribed for conditions such as community-acquired pneumonia, hospital-acquired- and ventilator-acquired pneumonia. Their utilization also scaled up in the Clinical Hospital in Shtip after the COVID-19 pandemic. Ceftriaxone utilization was constantly high in the study period, accounting for over 50% of monthly antibiotic consumption during 14 months in the period from January 2020 to December 2021. Our findings are in parallel with those of a study conducted in the United States showing a similar kind of rise in the consumption of ceftriaxone during the COVID-19 pandemic [16]. The widespread use of ceftriaxone, a third-generation cephalosporin, should be approached with caution due to its link to a higher incidence of extended-spectrum-β-lactamase (ESBL)-producing organisms [54]. A study conducted in an Italian university hospital confirmed significantly higher incidence of MDR bacterial infections in the COVID-19 departments compared to other medical departments with ESBL-producing *Klebsiella pneumoniae* accounting for most of the rise (29% versus 19%) [55].

Consumption of the third generation of cephalosporins and fluoroquinolones decreased in 2021 in comparison to 2020. A decline in fluoroquinolones usage confirmed in our study is in line with many other studies showing a reduction in fluoroquinolones throughout the period of the COVID-19 outbreak [12, 43, 56]. Fluoroquinolones are generally prescribed as empirical therapy due to their broad-spectrum activity, and typically not for the targeted antimicrobial therapy against causative microorganisms, to avoid the emergence of antimicrobial resistance. In 2020, there was a rise in the use of fluoroquinolones, which could be linked to the risk of ventilator-associated pneumonia (VAP) [57-61] allied with the mechanical ventilation required for severe COVID-19 cases. Fluoroquinolones have a broad spectrum of activity, including effectiveness against *Stenotrophomonas maltophilia*, a key pathogen in VAP [62], and COVID-19 increases the risk of VAP [22,63]. The decline in fluoroquinolone use can be explained by their limited indications, such as for genitourinary infections or hospital-acquired infections, in both children and adults. Conversely, some studies have reported a slight increase in their use. This discrepancy might occur if fluoroquinolones are employed for empirical treatment rather than targeting specific pathogens with a single antimicrobial therapy. This could be the reason for higher consumption of ciprofloxacin in our study during 2020 [43, 64, 65]. This drop-in usage may be attributed to the increased use of other antibiotics such as carbapenems and lincosamides. The observed increase in consumption trends in the use of meropenem, imipenem/cilastatin (carbapenem), clindamycin, and lincomycin (lincosamides) in 2021, overlays well with the third wave of infection, which was caused by the ß-variant of the SARS-CoV-2 virus [22, 66-68]. The results of our study are in line with reported results from other studies that confirmed an increase in the third and fourth generation cephalosporin and lincosamide consumption [31, 64, 65, 69, 70]. This may be related to the development of resistance in treated patients, inter-individual patient differences, or variations in the most common infections.

The usage of some other drugs, such as vancomycin (glycopeptide antibacterials) did not change in the period between 2020 and 2021 and was constantly low, accounting for a maximum of 2.5% of total antibiotic consumption in this period. Our results confirmed an increase in azithromycin consumption in April and May in 2020, followed by a decline of utilization, especially in 2021. The findings are consistent with other studies reporting increased use of azithromycin during the first wave of the COVID-19 pandemic, especially in combination with hydroxychloroquine [2, 69, 71-75]. This might be attributed to physicians' previous experience with azithromycin for respiratory infections or could be linked to its extensive off-label use for COVID-19 treatment in other countries due to azithromycin's in vitro antiviral effects encompassing reduced viral replication, inhibition of viral entry into host cells, and a potential impact on immune modulation [12].

Further studies on azithromycin benefits in COVID-19 patients did not reach satisfactory results, supportive of its usage in patients with mild to moderate forms of COVID-19 [12]. In the evaluated period, the usage of peroral antimicrobials was 21.46% in 2020, decreasing to 16.62% in 2021. Our study is similar to other studies evaluating rational antibiotic utilization during the COVID-19 pandemic and demonstrating a significantly high consumption of the WHO Watch category (Table **2**).

Changes in utilization of antimicrobials identified in relation to AWaRe classification were observed. The primary goal of the use of AWaRe is to reduce the use of antibiotics in the Watch and Reserve groups while increasing the usage of antibiotics in the Access group. The outcomes of this study revealed that the use of antibiotics in the Access group was below 20% (18.1% in 2020 and 19.86% in 2021). The Watch category of antimicrobials is more likely to be associated with the development of AMR, demanding continuous monitoring and urgent stewardship measures. Our findings are consistent with a published study investigating the consequences of the COVID-19 period on antibiotic usage in an inpatient setting [12]. The obtained data for the trends of antibiotic consumption in the Clinical Hospital in Shtip revealed that no antibiotics classified as Reserve group by the WHO AWaRe categorization were used.

In 2021, piperacillin and metronidazole were entirely discontinued, which could be attributed to availability issues or shifts in therapeutic practices. Cefotaxime and azithromycin experienced significant reductions of 77% and 78%, respectively, suggesting a move towards alternative antibiotics or adjustments in treatment protocols. Meanwhile, doxycycline has a modest decrease of 8%, indicating a minor shift in treatment preferences rather than a major change.

Conversely, clindamycin, lincomycin, and ertapenem saw significant rises, while the most dramatic change was observed in imipenem and the enzyme inhibitor. These data indicate a growing preference for these antibiotics, possibly due to their effectiveness in specific infections or updated guidelines. Moxifloxacin, meropenem and piperacillin, and an enzyme inhibitor were newly introduced in 2021, suggesting their recent incorporation into treatment protocols.

Overall, the data reflect a dynamic and evolving landscape of antibiotic usage. The observed trends indicate a shift towards newer or more effective treatments, with certain antibiotics being phased out in favor of alternatives. These insights underline the impact of therapeutic efficacy and changes in treatment guidelines on antibiotic usage patterns.

The COVID-19 pandemic has emerged as the most significant global health threat, requiring a crucial allocation of resources by healthcare systems worldwide for its ongoing management. All healthcare providers need to ensure that concurrent global health threats, such as antimicrobial resistance, are not overlooked during COVID-19 outbreaks, and that AMS is integrated as a key component of the immediate pandemic response [76-78]. Antimicrobial resistance should remain recognized as a major global health challenge that could jeopardize progress towards universal health coverage and health-related sustainable development goals [9]. The COVID-19 pandemic represented a significant public health threat that has also unsettled existing AMS programs, potentially promoting the rise of antimicrobial resistance among pathogens. Antimicrobial resistance appears to have been overlooked in hospitals in the Republic of North Macedonia during the pandemic, demanding urgent action for the effective reinstatement of AMS programs.

Our study can make an important contribution in evidencing the overprescribing and potential abuse, misuse, or irrational antibiotic use during the COVID-19 pandemic in the Clinical Hospital in Shtip. An increase in the use of non-evidence-based antimicrobials among COVID-19 patients was noticed. To optimize the rational use of antimicrobials, strategies should include promoting adherence to guidelines, promptly de-escalating or discontinuing therapy when there is no evidence of bacterial co-infection, selecting the appropriate antibiotic based on microbiological test results, and switching from intravenous to oral administration as soon as feasible [12, 41]. AMS programs have been and will continue to be an irreplaceable instrument in assuring the rational prescription and utilization of antimicrobials through education, research, and intervention.

Hospitals in North Macedonia could benefit from this insight into AMS. Assessing antibiotic consumption is crucial for AMS programs as it helps enhance clinical practices related to antibiotic use. A thorough investigation into the spread of antimicrobial resistance is needed to validate the impact of changes in the use of certain broad-spectrum antimicrobials and the increased use of antimicrobials in the Watch category. Hospital and community pharmacists are key factors in improving the situation in our country. This approach could result not only in control of antimicrobial resistance but also in a decrease in the economic burden in hospitals and at the national level.

However, several limitations may impact the generalizability of our findings, such as the retrospective study design. Our study was conducted at a single hospital, which makes it challenging to account for other variables that might have influenced the results, such as patient case, mix, and types of infections. Further research at the patient level is necessary. Although we assessed the trend in the consumption of antimicrobials for systemic use during 24 months of the COVID-19 pandemic in only one clinical hospital, this could help to generate a hypothesis for an extended study. Additionally, a multi-site study in more tertiary care facilities in the Republic of North Macedonia is required to gain a broader understanding of the impact of the COVID-19 pandemic on antibiotic use.

CONCLUSION

The study revealed a substantial increase in overall antibiotic consumption during the COVID-19 pandemic, particularly in 2021, with a high prevalence of broad-spectrum antibiotics from the Watch category, such as meropenem, moxifloxacin, and piperacillin combined with enzyme inhibitors. These antibiotics were newly introduced during the evaluated period. Additionally, antibiotics like lincomycin, ertapenem, imipenem with enzyme inhibitors (Watch category), and clindamycin (Access category) showed significant increases in use compared to 2020, as indicated by their rate of change. The notable use of Watch category antibiotics

raises concerns about the potential for increased antimicrobial resistance. This underscores the urgent need for the strict implementation of antimicrobial stewardship programs, particularly in ICU settings. The active involvement of hospital pharmacists is essential to monitor antibiotic use, enhance patient safety, and reduce the economic burden associated with inappropriate antibiotic prescribing.

STUDY LIMITATIONS

Several limitations may affect the generalizability of our findings. First, the retrospective study design may introduce inherent biases. Second, the study was conducted at a single hospital, which limits the ability to account for other variables that could have influenced the results, such as the patient case mix and types of infections. Furthermore, although we evaluated trends in the consumption of systemic antimicrobials during the 24 months of the COVID-19 pandemic in one clinical hospital, these findings primarily serve to generate hypotheses for extended investigations. Future research at the patient level and multi-site studies in additional tertiary care facilities across the Republic of North Macedonia are required to provide a broader understanding of the impact of the COVID-19 pandemic on antibiotic use.

AUTHORS' CONTRIBUTIONS

The authors confirm their contribution to the paper as follows: Investigation: BL; data collection: BE, TT, DM; analysis and interpretation of results: MSC; draft manuscript: ZN. All authors reviewed the results and approved the final version of the manuscript.

LIST OF ABBREVIATIONS

ABC	=	Antibiotic Consumption Calculator
AMR	=	Antimicrobial Resistance
AMS	=	Antimicrobial Stewardship Program
ARTIs	=	Acute Respiratory Tract Infections
ATC	=	Anatomical Therapeutic Chemical Classification System
AWaRe	=	Access, Watch, and Reserve (WHO classification of antibiotics)
BD	=	Bed-Day
CDC	=	Centers for Disease Control and Prevention
COVID-19	=	Coronavirus Disease 2019
DDD	=	Defined Daily Doses
ESBL	=	Extended-Spectrum β-Lactamase
EU	=	European Union
ICU	=	Intensive Care Unit
LMICs	=	Low- and Middle-Income Countries
MDR	=	Multi-Drug Resistant
OBD	=	Occupied Bed-Days
VAP	=	Ventilator-Associated Pneumonia
WHO	=	World Health Organization

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical approval of the study was obtained from the Research Ethics Committee of the Clinical Hospital Stip. The approval number is 03-423/2, dated 25.04.2022.

HUMAN AND ANIMAL RIGHTS

No animals were used in this research. All procedures performed in studies involving human participants were in accordance with the ethical standards of institutional and/or research committee and with the 1975 Declaration of Helsinki, as revised in 2013.

CONSENT FOR PUBLICATION

The study is a retrospective descriptive analysis conducted at the Clinical Hospital in Stip, North Macedonia, evaluating antibiotic consumption in the ICU over two years during the COVID-19 pandemic. The data were collected solely from administrative records, with no direct patient contact involved; hence, informed consent was not applicable in this case..

AVAILABILITY OF DATA AND MATERIALS

The data and supportive information are available within the article.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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