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Impact of the COVID-19 pandemic on antibiotic consumption in the Intensive Care Unit and Gynecology Ward at SHOGAT "Prof. Dr. D. Stamatov" Varna, Bulgaria

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One of the greatest threats to human health is bacteria's resistance to an increasing number of available antibiotics. This resistance can arise due to various factors like misuse and inappropriate antibiotic use in humans and animals. Our study aims to analyze the impact of the COVID-19 pandemic on antibiotic use in ICU and GW at the Specialized Hospital of Obstetrics and Gynecology for Active Treatment (SHOGAT) "Prof. Dr. D. Stamatov" Varna, Bulgaria. It is a retrospective analysis of data from 2017-2023 from two wards (ICU and GW) at SHOGAT. To calculate antibiotic consumption, we used the Anatomical Therapeutic Chemical/Defined Daily Dose (ATC/DDD) classification system which is an international standard for calculating antibiotic consumption in a unified technical unit - defined daily dose (DDD). The changes in antibiotic use in both wards of SHOGAT are related to COVID-19 and an adjustment in the hospital's antibiotic policy. A notable increase was observed in the use of two specific antibiotics: azithromycin and cefazolin. The high use of azithromycin in 2021 is explained by the fact that it was the main choice for patients with confirmed COVID-19. The increasing use of cefazolin is related to its application as the drug of choice for preoperative antibiotic prophylaxis. Strict adherence to antibiotic application protocols in the medical facility, along with the recommendations of EUCAST and the Bulgarian Association of Microbiologists, has limited the overuse of antimicrobial agents. This, in turn, leads to reduced treatment costs for patients and limits the development of resistant strains.

Keywords: antibiotic consumption, antibiotic stewardship, COVID-19, antibiotic guidelines

INTRODUCTION

Antibiotics are life-saving and cost-effective medicines, but the increasing resistance of pathogenic bacteria to available antibacterial therapy is one of the biggest threats to human health nowadays. In July 2022, Health Emergency Preparedness and Response (HERA) identified on an annual basis three specific high-impact health threats: pathogens with high pandemic potential; chemical, biological, radiological, and nuclear (CBRN) threats originating from accidental or deliberate release, and antimicrobial resistance [1]. The latest 2022 report from the European Centre for Disease Prevention and Control shows that the death rate from multidrug-resistant bacteria is comparable to that of HIV/AIDS, tuberculosis, and influenza combined. It is also estimated that approximately 70% of infections caused by antibiotic resistant bacteria are due to nosocomial infections [2].

Despite numerous programs to reduce usage and control prescription, resistance to clinically used antibiotics remains widespread, and the number of bacterial pathogens presenting multidrug resistance continues to rise [3]. The high consumption of antibiotics in our food chain and healthcare systems has drastically waned the effectiveness of antibacterial treatments, severely compromising our ability to manage infections. The development and introduction into clinical practice of new antibacterial therapies are inadequate to address the growing threat of antimicrobial resistance (AMR) [4]. According to the World Health Organisation (WHO) antibiotic pipeline data report, eleven new antibiotics have been approved since 2017. Only two of them represent a new class and have a new target of action (vaborbactam + meropenem and lefamulin) [5].

While not a novel paradigm, the One Health concept has seen a significant escalation in its importance in recent years, underscored by the advent of recent epidemics and pandemics, notably COVID-19. This has elucidated the complex interdependence between human, animal, plant, and environmental health, advocating against their isolated consideration. Concurrently, there has been a discernible surge in antimicrobial resistance (AMR) and the prevalence of zoonotic diseases

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(including COVID-19, avian influenza, and mpox) within the European region. Empirical evidence substantiates that identical pathogens proliferate amongst humans and animals, culminating in analogous pathologies primarily exacerbated by the homogeneous application of antibiotics across species. This homogeneity in treatment methodologies fosters an environment conducive to the amplification of AMR. In a preemptive measure, the European Union (EU) instituted a comprehensive prohibition on the utilization of antibiotics as feed additives for animals as early as 2006. Subsequently, in June 2017, the European Commission ratified the European One Health Action Plan against AMR [6]. An analytical review conducted in 2023 delineated the impediments to the efficacious enactment of AMR countermeasures within EU Member States, Norway, and Iceland [7].

According to Machowska and Lundborg [7], the drivers of the irrational use of antibiotics among healthcare providers in Europe are: knowledge, attitude, and perception of healthcare providers about antibiotic use and resistance; lack of adequate education for healthcare providers; pharmaceutical promotion; lack of rapid and sufficient diagnostic tests and local antibiotic susceptibility data; patient–doctor interaction; knowledge, attitude, and perception of pharmacists regarding antibiotic use and resistance [8]. In Europe, healthcare-associated infections (HAIs) have the highest public health burden compared to all other infectious diseases. Each year, 4.3 million patients in hospitals in the EU/EEA acquire at least one healthcare-associated infection during their stay in the hospital [9].

Antimicrobial stewardship (AMS) is a systematic approach to educate and support healthcare professionals to follow evidence-based guidelines for prescribing and administering antimicrobials [10]. AMS is the effort to measure and improve how antibiotics are prescribed by physicians and used by patients. Improving antibiotic prescribing and use is critical to effectively treat infections, protect patients from harms caused by unnecessary antibiotic use, and combat antibiotic resistance [11].

This work aimed to assess the impact of the COVID-19 pandemic on antibiotic usage in two wards: Intensive Care Unit (ICU) and Gynecology Ward (GW) at SHOGAT "Prof. Dr. D. Stamatov" Varna, Bulgaria. The analysis was conducted by reviewing antibiotic prescriptions and comparing annual antimicrobial consumption during the three years preceding the pandemic (2017–2019) with usage during various COVID-19 waves (2020–2023). Additionally, the study aimed to assess changes in antibiotic stewardship policies and their potential effects on antimicrobial use during this period.

EXPERIMENTAL

Study design

A retrospective investigation was conducted for seven years. The study was carried out in Varna, Bulgaria, at the Specialized Hospital of Obstetrics and Gynecology for Active Treatment "Prof. Dr. D. Stamatov" (SHOGAT). SHOGAT is a teaching hospital and has different wards, such as Intensive Care Units (ICU), Gynecology Ward (GW), Neonatal Ward (NW), Maternity Ward/ Labour Ward (MW/LW), High-Risk Pregnancy Ward (HRPW). The hospital has 140 beds [10 (7,14%) ICU, 10 (7,14%) NW intensive care beds, 40 (28,57%) NW and 80 (57,15%) medical. Of these 80 beds, 15 (10,72 %) are part of GW. All antibiotics for oral and parenteral use were set as inclusion criteria for the study. The limitation factor in the presented work is that antibiotic use was examined and analyzed only in two of the hospital wards (ICU and GW) because antibiotic use in them is higher.

Data collection

Data on antimicrobial use between January 2017 and December 2023 were extracted from the pharmacy information system. These data included the consumption of intravenous and oral antibiotics prescribed to inpatients. The collected data were validated by manually checking for errors. To calculate antibiotic consumption, we used the Anatomical Therapeutic Chemical/Defined Daily Dose (ATC/DDD) classification system which is an international standard for calculating antibiotic consumption in a unified technical unit defined daily dose (DDD) per 1000 inhabitants per day (IPD). When calculating antibiotic use in the separate wards, the number of occupied bed days in the ward is taken into account, while the total use is calculated based on occupied bed days in the hospital.

Classification of antibiotics

The used antibiotics were grouped according to their chemical structures into penicillins, cephalosporins, aminoglycosides, fluoroquinolones, tetracyclines, nitroimidazoles, and macrolides. The WHO AWaRe classification (Access, Watch, and Reserve) was used to categorise the antibiotics assessed.

Statistics and software

Antibiotic consumption was analysed using descriptive methods. The data are expressed as percentages and proportions. Data input, percentage calculation, and graphical visualization of the results were performed using Microsoft Excel.

RESULTS AND DISCUSSION

Calculated total antibiotic usage in SHOGAT "Prof. Dr. D. Stamatov" - Varna, Bulgaria by years, covering the period from 2017 to 2023, is presented in Table 1. The data in the table indicate that the total antibiotic usage in the hospital is considerably lower than the average reported for Europe. A 2022 EU/EEA report states that in the hospital sector, the population-weighted mean consumption of antibacterials for systemic use (ATC group J01) was 1,61 DDD per 1000 inhabitants per day (country range: 0.75–3.15), while in SHOGAT it is 0.40 DDD per 1000 inhabitants per day.

During the period 2013–2022, a statistically significant decrease in antibiotics use was observed at the EU/EEA level. Statistically significant decreasing trends were observed for six countries, and a statistically significant increasing trend was observed for two countries (Bulgaria and Croatia) [12]. This trend is also observed in the studied hospital, but despite this, the average values of antibiotic consumption (0.40 DDD/1000IPD) are lower compared to those in Bulgaria (1.72 DDD/1000IPD) and Europe (1.63 DDD/1000IPD) [12].

Table 1. Antibiotic consumption in SHOGAT hospital Varna, Bulgaria, DDD per 1000 inhabitants per day (IPD), from 2017 to 2023

	2017	2018	2019	2020	2021	2022	2023
Total antibiotic consumption *(DDD per 1000 IPD)*	0.339	0.294	0.236	0.419	0.521	0.518	0.445

Table 2. Antibiotics used in ICU and GW (DDD per 1000 IPD, 2017–2023)

ICU and GW antibiotics used *(DDD per 1000 inhabitants per day, from 2017 to 2023)*								
Ward	2017	2018	2019	2020	2021	2022	2023	Total
ICU	7.34	7.31	6.58	12.79	14.32	16. 7	12.46	77.67
GW	2.70	3.33	2.18	4.58	6.35	4.89	6.95	30.98
Total	10.04	10.64	8.76	17.37	20.67	21.76	19.41	108.65

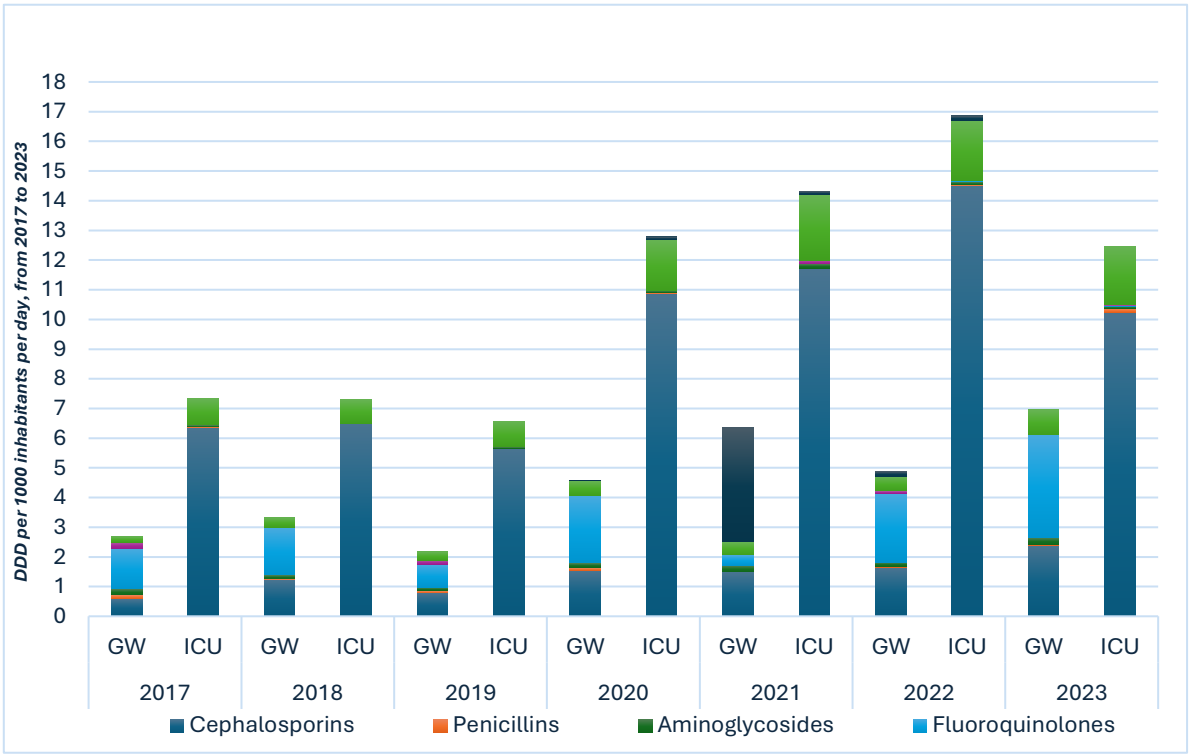


Figure 1. Antibiotics use in ICU and GW at SHOGAT "Prof. Dr. D. Stamatov", Varna, Bulgaria from 2017 – 2023 by chemical structure

These data can be explained by the fact that SHOGAT is a specialized hospital where patients with severe life-threatening infections are not treated. Table 2 presents data for antibiotic usage in two wards – ICU and GW. We chose these two wards because antibiotic consumption is higher than in other wards.

Table 2 shows a significant increase in antimicrobial use, particularly in intensive care units, with peaks in 2020 and 2021. The overall trend indicates that both ICU and GW have increased their use of antimicrobial agents, but the ICU demonstrates more significant variability and a higher average level of use.

A difference is observed between the groups of antibiotics used in the two wards (Fig. 1). In the ICU, the primary antimicrobial agents are cephalosporins, followed by nitroimidazoles (metronidazole). Quinolones (ciprofloxacin) are the preferred antimicrobial agents in the GW, followed by metronidazole as the secondary choice. Aminoglycosides are frequently used in the GW, while they are rarely used in the ICU. The use of penicillins is low in both wards.

Figure 1 illustrates the impact of the COVID-19 pandemic on antimicrobial usage in the hospital. The use of macrolides (azithromycin) has been observed since 2020. The highest consumption of azithromycin was observed in 2021 in GW. The COVID-19 pandemic was associated with an increase in the consumption of azithromycin, notably during the first waves of the pandemic [13]. After a systematic review and meta-analysis, Khan *et al*. reported that antimicrobial consumption in patients with COVID-19 in high-income countries was lower compared with lower and middle-income countries (58% versus 85%) [14].

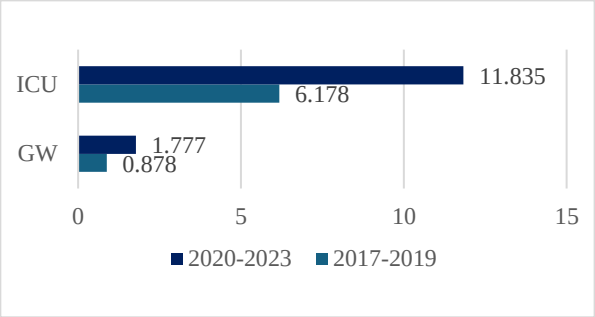
The significant reduction in the use of macrolides in 2022 is associated with the emergence of new studies and clinical data showing their limited effectiveness in the treatment of COVID-19 [15]. Data from Figure 1 indicate that macrolides were not used in 2023, which aligns with European and global trends. The measurable impact of the pandemic was a brief increase in macrolide consumption in 2021 compared to all other years.

The comparative analysis of cephalosporin use for the two considered periods (Fig. 2) shows a significant increase in both the GW ward (102.39%) and the ICU (91.57%) for the period 2020-2023.

Surgical site infections are an important complication of surgical procedures, and appropriate antibiotic prophylaxis can reduce the risk of infections during certain procedures [16].

The definition of surgical antibiotic prophylaxis is taken from the 2018 WHO publication “Prevention of infectious complications by administering an effective antimicrobial agent prior to exposure to contamination during surgery” [17]. To prevent infectious complications before exposure to contamination during surgery, WHO guideline recommended "Access group" antibiotics as the first-choice option in most cases. According to the recommendations of the Bulgarian Association of Microbiologists [18], a single dose of cefazolin 2g *i.v.* is applied for preoperative prophylaxis of caesarean section (or cefamandole, or cefuroxime), and as an alternative - metronidazole 500 mg (1000 mg) *i.v.*

The increased use of cephalosporins (cefazolin) after 2020 is associated with a change in the hospital's antibiotic policy. This policy is aligned with the recommendations of the Bulgarian Association of Microbiologists for preoperative prophylaxis in obstetrics and gynecology.



	ICU	GW
Cephalosporins use (2017-2019)	6.178	0.878
Cephalosporins use (2020-2023)	11.835	1.777
*Relative rate of change**	*1.92*	*2.02*

** Relative rate of change = DDD per 1000 IPD (2020-2023)/DDD per 1000 IPD (2017-2019)*

Figure 2. Cephalosporins consumption in two periods

Table 3 shows the detailed pattern of antibiotic prescriptions. The most prescribed antibiotics were cephalosporins (cefazolin, ceftriaxone, and ceftazidime), which account for nearly 70% of all antibiotics used in the hospital. The use of ceftriaxone (33.8%) and metronidazole (12.5%) in ICU and GW is similar to data from a study by Hodoșan *et al.*, conducted at the Emergency Clinical County Hospital of Oradea, Romania (26.46% and 13.05%, respectively) [19].

Table 3. Antibiotics used by WHO AWaRe category and consumption rates (DDD/1000IPD) from 2017 to 2023

Antimicrobials	WHO AWaRe category	DDD/1000IPD 2017-2023	DDD/1000 IPD% 2017-2023
Cefazolin	Access	38.414	35.5%
Amoxicillin	Access	0.321	0.%
Ceftriaxone	Watch	36.519	33.8%
Gentamycin	Access	1.724	1.6%
Ciprofloxacin	Watch	12.211	11.3%
Doxycycline	Access	0.5885	0.5%
Metronidazole	Access	13.5305	12.5%
Ampicillin	Access	0	0 %
Amikacin	Access	0.121	0.1%
Piperacillin/Tazobactam	Watch	0.2065	0.2%
Ampicillin/Sulbactam	Access	0.0635	0.1%
Azithromycin	Watch	4.3975	4.1%
Ceftazidime	Watch	0.005	0.005%
Meropenem	Watch	0.0105	0.01%
Vancomycin	Watch	0.0765	0.07%

Table 4. Antibiotics used according to WHO AWaRe category

	Access	Watch	Reserve
% of antibiotics used by WHO classification	60%	40%	0%

Table 5. Antimicrobial agents and their usage percentages by WHO AWaRe category

Antimicrobial agent	WHO AWaRe category	Percentage of usage (%)
Ceftriaxone	Watch	68.36
Ciprofloxacin	Watch	22.85
Azithromycin	Watch	8.23
Piperacillin/Tazobactam	Watch	0.39
Vancomycin	Watch	0.14
Meropenem	Watch	0.02
Ceftazidime	Watch	0.01

Table 4 presents a summary of the results of our study on total antibiotic use in both wards (ICU and GW) according to AWaRe classification. Notably, 60% of the used antimicrobial agents fall into the Access group, and 40% are from the Watch group. No use of antibiotics from the Reserve group was observed. In the annual report of the European Center for Disease Prevention and Control for 2022, it is stated that only 10 countries met or exceeded the EU target of at least 65% of antibiotic consumption being from the ‘Access’ group, as per WHO’s AWaRe classification of antibiotics. The number of EU Member States at or above the 65% target has not changed since 2019 [12]. Even though the use of 'Access' group antibiotics in Bulgaria does not meet the ECDC's set target, SHOGAT nearly achieves these target values.

In Table 5, we showed the results for the use of antibiotics from the 'Watch' group in ICU and GW from 2017 to 2023. Ceftriaxone is the most used antimicrobial in this group, with a significant usage percentage of 68.36%. Ciprofloxacin follows with a usage percentage of 22.85%, indicating its common use but at a lower frequency than ceftriaxone, and then comes azithromycin with 8.23%. Piperacillin/ tazobactam, vancomycin, meropenem, and ceftazidime are used less frequently, with percentages of 0.39%, 0.14%, 0.02%, and 0.01%, respectively.

CONCLUSION

The antibiotic use changes in both SHOGAT wards are related to COVID-19 and an adjustment in the hospital's antibiotic policy. Despite the observed increase in antibiotic prescriptions during the period 2020-2023, the overall antibiotic use in the hospital remains below the levels for Bulgaria and Europe/EEA. Additional measures are needed to promote the rational use of antibiotics by implementing the WHO AWaRe classification and increasing the prescription of antibiotics from the 'Access' group. WHO recommends that antibiotics from this group should constitute 65% of all antibiotics used. A more extensive study will

subsequently present the analyzed data on antibiotic use across all wards of SHOGAT.

Conflict of interest: *Authors declare no conflict of interest.*

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