MAPPING THE ANTIBIOTIC CONSUMPTION IN THE REPUBLIC OF MOLDOVA

Doina MACARI[1], Corina SCUTARI[1], Simona NEGRES[2], Mihail TODIRAS[1]

[1]*Nicolae Testemitanu* State University of Medicine and Pharmacy, Chisinau, Republic of Moldova
[2]*Carol Davila* University of Medicine and Pharmacy, Bucharest, Romania

Corresponding author: Doina Macari, e-mail: doina.macari@usmf.md

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Introduction*. Antibiotic consumption represents a crucial aspect of modern healthcare. Abuse and inappropriate use of antibacterial agents contribute to the phenomenon of bacterial resistance. The aim of the study was to determine antibiotic consumption in hospital conditions and map the results in order to highlight regions in the country with the highest levels of antibiotic consumption and the classes of antibiotics used.*

Material and methods. *Antibiotic consumption in hospitals (64 facilities) over a 4-year period (2018-2021) was determined using the defined daily dose (DDD) as the unit of measurement. The quantity of antibiotics consumed was expressed in DDD/1000 patient-days (hospitalization days), followed by mapping the results.*

Results. *A "very high" level of antibiotic consumption, expressed in DDD/1000 patient-days, was observed in the Falesti district, while a "medium" level of antibacterial agent consumption was observed in the Taraclia, Comrat, Ialoveni, Singerei, Glodeni, and Donduseni districts. The total consumption per antibiotic class revealed an increased use of Cephalosporins, Imidazole derivatives, Macrolides, Tetracyclines, Fluoroquinolones, and Aminoglycosides.*

Conclusions. *Mapping antibiotic consumption is an efficient tool in highlighting administrative-territorial regions with high antibiotic consumption and identifying the most frequently used antibiotic classes. Providing this information is useful for developing policies aimed at optimizing antibiotic use and minimizing resistance.*

Cuvinte-cheie: *cartografiere, consum de antibiotice, DDD, OMS, spitale.*

CARTOGRAFIEREA CONSUMULUI DE ANTIBIOTICE ÎN REPUBLICA MOLDOVA

Introducere. *Consumul de antibiotice reprezintă un aspect crucial al asistenței medicale moderne. Abuzul și utilizarea necorespunzătoare a preparatelor antibacteriene favorizează fenomenul de rezistență bacteriană. Scopul studiului a fost determinarea consumului de antibiotice în condiții de staționar în Republica Moldova și cartografierea rezultatelor obținute.*

Material și metode. *În acest studiu a fost determinat consumul de antibiotice în condiții de staționar (64 de spitale), pe o perioadă de patru ani (2018-2021), folosind ca unitate de măsură doza zilnică definită (DDD). Cantitatea de antibiotice consumată a fost exprimată în DDD/1000 zile-pacient (zile de spitalizare), ulterior fiind efectuată cartografierea rezultatelor.*

Rezultate. *Rezultatele înregistrate atestă un nivel „foarte mare" de consum de antibiotice exprimat în DDD/1000 zile de spitalizare în raionul Fălești și un nivel „mediu" de consum de preparate antibacteriene în raioanele Taraclia, Comrat, Ialoveni, Sîngerei, Glodeni, Dondușeni. Consumul total per clase de antibiotice a scos în evidență un consum sporit de cefalosporine, de derivați de imidazol, de macrolide, de tetracicline, de fluorochinolone și de aminoglicozide.*

Concluzii. *Cartografierea consumului de antibiotice reprezintă un instrument eficient de evidențiere a regiunilor administrativ-teritoriale în care consumul de antibiotice este ridicat, și a claselor de antibiotice cel mai frecvent utilizate. Aceste informații sunt utile pentru elaborarea de politici menite să optimizeze utilizarea antibioticelor și să minimizeze rezistența acestora.*

INTRODUCTION

Antibiotics are crucial for treating infectious diseases, but bacterial resistance poses a rapidly increasing global threat. A key driver of resistance is antibiotic use (1). Monitoring antibiotic consumption patterns over time and across countries could inform policies aimed at optimizing antibiotic prescribing and minimizing antibiotic resistance. This may involve setting and enforcing per capita consumption targets or supporting investments in alternatives to antibiotics (2).

According to the European Centre for Disease Prevention and Control, hospital consumption represents only 9% of the overall European Union/European Economic Area (EU/EEA) total consumption of antibacterials for systemic use. The continued decline in consumption between 2020 and 2021 is not immediately apparent when hospital and community sectors are combined. The overall EU/EEA population-weighted mean consumption in the hospital sector decreased linearly by 0.04 DDD per 1,000 inhabitants per day between 2016 and 2019. The largest annual decrease occurred in 2020 (0.11 DDD per 1,000 inhabitants per day), followed by a reduction of 0.05 DDD per 1,000 inhabitants per day in 2021. At the country-level, eight countries experienced increases in hospital consumption between 2019 and 2020, and 11 had increases between 2020 and 2021. Five countries (Bulgaria, Croatia, Greece, Portugal, and Slovakia) had higher hospital consumption in 2021 than in 2019. The overall EU/EEA population-weighted proportion of Antimicrobial Medicines Consumption (AMC) from broad spectrum sub-groups also showed consecutive annual increases during the period 2019–2021. The largest annual increase in the past 10 years occurred between 2020 and 2021 (3).

In the Republic of Moldova, antibiotics constitute approximately 10% of the total number of medicines, with a prevalence of antibiotic consumption at 42.7%. National results, based on data regarding the antimicrobial resistance profile of microorganisms involved in systemic infections, indicate a high level of resistance. Isolates of K. pneumoniae show increased resistance to cephalosporins (>96%), fluoroquinolones (>50%), and aminoglycosides (>90%). For *A. baumannii*, the resistance profile to fluoroquinolones is 100%, carbapenems >90%, and aminoglycosides >95%. *E. coli* strains exhibit resistance rates of >80% to penicillins, >65% to cephalosporins, and >55% to fluoroquinolones.

Currently, in the Republic of Moldova, 505 drugs are registered and classified according to the international code - ATC (Anatomical Therapeutic Chemical Classification) as systemic antibacterial agents. According to the Medicines and Medical Devices Agency (AMDM), there has been a constant increase in the number of antibiotics used in the last three years. In 2021, over 70 million packages were imported, representing a 10% increase compared to previous years, or over 20 boxes per capita within a year, which translates to almost two boxes per person per month (4, 5).

Therefore, there is a need to enhance the national surveillance system for antibacterial resistance and monitoring of antibiotic consumption both in hospital and outpatient settings. Studies on antibiotic consumption in hospital conditions in the Republic of Moldova are limited, which is why determining and mapping antibiotic consumption are crucial steps in preventing antibacterial resistance and promoting the rational use of antibiotics.

The aim of the study was to determine the consumption of antibiotics in hospitals in the Republic of Moldova and to map the results in order to highlight which regions of the country exhibit the highest levels of antibiotic consumption and the classes of antibiotics used.

MATERIAL AND METHODS

A comprehensive descriptive study was conducted to determine the consumption of antibacterial agents based on the geographical location of Public Health Institutions (IMSP) and the type of antibiotic delivered to IMSP.

The research utilized reports on the execution of public procurement contracts from the years 2018-2021, along with the number of hospitalization days of the healthcare units included in the study during the analyzed period.

The determination of antibacterial agent consumption was carried out in 64 IMSPs in the Republic of Moldova (the study did not include the Transnistrian region), using Defined Daily Dose (DDD) as the measurement unit recommended by the World Health Organization (WHO) for drug utilization studies (6).

The quantity of antibiotics consumed was expressed in DDD/1000 hospitalization days, with the DDD values from the 2022 version of the WHO's Anatomical Therapeutic Chemical Classification/Defined Daily Dose (ATC/DDD) system used for each antibiotic.

The practical calculation method of DDD/1000 patient days (hospitalization days) followed this algorithm:

Stage I: Examination of the antibacterial delivery report for each IMSP individually.
Stage II: Conversion of all concentrations into grams or million units (MU).
Stage III: Tabular insertion of columns: WHO DDD, and respective WHO DDD Unit.
Stage IV: Calculation of DDD.
Stage V: DDD calculation per 1000 hospitalization days.
Stage VI: Arrangement of antibacterial agents by classes.
Stage VII: The results obtained were entered into electronic databases and statistically processed using Microsoft Office Excel and IBM SPSS Statistics programs.

Based on the geographical location of IMSPs, the quantity of consumed antibiotics was centralized and distributed per district/municipality, followed by mapping the results.

Districts/municipalities were classified into 5 levels of antibiotic consumption based on the values obtained from the determination of DDD/1000 hospitalization days over the years 2018-2021.

Thus, the following levels were outlined: “very high” – 25.4-30 DDD/1000 hospitalization days, “high” – 20.7-25.4 DDD/1000 hospitalization days, “medium” – 16-20.7 DDD/1000 hospitalization days, “low” – 11.4-16 DDD/1000 hospitalization days, “very low” – 5-11.4 DDD/1000 hospitalization days.

RESULTS

After analyzing the distribution of districts/municipalities based on the level of antibiotic consumption, the research results revealed a “very low” level of antibacterial agent usage from 2018 to 2021 in the following districts of the Republic of Moldova (fig. 1): Cahul, Cimislia, Hincesti, Nisporeni, Straseni, Calarasi, Orhei, Telenesti, Rezina, Soldanesti, and in the Municipality of Balti.

The total antibiotic consumption in these districts during the years 2018-2021 ranged between 5-11.4 DDD/1000 hospitalization days.

A "low" level of antibacterial agent consumption was recorded in the following districts: Cantemir, Leova, Basarabeasca, Stefan Voda, Causeni, Anenii Noi, Criuleni, Ungheni, Floresti, Soroca, Drochia, Edinet, Briceni, and in the Municipality of Chisinau.

The total antibiotic consumption in these districts during the years 2018-2021 ranged between 11.4-16 DDD/1000 hospitalization days.

A "medium" level of antibacterial agent consumption was recorded in the following districts: Taraclia, Comrat, Ialoveni, Singerei, Glodeni, and Donduseni.

The total antibiotic consumption in these districts during the years 2018-2021 ranged between 16-20.7 DDD/1000 hospitalization days.

Districts with a "high" level of antibiotic consumption, ranging between 20.7-25.4, were not identified.

A "very high" level of antibacterial agent consumption was recorded in Falesti district, where the total antibiotic consumption during the years 2018-2021 ranged between 25.4-30 DDD/1000 hospitalization days.

The trend of consumption for antibacterial preparations for the years 2018-2021 within the Public Health Institutions (IMSP) of the Republic of Moldova, as shown in Figure 2, is as follows:

a) In 2018, the average total antibiotic consumption was 12.3 DDD/1000 hospitalization days.
b) In 2019, the average total antibiotic consumption was 11 DDD/1000 hospitalization days.
c) In 2020, the average total antibiotic consumption was 15.6 DDD/1000 hospitalization days.
d) In 2021, the average total antibiotic consumption was 12.01 DDD/1000 hospitalization days.

Thus, there is an observed trend of increased antibiotic consumption in hospitals in the Republic of Moldova in 2020, a period associated with the COVID-19 pandemic. Additionally, in 2021, the trend of antibiotic preparations consumption is decreasing in the hospital sector, constituting 12.01 DDD/1000 hospitalization days.

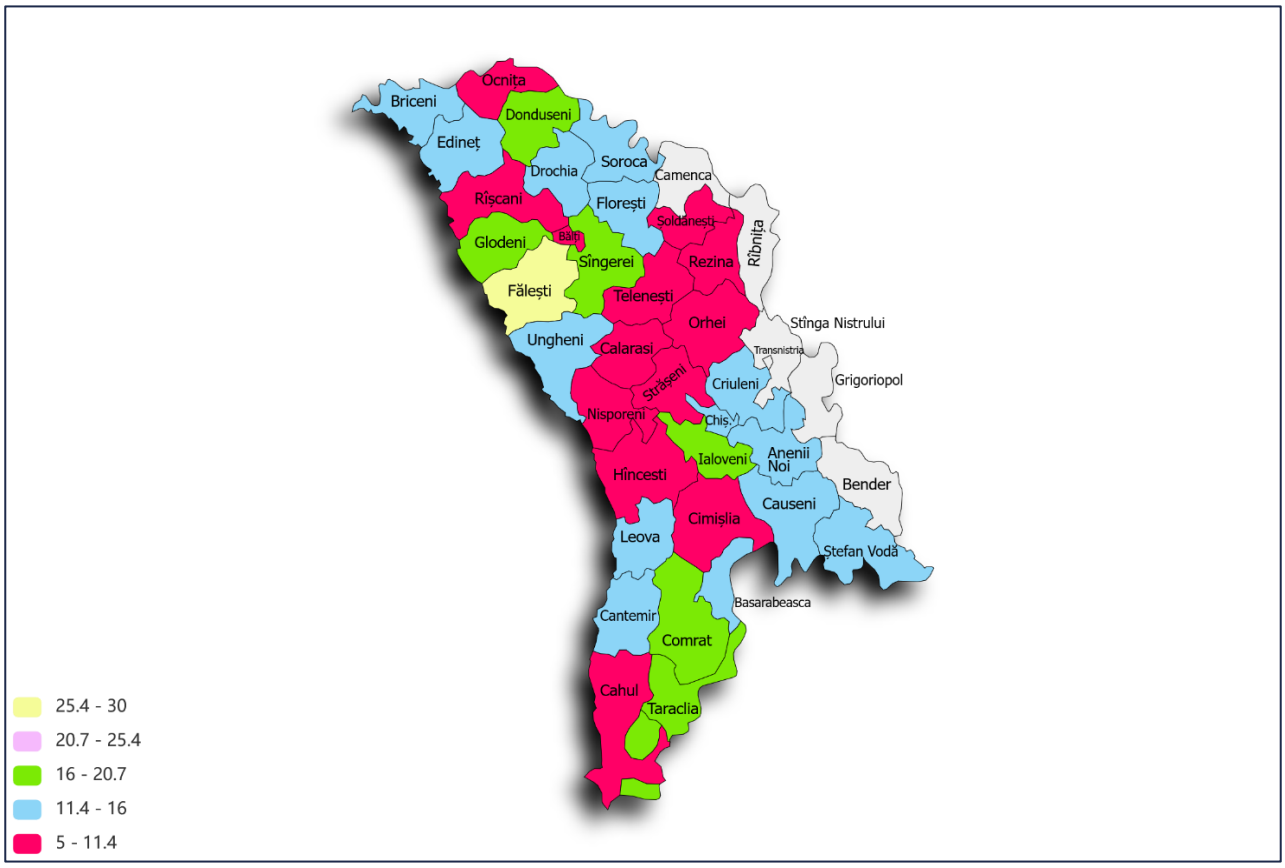

Figure 1. Mapping the antibiotic consumption in the Republic of Moldova based on administrative-territorial zone for the years 2018-2021, Expressed in DDD/1000 hospitalization days.

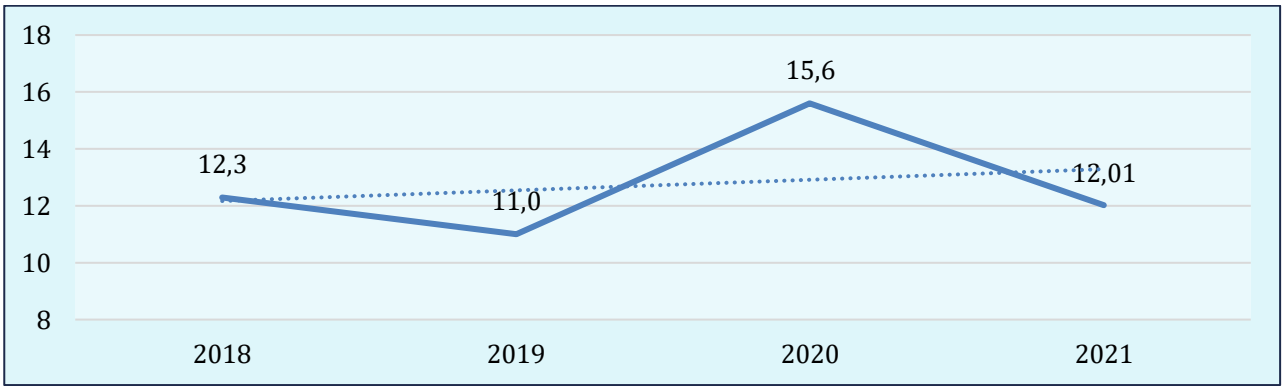

Figure 2. The trend of antibiotic consumption for the years 2018-2021, expressed in DDD/1000 hospitalization days.

Thus, there is an observed trend of increased antibiotic consumption in hospitals in the Republic of Moldova in 2020, a period associated with the COVID-19 pandemic. Additionally, in 2021, the trend of antibiotic preparations consumption is decreasing in the hospital sector, constituting 12.01 DDD/1000 hospitalization days.

Regarding the classes of consumed antibacterial preparations, as shown in Figure 3, it is presented as follows:

a) In 2018, there was an increased consumption of antibiotics from the following classes: Cephalosporins (21.2 DDD/1000 hospitalization days), Imidazole derivatives (16.1 DDD/1000 hospitalization days), Quinolones (13.6 DDD/1000 hospitalization days), and Tetracyclines (14.4 DDD/1000 hospitalization days).
b) In 2019, there was an increased consumption of antibiotics from the following classes: Cephalosporins (18.4 DDD/1000 hospitalization days),

Tetracyclines (15.5 DDD/1000 hospitalization days), Imidazole derivatives (14.4 DDD/1000 hospitalization days), and Macrolides (10.4 DDD/1000 hospitalization days).

c) In 2020, there was an increased consumption of antibiotics from the following classes: Cephalosporins (25.6 DDD/1000 hospitalization days), Macrolides (21.7 DDD/1000 hospitalization days), Tetracyclines (19.7 DDD/1000 hospitalization days), and Imidazole derivatives (15 DDD/1000 hospitalization days).

d) In 2021, there was an increased consumption of antibiotics from the following classes: Cephalosporins (17.4 DDD/1000 hospitalization days), Fluoroquinolones (15.4 DDD/1000 hospitalization days), Macrolides (12.9 DDD/1000 hospitalization days), Nitrofuran derivatives (9.9 DDD/1000 hospitalization days), and Aminoglycosides (9.5 DDD/1000 hospitalization days).

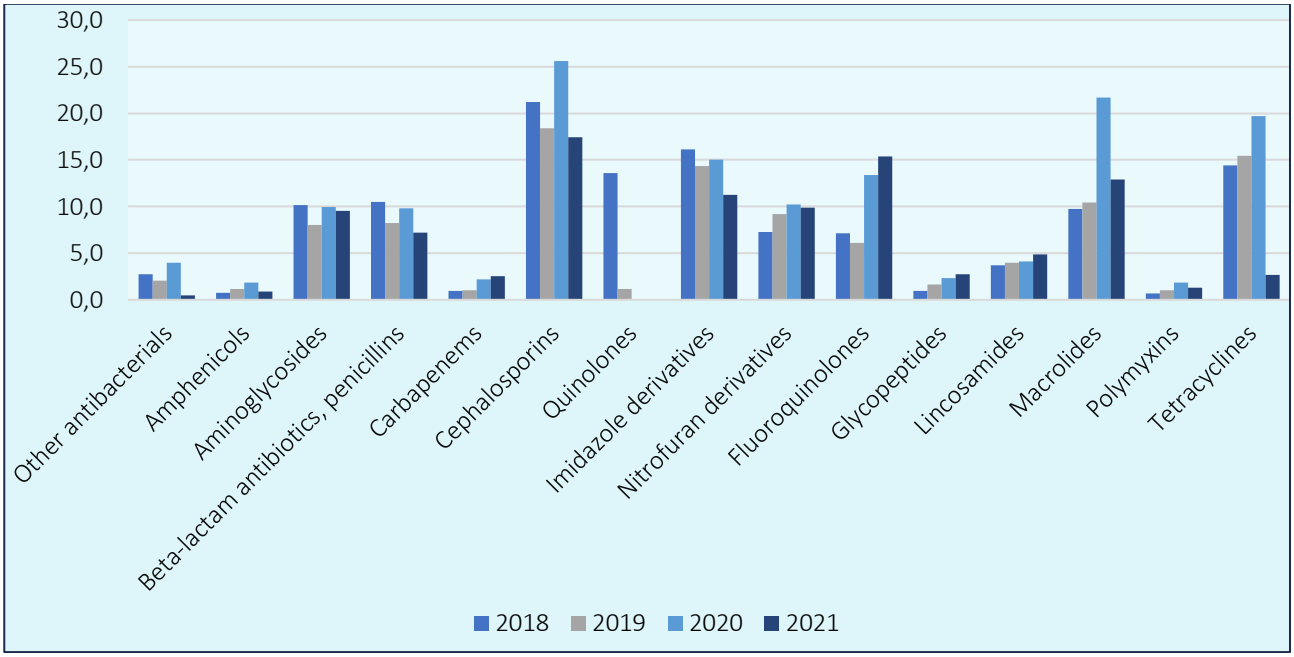

Figure 3. The consumption per class of antibiotics for the years 2018-2021, expressed in DDD/1000 hospitalization days.

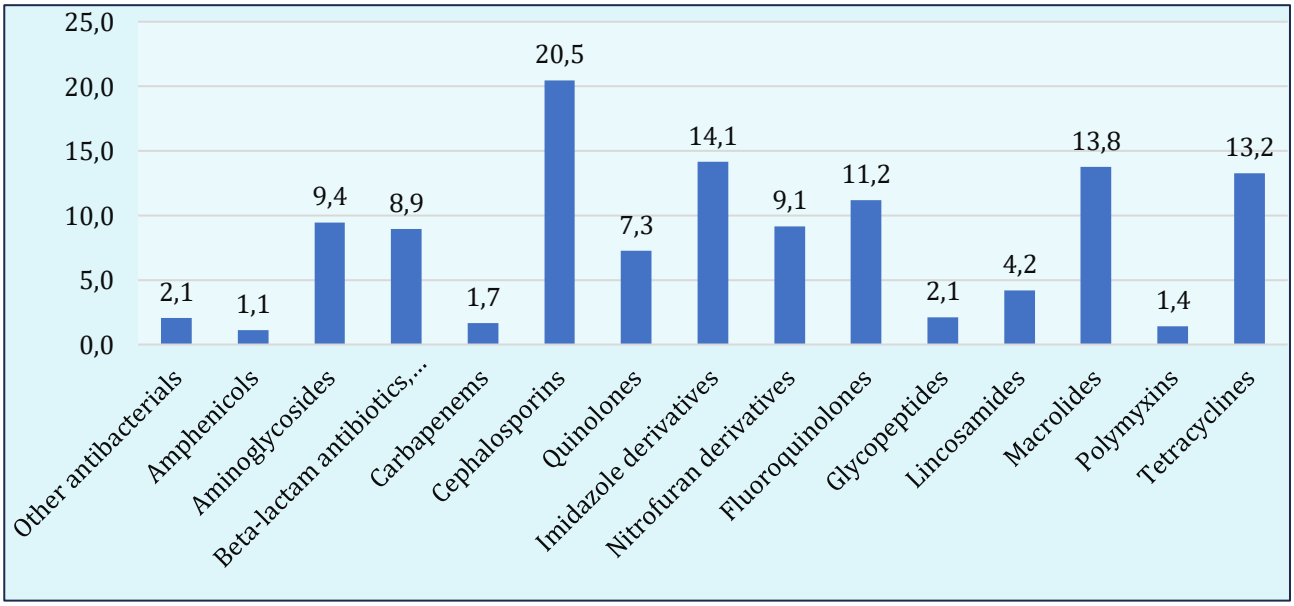

Figure 4. The total consumption per class of antibiotics for the years 2018-2021, expressed in DDD/1000 hospitalization days.

Following the centralization of data for the years 2018-2021, the total consumption per class of antibiotics highlighted an increased consumption for the following antibiotic groups (fig. 4): Cephalosporins (20.5 DDD/1000 hospitalization days), Imidazole derivatives (14.1 DDD/1000 hospitalization days), Macrolides (13.8 DDD/1000 hospitalization days), Tetracyclines (13.2 DDD/1000 hospitalization days), Fluoroquinolones (11.2 DDD/1000 hospitalization days), and Aminoglycosides (9.4 DDD/1000 hospitalization days).

DISCUSSIONS

Providing reliable national data on the consumption of antibacterial agents is mandatory to understand the epidemiology of antibiotic resistance, as antibiotic misuse is a key factor promoting bacterial resistance (5). While the majority of antibiotics are used in outpatient settings, the administration of antibiotics in hospitals is a major driver for the spread of multidrug-resistant bacteria responsible for nosocomial infections.

Thus, the conducted study serves as an efficient tool in providing valuable information for the development of new policies to prevent and combat nosocomial infections. The determined consumption levels reflect the situation only in hospital conditions; for a more comprehensive overview, it is necessary to assess antibiotic consumption in outpatient settings as well.

Regarding the antibiotic classes used in hospitals during the years 2018-2021, there is a predominant high consumption for antibiotics in the following classes: Cephalosporins, Imidazole derivatives, Macrolides, Tetracyclines, and Fluoroquinolones, and lower consumption for antibiotics in the classes: Amphenicols, Polymyxins, Carbapenems, Glycopeptides, and Lincosamides. The trend in antibiotic consumption is decreasing for the year 2021 by 23% compared to 2020.

Studies on antibiotic consumption are limited, as a major challenge in conducting these studies is the lack of data on antibiotic consumption in low- and middle-income countries (7). Strengthening national networks in the field of antimicrobial resistance and expanding subsequent participation in global and regional networks will enable the Republic of Moldova to adjust quality standards and operational procedures to international rigor and obtain comparable, standardized, and accurate data for evidence-based decision-making (4). Currently, monitoring of antimicrobial consumption relies on import data, and there is a clear need for the use of additional data sources, such as retail trade, including disaggregation by community and hospital sectors.

CONCLUSIONS

1. Mapping antibiotic consumption represents an efficient tool for highlighting the administrative-territorial regions with increased antibiotic use, contributing to the improvement of the national system for monitoring antimicrobial resistance and antibiotic consumption based on contemporary approaches. The study reveals a "very high" level of antibiotic consumption expressed in DDD/1000 hospitalization days in Falesti district and a "medium" level of antibacterial preparations consumption in the districts of Taraclia, Comrat, Ialoveni, Singerei, Glodeni, and Donduseni. Continuous monitoring of antibiotic consumption trends provides important information to competent authorities for implementing measures to reduce irrational antibiotic use, thereby decreasing the risk of resistant bacterial strains.
2. Determining the consumption of antibacterial preparations used in a hospital setting is an important step in estimating the costs associated with acquiring these preparations. It can signal the onset of bacterial resistance to certain classes of antibiotics and serve as an efficient tool to limit the misuse of drugs from a specific antibiotic class.

CONFLICT OF INTEREST

Authors have no conflict of interest to declare.

ETHICAL APPROVAL

Favorable opinion from the Research Ethics Committee No. 5 dated 12.07.2022, ref. no. 42 dated 26.05.2022, for the scientific research project titled: "Evaluation of antibiotic consumption and rational use of antibacterial preparations in hospitals."

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