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STUDY OF HOSPITAL USE OF ANTIMICROBIAL DRUGS INTENDED FOR PROPHYLAXIS AND TREATMENT OF OBSTETRIC AND GYNECOLOGICAL INFECTIONS

THESIS SUMMARY

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The dissertation comprises 138 pages, illustrated with 35 figures and 25 tables. The bibliography contains 234 sources. The numbering of figures and tables in the abstract does not correspond to those in the dissertation.

The public defence of the dissertation will take place on September 24, 2025, at 10:30 a.m. online via the Webex platform.

The defence materials are published on the website of the Medical University "Prof. Dr. Paraskev Stoyanov" – Varna.

“The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug, make them resistant"

Alexander Fleming, 1945

I would like to express my sincere gratitude and deep appreciation to my academic supervisors, Associate Professor Silvia Mihaylova and Professor Marieta Georgieva, for their professionalism, unwavering support, and the invaluable expertise they generously shared during the preparation of this dissertation.

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Last but certainly not least, I wish to extend my profound gratitude to my family and friends for their continuous encouragement and unwavering presence throughout this journey.

CONTENT

LIST OF MOST COMMONLY USED ABBREVIATIONS

MRSA	Methicillin-resistant staphylococcus aureus
VRE	Vancomycin-resistant enterococci
VRSA	Vancomycin-resistant staphylococcus aureus
WHO	Worlds health organisation
HAI	Hospital acquired infections
RSV	Respiratory syncytial virus
BPPL	Bacterial priority pathogens list
ESKAPE	*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa,* и *Enterobacter spp.*
E. faecium	*Enterococcus faecium*
S. aureus	*Staphylococcus aureus*
K. pneumoniae	*Klebsiella pneumoniae*
A. baumannii	*Acinetobacter baumannii*
P. aeruginosa	*Pseudomonas aeruginosa*
E. coli	*Escherichia coli*
AMP	antimicrobial resistance
EU/EEA	European union/ European Economic Area
PBP	penicillin-binding protein
ATP	Adenosine Triphosphate
DNA	Deoxyribonucleic Acid
tRNA	Transfer RNA
иРНК	Informational RNA
рРНК	Ribosomal RNA
HA-MRSA	Hospital-acquired MRSA
CA-MRSA	Community-associated MRSA
LA-MRSA	Livestock-associated MRSA
AME	Aminoglycoside-Modifying Enzyme
RND	resistance–nodulation–division
MIC	Minimum Inhibitory Concentration
VAP	Ventilator-associated pneumonia
ESBL	Extended-Spectrum β-Lactamase
HR	Heteroresistance

ECDC	European Centre for Disease Prevention and Control
QS	Quorum sensing
TLC	Thin-Layer Chromatography
HPLC	High-Performance Liquid Chromatography
AMS	Antimicrobial stewardship
SSI	Surgical site infections
MW	Maternity Ward
GW	Gynecology Ward
ICU	Intensive Care Unit
HRPW	High-Risk Pregnancy Ward
AHL	N-acyl homoserine lactone

INTRODUCTION

The treatment of bacterial infections caused by resistant pathogens represents one of the most significant challenges facing modern medicine. In Europe, these infections are responsible for approximately 35,000 deaths annually. According to projections by the World Health Organisation, by the year 2050, antimicrobial resistance (AMR) is expected to claim the lives of more than 10 million people worldwide.

The emergence and spread of resistant bacterial strains can be attributed to a range of factors. Among the most common are the presence of intrinsic or acquired resistance, horizontal gene transfer, biofilm formation, cross-resistance, and heteroresistance.

Furthermore, the irrational use of antibiotics - both in outpatient and inpatient settings, significantly accelerates the selection and dissemination of resistant microorganisms. This includes the administration of antibiotics without a justified medical indication, the use of inappropriate antimicrobial agents, incorrect dosing or treatment duration, self-medication without medical supervision, and other improper practices.

The implementation of antimicrobial stewardship programs constitutes a crucial mechanism in the global effort to combat antibiotic resistance. Systematic monitoring and analysis of antibiotic consumption at the local, national, and international levels enable the assessment of current practices, the identification of critical areas for intervention, and the development of effective strategies aimed at optimising antimicrobial therapy. These efforts also include limiting the use of specific classes of antibiotics when appropriate.

I. AIM AND OBJECTIVES

The findings of the literature review provide the foundation for defining the aim and objectives of the present dissertation.

Aim:

To investigate and analyse the hospital use of antimicrobial agents intended for the prophylaxis and treatment of obstetric and gynecological infections at the Specialised Hospital of Obstetrics and Gynecology for Active Treatment "Prof. Dr. D. Stamatov" – Varna over a 12-year period.

Based on the aim, the following objectives were set:

1. Collect and systematise of primary data on antibiotic use for the period 2012–2023 in four wards (Intensive Care Unit (ICU), Gynecology Ward (GW), Maternity Ward (MW), and High-Risk Pregnancy Ward (HRPW)) at the SHOGAT "Prof. Dr. D. Stamatov" – Varna.

2. To analyse the ratio between the Access, Watch, and Reserve groups according to the WHO AWaRe classification in hospital practice and to assess the extent of antibiotic use with an increased risk of developing antimicrobial resistance.

3. To analyse trends in hospital antibiotic use at the SHOGAT "Prof. Dr. D. Stamatov" – Varna for the period 2012–2023, measured in DDD/100 bed-days.

4. Selection of a statistical processing method (dynamic analysis) and significance level ($\alpha = 0.05$), and retrospective analysis of antibiotic use at the SHOGAT "Prof. Dr. D. Stamatov" – Varna.

5. Analysis of trends in antibiotic use in the different wards (Intensive Care Unit, Gynecology Ward, Maternity Ward, and High-Risk Pregnancy Ward) at the Specialised Obstetrics and Gynecology Hospital for Active Treatment “Prof. Dr. D. Stamatov” – Varna.

6. Prospective analysis of hospital use of major antibiotic groups in the four wards (Intensive Care Unit, Gynecology Ward, Maternity Ward, and High-Risk Pregnancy Ward) of the SHOGAT “Prof. Dr. D. Stamatov” – Varna for the period 2024–2026, based on statistically significant models.

II. MATERIALS AND METHODS

Data Collection

The study was conducted at the Specialised Hospital of Obstetrics and Gynecology for Active Treatment "Prof. Dr. Dimitar Stamatov" – Varna. The information was extracted from the complete drug usage database of the medical institution for the period 2012 – 2023. These data include the use of antibiotics (intravenous (*i.v.*) and oral (*per os*)) in four wards (ICU, GW, MW, HRPW), prescribed to patients admitted for treatment in the hospital. The collected data were validated through manual error detection.

Information on antibiotic use in the Neonatology Ward is not included in the present study. The main reason is that antibiotic dosages for newborns differ from those for adults. They depend on the weight, age, and clinical condition of the newborn, and the doses are adjusted individually. This makes the use of standard Defined Daily Doses (DDD), which are determined for adults, inaccurate for newborns, especially in comparative analysis.

Calculation of Antibiotic Use

For the calculation of antibiotic use in the different wards, the number of bed-days in the respective ward was taken into account, while the total usage was calculated based on the hospital's bed-days.

We use the Anatomical Therapeutic Chemical/Defined Daily Dose (ATC/DDD) classification system, which is an international standard for calculating antibiotic use in a unified technical unit – defined daily dose (DDD) per 100 bed-days.

$$Antibiotic\ Use = \frac{Total\ number\ of\ DDDs\ used}{Total\ number\ of\ bed\ days} \text{ x } 100$$

Classification of Antibiotics

The antibiotics used are grouped according to their chemical classification. They are divided into the following pharmacological groups: penicillins, cephalosporins, aminoglycosides, fluoroquinolones, tetracyclines, nitroimidazoles, and macrolides (Table 1).

***Table 1**. Classification of antibiotics used according to their chemical structure*

<table>
<tr><th colspan="7">β-LACTAM ANTIBIOTICS</th></tr>
<tr><th>Penicillins</th><th colspan="3">Cephalosporins</th><th colspan="3">Carbapenems</th></tr>
<tr><td>amoxicillin</td><td colspan="3">cefazolin</td><td colspan="3">imipenem</td></tr>
<tr><td>ampicillin</td><td colspan="3">ceftriaxone</td><td colspan="3">meropenem</td></tr>
<tr><td>ampicillin per os</td><td colspan="3">cefuroxime</td><td colspan="3"></td></tr>
<tr><td>ampicillin/sulbactam</td><td colspan="6" rowspan="2"></td></tr>
<tr><td>piperacillin</td></tr>
<tr><th colspan="7">GROUPS OF ANTIBIOTICS</th></tr>
<tr><th>Aminoglycosides</th><th>Tetracyclines</th><th>Macrolides</th><th>Fluoroquinolones</th><th>Lincosamides</th><th>Glycopeptides</th><th>Nitroimidazole derivatives</th></tr>
<tr><td>amikacin</td><td rowspan="2">doxycycline per os</td><td rowspan="2">azithromycin per os</td><td>ciprofloxacin per os</td><td rowspan="2">clindamycin</td><td rowspan="2">vancomycin</td><td rowspan="2">metronidazole</td></tr>
<tr><td>gentamycin</td><td>ciprofloxacin i.v.</td></tr>
</table>

Statistical Data Processing

IBM SPSS Statistics software, version 19, was used for the statistical processing of the data. The following statistical indicators are provided in all analyses: regression coefficients (b0 and b1), correlation coefficient (R), coefficient of determination (R^2), standard error of the estimate, as well as an analysis of variance table (ANOVA).

Interpretation of the correlation coefficient:

$0 < R < 0.3$ – weak correlation

$0.3 < R < 0.5$ – moderate correlation

$0.5 < R < 0.7$ – significant correlation

$0.7 < R < 0.9$ – high correlation

$0.9 < R < 1$ – very high correlation

The models presented and used for the analysis of the data include the following.

Linear model	**Complex-composite model**
$Y = b0 + b1.t$	$Y = b0 .b1^{t}$
Logarithmic model	**S-shaped model**
$Y = b0 + b1.\ln(t)$	$Y = e^{(b0 + (b1/t)}$
Inverse model	**Logistics model**
$Y = b0 + (b1 / t)$	$Y = \ln (b0) + \ln(b1)^{t}$

Quadratic model

$$Y = b0 + b1.t + b2.t^2$$

Growth model

$$\ln(Y) = b0 + b1^t$$

Cubic model

$$Y = b0 + b1.t + b2\ .t^2 + b3.t^3$$

Exponential model

$$\ln(Y) = \ln(b0) + b1^t$$

Step model

$$Y = b0.\ t^{b1}$$

For each of these models, an evaluation of the coefficients was performed, and the statistical indicators were analysed to determine the most appropriate model for representing the data. In addition, an analysis of variance (ANOVA) was conducted to assess the significance of the regression models.

III. RESULTS AND DISCUSSION

The study was carried out through a retrospective and prospective analysis of data on antibiotic use. The retrospective analysis by wards covers a 12-year period before the start of the study (2012–2023). The data used were extracted from the pharmacy software “Gama Store”, following authorisation from Prof. Dr. E. Kovachev, MD, PhD (Managing Director of the SHOGAT "Prof. Dr. D. Stamatov"). The prospective analysis was based on the statistically significant mathematical models obtained.

1. Systematisation of Primary Data on Antibiotic Use at SHOGAT "Prof. Dr. D. Stamatov" for the Period 2012–2023

The primary data on antibiotic use from the four wards are presented in tables (Tables 2–13), each table containing information for a specific calendar year. Each table is organised by ward and displays the use of various types of antibiotics in the respective wards. The overall values of antibiotic use are reported in a standardised technical unit – defined daily dose (DDD) per 100 bed-days (DDD/100 bed-days).

Table 2. *Systematised data on antibiotic use by wards in 2012 (DDD/100 bed-days)*

Antibiotic use for 2012 (DDD/100 bed-days)					
Antibiotic (INN)	**Ward**				
	MW	**GW**	**ICU**	**HRPW**	**Total**
amikacin	0,1	0	0	0	0,05
amoxicillin	0	0	0	0	0
ampicillin	0	0	0	0	0
ampicillin *per os*	6,24	1,37	0,2	4,38	4,89
ampicillin/sulbactam	0	0	0	0	0
azithromycin *per os*	0	0	0	0	0
cefazolin	0,8	3,33	21,81	0,33	3,93
ceftriaxone	1,1	13,92	32,33	2,23	7,65
cefuroxime	0,11	1,04	6,42	0	1,08
ciprofloxacin *per os*	0,01	8,88	0	0,06	1,48
ciprofloxacin *i.v.*	0	0,04	0	0	0,005
clindamycin	0,02	0,05	0	0	0,02
doxycycline *per os*	0	8,06	0	0,06	1,22
fluconazole	0	0	0	0	0
gentamycin	0,32	6,18	5,53	0,11	1,8

Antibiotic use for 2012 (DDD/100 bed-days)					
Antibiotic (INN)	**Ward**				
	MW	**GW**	**ICU**	**HRPW**	**Total**
imipenem	0	0	0	0	0
meropenem	0	0	0	0	0
metronidazole	0,7	8,07	12,52	0,06	3,2
piperacillin	0,02	0	0	0	0,01
vancomycin	0	0	0	0	0

Table 3. *Systematised data on antibiotic use by* wards *in 2013 (DDD/100 bed-days)*

Antibiotic use for 2013 (DDD/100 bed-days)					
Antibiotic (INN)	**Ward**				
	MW	**GW**	**ICU**	**HRPW**	**Total**
amikacin	0	0,22	0	0,18	0,06
amoxicillin	0	0	0	0	0
ampicillin	0	0	0	0	0
ampicillin *per os*	5,3	0,34	0	4,66	3,71
ampicillin/sulbactam	0,04	0	0,09	0	0,03
azithromycin *per os*	0	0	0	0	0

Antibiotic use for 2013 (DDD/100 bed-days)					
Antibiotic (INN)	**Ward**				
	MW	**GW**	**ICU**	**HRPW**	**Total**
cefazolin	1,15	0,11	31,8	0,06	5,27
ceftriaxone	1,07	17,07	23,65	5,07	7,37
cefuroxime	0	0	0	0	0
ciprofloxacin *per os*	0,11	8,5	0,19	0,15	1,31
ciprofloxacin *i.v.*	0,004	0	0	0	0,002
clindamycin	0,05	0	0	0	0,03
doxycycline *per os*	0	5,62	0	0,18	0,83
fluconazole	0	0	0	0	0
gentamycin	0,53	5,98	5,82	0,06	2,02
imipenem	0,04	0	0	0,27	0,07
meropenem	0	0	0	0	0
metronidazole	0,81	7,19	10,29	0,12	2,99
piperacillin	0	0	0	0	0
vancomycin	0	0	0	0,06	0,01

Table 4. *Systematised data on antibiotic use by wards in 2014 (DDD/100 bed-days)*

Antibiotic use for 2014 (DDD/100 bed-days)					
Antibiotic (INN)	**Ward**				
	MW	**GW**	**ICU**	**HRPW**	**Total**
amikacin	0,04	0,02	0,04	0,03	0,03
amoxicillin	4,13	0,1	0	2,91	2,76
ampicillin	0	0	0	0	0
ampicillin *per os*	0,9	0	0	0,58	0,59
ampicillin/sulbactam	0	0	0,01	0,02	0,005
azithromycin *per os*	0	0	0	0	0
cefazolin	0,44	0,05	25,6	0	3,78
ceftriaxone	2,11	17,48	35,5	3,85	9,23
cefuroxime	0	0	0	0,23	0,04
ciprofloxacin *per os*	0	5,81	0,12	0,03	0,17
ciprofloxacin *i.v.*	0,006	0	0	0	0,003
clindamycin	0,02	0	0	0	0,009
doxycycline *per os*	0	4,73	0	0,28	0,73
fluconazole	0	0	0	0	0
gentamycin	0,52	6,95	7,73	0,05	2,35

Antibiotic use for 2014 (DDD/100 bed-days)					
Antibiotic (INN)	**Ward**				
	MW	**GW**	**ICU**	**HRPW**	**Total**
imipenem	0,03	0	0	0	0,01
meropenem	0	0	0	0	0
metronidazole	0,74	9,32	14,69	0,02	3,36
piperacillin	0	0	0	0	0
vancomycin	0,04	0	0,17	0	0,04

Table 5. *Systematised data on antibiotic use by wards in 2015 (DDD/100 bed-days)*

Antibiotic use for 2015 (DDD/100 bed-days)					
Antibiotic (INN)	**Ward**				
	MW	**GW**	**ICU**	**HRPW**	**Total**
amikacin	0,21	0,21	0,1	0	0,16
amoxicillin	4,49	0,89	0,15	7,83	3,9
ampicillin	0	0	0	0	0
ampicillin *per os*	0	0	0	0	0
ampicillin/sulbactam	0	0	0	0	0
azithromycin *per os*	0	0	0	0	0

Antibiotic use for 2015 (DDD/100 bed-days)					
Antibiotic (INN)	**Ward**				
	MW	**GW**	**ICU**	**HRPW**	**Total**
cefazolin	0,16	0,16	20,72	0,02	3,3
ceftriaxone	2,71	21,06	52,76	3,35	13,15
cefuroxime	0	0	0	0	0
ciprofloxacin *per os*	0,19	10,96	0,04	0,18	1,71
ciprofloxacin *i.v.*	0	0	0	0	0
clindamycin	0	0	0	0	0
doxycycline *per os*	0	2,06	0	0,6	0,4
fluconazole	0	0	0	0	0
gentamycin	0,47	6,97	8,76	0,08	2,59
imipenem	0	0	0	0	0
meropenem	0	0	0,04	0,11	0,03
metronidazole	0,78	10,82	22	0,04	5,4
piperacillin	0	0	0	0	0
vancomycin	0,06	0,56	0	0	0,11

Table 6. *Systematised data on antibiotic use by wards in 2016 (DDD/100 bed-days)*

Antibiotic use for 2016 (DDD/100 bed-days)					
Antibiotic (INN)	**Ward**				
	MW	**GW**	**ICU**	**HRPW**	**Total**
amikacin	0,06	0,22	0,17	0	0,09
amoxicillin	3,72	0,17	0	9,97	3,61
ampicillin	0	0	0	0	0
ampicillin oral	0	0	0	0	0
ampicillin/sulbactam	0	0	0	0	0
azithromycin *per os*	0	0	0	0	0
cefazolin	0,52	0,06	24,44	0,03	4,21
ceftriaxone	2,18	12,85	41,56	4,15	10,32
cefuroxime	0	0	0	0	0
ciprofloxacin *per os*	0,07	13,95	0,04	0,23	2,06
ciprofloxacin *i.v.*	0,04	0	0	0	0,02
clindamycin	0	0	0	0	0
doxycycline *per os*	0	0,95	0	0	0,14
fluconazole	0	0	0	0	0
gentamycin	0,56	3,24	2,79	0,08	1,22

Antibiotic use for 2016 (DDD/100 bed-days)					
Antibiotic (INN)	**Ward**				
	MW	**GW**	**ICU**	**HRPW**	**Total**
imipenem	0	0	0	0	0
meropenem	0	0	0	0	0
metronidazole	0,24	6,4	20,41	0,03	4,43
piperacillin	0,05	0	0	0	0,02
vancomycin	0,05	0	0,08	0	0,04

Table 7. *Systematised data on antibiotic use by wards in 2017 (DDD/100 bed-days)*

Antibiotic use for 2017 (DDD/100 bed-days)					
Antibiotic (INN)	**Ward**				
	MW	**GW**	**ICU**	**HRPW**	**Total**
amikacin	0	0	0	0	0
amoxicillin	3,76	0,81	0,1	5,96	3,05
ampicillin	0	0	0	0	0
ampicillin *per os*	0	0	0	0	0
ampicillin/sulbactam	0	0	0	0	0
azithromycin *per os*	0	0	0	0	0

Antibiotic use for 2017 (DDD/100 bed-days)					
Antibiotic (INN)	**Ward**				
	MW	**GW**	**ICU**	**HRPW**	**Total**
cefazolin	0,38	0,06	13,52	0	2,44
ceftriaxone	3,36	6,03	50,11	3,75	10,92
cefuroxime	0	0	0	0	0
ciprofloxacin *per os*	0	13,59	0	0,12	2,12
ciprofloxacin *i.v.*	0	0	0	0	0
clindamycin	0	0	0	0	0
doxycycline *per os*	0	2,14	0	0	0,33
fluconazole	0	0	0	0	0
gentamycin	0,48	2,09	0,65	0,03	0,69
imipenem	0	0	0	0	0
meropenem	0	0	0	0	0
metronidazole	0,37	2,01	8,97	0	1,99
piperacillin	0	0	0	0	0
vancomycin	0	0	0	0	0

Table 8. *Systematised data on antibiotic use by wards in 2018 (DDD/100 bed-days)*

Antibiotic use for 2018 (DDD/100 bed-days)					
Antibiotic (INN)	**Ward**				
	MW	**GW**	**ICU**	**HRPW**	**Total**
amikacin	0	0	0	0	0
amoxicillin	3,62	0,17	0	7,82	3,28
ampicillin	0	0	0	0,042	0,006
ampicillin *per os*	0	0	0	0	0
ampicillin/sulbactam	0	0	0	0	0
azithromycin *per os*	0	0	0	0	0
cefazolin	0,14	0,23	9,45	0	1,35
ceftriaxone	1,92	9,56	52,26	3,96	9,96
cefuroxime	0	0	0	0	0
ciprofloxacin *per os*	0	15,8	0	0,09	2,35
ciprofloxacin *i.v.*	0	0	0	0	0
clindamycin	0	0	0	0	0
doxycycline *per os*	0	0	0	0	0
fluconazole	0	0	0	0	0
gentamycin	0,2	1,28	0,98	0,13	0,45

Antibiotic use for 2018 (DDD/100 bed-days)					
Antibiotic (INN)	**Ward**				
	MW	**GW**	**ICU**	**HRPW**	**Total**
imipenem	0	0	0	0	0
meropenem	0	0	0	0	0
metronidazole	0,22	3,14	7,4	0	1,56
piperacillin	0	0	0	0	0
vancomycin	0,07	0	0	0	0,04

Table 9. *Systematised data on antibiotic use by wards in 2012 (DDD/100 bed-days)*

Antibiotic use for 2019 (DDD/100 bed-days)					
Antibiotic (INN)	**Ward**				
	MW	**GW**	**ICU**	**HRPW**	**Total**
amikacin	0,06	0	0	0	0,034
amoxicillin	1,94	0,69	0	5,26	2,01
ampicillin	0	0	0	0	0
ampicillin *per os*	0	0	0	0	0
ampicillin/sulbactam	0,04	0	0	0	0,02
azithromycin *per os*	0	0	0	0	0

Antibiotic use for 2019 (DDD/100 bed-days)					
Antibiotic (INN)	**Ward**				
	MW	**GW**	**ICU**	**HRPW**	**Total**
cefazolin	0,59	4,29	42,37	0	5,56
ceftriaxone	1,79	7,94	40,02	2,83	7,06
cefuroxime	0	0	0	0	0
ciprofloxacin *per os*	0	11,79	0	0	2,08
ciprofloxacin *i.v.*	0,01	0	0	0	0,007
clindamycin	0	0	0	0	0
doxycycline *per os*	0	1,45	0	0	0,26
fluconazole	0	0	0	0	0
gentamycin	0,24	1,71	0,68	0,05	0,56
imipenem	0	0	0	0	0
meropenem	0	0	0	0	0
metronidazole	0,53	4,57	13,21	0,19	2,53
piperacillin	0,03	0,2	0	0	0,05
vancomycin	0	0	0	0	0

Table 10. *Systematised data on antibiotic use by wards in 2020 (DDD/100 bed-days)*

Antibiotic use for 2020 (DDD/100 bed-days)					
Antibiotic (INN)	**Ward**				
	MW	**GW**	**ICU**	**HRPW**	**Total**
amikacin	0,1	0	0	0	0,006
amoxicillin	2,59	0,58	0	9,67	3,2
ampicillin	0	0	0	0	0
ampicillin *per os*	0	0	0	0	0
ampicillin/sulbactam	0	0	0,01	0	0,002
azithromycin *per os*	0,12	0,08	1,08	0	0,2
cefazolin	1,55	1,19	78,26	0	9,69
ceftriaxone	2,58	14,31	29,66	5,68	7,76
cefuroxime	0	0	0	0	0
ciprofloxacin *per os*	0	22,98	0	0	3,3
ciprofloxacin *i.v.*	0	0	0	0	0
clindamycin	0	0	0	0	0
doxycycline *per os*	0	0	0	0	0
fluconazole	0	0	0	0	0
gentamycin	0,42	1,59	0,48	0,06	0,54

Antibiotic use for 2020 (DDD/100 bed-days)					
Antibiotic (INN)	**Ward**				
	MW	**GW**	**ICU**	**HRPW**	**Total**
imipenem	0	0	0	0	0
meropenem	0	0	0	0	0
metronidazole	0,88	4,87	17,07	0	3,09
piperacillin	0,02	0	0	0,3	0,05
vancomycin	0	0	0	0	0

Table 11. *Systematised data on antibiotic use by wards in 2021 (DDD/100 bed-days)*

Antibiotic use for 2021 (DDD/100 bed-days)					
Antibiotic (INN)	**Ward**				
	MW	**GW**	**ICU**	**HRPW**	**Total**
amikacin	0	0,26	0,48	0	0,1
amoxicillin	1,58	0	0	8,15	2,18
ampicillin	0,04	0	0	0	0,02
ampicillin *per os*	0	0	0	0	0
ampicillin/sulbactam	0	0	0	0,05	0,007
azithromycin *per os*	0,58	38,4	1,18	1,25	6,57

Antibiotic use for 2021 (DDD/100 bed-days)					
Antibiotic (INN)	**Ward**				
	MW	**GW**	**ICU**	**HRPW**	**Total**
cefazolin	1,76	1,71	88,45	0	11,32
ceftriaxone	5,46	13,3	28,8	8,22	9,75
cefuroxime	0	0	0	0	0
ciprofloxacin *per os*	0	3,54	0	0	0,55
ciprofloxacin *i.v.*	0	0	0	0	0
clindamycin	0	0	0	0	0
doxycycline *per os*	0,58	0	1,22	0	0,48
fluconazole	0	0	0	0	0
gentamycin	0,41	1,87	1,05	0,06	0,65
imipenem	0	0	0	0	0
meropenem	0,04	0	0	0	0,02
metronidazole	1,34	4,45	22,03	0	3,96
piperacillin	0	0	0	0	0
vancomycin	0	0,25	0	0	0,04

Table 12. *Systematised data on antibiotic use by wards in 2022 (DDD/100 bed-days)*

Antibiotic use for 2022 (DDD/100 bed-days)					
Antibiotic (INN)	**Ward**				
	MW	**GW**	**ICU**	**HRPW**	**Total**
amikacin	0	0,05	0	0	0,007
amoxicillin	1,79	0,13	0	13,09	2,52
ampicillin	0	0	0	0	0
ampicillin *per os*	0	0	0	0	0
ampicillin/sulbactam	0,01	0	0,2	0,02	0,03
azithromycin *per os*	0,68	5,7	5,4	2,5	2,24
cefazolin	1,11	1,61	88,41	0,03	10,71
ceftriaxone	5,7	14,42	32,15	8,53	10,36
cefuroxime	0	0	0	0	0
ciprofloxacin *per os*	0	23,1	0,37	0	3,47
ciprofloxacin *i.v.*	0	0	0	0	0
clindamycin	0	0	0	0	0
doxycycline *per os*	0,14	0,8	0,13	0	0,22
fluconazole	0	0,25	0,2	0	0,06
gentamycin	0,2	1,41	1,08	0,1	0,46

Antibiotic use for 2022 (DDD/100 bed-days)					
Antibiotic (INN)	Ward				
	MW	GW	ICU	HRPW	Total
imipenem	0	0	0	0	0
meropenem	0	0	0,07	0,19	0,04
metronidazole	1,08	4,58	20,24	1,26	3,78
piperacillin	0,07	0,06	0,25	0	0,07
vancomycin	0	0	0	0	0

Total 13. *Systematised data on antibiotic use by wards in 2023 (DDD/100 bed-days)*

Antibiotic use for 2023 (DDD/100 bed-days)					
Antibiotic (INN)	Ward				
	MW	GW	ICU	HRPW	Total
amikacin	0,06	0,28	0	0	0,07
amoxicillin	1,15	0,11	0	4,34	1,51
ampicillin	0	0	0	0	0
ampicillin *per os*	0	0	0	0	0
ampicillin/sulbactam	0,03	0,02	0,06	0,23	0,07
azithromycin *per os*	0	0	0	0	0

Antibiotic use for 2023 (DDD/100 bed-days)					
Antibiotic (INN)	**Ward**				
	MW	**GW**	**ICU**	**HRPW**	**Total**
cefazolin	0,67	0,44	69,78	0,13	6,62
ceftriaxone	4,68	24,27	51,76	7,52	13,08
cefuroxime	0,06	0	7,3	0	0,78
ciprofloxacin *per os*	0,1	37,29	0,23	0,1	5,37
ciprofloxacin *i.v.*	0	0	0	0	0
clindamycin	0	0,07	0	0	0,01
doxycycline *per os*	0	0	0,02	0	0,002
fluconazole	0	0	0	0	0
gentamycin	0,31	2,31	0,59	0,12	0,59
imipenem	0	0	0	0	0
meropenem	0	0	0	0	0
metronidazole	0,85	8,9	21	0,92	4,05
piperacillin	0	0	0	0	0
vancomycin	0	0	0	0	0

Following the analysis of antibiotic use in the hospital, it was observed that the most commonly used antibiotics are cephalosporins, particularly in the ICU and GW. Fluoroquinolones are also widely used in the GW, with a noticeable increase in their usage over the years. Metronidazole is widely used in both the ICU and GW, with a rising trend in its application. Aminoglycosides, although used in smaller amounts, are also utilised across the different units. One of the wards with the highest antibiotic consumption is the ICU, where the largest quantities of cephalosporins and metronidazole are administered. In the GW, there is a high usage of fluoroquinolones, metronidazole, and ceftriaxone. In the HRPW, antibiotic use is relatively low, but oral penicillins and metronidazole are still used. In the MW, antibiotic use is also comparatively lower; however, oral penicillins and aminoglycosides are still in use. The main trends in antibiotic use include increasing consumption of cephalosporins and fluoroquinolones, particularly in the intensive care unit. The use of carbapenems (imipenem, meropenem) remains low, which can be considered a positive indicator of the control of antimicrobial resistance. The sharp increase in the use of azithromycin in 2021 is related to the COVID-19 pandemic and its inclusion as a first-line treatment for confirmed infections.

Table 14. *Antibiotic use (DDD/100 bed-days, %) in SHOGAT "Prof. Dr. D. Stamatov" - Varna, according to the WHO AWaRe classification*

Antibiotics	**WHO AWaRe classification**	**DDD/100 bed-days (total) 2012-2023**	**DDD/100 bed-days % (total) 2012-2023**
cefazolin	Access	68,18	21.36
amoxicillin	Access	28,02	8.78
ceftriaxone	Watch	116,61	36.52
gentamycin	Access	13,92	4.36
ciprofloxacin	Watch	25,97	8.14
ciprofloxacin *i.v.*	Watch	0,04	0.01
doxycycline	Access	4,61	1.44

Antibiotics	WHO AWaRe classification	DDD/100 bed-days (total) 2012-2023	DDD/100 bed-days % (total) 2012-2023
metronidazole	Access	40,34	12.64
ampicillin	Access	0,03	0.01
ampicillin *per os*	Access	9,19	2.88
amikacin	Access	0,61	0.19
piperacillin/tazobactam	Watch	0,2	0.06
ampicillin/sulbactam	Access	0,16	0.05
azithromycin	Watch	9,01	2.82
cefuroxime	Watch	1,90	0.60
meropenem	Watch	0,09	0.03
vancomycin	Watch	0,28	0.09
clindamycin	Access	0,07	0.02
imipenem	Watch	0,08	0.03

The analysis of antibiotic use data (Table 14) for the period 2012–2023 shows that the most frequently used antibiotic is ceftriaxone (Watch group), with 116.61 DDD/100 bed-days, accounting for 36.52% of the total use. It is followed by cefazolin (Access group), with 68.18 DDD/100 bed-days, representing a share of 21.36%. Among the antibiotics in the Access group, significant use is observed for amoxicillin (28.02 DDD/100 bed-days, 8.78%) and metronidazole (40.34 DDD/100 bed-days, 12.64%). Gentamycin also shows a relatively high use – 13.92 DDD/100 bed-days (4.36%). In addition to ceftriaxone, Watch antibiotics include ciprofloxacin (25.97 DDD/100 bed-days, 8.14%), azithromycin (9.01 DDD/100 bed-days, 2.82%), and cefuroxime (1.90 DDD/100 bed-days, 0.60%). The use of carbapenems (meropenem, imipenem) and glycopeptides (vancomycin) is significantly lower – below 0.1 DDD/100 bed-days.

The antibiotics with the lowest usage are ampicillin (0.03 DDD/100 bed-days, 0.01%), piperacillin/tazobactam (0.2 DDD/100 bed-days, 0.06%), and clindamycin (0.07 DDD/100 bed-days, 0.02%).

2. **Analysis of antibiotics usage according to the Access, Watch, and Reserve groups of the WHO AWaRe classification.**

Table 15. *Antibiotics used in SHOGAT "Prof. Dr. D. Stamatov" - Varna by Access, Watch and Reserve groups of the AWaRe classification - percentage distribution*

	Access (%)	**Watch (%)**	**Reserve (%)**
% of antibiotics used by WHO classification	51.70	48.30	0

The analysis from Table 15 regarding the distribution of antibiotic use according to the WHO AWaRe classification shows that 51.70% of the antibiotics used belong to the Access group, while 48.30% fall under the Watch group. No antibiotic use from the Reserve group was reported (0%).

Antibiotics from the Access group are recommended by the WHO for broad application due to their proven effectiveness and the lower risk of contributing to the development of antimicrobial resistance.

On the other hand, antibiotics from the Watch group, which are associated with a higher risk of resistance development and are recommended to be used with greater caution, constitute a significant portion of total usage (48.30%). This ratio indicates that nearly half of the antibiotics used fall into the group that requires stricter control.

The absence of antibiotics from the Reserve group (0%) may be interpreted as an indication that these agents, intended for the treatment of multidrug-resistant infections, were not necessary during the study period. This may suggest an effective management of antibiotic therapy or a lower incidence of resistant infections requiring treatment with Reserve antibiotics.

Table 16. *Use of antibiotics from the Watch group of the AWaRe classification in SHOGAT "Prof. Dr. D. Stamatov" - Varna (%), for 12 years*

Antibiotic	WHO AWaRe classification	Usage in percent (%)
ceftriaxone	Watch	75,66
ciprofloxacin *per os*	Watch	16,84
ciprofloxacin *i.v.*	Watch	0.03
azithromycin	Watch	5,84
piperacillin/tazobactam	Watch	0,13
vancomycin	Watch	0,18
meropenem	Watch	0,06
cefuroxime	Watch	1,23
imipenem	Watch	0,05

The analysis of the data in Table 16 indicates that during the 12-year observation period, ceftriaxone had the highest share of use – 75.66% –making it the antibiotic most frequently used by the Watch group. It is followed by ciprofloxacin, which represents 16.84% of the total use. Other antibiotics show significantly lower values: azithromycin (5.84%), cefuroxime (1.23%), and vancomycin (0.18%).

Antibiotics used in very small quantities include piperacillin/tazobactam (0.13%), meropenem (0.06%), imipenem (0.05%), and intravenous ciprofloxacin (0.03%). The low usage of carbapenems (meropenem, imipenem) and vancomycin reflects the limited application of broad-spectrum reserve antibiotics, which indicates controlled use aimed at reducing antimicrobial resistance.

3. Analysis of trends in hospital antibiotic use in SHOGAT "Prof. Dr. D. Stamatov" - Varna for the period 2012–2023, measured in DDD/100 bed-days

The data in Figure 1 presents the summarised results of the total hospital antibiotic consumption at SHOGAT "Prof. Dr. D. Stamatov" – Varna for the period 2012–2023, expressed in DDD/100 bed-days.

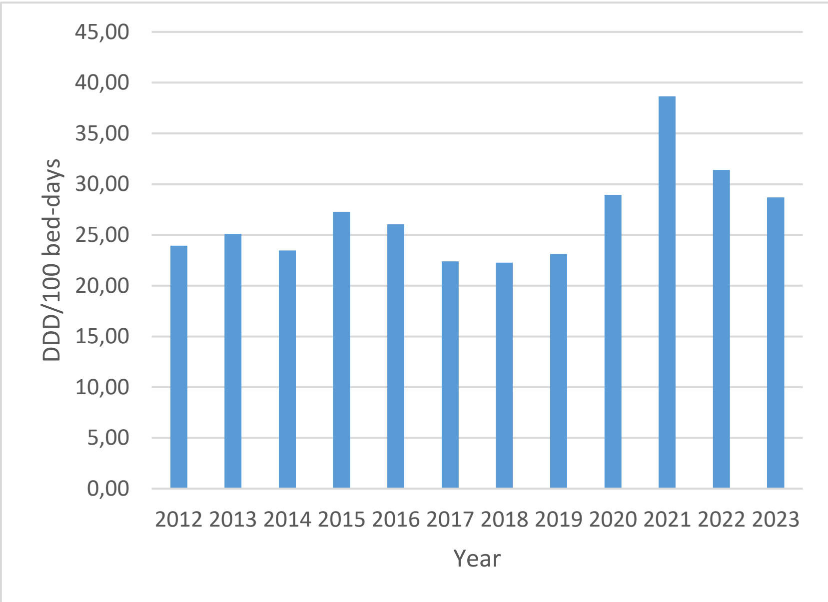

Figure 1. *Summary data on antibiotic use in SHOGAT "Prof. Dr. D. Stamatov" - Varna during the period 2012–2023.*

Various dynamic and clearly defined fluctuations are observed during the 12-year observation period. At the beginning of the period, in 2012, the total antibiotic consumption was 23.95 DDD/100 bed-days, followed by a slight increase to 25.10 DDD/100 in 2013, and a subsequent decrease in 2014 (23.45 DDD/100). In 2015 and 2016, an increase in consumption was recorded, reaching 27.29 and 26.05

DDD/100, respectively, before a gradual decline over the following two years—down to the lowest value of 22.25 DDD/100 bed-days in 2018. After 2018, the trend reversed and from 2019 onward a steady increase was observed, reaching a peak in 2021 with the highest value throughout the period: 38.65 DDD/100 bed-days. This sharp increase coincides with the peak phase of the COVID-19 pandemic in Bulgaria, suggesting a possible link between increased antibiotic use and complications related to the SARS-CoV-2 virus, as well as changes in clinical practice, higher hospitalisation rates, and modifications in empirical therapy in patients with infections of unclear aetiology. After 2021, a decline is observed, with the value decreasing to 31.42 DDD/100 in 2022 and to 28.69 DDD/100 bed-days in 2023, which nevertheless remains significantly higher compared to prepandemic levels.

The upward trend during the period 2019–2021 and its subsequent decline in 2022–2023 highlight the influence of external factors on hospital antibiotic consumption, including exceptional epidemic situations, changes in treatment protocols, and potentially stricter control in the following years. These findings emphasise the need for sustainable monitoring and stewardship programs for antibiotic use in hospital settings, especially in the context of global health challenges.

Based on the results obtained from Tables 8–19 and Figure 1, we conducted a comparative analysis of hospital antibiotic use in 2021 (the highest recorded consumption at SHOGAT) between SHOGAT "Prof. Dr. D. Stamatov" – Varna and 27 EU/EEA member states.

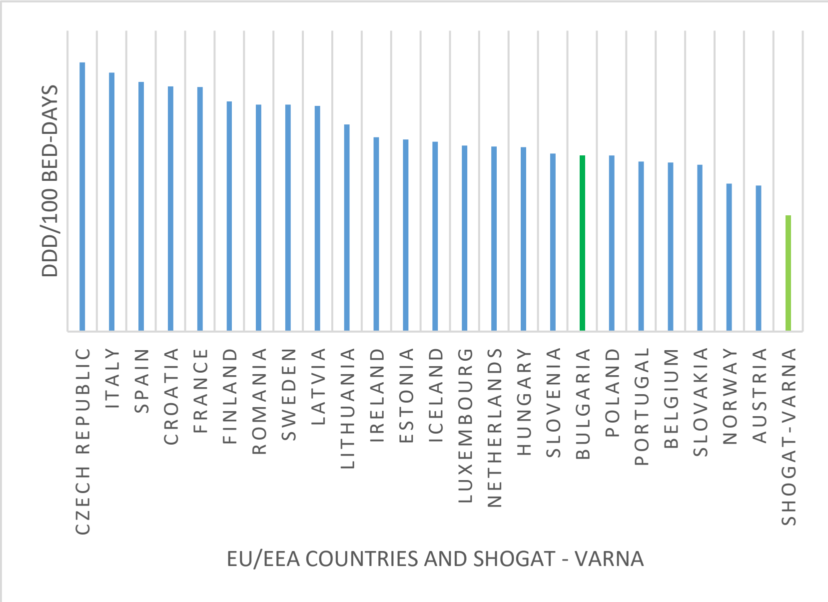

Figure 2. *Comparative analysis of hospital antibiotic use in EU/EEA countries and SHOGAT "Prof. Dr. D. Stamatov" - Varna in 2021.*

Figure 2 illustrates the levels of hospital antibiotic consumption in 24 of 30 EU/EEA countries, measured in defined daily doses (DDD) per 100 bed-days for the year 2021, and includes the value reported by SHOGAT "Prof. Dr. D. Stamatov" – Varna. The data reveal significant differences among the countries, ranging from less than 50 DDD/100 bed-days (Norway – 49.2; Austria – 48.5) to values exceeding 85 DDD/100 bed-days (Czech Republic – 89.5; Italy – 86.1; Spain – 83.0).

SHOGAT – Varna stands out with the lowest recorded value – 38.65 DDD/100 bed-days, which is substantially below the average level for EU/EEA countries. This value is nearly 10 units lower even compared to the countries with the lowest antibiotic consumption in Europe. At the national level, the observed antibiotic use in this healthcare facility is significantly lower than the value for Bulgaria (58.5 DDD/100 bed-days), indicating the effective implementation of the strategies for rational antibiotic use developed at SHOGAT "Prof. Dr. D. Stamatov" – Varna. This result can be viewed as a positive indicator of antibiotic policy, particularly in the context of increased overall antibiotic consumption during the COVID-19 pandemic.

One of the contributing factors to the observed lower antibiotic use at SHOGAT "Prof. Dr. D. Stamatov" – Varna is related to its specialised profile as an obstetric and gynecological medical facility, in which the spectrum of treated infections and the need for broad-spectrum antimicrobial therapy are more limited compared to general hospitals.

A comparative analysis of antibiotic use in Bulgaria clearly shows that the choice of metric used to measure antibiotic consumption significantly influences the interpretation of the data. In a 2024 study by Rubinić et al., hospital antibiotic use in EU/EEA countries was assessed for the period 2017 to 2021 through the comparison of different indicators. When DDD per 100 bed-days is used, Bulgaria is among the countries with the lowest hospital antibiotic consumption in Europe throughout the entire study period. In contrast, when the metric DDD per 1,000 inhabitants per day is applied, Bulgaria ranks second among all countries studied by the authors.

From this, it can be concluded that to obtain a more comprehensive and objective picture of actual antibiotic consumption, both methods should be used in combination. This allows for more accurate analysis and better understanding of antibiotic therapy patterns.

4. Retrospective analysis of antibiotic use in SHOGAT "Prof. Dr. D. Stamatov" - Varna

4.1. Retrospective analysis of antibiotic use by groups and wards

A retrospective analysis of antibiotic use (by group) was conducted across the four wards (GW, MW, ICU, HRPW) at SHOGAT "Prof. Dr. D. Stamatov" – Varna. Table 17 presents only the results for the statistically significant models identified.

Table 17. Modelling the trend of antibiotic use by groups and wards in SHOGAT "Prof. Dr. D. Stamatov" - Varna for the period 2012 - 2023.

Antibiotic group	Ward	R	R^2	SEE*	sig.	F	Model
Penicillins	MW	0,976	0,953	0,375	0,000	202,015	linear
Cephalosporins	MW	0,826	0,682	1,154	0,006	9,643	quadratic
	GW	0,805	0,649	3,452	0,032	4,924	cubic
	ICU	0,902	0,813	0,142	0,000	43,562	exponential
	HRPW	0,837	0,701	1,264	0,004	10,528	quadratic
Fluoroquinolones	GW	0,778	0,606	6,841	0,049	4,101	cubic
Tetracyclines	GW	0,979	0,959	0,632	0,000	61,730	cubic
Nitroimidazole derivatives	GW	0,790	0,624	1,939	0,041	4,419	cubic
	HRPW	0,840	0,705	0,265	0,016	6,369	cubic
Lincosamides	MW	0,784	0,615	0,011	0,014	7,191	quadratic

Antibiotic group	Ward	R	R^2	SEE*	sig.	F	Model
	GW	0,782	0,612	0,017	0,046	4,210	cubic
Aminoglycosides	GW	0,920	0,846	1,082	0,001	14,596	cubic
	ICU	0,803	0,644	0,685	0,002	18,107	exponential

*Std. Error of the Estimate

As a result of the conducted statistical analysis, only one statistically significant model was identified, which describes the use of penicillins in the MW (Figure 3). The analysis revealed a clear and reliable trend in the dynamics of antibiotic use within this group, which can be described by a linear regression model. The model obtained demonstrates a strong statistical relationship between time and the use of penicillins in MW, with a correlation coefficient of $R = 0.976$. This indicates a very high degree of linear dependence. The coefficient of determination $R^2 = 0.953$ shows that 95.3% of the variation in usage is explained by the time factor. All parameters included in the model are statistically significant at a significance level of $p < 0.001$. The resulting regression equation is the following:

$$Y = -0{,}446 \cdot t + 6{,}398,$$

where Y represents the amount of penicillins used and t — time, measured in arbitrary periods. The negative slope of the line indicates an inversely proportional relationship — with each passing unit of time, the use of penicillins decreases on average by 0.446 units. In conclusion, within the period examined, a statistically significant and sustained decrease in penicillins use is observed in MW is observed.

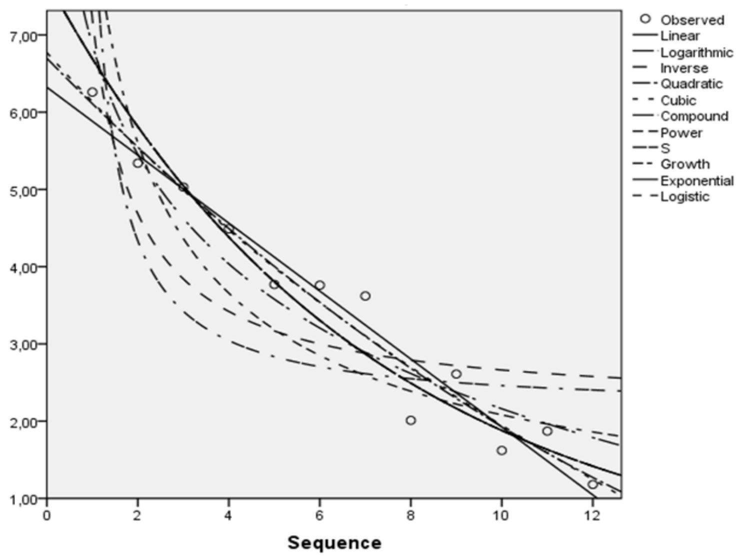

Figure 3. *Graphical representation of the statistical models used describing the use of penicillins in MW*

During the statistical analysis, statistically significant models were found for the use of cephalosporins in all hospital wards. The use of cephalosporins in the four wards is described by different statistical models, but each of them shows increasing usage.

In MW, the antibiotic trend in the use from this group is most accurately described by a quadratic regression model, which showed the highest correlation coefficient and the lowest standard error (Figure 4). The model is statistically significant ($p = 0.006$), which confirms the reliability of the results obtained. The regression equation describing the dynamics of cephalosporin use over time is as follows:

$$Y = 0{,}044 \cdot t^2 - 0{,}164 \cdot t + 2{,}38,$$

where Y represents the amount of cephalosporins used, and t is time measured in arbitrary units. The form of the equation indicates an increasing trend – after an initial slight decline, the use of cephalosporins shows a steady increase in the later periods. The data obtained for the studied time period indicate that in MW there is a progressive increase in the use of cephalosporins. This is an indicator that should be carefully analysed in the context of antimicrobial resistance.

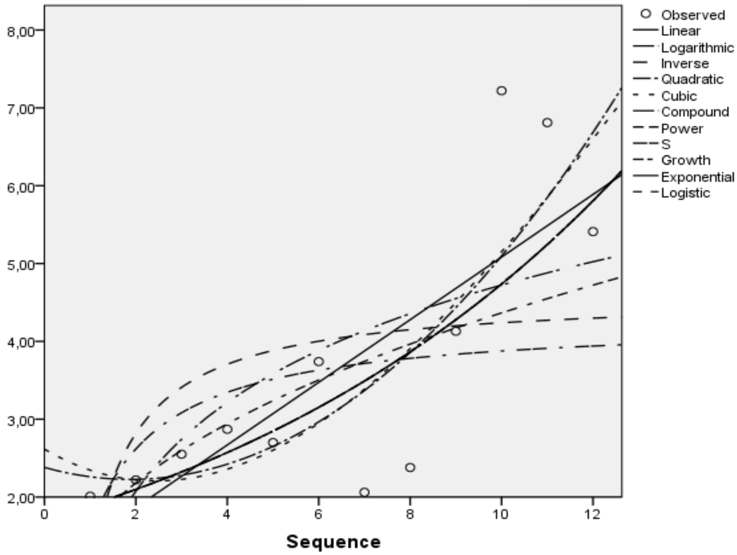

Figure 4. *Graphical representation of the statistical models used describing the use of cephalosporins in MW*

Analysis of cephalosporin use in the GW reveals the presence of a statistically significant model that describes the trend over time (Figure 5). Among the models considered, the cubic regression model demonstrated the highest correlation coefficient and the lowest error value, making it the most appropriate for describing the data. The model is statistically significant at a significance level of $p = 0.032$, confirming the reliability of the observed relationships. The model is described by the following regression equation:

$$Y = 0{,}052 \cdot t^3 - 0{,}676 \cdot t^2 + 1{,}214 \cdot t + 18{,}135,$$

where Y denotes the amount of cephalosporins used, and t represents time, expressed in arbitrary periods. The form of the equation suggests the presence of a nonlinear and accelerating trend, in which, after initial fluctuations, an increasing use of cephalosporins in GW is observed.

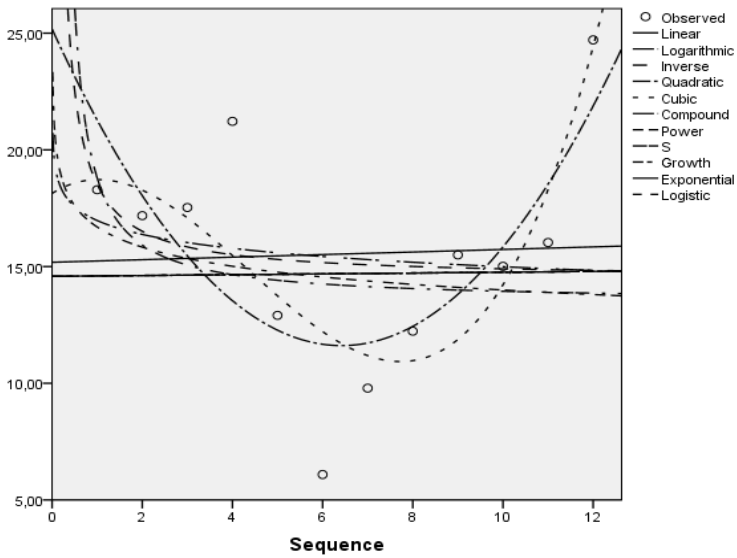

Figure 5. *Graphical representation of the statistical models used describing the use of cephalosporins in GW*

The statistical analysis of the use of cephalosporin in ICU shows that the exponential regression model best describes the consumption trend (Figure 6). It shows the highest value of the correlation coefficient ($R = 0.902$) and the lowest error. The model is statistically significant at a significance level of $p < 0.000$, indicating a high reliability of the established relationship. The resulting regression equation is the following:

$$Y = 47{,}739 \cdot e^{(1{,}082 \cdot t)},$$

where Y denotes the amount of cephalosporins used, and t represents time in arbitrary units. The function exhibits a typical exponential dynamic—with an accelerated increase in consumption over time. The observed exponential trend is an indicator of a significant increase in the use of cephalosporins in critical units such as the ICU.

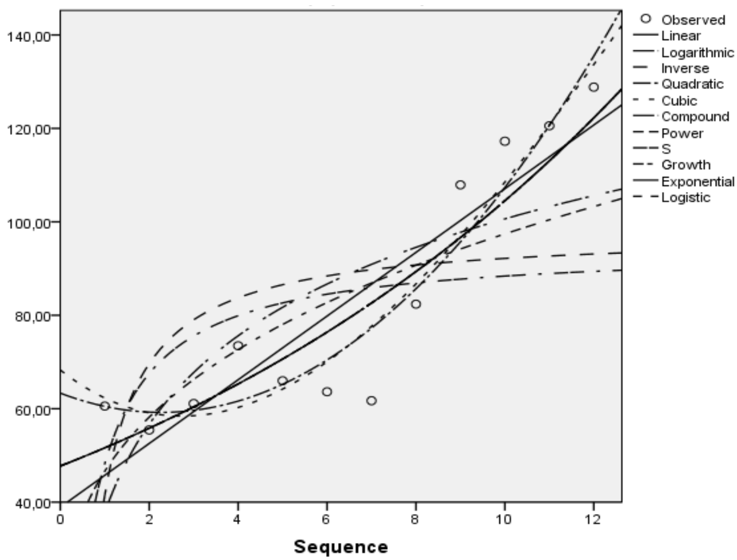

Figure 6. *Graphical representation of the statistical models used describing the use of cephalosporins in ICU*

In HRPW, the trend in the use of antibiotics from the cephalosporin group is best described by a quadratic regression model (Figure 7). The selected model is characterised by a high correlation coefficient (R = 0.837) and a low error value, which makes it statistically justified and applicable for interpreting the data. The model is statistically significant at a significance level of p = 0.016, which confirms its validity. The equation describing the model is as follows:

$$Y = 0{,}072 \cdot t^2 - 0{,}507 \cdot t + 4{,}38,$$

where Y represents the amount of cephalosporins used and t denotes time. The model reflects an increasing trend in usage, with an initial slight decline followed by a sustained rise.

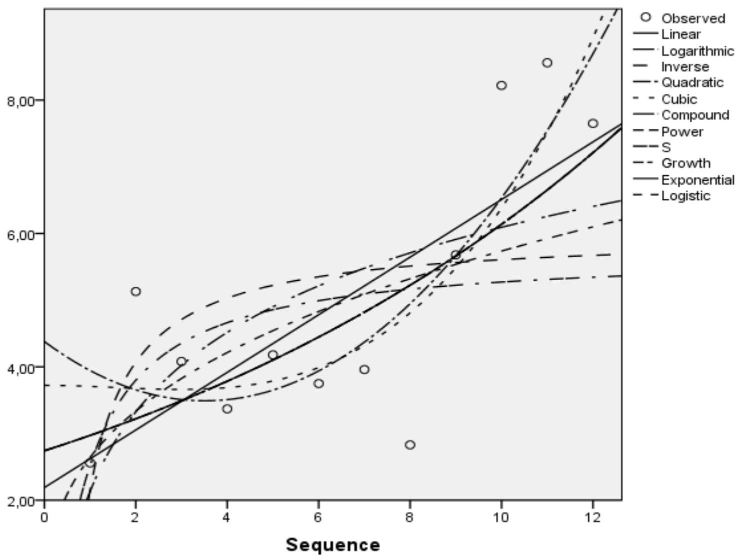

Figure 7. *Graphical representation of the statistical models used describing the use of cephalosporins in HRPW*

Regarding the use of antibiotics from the fluoroquinolone group, the conducted statistical analysis showed that a statistically significant model of use was established only in GW. The trend in its consumption is best described by a cubic regression model (Figure 8), which demonstrates a correlation coefficient of $R = 0.778$ and a statistical significance $p = 0.049$. The resulting regression equation is the following:

$$Y = 0{,}086 \cdot t^3 - 1{,}433 \cdot t^2 + 7{,}567 \cdot t - 0{,}567,$$

where Y represents the amount of fluoroquinolones used, and t denotes time. The equation reflects an increasing trend in the use of fluoroquinolones during the studied period.

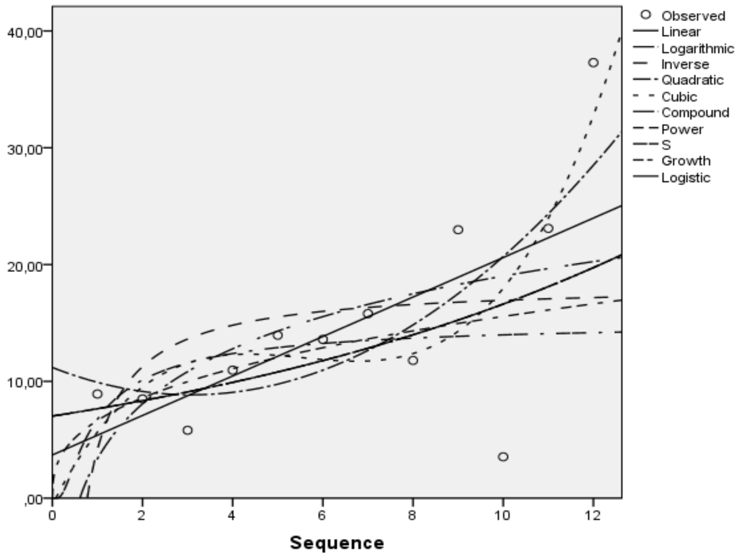

Figure 8. *Graphical representation of the statistical models used describing the use of fluoroquinolones in GW*

For antibiotics from the tetracycline group, a statistically significant model was also identified only in GW, with the most accurate description of the data achieved through a cubic regression model (Figure 9). The correlation coefficient is exceptionally high ($R = 0.979$), and the model is highly significant $p < 0.000$. The regression equation of the model is:

$$Y = -0{,}013 \cdot t^3 + 0{,}379 \cdot t^2 - 3{,}554 \cdot t + 11{,}423,$$

where Y represents the quantity of tetracyclines used and t denotes time, indicating a clear trend toward a decrease in the use over the observed period.

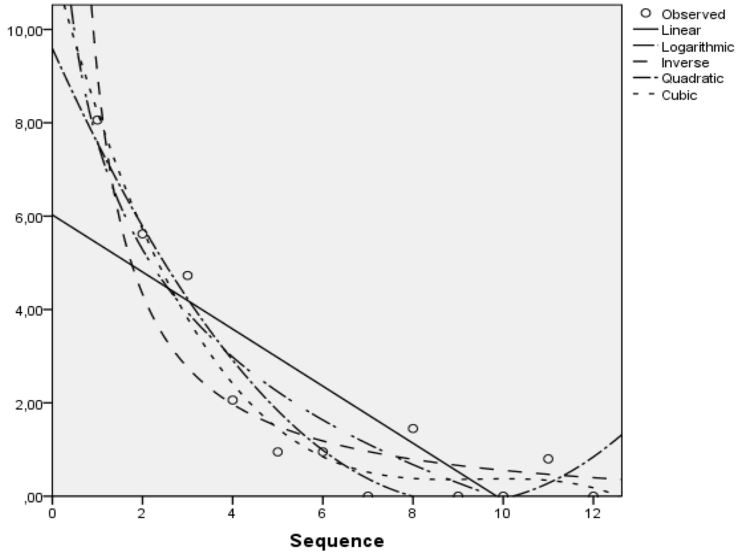

Figure 9. *Graphical representation of the statistical models used describing the use of tetracyclines in GW*

In the conducted statistical analysis, a statistically significant model for the use of nitroimidazole derivatives was identified in the GW and HRPW. Their consumption is best described by a cubic model.

In the GW, a cubic regression model most accurately describes the use of nitroimidazole derivatives, with a correlation coefficient of $R = 0.79$ and good statistical significance at $p = 0.041$ (Figure 10). The model equation is as follows:

$$Y = 0{,}041 \cdot t^3 - 0{,}672 \cdot t^2 + 2{,}443 \cdot t + 6{,}143,$$

where Y represents the quantity of nitroimidazole derivatives used, and t denotes time. An uneven but slightly increasing trend in usage is observed.

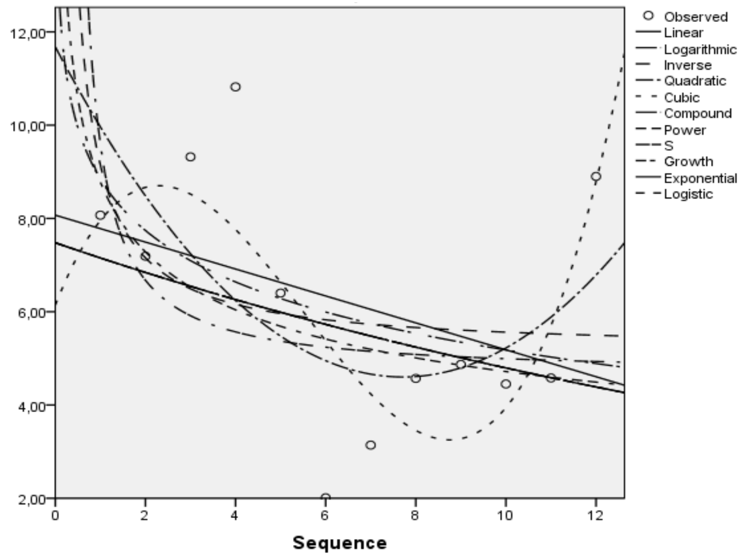

Figure 10. *Graphical representation of the statistical models used, describing the use of nitroimidazole derivatives in GW*

The cubic model that describes the dynamics of the use of the nitroimidazole derivative in the HRPW is characterised by a good correlation coefficient of $R = 0.84$, indicating a high degree of conformity between empirical data and the theoretical function (Figure 11). The statistical significance of the model is confirmed at $p = 0.016$, which demonstrates the reliability of the conclusions drawn. The resulting regression equation is the following:

$$Y = 0{,}003 \cdot t^3 - 0{,}039 \cdot t^2 + 0{,}124 \cdot t - 0{,}028.$$

The shape of the function reflects an uneven but upward trend in the use of nitroimidazole derivatives within the analysed time interval. A slight instability is observed in the initial periods, followed by a clearly expressed increase in values toward the end of the observation.

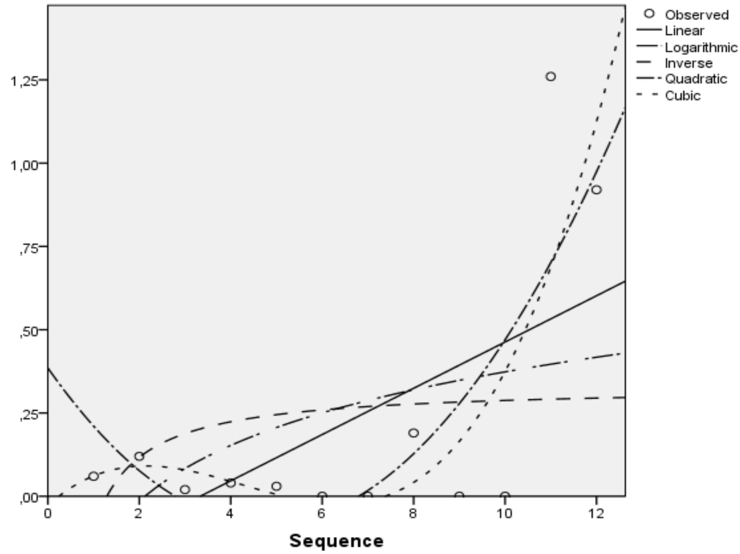

Figure 11. *Graphical representation of the statistical models used describing the use of nitroimidazole derivatives in the HRPW*

In the conducted statistical analysis, statistically significant models for the use of lincosamides were established in the MW and GW. It is important to note that this group of antibiotics was not used at all in the ICU and HRPW. Lincosamides are not administered in HRPW, as they fall into category B of the risk classification. Although the categorisation of antibiotics into letter categories (A, B, C, D, and X) has not been used since 2015, it still finds application in routine clinical practice. Lincosamides cross the placental barrier, and their use in pregnant women is limited. They are not administered in the ICU, as they are not considered a first-line treatment option in contemporary guidelines for antimicrobial therapy in obstetrics and gynecology. The overall use of lincosamides in the hospital can be represented by a statistically significant model.

In MW, the trend in the use of lincosamides is best described by a quadratic regression model (Figure 12), which is characterised by a statistically significant result of $p = 0.014$ and a correlation coefficient of $R = 0.784$. This result indicates a moderately strong relationship between time and antibiotic use. The equation of the established model is as follows:

$$Y = 0{,}001 \cdot t^2 - 0{,}011 \cdot t + 0{,}044,$$

with the graphical interpretation of the model revealing a tendency toward a decrease in the use of lincosamides over time, particularly in the second half of the observed period.

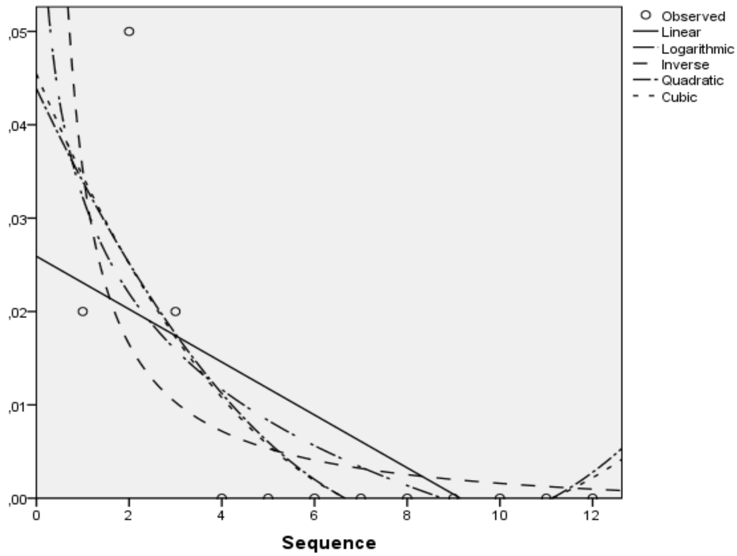

Figure 12. *Graphical representation of the statistical models used describing the use of lincosamides in MW*

In the GW, the model that best represents the dynamics of lincosamide use is cubic (Figure 13), with a good correlation coefficient of $R = 0.782$ and statistical significance of $p = 0.046$. This indicates the reliability of the established model. The regression equation is as follows:

$$Y = 8{,}5 \cdot 10^{-5} \cdot t^3 - 1{,}83 \cdot 10^{-5} \cdot t^2 - 0{,}012 \cdot t + 0{,}043,$$

which reflects an uneven but moderately increasing trend in the use of lincosamides in the ward.

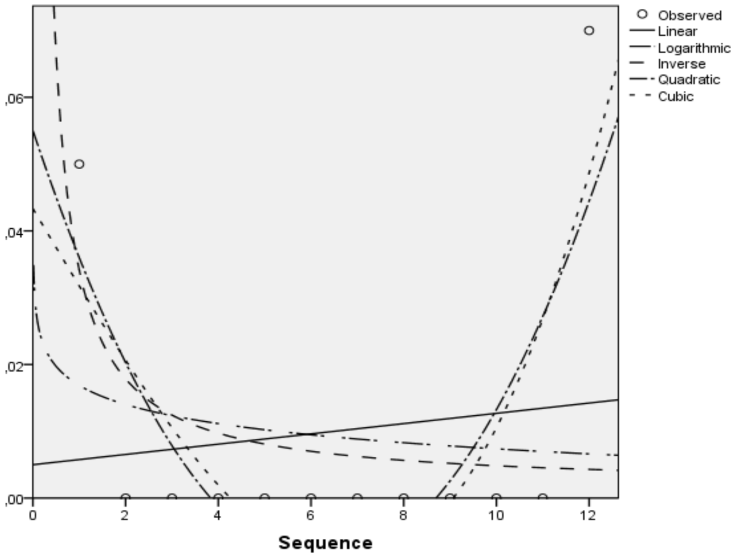

Figure 13. *Graphical representation of the statistical models used describing the use of lincosamides in GW*

In the conducted statistical analysis, statistically significant models for aminoglycoside use were identified in the GW and the ICU.

Analysis of aminoglycoside use in GW shows that the best-fitting model is cubic, demonstrating a high correlation coefficient $R = 0.92$ and statistical significance $p = 0.001$ (Figure 14). These values indicate a strong and reliable relationship between time and changes in the consumption of this group of antibiotics. The regression equation is the following.

$$Y = 0{,}023 \cdot t^3 - 0{,}378 \cdot t^2 + 1{,}017 \cdot t + 5{,}883,$$

which describes a trend toward decreasing aminoglycoside use in the long term. This may result from changes in antimicrobial resistance or substitution with other antibiotic groups.

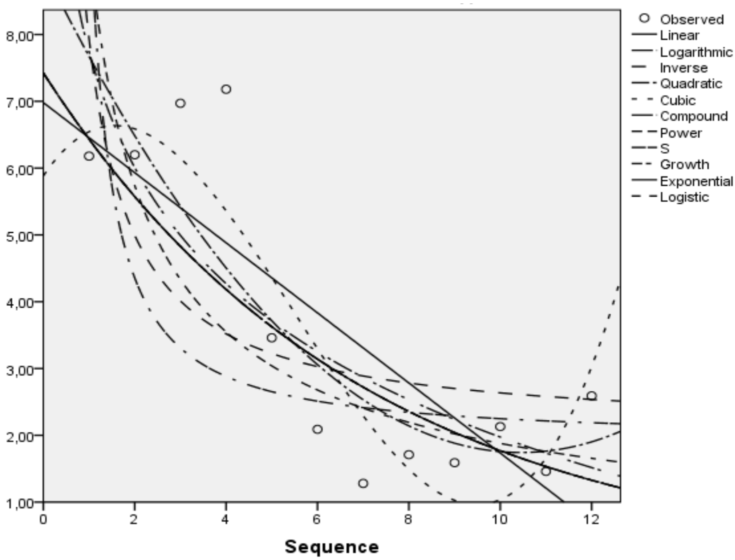

Figure 14. *Graphical representation of the statistical models used describing the use of aminoglycosides in GW*

In ICU, the exponential model best describes the trend in aminoglycoside use (Figure 15). It is characterised by a correlation coefficient of $R = 0.803$ and high statistical significance, $p = 0.002$, making it reliable for interpreting the usage dynamics. The equation of this model is the following.

$$Y = 8{,}883 \cdot e^{(-0{,}244 \cdot t)},$$

which shows a clear and stable trend of decreasing aminoglycoside use in the ICU.

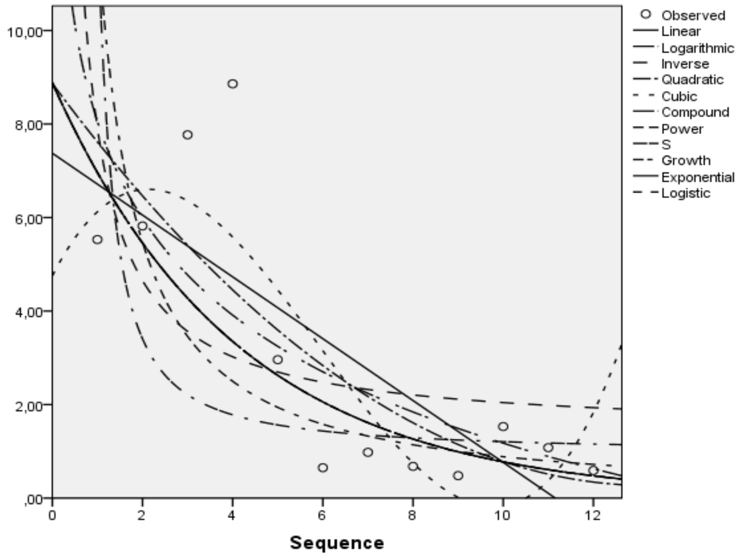

Figure 15. *Graphical representation of the statistical models used describing the use of aminoglycosides in ICU*

4.2. Modelling the trend of development of the total use of antibiotics in SHOGAT "Prof. Dr. D. Stamatov" - Varna for the period 2012-2023.

In this part, the results of modelling the trends in the overall antibiotic use (by groups) are presented (Table 18), without taking into account the use by wards, at SHOGAT “Prof. Dr. D. Stamatov” – Varna.

Table 18. *Trend of development of the total use of antibiotics in SHOGAT "Prof. Dr. D. Stamatov" - Varna for the period 2012-2023.*

	R	**R^2**	**SEE***	**sig.**	**F**	**Model**
Penicillins	0,865	0,749	0,477	0,000	29,781	linear
Cephalosporins	0,828	0,682	2,250	0,005	9,838	quadratic
Tetracyclines	0,934	0,872	0,161	0,001	18,198	cubic
Lincosamides	0,873	0,762	0,005	0,002	14,409	quadratic
Aminoglycosides	0,818	0,669	0,407	0,001	20,170	exponential
Total	**0,685**	**0,469**	**0,698**	**0,148**	**2,359**	**cubic**

* Std. Error of the Estimate

The results of the statistical analysis indicate that the linear model is the most suitable for describing the trend in overall use of penicillins in the healthcare facility (Figure 16). The obtained correlation coefficient $R = 0.865$ shows a strong linear relationship between time and the amount of penicillins used, while the coefficient of determination $R^2 = 0.749$ means that 74.9% of the variation in use can be explained by time. The model is statistically significant at $p < 0.001$, which attests to the reliability of the analysis. The regression equation is the following.

$$Y = -0{,}218 \cdot t + 4{,}549,$$

where t denotes the time period, and Y represents the predicted use of penicillins. The negative coefficient for t confirms that with each passing year, the use decreases on average by 0.218 units, indicating a clear trend towards a reduced application of this group of antibiotics.

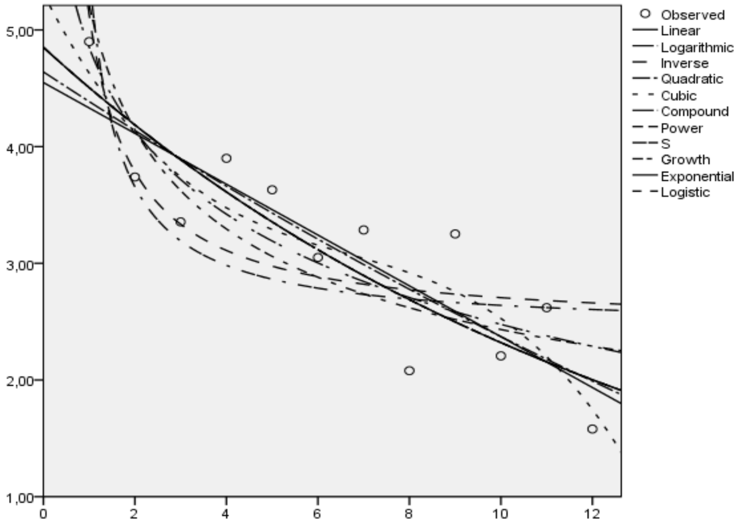

Figure 16. *Graphical presentation of the statistical models used, describing the general use of penicillins in SHOGAT "Prof. Dr. D. Stamatov" - Varna*

The analysis reveals that the quadratic model most accurately describes the trend of the overall use of cephalosporin in the healthcare facility (Figure 17). With a correlation coefficient of $R = 0.828$ and a low degree of error, the model is statistically significant at $p = 0.005$ and provides a reliable representation of the dynamics of consumption. The regression equation is the following.

$$Y = 0{,}118 \cdot t^2 - 0{,}781 \cdot t + 14{,}245,$$

which describes an increasing trend in the use of cephalosporins. The initial decline, caused by the negative coefficient of the linear term, is quickly offset by the positive quadratic component, indicating a rise in usage over time.

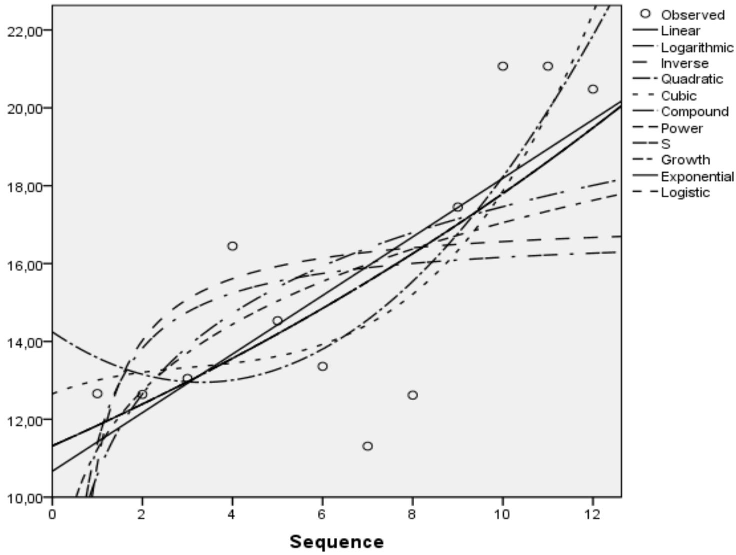

Figure 17. *Graphical presentation of the statistical models used, describing the overall use of cephalosporins in SHOGAT "Prof. Dr. D. Stamatov" - Varna*

The trend in overall use of tetracyclines in the healthcare facility is best described by a cubic model, which shows an exceptionally strong correlation with time (R = 0.934) and high statistical significance p = 0.001 (Figure 18). This indicates a strong and reliable relationship between time and the use of these antibiotics. The model equation is as follows:

$$Y = –0,003 \cdot t^3 + 0,079 \cdot t^2 – 0,644 \cdot t + 1,850,$$

which demonstrates a clearly expressed trend toward a decrease in the use of tetracycline, especially in the latter periods of the study. The form of the equation suggests that the use may initially have fluctuated, but the overall trend is downward.

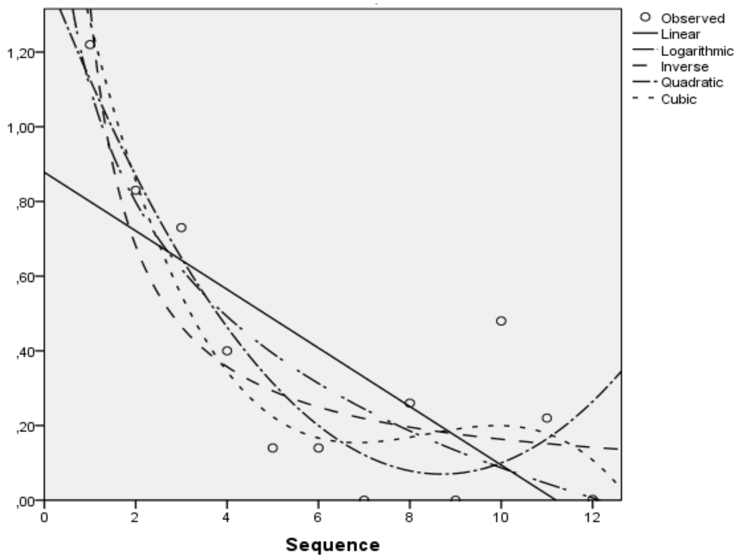

Figure 18. *Graphical presentation of the statistical models used, describing the general use of tetracyclines in SHOGAT "Prof. Dr. D. Stamatov" - Varna*

Quadratic regression best explains the dynamics of the overall use of lincosamides, with a correlation coefficient $R = 0.873$ and a statistical significance $p = 0.002$ (Figure 19). This model indicates a reliable relationship between changes over time and the use of this group of antibiotics. The mathematical model is described by the following equation:

$$Y = 0,001 \cdot t^2 - 0,009 \cdot t + 0,034,$$

which represents a trend toward a gradual decrease in usage. Although the quadratic model includes a positive second-degree term, the dominant linear component with a negative sign influences the overall trend. Thus, a slight but consistent decline in the use of lincosamides in healthcare facilities is observed.

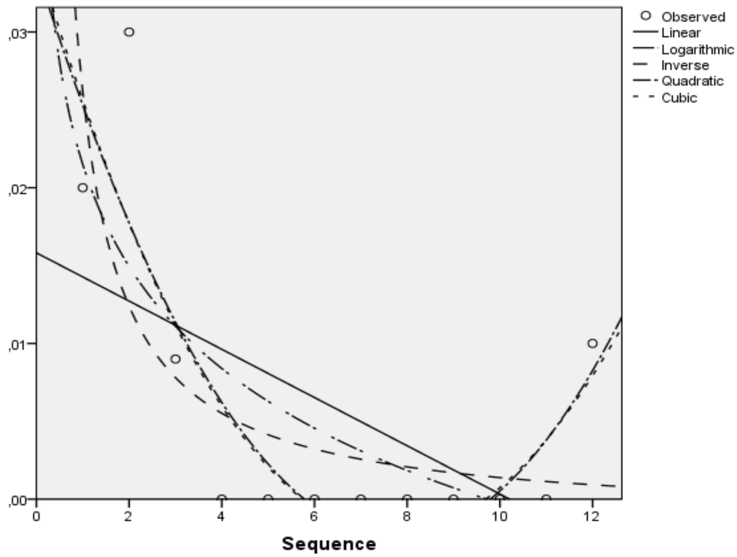

Figure 19. *Graphical presentation of the statistical models used, describing the general use of lincosamides in SHOGAT "Prof. Dr. D. Stamatov" - Varna*

The exponential model best describes aminoglycosides, demonstrating a correlation coefficient R = 0.818 and statistical significance p = 0.001 (Figure 20). The exponential nature of the model allows for more accurate interpretation in cases of rapid decrease in usage. The equation of the model is as follows:

$$Y = 2{,}644 \cdot e^{(-0{,}153 \cdot t)},$$

, which clearly depicts an exponential decline in the use of aminoglycosides over time.

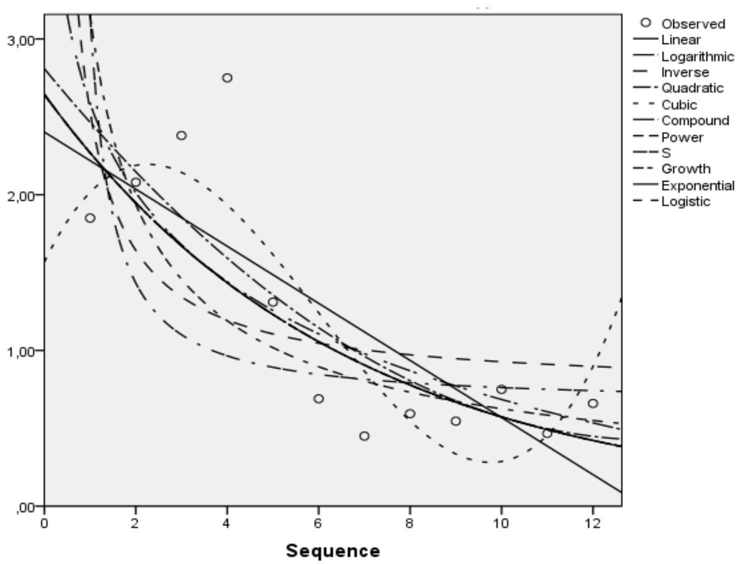

Figure 20. *Graphical presentation of the statistical models used, describing the general use of aminoglycosides in SHOGAT "Prof. Dr. D. Stamatov" - Varna*

To analyse the dynamics of overall antibiotic use at SHOGAT "Prof. Dr. D. Stamatov" – Varna for the entire study period (2012–2023), regression modelling was applied, the cubic model providing the best description of the trends. This model has the highest correlation coefficient R = 0.685 compared to other alternatives tested, indicating a moderately strong relationship between time and antibiotic consumption. The regression model equation is as follows:

$$Y = 0{,}018 \cdot t^3 - 0{,}116 \cdot t^2 - 0{,}318 \cdot t + 26{,}069,$$

where t represents the time period and Y the predicted amount of antibiotics used. The graphical form of this model (Figure 21) shows a non-uniform trend characterised by a decrease in overall use until the middle of the period, followed by a subsequent increase in later years. Despite the relatively good correlation coefficient, it is important to note that the model is not statistically significant, with p = 0.148.

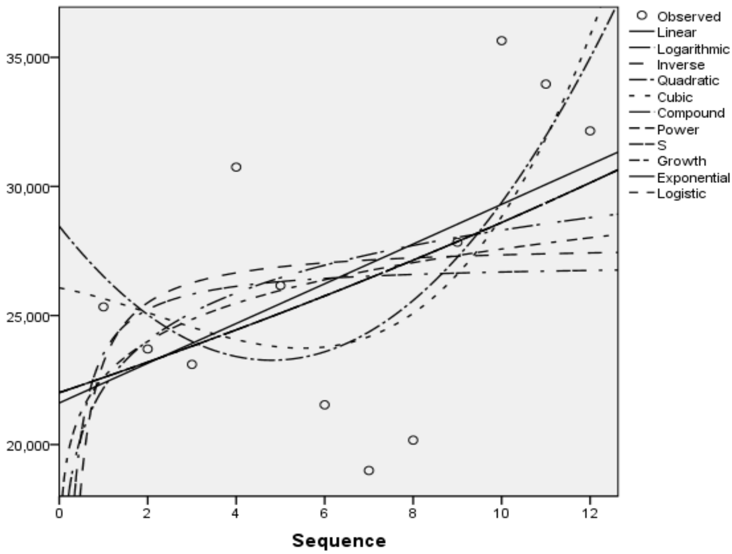

Figure 21. *Graphical presentation of the statistical models used, describing the TOTAL use of antibiotics in SHOGAT "Prof. Dr. D. Stamatov" - Varna*

The irregular pattern observed in the overall use of antimicrobial agents in hospital may be the result of random fluctuations. For example, the limited use of certain groups of antibiotics in the analysed wards (antimycotics, carbapenems, and glycopeptides) does not allow for differentiated statistical analysis of their use; however, the consumption values of these agents are included in the total hospital antibiotic usage.

Another example is the use of macrolides (azithromycin), which has been observed since 2020 (Table 10). The highest consumption of azithromycin was recorded in 2021 in the GW. The COVID-19 pandemic is associated with an increased use of azithromycin, particularly during the early waves of the pandemic. The significant decline in macrolide use in 2022 is related to emerging studies and clinical data that demonstrate their limited efficacy in the treatment of COVID-19. Data from Table 13 shows that macrolides were barely used in 2023, aligning with European and global trends.

However, the model provides a useful indicative perspective on possible fluctuations in antibiotic use within the hospital and highlights the need for prolonged monitoring or further analysis.

5. **Prospective analysis of hospital use of main antibiotic groups in various wards of SHOGAT "Prof. Dr. D. Stamatov" - Varna for the period 2024–2026, based on statistically significant models.**

Based on the statistically significant models, a forecast for the use of the respective type of antibiotic for the next three years has been formulated, using the most recently reported value as a baseline. The results of the forecasts are presented in Table 19.

Table 19. *Forecast trends in antibiotic use (DDD/100 bed-days) for the period 2024–2026.*

Antibiotic group and place of use	2024	2025	2026
Penicillins			
– Maternity ward	0.600	0.154	-0.292
– Total in SHOGAT	1.715	1.497	1.279
Cephalosporins			

Antibiotic group and place of use	**2024**	**2025**	**2026**
– Gynecology ward	33.917	45.323	59.745
– Maternity ward	7.684	8.708	9.820
– Intensive Care Unit	131.191	141.800	153.267
– High-Risk Pregnancy Ward	10.357	11.794	13.375
– Total for SHOGAT	24.034	26.439	29.080
Fluoroquinolones			
– Gynecology ward	44.569	60.487	80.763
Tetracyclines			
– Gynecology ward	0.711	0.279	-0.487
– Total for SHOGAT	0.238	0.086	-0.160
Nitroimidazole derivatives			
– Gynecology ward	14.411	21.137	29.963
– High-Risk Pregnancy Ward	1.584	2.296	3.182
Lincosamides			
– Maternity ward	-0.006	-0.008	-0.009
– Gynecology ward	0.071	0.105	0.146

Antibiotic group and place of use	2024	2025	2026
– Total for SHOGAT	0.086	0.104	0.124
Aminoglycosides			
– Gynecology ward	5.753	9.145	13.713
– Intensive Care Unit	0.376	0.295	0.231
– Total for SHOGAT	0.364	0.312	0.268

Penicillins

The forecast values indicate a gradual decrease in the overall use of penicillins in the healthcare facility, the projected value for 2024 being 1.715 DDD/100 bed-days, for 2025 – 1.497 DDD/100 bed-days, and for 2026 – 1.279 DDD/100 bed-days. A pronounced trend toward a decrease in the use of this group of antibiotics is also observed for the MW. In 2024, the predicted value is 0.600 DDD/100 bed-days, in 2025 it decreases to 0.154 DDD/100 bed-days, and in 2026 it is expected to decline to –0.292 DDD/100 bed-days (Table 19).

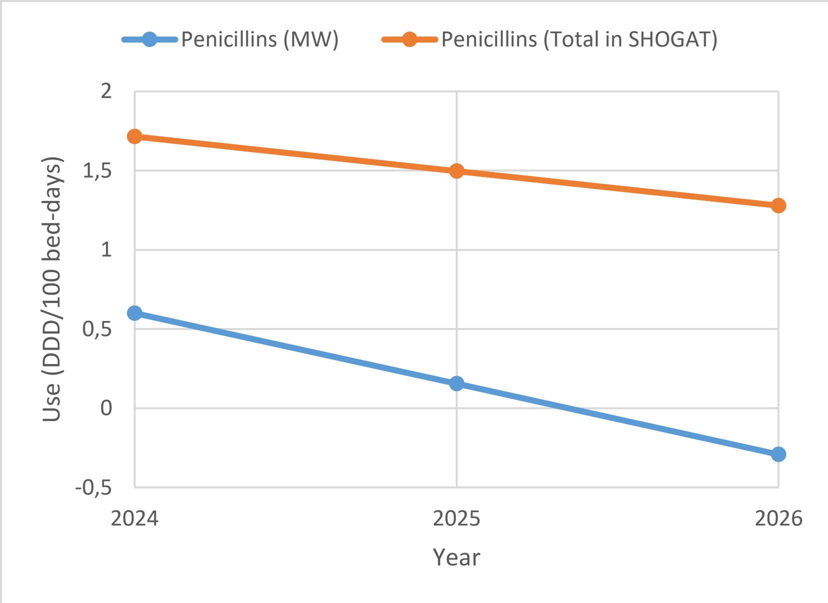

Figure 22. *Trends in penicillins use (DDD/100 bed-days) - prospective analysis*

The data in Figure 22 show that the forecasted values predict an overall almost constant use of penicillins, with a slight decrease during the period 2024–2026. However, in the MW, a sharp decline is forecasted, with the value becoming negative in 2026, suggesting a cessation of their use.

Cephalosporins

The forecast values predict a significant increase in the use of cephalosporins in the GW, with usage projected at 33.917 DDD/100 bed-days for 2024, 45.323 DDD/100 bed-days for 2025, and 59.745 DDD/100 bed-days for 2026. The projected use of cephalosporins in the MW also shows an increase — 7.684 DDD/100 bed-days for 2024, 8.708 DDD/100 bed-days for 2025, and 9.820 DDD/100 bed-days for

2026. The data for the ICU show the highest and most stable upward trend — 131.191 DDD/100 bed-days for 2024, 141.800 DDD/100 bed-days for 2025, and 153.267 DDD/100 bed-days for 2026. The projected use of cephalosporins on the HRPW ward shows a slight increase — 10.357 DDD/100 bed-days for 2024, 11.794 DDD/100 bed-days for 2025, and 13.375 DDD/100 bed-days for 2026. The overall expected use of cephalosporins shows a steady growth — 24.034 DDD/100 bed-days for 2024, 26.439 DDD/100 bed-days for 2025, and 29.080 DDD/100 bed-days for 2026 (Table 19).

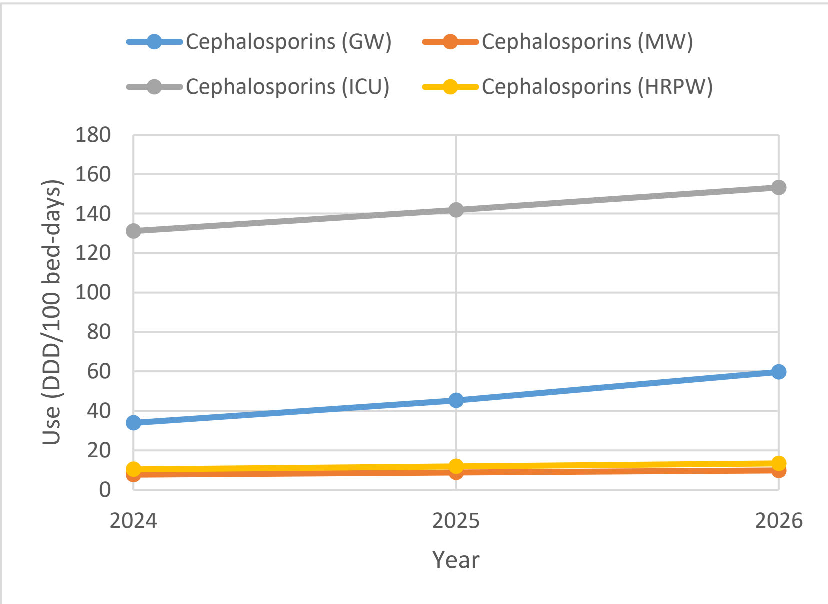

Figure 23. *Trends in the use of cephalosporins (DDD/100 bed-days) - prospective analysis*

Cephalosporins remain one of the most commonly used groups of antibiotics, with a projected increase in usage in all wards. The most significant increase is expected in GW and the ICU, where the forecasts indicate a sustained upward trend (Figure 23).

The increasing use of cephalosporins in the healthcare facility is due to several key factors, primarily related to the use of cefazolin and ceftriaxone. Cefazolin has been established as the drug of choice for antibiotic prophylaxis, which explains its widespread application. The use of ceftriaxone is directly related to its proven effectiveness and its establishment as a preferred agent in obstetric and gynecological practice.

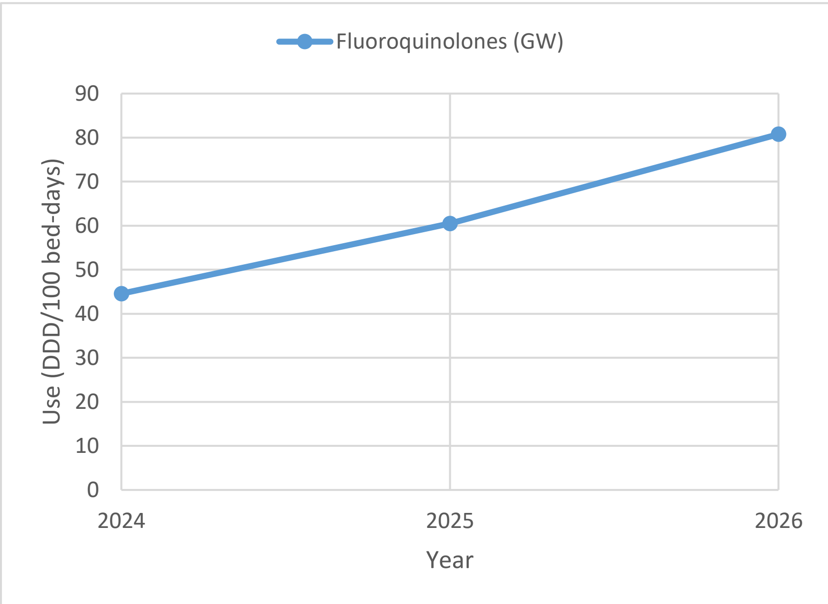

Figure 24. *Trends in the use of fluoroquinolones (DDD/100 bed-days) - a prospective analysis*

The trend of increasing use (Figure 24) of ciprofloxacin can be explained by two main reasons. First, an increase in the number of hospitalised patients is observed in the GW. Second, this antibiotic is widely accepted and established in clinical practice as a preferred agent for treatment in conservative gynecology. These factors collectively contribute to its increased application.

Tetracyclines

The forecast values for the use of tetracyclines in the GW show a decreasing trend — 0.711 DDD/100 bed-days for 2024, 0.279 DDD/100 bed-days for 2025, and –0.487 DDD/100 bed-days for 2026. The forecast values for the overall use of tetracyclines in the healthcare facility also show a decline — 0.238 DDD/100 bed-days for 2024, 0.086 DDD/100 bed-days for 2025, and –0.160 DDD/100 bed-days for 2026 (Table 19).

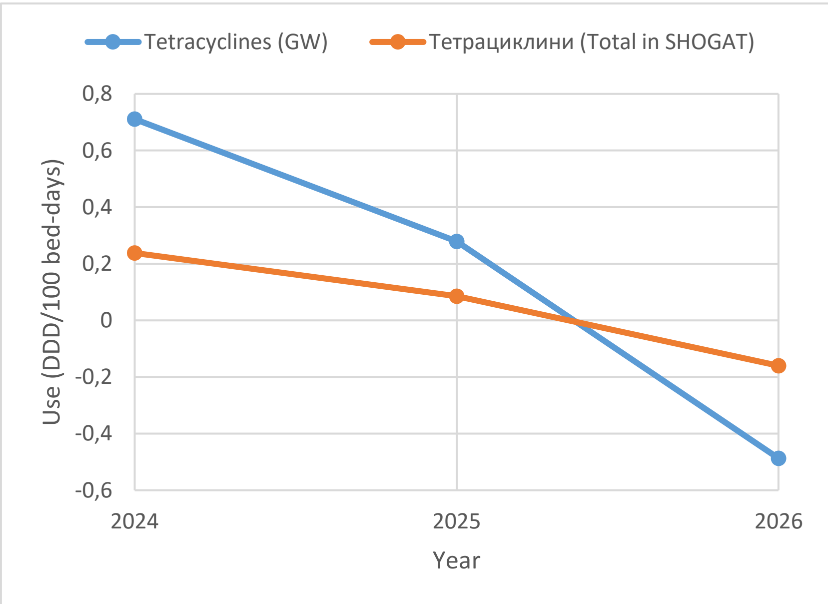

Figure 25. *Trends in tetracycline use (DDD/100 bed-days) - prospective analysis*

From the graphs in Figure 25, a clear decrease in tetracyclines use can be observed, both in the GW and in their overall use in the hospital.

Nitroimidazole derivatives (metronidazole)

The forecast values predict an almost twofold increase in the use of metronidazole, both in the GW — 14.411 DDD/100 bed-days for 2024, 21.137 DDD/100 bed-days for 2025, and 29.963 DDD/100 bed-days for 2026, and in the HRPW — 1.584 DDD/100 bed-days for 2024, 2.296 DDD/100 bed-days for 2025, and 3.182 DDD/100 bed-days for 2026 (Table 19 and Figure 26).

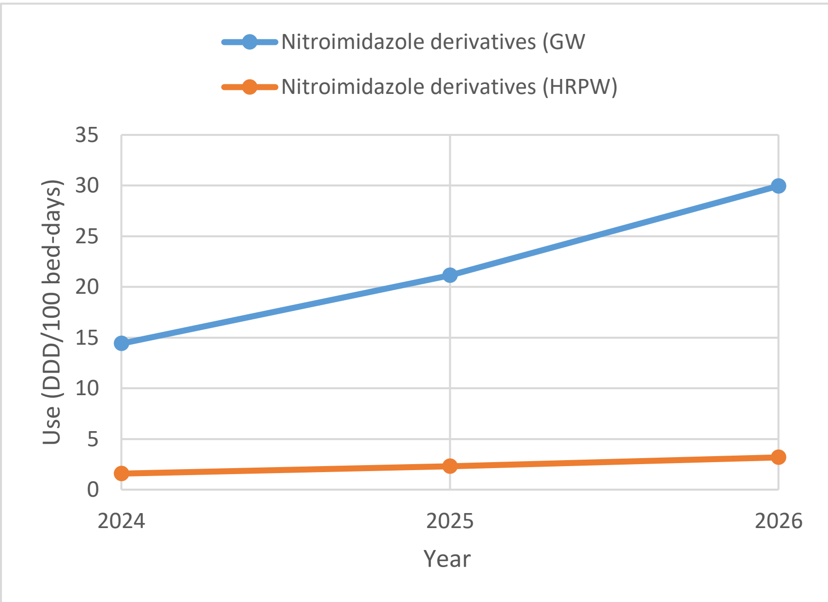

Figure 26. *Trends in the use of imidazole derivatives (DDD/100 bed-days) - prospective analysis*

Lincosamides

The forecasted use of lincosamides by ward and overall for the hospital shows a varying trend. In the MW, a continuing trend toward a decrease in the use of this group of antibiotics is observed — –0.006 DDD/100 bed-days for 2024, –0.008 DDD/100 bed-days for 2025, and –0.009 DDD/100 bed-days for 2026. The forecasted values predict a slight increase in the use of lincosamides in the GW — 0.071 DDD/100 bed-days for 2024, 0.105 DDD/100 bed-days for 2025, and 0.146 DDD/100 bed-days for 2026. The overall projected use of lincosamides in the healthcare facility also predicts a moderate increase in the use of this group of antibiotics — 0.086 DDD/100 bed-days for 2024, 0.104 DDD/100 bed-days for 2025, and 0.124 DDD/100 bed-days for 2026 (Table 19).

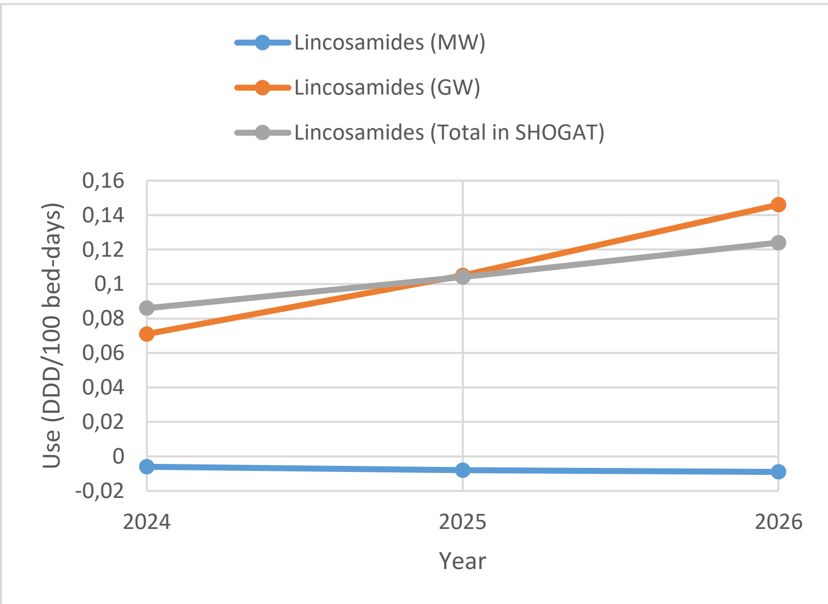

***Figure 27.** Trends in the use of lincosamides (DDD/100 bed-days) - prospective analysis*

Statistical models for predicting the use of lincosamides show relative stability in the overall use of this group of antibiotics. In the MW, the values remain negative, indicating that their use will likely be completely discontinued in this unit. However, in the GW, the forecasts indicate a slight increase (Figure 27).

Aminoglycosides

According to the forecast values, a distinct increase in the use of aminoglycosides is observed in the GW — 5.753 DDD/100 bed-days for 2024, 9.145 DDD/100 bed-days for 2025, and 13.713 DDD/100 bed-days for 2026. In the ICU, the data suggest a slight decrease in use — 0.376 DDD/100 bed-days for 2024, 0.295 DDD/100 bed-days for 2025, and 0.231 DDD/100 bed-days for 2026. The same trends are observed for the overall hospital use of aminoglycosides — 0.364 DDD/100 bed-days for 2024, 0.312 DDD/100 bed-days for 2025, and 0.268 DDD/100 bed-days for 2026 (Table 19).

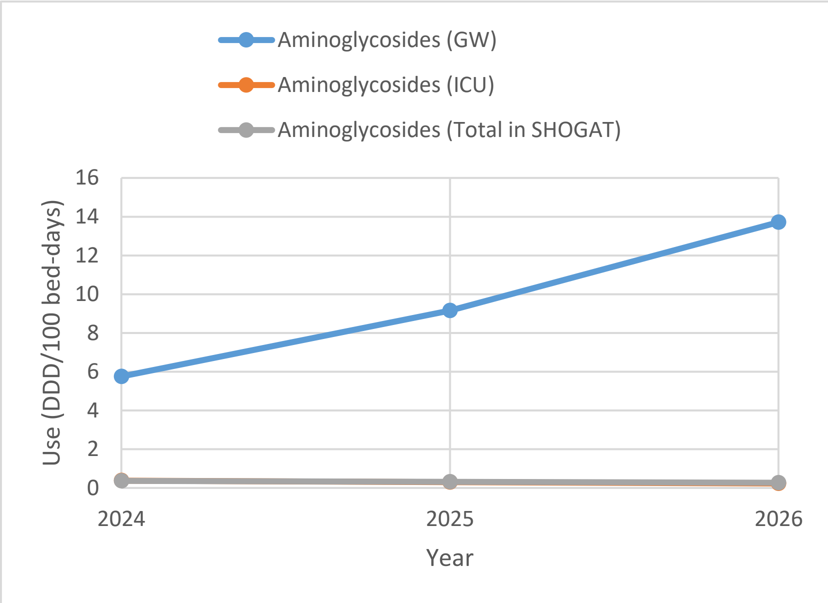

Figure 28. *Trends in aminoglycoside use (DDD/100 bed-days) - prospective analysis*

The overall forecast for aminoglycosides showed relative stability or minimal decline by the end of the period. In the graph, only one line is distinguishable for the ICU and the overall hospital use, as the values are very close to each other. The difference between them is minimal, making the lines almost entirely overlapping and visually indistinguishable (Figure 28).

Summary of the results of the prospective analysis

In the analysis of forecast values for antibiotic use from 2024 to 2026, there are instances where the models predict negative values (Table 19). This applies to:

- The use of penicillins in MW – forecasted values: 0.600 DDD/100 bed-days (2024), 0.154 DDD/100 bed-days (2025), -0.292 DDD/100 bed-days (2026).

- The use of tetracyclines in GW – forecasted values: 0.711 DDD/100 bed-days (2024), 0.279 DDD/100 bed-days (2025), -0.487 DDD/100 bed-days (2026).
- The total use of tetracyclines – forecasted values: 0.238 DDD/100 bed-days (2024), 0.086 DDD/100 bed-days (2025), -0.160 DDD/100 bed-days (2026).
- The use of lincosamides in the MW – forecasted values: -0.006 DDD/100 bed-days (2024), -0.008 DDD/100 bed-days (2025), -0.009 DDD/100 bed-days (2026).

Negative values should not be literally interpreted as actual negative usage, since antibiotic use cannot be less than zero. These values should be understood as a statistical reflection of a continuing trend toward decreasing the use of certain antibiotics, which may lead to complete elimination in the respective units.

The increase in antibiotic use in certain hospital wards can be explained by a combination of various factors. During the forecast period 2024–2026, a clearly expressed trend towards increased use of certain groups of antibiotics is observed, particularly in the gynecology ward, intensive care unit, and the high-risk pregnancy ward.

First, the forecast for a significant increase in the use of cephalosporins is due to the establishment of cefazolin as the agent of choice for antibiotic prophylaxis in obstetric-gynecological practice. Additionally, ceftriaxone is increasingly used as a result of its high efficacy and broad-spectrum action. In the updated BPPL of 2024, third-generation cephalosporins show decreasing levels of resistance to ESKAPE pathogens, with the exception of *E. coli*. This explains why, in the GW, the forecasted use of cephalosporins rises from 33.917 DDD/100 bed-days in 2024 to 59.745 DDD/100 bed-days in 2026, and in the ICU – from 131.191 to 153.267 DDD/100 bed-days over the same period.

Simultaneously, the trend in the use of fluoroquinolones also shows an increase in the GW – from 44.569 DDD/100 bed-days in 2024 to 80.763 DDD/100 bed-days in 2026. This is explained both by their established role in the treatment of complicated urogenital infections and by the increasing number of hospitalised patients, which inevitably leads to a greater need for antibiotic treatment.

For aminoglycosides, although their use is more limited, an increasing trend is also predicted in the GW – from 5.753 to 13.713 DDD/100 bed-days for the period 2024–2026. This is an indicator of their targeted application in certain severe or mixed bacterial infections, as well as likely as part of combination antibiotic therapies with cephalosporins.

A similar trend is observed for nitroimidazole derivatives, whose application in the GW can almost double during the forecast period – from 14.411 to 29.963 DDD/100 bed-days. This is due to the established role of metronidazole (the only representative of the nitroimidazole group registered in Bulgaria) in the treatment of anaerobic infections, which are frequently encountered in gynecological practice.

IV. CONCLUSIONS

1. The use of multiple regression models with varying degrees of complexity allowed not only to track the dynamics of antibiotic consumption over a 12-year period but also to assess the predictability of the observed processes. The cubic model stood out with the highest correlation; however, the results highlight the limitations of the univariate approach when dealing with complex clinical data and the need for multivariate analysis in future studies.

2. Units such as the ICU were identified where an increase in the use of certain antibiotics is observed, necessitating additional microbiological and clinical monitoring.

3. During the review period, the ICU consistently showed the highest levels of use of cephalosporin (cefazolin, ceftriaxone) and metronidazole. In the gynecology ward, an increasing use of ciprofloxacin was observed, whereas the High-risk pregnancy ward used relatively small but steady amounts of amoxicillin and metronidazole.

4. The extremely low frequency of antibiotics from the WHO AWaRe Watch group, such as carbapenems and vancomycin, confirms the success of the local antibiotic policy as well as the absence of broad-spectrum resistance at SHOGAT "Prof. Dr. D. Stamatov" – Varna.

5. The oral use of ampicillin and doxycycline is low, mainly limited to the early stage of the analysed period, subsequently showing a decreasing trend.

6. Modelling the time dependence of overall antibiotic use at SHOGAT "Prof. Dr. D. Stamatov" – Varna for the period 2012–2023

using a cubic regression model reveals a non-uniform trend, with an initial decline followed by an increase. Although the model demonstrates a relatively good correlation coefficient $R = 0.685$, the lack of statistical significance $p = 0.148$ limits the possibility of reliable long-term trend generalisation and requires the inclusion of additional data.

7. Prospective analysis for the period 2024–2026 reveals a variable nature of antibiotic use between wards and groups. A sustained increasing trend is observed for cephalosporins and fluoroquinolones, while penicillins and tetracyclines show a marked decline.

V. CONTRIBUTIONS

Contributions of a scientific and theoretical nature

1. This study is the first of its kind within SHOGAT "Prof. Dr. D. Stamatov" – Varna, providing a foundation for comparison with future clinical and scientific research.

2. The application of regression analysis of varying complexity (up to cubic) demonstrated effectiveness in modelling real clinical data and offers a statistical framework for future similar studies.

3. The statistical models developed based on the available data can be used for comparative analysis of antibiotic use between wards. This may serve as a basis for future predictive analyses and protocols related to rational antimicrobial policy.

4. The results of the analysis provide a scientific basis for optimising antibiotic therapy, tailored to resistance trends and the needs/specifications of different wards.

5. The dissertation offers a statistical approach to modelling and forecasting hospital antibiotic use, adapted to the structure of SHOGAT. This enables long-term planning of drug needs and effective monitoring of antibacterial therapy.

Contributions of a scientific and applied nature

1. For the first time, a systematic retrospective study of antibiotic consumption (DDD/100 bed-days) was conducted over a 12-year period at SHOGAT "Prof. Dr. D. Stamatov" – Varna.

2. The use of a standardised unit (DDD/100 bed-days) ensures the comparability of results and allows both intra-hospital and inter-hospital control.

3. For the first time, a quantitative prospective analysis of antibiotic use was performed at SHOGAT "Prof. Dr. D. Stamatov" –

Varna, contributing to existing national-level data and potentially helping identify risk trends.

4. The statistical models used in the analysis could be further developed and integrated into hospital information systems to enable real-time monitoring of trends, forecasting peak demands, optimising supplies, and automatic generation of deviation alerts.

5. The applied quantitative approach and models can be adapted and optimised for implementation in other hospital structures, granting the study strategic value for the creation of national algorithms for control and monitoring of antibiotic consumption.