REVIEW

Subject: Dissertation for the degree of Doctor of Science - Scientific field: 7. Health Care and Sports, Professional field – 7.3 Pharmacy, Scientific specialty "Pharmacology (including Pharmacokinetics and Chemotherapy)"

by Prof. Irina Nikolova Nikolova, MD, member of the scientific jury, in compliance with Order No. P-109-335 of 29 July 2025 of the Rector of MU-Varna.

Author of the dissertation: Mag. Pharm. **Plamen Stefkov Bekyarov**, PhD student at the Department of Pharmacology, Toxicology, and Pharmacotherapy, Faculty of Pharmacy, Medical University of Varna, with scientific supervisors Assoc. Prof. Silvia Georgieva Mihaylova, PhD, and Prof. Marieta Petrova Georgieva, MD.

Thesis topic: "Study of the hospital use of antimicrobial drugs intended for the prevention and treatment of obstetric and gynecological infections"

The dissertation is devoted to the analysis of the rational hospital use of antimicrobial drugs in the prevention and treatment of obstetric and gynecological infections at the Prof. Dr. D. Stamatov Military Medical Academy Hospital – Varna for a period of 12 years, using quantitative and qualitative measures at the national and regional level, in accordance with treatment standards and valid national and international pharmacotherapeutic guidelines.

PhD student Plamen Bekyarov graduated in Pharmacy from MU-Varna in 2017 and obtained a specialization in Clinical Pharmacy in 2022.

Plamen Bekyarov was enrolled as a full-time PhD student in February 2023.

The dissertation is 138 pages in length, with the literature review covering approximately 50 pages, the results and discussion covering about 50 pages, and 234 citations serving as references.

1. Literature review

The literature review is presented in six sections, concluding with a summary of the effective management of antimicrobial resistance, a global problem. The concept of Antimicrobial Stewardship (AMS) has been developed as a key factor in limiting resistance and improving therapeutic outcomes in hospital practice. AMS itself is a behavioral process that requires a multidisciplinary approach tailored to the institution in question, combining regulatory and educational measures.

It is impressive that the literature used spans a 100-year range, demonstrating that the doctoral student has thoroughly studied antibiotic use from the synthesis of penicillin in

1929 to its current widespread use, which has led to antimicrobial resistance and the concept of Antimicrobial Stewardship Programs (ASPs). Half of the cited literature sources are from the past decade.

The literature review includes a special section on pathogens that pose a critical threat to humanity, namely Acinetobacter, Pseudomonas, and Enterobacteriaceae, for which pan-resistance is increasingly reported. It is emphasized that these species are most often the cause of severe and even fatal nosocomial infections.

The mechanisms of action of antibiotics and the mechanisms of development of resistance to different groups of antimicrobial drugs are discussed in detail.

Logically, at the end of the literature review, the rational use of antimicrobial drugs in hospital care and the introduction of ASP for coordinated management of antimicrobial resistance are discussed. It has been established that there is no easy and universal way to introduce ASP, as it is a multifactorial and behavioral process that must be introduced and adapted at the institutional level.

Special attention is given to the specifics of obstetrics and gynecology departments, emphasizing that antibiotic use in pregnant women, women in labor, and women of childbearing age can also have an impact on fertility, newborns, and society as a whole. The incorrect/irrational use of antimicrobial drugs in humans is one of the key factors in the development of resistance.

2. Goal and objectives

The goal of the dissertation is correctly formulated. Six objectives have been formulated to achieve the stated goal.

3. Materials and methods

For the purposes of the dissertation, the database on drug use in four departments of the Prof. Dr. Dimitar Stamov Specialized Hospital for Obstetrics, Gynecology, and Neonatology in Varna for the period 2012-2023, including patients admitted for hospital treatment. A retrospective and prospective analysis of antimicrobial drug use by the department was conducted.

The indicator used was DDD/100 bed days, a standardized unit that ensured comparability of results and allowed for both intra-hospital and inter-hospital comparisons. The indicator used was DDD/100 bed days, a standardised unit that ensures comparability of results and allows for intra-hospital and inter-hospital control.

Multiple regression models were used to track the dynamics of antibiotic use over a 12-year period and to make a prospective assessment of the observed processes. The data were statistically processed.

4. Results and Discussion

Antimicrobial consumption, measured in defined daily doses per 100 bed-days (DDD/100 BD), was analyzed across departments and years. The highest consumption rates were observed in the Intensive Care Unit (ICU) and the Gynecology Department (GD). A marked temporal increase in the use of fluoroquinolones and metronidazole was noted across these units. Statistical analysis identified a significant upward trend in fluoroquinolone consumption, specifically within the GD. Additionally, both the ICU and GD exhibited high utilization rates of cephalosporins.

Conversely, as expected, lower consumption was noted in obstetric units (Maternity and Pathological Pregnancy Wards). Ceftriaxone was the most commonly used antibiotic hospital-wide, followed by cefazolin and metronidazole. A significant statistical model confirmed an increasing trend in cephalosporines use across all departments. On the contrary, a clear declining trend was observed for penicillins, lincosamides, and aminoglycosides. The low consumption of carbapenems (meropenem, imipenem) and vancomycin indicates restricted use of broad-spectrum antibiotics, reflecting controlled prescribing practices aimed at curbing antimicrobial resistance.

The analysis identifies a general trend of marked fluctuation in antimicrobial drug consumption, with pronounced shifts occurring during the COVID-19 pandemic. In a comparative context, data from 24 EU/EEA countries show substantial national variations. Within this framework, SBAGAL-Varna is a notable outlier, demonstrating the lowest recorded consumption rate. This value is significantly beneath the EU/EEA mean and is also considerably lower than the Bulgarian national average, strongly suggesting the presence of effective stewardship, rational antibiotic use, and a correct antibiotic policy at SBAGAL "Prof. Dr. D. Stamatov" – Varna. A contributing factor to this result is the significantly lower baseline requirement for antibiotics in its obstetric and gynecological patient population compared to general multi-profile hospitals.

To analyze antibiotic usage trends, a retrospective analysis was conducted across different drug groups and hospital departments, utilizing a suite of regression models (linear, quadratic, cubic, exponential, and logarithmic). This analysis served as the foundation for a prospective forecast of hospital antimicrobial drug consumption for the period 2024-2026. The forecast values reveal a projected gradual decline in the overall use of penicillins and tetracyclines, contrasted by a concerning increase in the consumption of metronidazole, lincosamides, aminoglycosides, cephalosporins, and fluoroquinolones. These trends, which are recognized as multifactorial processes, have been analyzed in detail. This critical assessment will directly contribute to the formulation of targeted institutional ASP protocols to address these shifting usage patterns.

In summary, the doctoral thesis of Mag. Pharm. Plamen Bekyarov tackles a highly relevant and globally significant topic with strong potential for further investigation. The extensive literature review reveals the candidate's expert command of antimicrobial drugs, therapy, and ASP. A clearly articulated aim is supported by tasks designed for a thorough retrospective and prospective analysis of antibiotic use.

The dissertation's aim is clearly defined and supported by well-formulated tasks that involve both retrospective and prospective analyses of rational antibiotic use. A robust methodological framework was appropriately selected to achieve these objectives. All methods are described in meticulous detail, ensuring the study's reproducibility and showcasing the candidate's proficiency in data analysis, evaluation, interpretation, and statistical processing.

The analysis is based on data extracted from the Gama Store pharmacy software, used with the permission of SBAGAL manager Prof. Dr. D. Stamov. The results were processed using IBM SPSS Statistics version 19 and are effectively illustrated through 35 figures and 25 tables.

The study period (2012-2023) encompasses the COVID-19 pandemic, a well-known confounding factor that could significantly affect the results related to antibiotic use. Despite this, its inclusion is highly valuable. It provides a baseline for future comparative analyses on the impact of sudden, large-scale antibiotic use on antimicrobial resistance (AMR). As a result, the findings strongly support the development of tailored, sustainable programs for monitoring and managing antibiotic use. Additionally, they highlight the importance of ongoing surveillance, predictive modeling, and further analysis to strengthen these efforts. The generated data carry institutional and national significance for creating algorithms to promote rational antibiotic use and control antimicrobial resistance.

Six principal conclusions have been drawn from the results: five key conclusions demonstrating significance in scientific-theoretical domains and five key conclusions demonstrating significance in scientific-applied domains.

The dissertation's primary contribution is the development of a novel statistical approach for modeling and forecasting hospital antibiotic use. The constructed models enable the identification of risk trends, optimization of drug utilization, forecasting of long-term drug needs, and effective monitoring of drug therapy across diverse multidisciplinary hospital structures. Consequently, the data and results hold substantial institutional and national importance for informing algorithms that aim to promote rational antibiotic use and to control antimicrobial resistance. The abstract succinctly and accurately encapsulates the dissertation's core content, with appropriate emphasis placed on the analysis outcomes, their interpretation, and the study's tripartite contributions to theory, methodology, and practical application. Their dissemination further underscores the

significance of these findings, as evidenced by four peer-reviewed publications derived directly from the thesis research, as well as presentations at one international and one national scientific conference.

Conclusion

The dissertation is well-structured and concise. The amount of work done is sufficient, using an adequate range of research approaches and methods, and the data analysed is well processed and illustrated. The work presented, along with the scientific metrics, clearly demonstrates the PhD student's personal contribution to the realization of the research programme. Undoubtedly, in the process of developing the PhD thesis, Mag. Pharm. Plamen Stefkov Bekyarov has acquired sufficient theoretical knowledge and practical skills to obtain the PhD degree. Therefore, the presented data and considerations provide me with grounds to confidently conclude that the submitted thesis meets the national and institutional regulatory requirements and the relevant quantitative criteria applicable to the present procedure. It is my distinct pleasure to recommend that the Honourable Members of the Scientific Jury vote in favor of awarding the educational and scientific degree of "Doctor" to Mag. Pharm. Plamen Stefkov Bekyarov.

Sofia 29.08.2025

Reviewed by

/Prof. Irina Nikolova, MD, PhD