



**MEDICAL UNIVERSITY  
"PROF. DR. PARASKEV STOYANOV" - VARNA**

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**FACULTY OF PUBLIC HEALTH  
Department of Social Medicine and Healthcare Organization**

**Deyana Ivanova Ilieva**

**SURVEILLANCE AND CONTROL OF  
HEALTHCARE-ASSOCIATED INFECTIONS – MODERN  
CHALLENGES**

**ABSTRACT**

of dissertation work  
for awarding an educational and scientific degree "Doctor"

**Scientific supervisors:**

Prof. Dr. Desislava Vankova, MD, DSc

Prof. Dr. Tsonko Paunov, MD

Varna, 2025



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Varna, 2025

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The dissertation is illustrated with 15 tables, 47 figures and one appendix. The bibliography includes 300 literature sources, of which 14 are in Cyrillic and 286 in Latin.

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Note: In the abstract, the numbers of the figures and tables do not correspond to the numbers in the dissertation.

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## ABBREVIATIONS

A. baumannii – Acinetobacter baumannii  
AB – Antibiotic  
AMR – Antimicrobial resistance  
ATP – Adenosine triphosphate  
C. difficile – Clostridium difficile  
CAIC – Clinic of Anesthesiology and Intensive Care  
CDC - Centers for Disease Control and Prevention  
CI – Confidence Interval  
DDD – Disinfection, disinsection, deratization  
E. coli – Escherichia coli  
ECDC – European Center for Disease Prevention and Control  
EEA – European Economic Area  
ENT – Otolaryngology  
Enterobacter cloacae – E. cloacae  
ESBL – Extended-Spectrum Beta-Lactamases  
EU – European Union  
HAI – Healthcare-associated infection  
ICT – Infection Control Team  
ICU –Intensive Care Unit  
K. pneumoniae – Klebsiella pneumoniae  
MRSA – Methicillin-Resistant staphylococcus aureus  
NCPHA – National center by public health and analytics  
P. aeruginosa – Pseudomonas aeruginosa  
PCHO - Pediatric Clinic of Hematology and Oncology  
RHI – Regional health inspectorate  
S. aureus – Staphylococcus aureus  
SD – Standard Deviation

SENIC – Study on the Efficacy of Nosocomial Infection Control

SSI – Surgical site infection place

VAP – Ventilation-associated pneumonia

WHO – World Health Organization

## INTRODUCTION

Nosocomial infections, also referred to as iatrogenic or hospital-acquired infections, have accompanied the development of medicine since its inception and continue to represent one of the most serious challenges facing healthcare systems worldwide. In contemporary scientific literature, as well as in key documents issued by the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC), the term “**healthcare-associated infections**” (HAI) is increasingly used and accepted as a preferred and unifying concept (Horan TC et al., 2008; WHO, 2011). The use of this term emphasizes the direct relationship between the occurrence of infection and the provision of healthcare, which constitutes its main conceptual characteristic. These infections are typically acquired during the delivery of medical care, including diagnostic, therapeutic, or preventive procedures. A defining feature of HAI is the absence of clinical signs of infection at the time of patient admission. The various terms used to describe this group of infections are employed interchangeably in the scientific literature and are likewise applied unambiguously in the present work.

HAI may occur at different stages of healthcare delivery: during hospitalization, outpatient treatment, diagnostic and preventive procedures, as well as after hospital discharge or completion of outpatient care or examinations.

It is an undeniable fact that antimicrobial resistance (AMR) represents a global health problem of high social significance with substantial economic consequences. AMR constitutes a major challenge for public health systems, with significant and often difficult-to-measure impacts on patients’ health, work capacity, and quality of life. It is among the most common adverse events in healthcare and has a direct impact on patient safety. The significant morbidity and mortality associated with AMR place a heavy burden on patients, their families, and healthcare systems, while also generating negative public attitudes toward healthcare institutions and public health services.

The emergence and spread of AMR among pathogenic microorganisms is one of the most alarming challenges facing public health worldwide. A particularly serious problem arises when bacteria that are generally susceptible to antibiotics acquire resistance as a result of genetic changes (acquired resistance). Resistant strains remain viable in the presence of antimicrobial agents and continue to multiply, leading to prolonged disease courses and an increased risk of fatal outcomes. Infections caused by resistant bacteria often require more intensive care and the use of alternative, more expensive antimicrobial agents, which may be associated with more severe adverse effects.

Reducing the risk of HAI requires intersectoral medical initiatives that integrate surveillance systems, infection prevention and control measures, and clinical risk management methodologies. As early as the 1980s, the results of the SENIC study (Study on the Efficacy of Nosocomial Infection Control), conducted by CDC, identified four key components necessary for effective prevention of nosocomial infections:

1. Systematic surveillance of infections;
2. Implementation of specific infection control measures;
3. Availability of a designated infection control specialist or nurse;

#### 4. Involvement of a hospital epidemiologist (Haley RW et al., 1985).

Effective prevention and control measures are essential to reduce the occurrence of HAI and the events or conditions that increase their risk. These measures are an integral part of the safe, effective, and high-quality provision of healthcare services and are of critical importance for maintaining low morbidity and mortality associated with HAI.

Surveillance of HAI is among the priority activities in healthcare related to the prevention of infectious diseases. It is primarily carried out by the Infection Control Team (ICT). This epidemiological approach has been recognized as one of the most effective methods for HAI control. Surveillance is defined as a systematic, active, and continuous process of monitoring the occurrence and spread of HAI, as well as events that increase infection risk, combined with the provision of regular feedback to clinical units regarding the results of implemented measures and preventive interventions. Surveillance data contribute to improved healthcare organization efficiency and reduction of adverse outcomes.

The main activities of the healthcare sector related to epidemiological surveillance of HAI are aimed at early and timely detection and diagnosis of infections, limiting the occurrence and spread of AMR, and ensuring a safe patient environment. In this context, “patient safety” is understood as the absence of unnecessary or potential harm to patients associated with healthcare delivery.

Surveillance data may be used to establish baseline levels of endemic infections, identify epidemics and outbreaks, provide information on the occurrence of infectious events, evaluate the effectiveness of control measures, support the implementation of appropriate infection prevention practices, improve medical care, protect against malpractice claims, enable comparative analyses, facilitate problem-solving and scientific research, and support planning and assessment of the impact of implemented recommendations.

## I. AIM, OBJECTIVES AND METHODOLOGY OF THE STUDY

### 1. Aim

The aim of this dissertation is to analyze and evaluate the system for prevention, surveillance and control on HAI at University Hospital “St. Marina” – Varna " St. Marina " - EAD, as well as to investigate morbidity, etiological and clinical structure of HAI in period 2013–2022. The results from the analysis will be used for development of an integrated model for management of HAI in the conditions of the modern hospital environment.

### 2. Objectives

To achieve the goal of the dissertation, the following objectives have been formulated:

**2.1 . To investigate the system for prevention, surveillance and control of HAI at University Hospital “St. Marina” – Varna for the period 2013–2022 through an analysis of the following areas:**

2.1.1. Organization of prevention, surveillance and control of HAI;

2.1.2. Activities related to disinfections, disinfestations and deratizations (DDD);

2.1.3. Internal control of disinfection;

2.1.4. Epidemic outbreaks that have occurred.

**2.2. To study the epidemiological characteristics of HAI at University Hospital “St. Marina” – Varna for the period 2013–2022 through analysis of:**

2.2.1. Trends in the incidence of HAI and their relationship with antibiotic use;

2.2.2. Frequency of HAI and antibiotic use in different clinical units, grouped according to the degree of risk, with assessment of the normality of the distributions using the Kolmogorov – Smirnov criterion ;

2.2.3. Etiological structure of HAI;

2.2.4. Clinical structure of HAI ;

2.2.5. Impact of the COVID-19 pandemic on the morbidity and structure of the ICU.

The aims and objectives of the study involve clarifying a number of relationships related to the incidence of HAI, their etiological and clinical structure, as well as the effectiveness of the surveillance and control system. In this context, the working hypotheses of the study were formulated.

### 3. Working hypotheses

**3.1.** The incidence of HAI and antibiotic resistance use at University Hospital “St. Marina” – Varna have an increasing trend for the studied 10 - year period (2013–2022).

**3.2.** The etiological structure of HAI is dominated by gram-negative bacteria such as *Acinetobacter baumannii*, *P. pseudomonas aeruginosa* and *Klebsiella pneumoniae*.

**3.3.** In the clinical structure of HAI at University Hospital “St. Marina”, the leading positions are occupied by pneumonia, urinary tract infections, and surgical site infections.

**3.4.** An increase in the number of registered HAI cases during the COVID-19 pandemic, compared with the pre-COVID-19 period.

**3.5.** A higher incidence of in-hospital outbreaks in wards caring for patients with compromised immune systems, such as intensive care units (ICU) and oncohematology clinics.

**3.6.** An effective system for the surveillance and control of HAI requires a well-structured ICT, integrated across all hospital wards, with clearly defined responsibilities and active involvement of hospital management.

#### **4. Methodology**

*Study Design* : Retrospective epidemiological study

*Monitoring period* : The study was conducted as a retrospective analysis, covering the period 2013–2022.

*Study population* : The present analysis covers patients hospitalized at the University Hospital "St. Marina" - Varna, in the period 2013–2022, identified as cases of HAI according to the criteria of the European Centre for Disease Prevention and Control (ECDC) and according to the requirements of The National medical standard for prevention and control of HAI in the Republic of Bulgaria, as well as in accordance with the guidelines of WHO and CDC . Patients are stratified by:

- Year of observation;
- Clinic/Department;
- Type of infection (pneumonia, urinary tract infections, surgical site, etc.);
- Etiological agent.

*Diagnostic criteria* : The determination on the cases of the HAI has been carried out according to the criteria of ECDC, the requirements on Medical standard for prevention and control of the HAI in the Republic Bulgaria , as well as in accordance with the guidelines on WHO and CDC.

##### **4.1. Materials**

To achieve the aims and objectives of the dissertation, a broad and diverse range of materials was utilized, encompassing both primary data collected within University Hospital “St. Marina” – Varna and secondary sources at the national and international levels. The materials include scientific publications, regulatory and normative documents, hospital programs and reports, official forms and registers, patients’ medical records, as well as data derived from epidemiological studies and microbiological surveillance. The collected information provides a comprehensive and objective basis for assessing HAI within the hospital environment.

**The following groups of materials were used in the study:**

**4.1.1.** Specialized Bulgarian and international scientific literature, including articles, monographs, and systematic reviews, as well as international guidelines and reports issued by the WHO, ECDC, and CDC;

**4.1.2.** National regulations related to the prevention and control of HAI and the containment of AMR;

**4.1.3.** Hospital programs, including:

- Program for prevention and control of HAI;
- Program to limit the spread of AMR;

- Disinfection and sterilization program;
- Hospital waste management program.

4.1.4. Reports and plans of the Hospital Infection Control Committee, including annual analyses, recommendations, and organizational measures;

4.1.5. Data from Form 3-05, compiled quarterly for all clinics and departments of University Hospital “St. Marina” – Varna and sent electronically to the Regional Health Inspectorate (RHI) - Varna, and the National Center for Public Health and Analyses (NCPHA)

4.1.6. Data from the medical records of patients, collected during own epidemiological prospective and retrospective studies of the incidence of HAI in the clinics of University Hospital “St. Marina” – Varna;

4.1.7. Data from studies and management of epidemic outbreaks from the HAI;

4.1.8. Protocols with results of internal microbiological laboratory control conducted at University Hospital “St. Marina” – Varna for the period 2013–2022;

4.1.9. Diaries for DDD events held on the territory of University Hospital “St. Marina” – Varna for the period 2013–2022;

4.1.10. Annual information bulletins, including a report on the activities of the various structural units of University Hospital “St. Marina” – Varna for the period 2013–2022;

4.1.11. National analysis of registered cases of HAI in Bulgaria for the period 2016–2022 (Sofia: Ministry of Health);

4.1.12. Analysis of registration data for HAI, their relative share, nosological and etiological structure on the territory of Varna region for the period 2013–2022 (Varna: RHI);

4.1.13. Ethical approval: the study was conducted in compliance with ethical standards and was approved by the Research Ethics Committee at the Medical University - Varna, protocol No. 117/26.05.2022.

## **4.2. Methods**

### **4.2.1. Documentary method**

This approach was applied to systematically analyze the available documentation related to the prevention and control of HAI. The analyzed materials included hospital registers and reports, internal protocols, microbiological surveillance data, antibiotic utilization data, as well as documentation related to the activities of the ICT. This approach ensures completeness of the information and enables the assessment of trends and the etiological structure of HAI during the studied period.

### **4.2.2 . Theoretical method**

A review of Bulgarian and foreign scientific literature, as well as international and national regulatory documents (ECDC, WHO, CDC, Medical Standard for Prevention and Control of HAI, etc.) was conducted.

### **4.2.3. Epidemiological method**

A retrospective epidemiological study was applied to analyze the incidence of HAI for the period 2013–2022, stratified by year, clinic, nosological form and etiological agent. The etiological structure of infections

was established based on the results of microbiological studies of clinical materials from patients with HAI. A comparative epidemiological analysis was also performed between the pre -COVID period (2013–2019) and the pandemic period (2020–2022), as well as an analysis of hospital outbreaks in wards with high-risk patients. A descriptive approach (time, place, affected population) and analytical elements were used to assess the factors for their occurrence.

#### **4.2.4. Statistical methods**

- Statistical grouping of data;
- Descriptive methods;
- Checking the normality of distributions (Kolmogorov – Smirnov);
- Correlation analysis.

##### ***Statistical grouping of data***

In order to build an empirical model, it is necessary to register information about individual statistical units (patients). It is important to take into account the following factors: time and place of observation, registration period, monitoring bodies.

Statistical clustering of data is a fundamental part of the process of any statistical study, providing an opportunity to penetrate the structure of the studied phenomenon and to reveal trends and dependencies. In this dissertation, through statistical clustering of data, empirical distributions of one-dimensional and two-dimensional nature are obtained.

##### ***Descriptive methods***

Descriptive methods have a direct relationship with the distribution of statistical units according to the meanings of their characteristics. The following descriptive tools have been applied in the dissertation:

- arithmetic mean, mode and median in order to establish central tendencies;
- standard deviation (SD) in order to establish the difference between units;
- coefficient of asymmetry, coefficient of kurtosis in order to identify deviations from standard distributions.

The graphical representation of the empirical distribution is an essential part of the descriptive statistical methodology. The following graphical representations are applied: histogram, structural diagram, bar chart.

##### ***Checking the normality of distributions ( Kolmogorov – Smirnov )***

To determine the applicability of parametric statistical methods, a normality test of the sampling distributions was performed. It was performed using the Kolmogorov – Smirnov test , which allows comparing the empirical distribution of the data with a theoretical normal distribution.

##### ***Correlation analysis***

Correlation analysis is a statistical method that measures the strength and direction of the correlation relationship between two or more phenomena. When developing a correlational model is essential the correct defining the independent variable X (factor) and the dependent variable variable Y (consequence). It is important to assess whether the resulting correlational coefficient r is statistically significant. In the context of testing correlation models in SPSS the dictision for statistical significance is reduced to

comparison of perceived standard significance level (risk of error  $\alpha$ ) and calculated borderline level of significance  $p$ . The dissertation paper applies the parametric correlational Brave coefficient.

*Software*

Statistical data processing has been carried out with SPSS (version 26.0).

## **II. RESULTS AND DISCUSSION**

### **1. Study the system for prevention, surveillance and control of HAI at University Hospital “St. Marina” – Varna for the period 2013–2022.**

#### **1.1. System for surveillance and control of HAI at University Hospital “St. Marina” – Varna**

Surveillance and control of HAI at University Hospital “St. Marina” – Varna are implemented through a coordinated system in which the head of the medical facility plays a key role. Management of the risk of HAI occurrence is carried out in close cooperation with the ICT, the Hospital Infection Control Committee, the Antibiotic Policy Committee, the Microbiology Laboratory, clinical wards and units, the chief nurse, senior nurses, and other relevant structures.

Hospital management is responsible for strategic planning and the implementation of safe working systems aimed at reducing and eliminating the risk of HAI. Throughout the study period, the ICT has consistently received institutional support, expressed both through the provision of resources and through the creation of conditions for the introduction of innovative practices. During this period, two contactless room disinfection devices were procured and implemented, including aerosol disinfection systems, the EnSURE Express sampling system, and an ultraviolet C (UV-C) disinfection robot, significantly enhancing the effectiveness of monitoring and control of the hospital environment.

A substantial contribution to the modernization of the system was also the management’s support for the implementation in 2018 of the ENCOMPASS program – an international training and improvement program for cleaning and disinfection outcomes, based on scientific evidence and standardized quality indicators. Guided by the principle “Making the invisible visible,” this initiative represents an important step toward the systematization and digitalization of the hygiene control process.

Since 2019, the team has had access to the information system “Gamma Code Master,” which provides comprehensive electronic traceability of the diagnostic and treatment process, including access to patients’ medical records and microbiological test results. This system significantly facilitates the monitoring, control, and follow-up of infectious cases.

By order of the Executive Director, responsible persons – senior nurses – have been appointed in each clinical unit of University Hospital “St. Marina.” They play a key role in the system for prevention, surveillance, and control of HAI. Their responsibilities include not only the operational implementation of specific anti-epidemic measures, but also the regular reporting of epidemiological information to the ICT. These functions encompass monitoring compliance with hygiene standards, assisting in the implementation of corrective actions, and participating in staff training programs.

##### **1.1.1. Role and structure of the ICT**

ICT is the central operational body responsible for the prevention and surveillance of HAI at University Hospital “St. Marina.” It serves as the key link between routine clinical practice, infection prevention and control, and the safety of the hospital environment. The importance of the ICT extends beyond its regulatory and supervisory functions, encompassing active methodological, organizational, and training activities aimed at improving the quality of patient care and ensuring patient safety.

## **Composition of the Infection Control Team**

Until 2020, the ICT consisted of a hospital epidemiologist with a specialty in *Epidemiology of Infectious Diseases* and a public health inspector. During the COVID-19 pandemic, in response to the increased demands for epidemiological surveillance, the team was expanded—initially through the appointment of an additional public health inspector and subsequently by a second inspector.

The ICT is provided with a dedicated office equipped with four workstations, computer hardware, and audiovisual equipment for training activities. In support of its operational functions, two disinfection technicians are assigned to the team and deployed across the hospital's two main sites (the Therapeutic Complex and the Infectious Diseases Clinic).

The activities of the ICT are closely integrated with those of the hospital's microbiology laboratory and the occupational health service, both of which play a key role in diagnostics, epidemiological surveillance, and risk management.

## **Responsibilities of the Infection Control Team**

The Infection Control Team performs the following key functions:

- risk assessment through systematic analysis of infectious disease risks in different clinics and hospital units;
- analysis of available data from registered infections, laboratory results, and clinical reports;
- monitoring of infection incidence, including cases occurring in intensive care units;
- reporting and interpretation of epidemiological information to hospital management and the Hospital Infection Control Committee;
- development, implementation, approval, and evaluation of annual programs for the prevention and control of HAI and the containment of AMR, as well as disinfection and sterilization programs;
- organization of training activities, including regular courses and practical seminars for healthcare personnel aimed at implementing modern technologies and standardized practices;
- development and implementation of standardized operating procedures in accordance with the national Medical Standard for the Prevention and Control of HAI;
- control of disinfection and sterilization processes through monitoring of applied methods and agents, including internal audits and environmental sampling;
- timely identification, documentation, and management of outbreaks, in cooperation with the RHI and the NCPHA.

The ICT performs a dual role: a preventive role, through risk assessment, training, and standardization, and an operational role, through control, monitoring, and response to incidents

### **1.1.2. Program for prevention and control of HAI and containment the spread of AMR**

The Program for the Prevention and Control of HAI and the containment of AMR at University Hospital "St. Marina" – Varna represents a fundamental institutional document regulating hospital policy

and specific measures for managing infectious risks. The program is developed annually by the Infection Control Team (ICT) and submitted for approval to hospital management.

The content of the program is aligned with the national Medical Standard for the Prevention and Control of HAI, as well as with the requirements of the Regulation on Acute Infectious Diseases, and includes:

- Assessment of infection risk for patients and third parties in clinical units;
- Assessment of infection risk for healthcare personnel, including immunization status and use of personal protective equipment;
- Specific measures for surveillance and control of hai and amr during the reporting year, including prevention of sharps injuries;
- Assessment of epidemic preparedness and an outbreak management plan;
- A plan for improving staff qualifications in the field of infection control, covering ict members, clinic-based hai coordinators, clinical staff, central service personnel, newly appointed employees, and periodic training on procedures, sharps injury prevention, and standard operating procedures (use of personal protective equipment, asepsis, etc.);
- Hospital policies on waste management and disinfection.

### **Main objectives of the program**

The main objectives of the program include:

- early detection, registration, reporting, and notification of HAI to the Regional Health Inspectorate;
- implementation of measures to improve hospital facilities and infrastructure;
- ensuring appropriate aseptic and antiseptic practices during medical procedures;
- optimization of the hospital disinfection policy;
- improvement of clinical and microbiological patient care;
- development and implementation of a modern hospital antibiotic policy;
- enhancement of healthcare workers' qualifications in matters related to HAI;
- assessment and mitigation of infection risks for staff, patients, and third parties in medical and diagnostic units, including measures related to immune status, immunizations, and personal protective equipment.

### **Implementation of the Program for Prevention and Control of HAI**

The implementation of the program is ensured through the following activities:

- Upon employment at the University Hospital, medical staff are familiarized by the ICT with the Medical Standard for the Prevention and Control of HAI, the Regulation on Acute Infectious Diseases, and relevant methodological guidelines according to the department profile.

- Treating physicians actively obtain focused epidemiological histories to identify criteria for HAI, acute infectious diseases, or contact with infectious cases, while carefully considering the results of outpatient microbiological and virological investigations.
- In cases of difficulties in diagnosing or treating HAI or acute infectious diseases, treating physicians conduct timely consultations with the ICT and a microbiologist.
- Every case of HAI is reported to the ICT, with particular attention given to clarifying the source of infection and implementing measures to prevent spread among patients and staff.
- In each clinic and ward, an HAI register is maintained, documenting HAI detected in the unit, imported HAI, and cases occurring after hospital discharge and reported by general practitioners or specialists outside the hospital.
- ICT members and microbiologists participate in outbreak investigations and epidemiological assessments.
- The ICT conducts active reviews of medical records to identify unreported or unregistered HAI.
- Detected and suspected HAI are reported daily during morning clinical meetings to ensure timely implementation of appropriate anti-epidemic measures. The ICT analyzes the causes of HAI and initiates corrective actions.
- In the event of a suspected HAI outbreak, the Executive Director, the Chair of the Hospital Infection Control Committee, and the ICT are immediately notified, followed by notification of the Regional Health Inspectorate.
- At the end of each quarter, based on entries in the HAI Register, Form 3-05 is completed in the hospital wards and submitted electronically to the ICT, the RHI and NCPHA.
- When criteria or suspicion of HAI are identified during autopsy, the physician informs the ICT, documents the findings in the autopsy report, collects samples for microbiological testing, and organizes their transport.
- Periodic microbiological screening of staff in high-risk units is performed to detect methicillin-resistant *Staphylococcus aureus* (MRSA), enabling timely identification of persistent carriers and implementation of decolonization measures.
- When evidence of infectious disease or carriage of epidemiologically significant pathogens posing a risk of HAI is identified in a hospital employee, immediate measures are undertaken, including temporary removal from the work environment and treatment until negative microbiological results are achieved, followed by possible reassignment.
- The Hospital Infection Control Committee reviews registered infections at its meetings, examines recommendations and prescriptions issued by the RHI, and adopts measures to ensure compliance with hygiene and anti-epidemic requirements within the hospital.

### **1.1.3. Program for implementation of disinfection and sterilization at University Hospital “St. Marina” – Varna**

The disinfection and sterilization program is a key element of the HAI control system and is regularly updated by the ICT in response to changes in the biocidal products used, the introduction of new technologies, or the emergence of epidemiological indications. The program regulates both preventive and focal disinfection and sterilization activities, covering all hospital units.

Based on this program, each clinic and department develops individual disinfection plans tailored to the specific infection risks, the clinical profile of the unit, and the characteristics of the patient population. When selecting disinfectants, their efficacy, spectrum of action, and required exposure time are taken into account, with reliance on modern, highly effective biocides authorized for use by the Ministry of Health. Particular attention is paid to their hypoallergenic properties and low toxicity to ensure the safety of both staff and patients.

Special emphasis within the program is placed on epidemiologically significant objects that may act as factors in the transmission of infections, including:

- hands and skin of healthcare personnel;
- medical instruments and equipment;
- specialized medical devices and supplies;
- surfaces and hospital premises;
- patient care items.

#### **1.1.4. Antibiotic policy at University Hospital “St. Marina” – Varna**

The antibiotic (AB) policy at the University Hospital is periodically updated, taking into account the specificity of the treated pathology, the local clinical structure of infections, local patterns of antimicrobial resistance, and the principles of controlled AB use. By order of the hospital’s Executive Director, an Antibiotic Policy Committee has been established, comprising recognized specialists from various medical fields who routinely apply antibiotic therapy in their clinical practice.

The objectives of the Antibiotic Policy Committee are:

- to promote the safe, effective, cost-efficient, and rational use of antibiotics;
- to improve the quality of patient care;
- to minimize the unfavorable consequences of bacterial resistance, both currently and in the future.

Strategies for achieving these objectives include:

- adherence to clinical guidelines and algorithms for the diagnosis and treatment of infectious diseases;
- regulation of antibacterial prescribing through classification of antibiotics into three main groups: unrestricted use, restricted use, and strategic antibiotics subject to strict limitations;
- consultation of patients with complicated, persistent, or severe infections and participation in multidisciplinary medical case conferences;
- close cooperation with the Hospital Infection Control Committee, including joint meetings and reciprocal presentation of results related to antibiotic use, incidence and structure of HAI, and antimicrobial resistance patterns;

- annual presentation of data on antibiotic consumption to clinical teams at University Hospital “St. Marina” through open medical meetings and publication on the hospital intranet “Antibiotic Policy” page;
- promotion of awareness regarding antimicrobial resistance through participation in symposia and congresses, publication of articles in medical journals and newspapers, and delivery of lectures to students, outpatient physicians, and clinical staff.

#### **1.1.5. Commission for the control of HAI**

The Chair of the Commission for the control of HAI is the hospital epidemiologist, while the Deputy Chair is the Head of the Occupational Health and Safety Service. The composition of the Commission is updated annually by order of the Executive Director. The Commission holds regular meetings at least twice a year. In the event of an epidemic outbreak or suspicion of an outbreak, an extraordinary meeting is convened to propose appropriate anti-epidemic measures and to supervise their implementation.

The organization, prevention, and control of injuries caused by sharp objects at the University Hospital are jointly managed by the ICT and the Occupational Health and Safety Service. The ICT maintains close collaboration with this service not only with regard to sharps injuries, but also in the prevention and control of HAI and acute infectious diseases.

Other units with which the ICT works in close cooperation include the microbiology laboratory and the Antibiotic Policy Committee. The microbiology laboratory plays a key role in the diagnosis of infections and in guiding the selection of appropriate antimicrobial therapy. It supports the ICT in epidemiological investigations by identifying the infectious agent, determining the source of infection, and clarifying the mechanisms of transmission. In addition, the laboratory has an essential role in HAI control through participation in epidemiological surveillance and outbreak management, bacterial typing, and timely reporting to the ICT of newly identified pathogens and strains with unusual antimicrobial resistance patterns.

#### **1.1.6. Recording and management of an explosion by HAI**

Behavior during an epidemic outbreak is planned in advance. The ICT has developed a plan for the management of HAI outbreaks, which has been approved by the Executive Director of the University Hospital and is subject to annual revision. The plan defines two main phases of response: a proactive (preparatory) phase and a reactive phase. The proactive phase specifies the responsibilities and competencies of the outbreak control team, determines the type and scope of laboratory investigations, and defines the procedures for sending samples to the reference laboratory of the National Center of Infectious and Parasitic Diseases. It also regulates the procedures for notification and cooperation with other services that may be involved in outbreak management. Given that HAI outbreaks are often of public and media interest, the plan also defines the role of the hospital’s public relations representative.

The reactive phase includes identification of events indicative of a potential HAI outbreak, assessment of the situation based on available information, and a decision to establish an outbreak control team. This phase encompasses case investigation, reporting according to established procedures upon confirmation of an outbreak, assessment of the epidemiological situation, and determination of appropriate

control measures. Additional activities include prevention of further transmission, identification of the source of infection and transmission routes, evaluation of collected data, and implementation of targeted anti-epidemic measures. The reactive phase concludes with termination of outbreak control activities, determination of safety assurance measures, and a final analysis and evaluation identifying gaps and defining future prevention strategies. The final documentation serves as a basis for optimizing preventive approaches for subsequent outbreaks.

#### **1.1.7. Control of activities on disinfection and sterilization**

The ICT monitors the hospital environment using two complementary methods: microbiological laboratory surveillance, with samples processed by the Microbiology Laboratory of University Hospital “St. Marina,” and a rapid nucleotide-based test for surface protein contamination, introduced in early 2016. Internal microbiological monitoring is conducted both on a scheduled basis and in response to epidemiological indications. Planned mandatory microbiological surveillance is performed at different frequencies depending on the risk profile of the clinical units: twice per year in low-risk clinics, four times per year in medium-risk units, and monthly in high-risk units. The rapid surface contamination test is applied with varying intensity and is typically combined with routine hygiene inspections, which are conducted quarterly in cooperation with the chief nurse.

#### **Preparation and implementation of procedures on prevention and control of the most common registered HAI bundles**

Since 2015, targeted measures have been developed to improve the quality and safety of medical procedures and interventions, patient care, and treatment outcomes. Following the registration of an epidemic outbreak caused by *Enterobacter cloacae*, isolated from blood cultures in 10 patients in the Hemodialysis Clinic, the Commission for the control of HAI decided to develop and implement care bundles aimed at infection prevention and patient safety.

#### **1.1.8. Training of medical personnel**

Staff training on hand disinfection is conducted annually. The training includes both theoretical and practical components and is tailored to the specific professional roles of participants, including physicians, healthcare professionals, orderlies, and maintenance staff (technicians, hygienists, etc.). Upon completion of the training, all participants are issued a certificate confirming successful completion of training in hygienic hand disinfection. In addition, collegiums and short seminars are held with physicians working in high-risk clinical units at least twice a year. Training topics are selected based on the specific epidemiological situation and identified infection control needs.

#### **1.1.9 . Waste management activities**

Effective management of hospital waste leads to the achievement of several significant outcomes:

- prevention of the occurrence of HAI;
- reduction of the risk of occupational accidents, infections, and injuries associated with handling hospital waste, particularly sharps and cutting objects;

- By order of the Executive Director of University Hospital “St. Marina” - Varna , designated individuals are assigned responsibilities related to hospital waste management activities. Waste management regulations have been introduced in accordance with current legal requirements, clearly defining the rights and obligations of all personnel working within the healthcare facility. In addition, joint actions are undertaken in cooperation with control authorities to improve the effectiveness of hospital waste management.

## **Discussion**

The data from this study indicate that University Hospital “St. Marina” – Varna has established a structured and functional system for infection control that incorporates all key components recommended by leading international organizations such as the WHO, ECDC, and CDC. The hospital maintains a specialized ICT that coordinates activities related to the surveillance, prevention, and containment of HAI. The expansion of the ICT in recent years, particularly during the COVID-19 pandemic, demonstrates the institution’s flexibility and commitment to addressing emerging epidemiological risks. This process is consistent with WHO recommendations regarding adaptability and capacity of infection control systems in emergency situations.

Effective coordination is observed between the different levels of management, including hospital leadership, the HAI Committee, the Antibiotic Policy Committee, the ICT, the microbiology laboratory, and clinical units. This interdisciplinary approach aligns with the WHO concept of fostering a culture of safety and sustainability within healthcare facilities (WHO, 2018).

Despite the progress achieved, challenges remain, particularly in relation to human resources and the level of digitalization. There is a discrepancy between the hospital’s capacity (1,292 inpatient beds and 175 short-term stay beds, totaling 1,467 beds) and the number of ICT staff, which remains below recommended levels. International standards endorsed by the WHO and professional organizations such as the Association for Professionals in Infection Control and Epidemiology indicate a minimum threshold of one trained infection control specialist per 250 beds, while contemporary models recommend between 0.8 and 1.0 specialists per 100 beds (Bartles R et al., 2024). This suggests that, at full capacity, the hospital would require at least six infection control specialists to ensure optimal coverage.

At University Hospital “St. Marina” – Varna, key elements of effective infection control are implemented, including standardized operating procedures, hand hygiene programs, antimicrobial stewardship, and the application of care bundles in high-risk units. However, comparison with leading European models in Sweden, Germany, and the Netherlands reveals notable differences in the degree of digitalization and national integration. At “St. Marina,” surveillance is conducted through continuous monitoring by the ICT, which actively identifies and analyzes cases of HAI, antimicrobial resistance, and potential outbreaks. While this model ensures high sensitivity, it remains largely manual and dependent on expert interpretation.

In Sweden, the national SmiNet system, managed by the Public Health Agency of Sweden, enables automated electronic reporting of infectious diseases and two-way data exchange between healthcare institutions and public authorities. In Germany, the KISS system, administered by the Robert Koch Institute,

integrates hospital data into standardized modules and enables national benchmarking. The Netherlands employs integrated platforms such as PREZIES and ISIS-AR, which combine epidemiological surveillance and antimicrobial resistance monitoring within the “One Health” framework (RIVM, PREZIES, 2024).

In several European countries, electronic surveillance systems incorporate predefined alert thresholds that automatically signal deviations from expected infection levels or the emergence of new clusters. In Germany, the KISS system applies standardized alert criteria, such as the detection of two or more identical isolates within 72 hours or values exceeding national median indicators for a specific infection type. In the Netherlands, the PREZIES platform automatically reports deviations in the incidence of methicillin-resistant *Staphylococcus aureus* (MRSA) and extended-spectrum beta-lactamase (ESBL)-producing isolates, generating early alerts for epidemiological investigation. A similar principle is embedded in the Swedish SmiNet system, which integrates microbiological and clinical data to provide real-time alerts when unusual infection patterns or clusters are detected. According to the WHO and ECDC, the implementation of such automated alert systems is considered the gold standard in modern infection surveillance, as it significantly enhances the sensitivity and timeliness of detecting infectious disease events.

In this context, the system at University Hospital “St. Marina” – Varna does not yet include an automated electronic surveillance platform capable of real-time notification, analysis, visualization, and national benchmarking. This represents a structural limitation compared with leading European practices. The WHO and ECDC emphasize that digitalization of surveillance is a key prerequisite for early detection of epidemiological signals and standardized reporting.

The hospital’s antimicrobial policy is well established and coordinated by the Antibiotic Policy Committee, which regulates antimicrobial prescribing and monitors antibiotic use. However, at present, Bulgaria lacks a centralized integrated system that automatically links microbiological results with antimicrobial stewardship data and rational use programs, while also enabling real-time national benchmarking. Currently, data are generated through separate channels, including the National Health Information System, which supports electronic prescriptions, and the National Reference Laboratory for Control and Monitoring of Antimicrobial Resistance at the National Center of Infectious and Parasitic Diseases, which conducts national AMR surveillance. These systems operate independently, without an integrated operational platform for automated data exchange and analysis. The absence of such integration limits the comparability of hospital-level surveillance results with national and international standardized indicators, as implemented in most EU countries.

With regard to training, University Hospital “St. Marina” – Varna demonstrates favorable outcomes, including annual training in hand hygiene and disinfection, staff certification, and participation in the international ENCOMPASS program based on standardized quality indicators. Similar approaches are applied in Sweden, Germany, and the Netherlands, where training and compliance are supported through mandatory annual programs and independent audits.

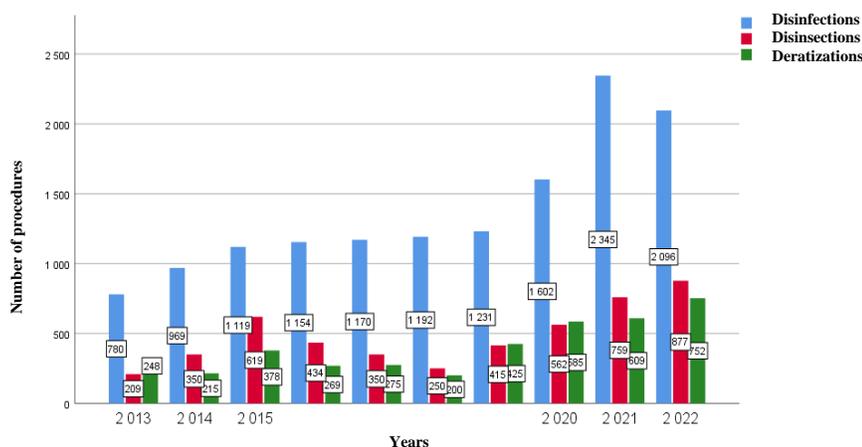
In conclusion, the system for surveillance and control of HAI at University Hospital “St. Marina” – Varna can be characterized as well structured, functional, and quality-oriented. It corresponds to the core components defined by the WHO and ECDC, particularly in terms of internal organization, staff training, and antimicrobial policy. The main differences compared with leading European models relate to the

absence of an automated electronic surveillance system, limited staffing capacity, and the lack of national benchmarking. Further development through the implementation of electronic surveillance tools, integration of microbiological and pharmaceutical data, and participation in national monitoring programs would align the system at University Hospital “St. Marina” – Varna more closely with the sustainable and proven effective models applied in Sweden, Germany, and the Netherlands.

### 1.2. Analysis of the activity of disinfections, disinsections and deratizations at the University Hospital " St. Marina " for the period 2013-2022 Mr.

The analysis of the performed DDD activities are necessary because as these events are essential components of the system for prevention and control of HAI. In Fig. 1 is presented the dynamics of disinfections, disinsections and deratizations carried out for the period 2013–2022, which allows to track the trends and volume of events held in the weather.

Fig. 1. Dynamics of disinfections, disinsections and deratizations for the period 2013-2022.



For the period 2013–2022, a clear increase in DDD activities was observed. The number of disinfections performed ranged from a minimum of 780 in 2013 to a maximum of 2,345 in 2021, with a mean annual value of 1,365.8 (SD = 498.9). Disinsection activities demonstrated a similar pattern, with a mean annual value of 482.5 (SD = 218.1) and values ranging between 209 and 877 procedures per year. After fluctuating levels up to 2018, a sustained increase was observed during the period 2019–2021, followed by a pronounced peak in 2022 (877). Deratization activities showed the lowest recorded value in 2018 (200 procedures) and the highest in 2022 (752 procedures), with a mean annual value of 395.6 (SD = 192.3) (Fig. 1).

### Discussion

The analysis of DDD activities during the period 2013–2022 reveals marked changes in their frequency, reflecting both local epidemiological conditions and the impact of global events, most notably the COVID-19 pandemic. The substantial increase in the number of disinfections coincides with the COVID-19 period, during which disinfection became a key intervention for limiting the spread of SARS-CoV-2.

Disinsection and deratization activities also exhibited an overall upward trend. Although less pronounced than the increase in disinfection procedures, this pattern indicates intensified control of environmental factors such as insects and rodents, which may contribute to the transmission of pathogens in both hospital and community settings.

Comparison with available European data suggests that similar trends have been observed at the continental level. Market analyses indicate that the value of the European surface disinfectants market reached approximately USD 1.63 billion in 2023 and is projected to increase to USD 2.56 billion by 2030, with an average annual growth rate of 6.7% [Bock LJ et al., 2022]. Although these figures represent economic indicators rather than direct epidemiological measures, they clearly demonstrate sustained growth in disinfectant consumption and support the conclusion that the observed increase in local DDD activities aligns with broader European trends toward strengthening infection prevention and control measures.

### **1.3. Analysis of disinfection control (internal) at the University Hospital " St. Marina " for the period 2013-2022.**

Monitoring of internal disinfection control is directly related to the prevention of HAI, as positive samples from surfaces, air, or medical equipment represent potential reservoirs of pathogenic microorganisms. To assess the effectiveness of implemented anti-epidemic measures at University Hospital “St. Marina” – Varna, internal disinfection control was systematically monitored. This monitoring was conducted using multiple complementary approaches, including microbiological testing (surface swabs, samples collected using the Kelsey method, and air sampling) and non-microbiological methods for detecting residual organic contamination, such as adenosine triphosphate (ATP) testing using the UltraSnap system.

The results of the monitoring conducted during the period 2013–2022 are summarized in Table 1. Over the ten-year period, a total of 7,704 samples were analyzed, of which 947 yielded positive results. The total number of samples collected annually ranged from 162 in 2021 (the lowest value) to 1,128 in 2018 (the highest value), with a mean annual number of 770.4 samples.

The number of positive samples ranged from 25 in 2020 (the lowest value) to 152 in 2017 (the highest value). The annual volume of sampling remained relatively high and stable during the period 2013–2018, with values ranging from 872 to 1,128 samples per year. In contrast, a sharp decline in the number of samples was observed in 2019 and 2020 (634 and 223 samples, respectively), with the lowest value for the entire study period recorded in 2021 (162 samples). In 2022, the number of samples partially recovered to 756, although it remained below the pre-2019 levels (Table 1).

*Table 1. Number of samples tested and relative share of positive results in disinfection control (2013–2022) at University Hospital “St. Marina” – Varna – Varna*

Year	Number samples	Number (+) samples	% (+) samples /total number of samples
2013	872	106	12.2
2014	963	111	11.5

2015	873	87	10.0
2016	1051	103	9.8
2017	1042	152	14.6
2018	1128	150	13.3
2019	634	71	11.2
2020	223	25	11.2
2021	162	40	24.7
2022	756	82	10.8
Total number	7074	947	

The proportion of positive samples relative to the total number of samples ranged from 9.8% in 2016 to 24.7% in 2021. During the period 2013–2016, the values remained relatively stable, between 9.8% and 12.2%. An increase was observed in 2017 and 2018 (14.6% and 13.3%, respectively), followed by a decrease in 2019–2020, when the proportion of positive samples stabilized at approximately 11.2%. In 2021, a pronounced peak of 24.7% was recorded, coinciding with the lowest total number of collected samples. In 2022, the indicator returned to levels comparable to previous years (10.8%) (Table 1).

Figure 2 presents the number of surface swab samples collected and the number of positive results obtained at University Hospital “St. Marina” – Varna during the period 2013–2022. The dynamics of surface swab sampling at University Hospital “St. Marina” – Varna over the study period show marked fluctuations. The highest level of sampling activity was observed during 2013–2015, with up to 887 samples collected annually and more than 100 positive results. This was followed by a decline in 2016 and a partial recovery in 2017–2018. The lowest levels of activity were recorded during 2019–2021, with up to 160 samples and 18–40 positive results per year. In 2022, a renewal of control activities was observed, with 688 samples collected and 68 positive results (Fig. 2).

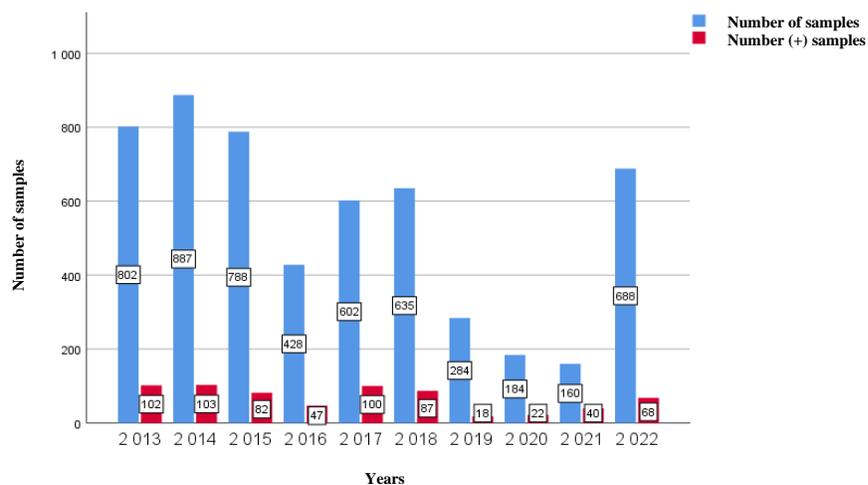
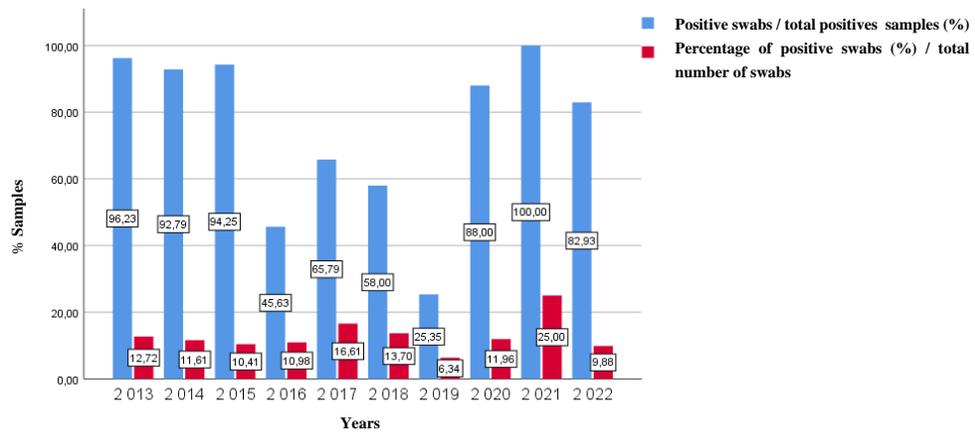


Fig. 2. Dynamics of the number of flushing operations performed and positive results of microbiological control of disinfection (2013–2022)

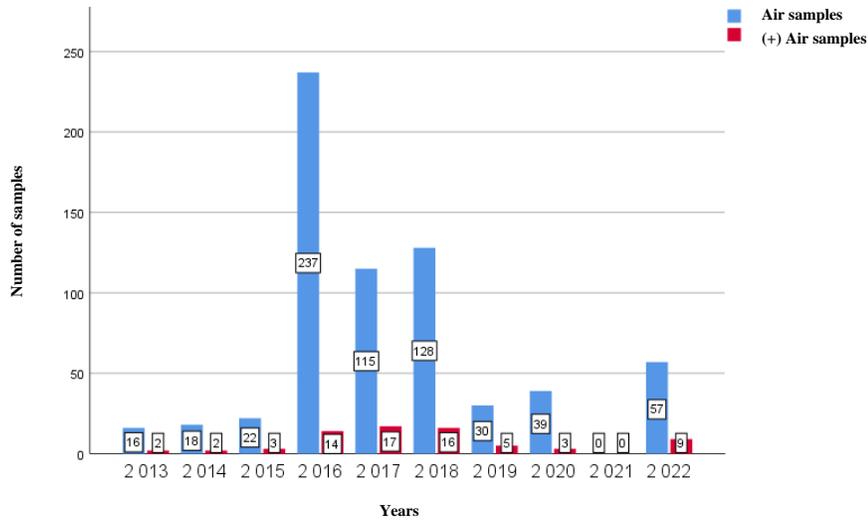
Figure 3 presents two relative indicators related to surface swab results for the period 2013–2022: the proportion of positive surface swabs among all positive samples and the proportion of positive surface swabs relative to the total number of collected swabs.

The proportion of positive surface swabs among all positive samples varies between 25% and 100%, with the highest value observed in 2021. The proportion of positive surface swabs relative to the total number of collected swabs generally ranges between 6% and 25%, again reaching its peak in 2021. A decrease in these values is observed in 2022 (Fig. 3).



*Fig. 3. Relative share of positive swabs compared to the total number of positive samples and compared to all swabs performed for the period 2013–2022.*

The total number of air samples varied considerably over the study period. The lowest numbers were recorded in 2013–2015, ranging from 16 to 22 samples per year, while the highest number was observed in 2016 (237 samples). In subsequent years, a gradual decrease was noted, with 115 and 128 samples collected in 2017 and 2018, respectively. In 2019–2020, the number of air samples declined further to 30–39 per year. No air sampling was conducted in 2021, whereas in 2022 the number increased again to 57 samples. The number of positive air samples generally ranged between 2 and 5 per year, except during the period 2016–2018, when higher values of 14–17 positive samples were recorded (Fig. 4).



*Fig. 4. Dynamics of the number of air samples taken and positive results in microbiological control of disinfection (2013–2022)*

The proportion of positive relative to the total number of air samples was lowest at the beginning of the study period (1.9% in 2013) and increased to a maximum of 13.6% in 2016, after which it fluctuated within the range of 7.0% to 12.0%. In 2021, no positive air samples were reported due to the absence of air sampling rather than an actual zero positivity rate (Fig. 5). The proportion of positive air samples relative to the total number of all positive samples remained within relatively narrow limits throughout the study period. The lowest value was recorded in 2016 (5.9%), when the highest number of air samples was collected but the number of positive results remained relatively limited. The highest values were observed in 2019 (16.7%) and 2022 (15.8%), reflecting a higher relative contribution of positive air samples against a background of a smaller absolute number of collected samples. In the remaining years, this indicator generally ranged between 10% and 15%. No values were reported for 2021 due to the absence of air sampling (Fig. 5).

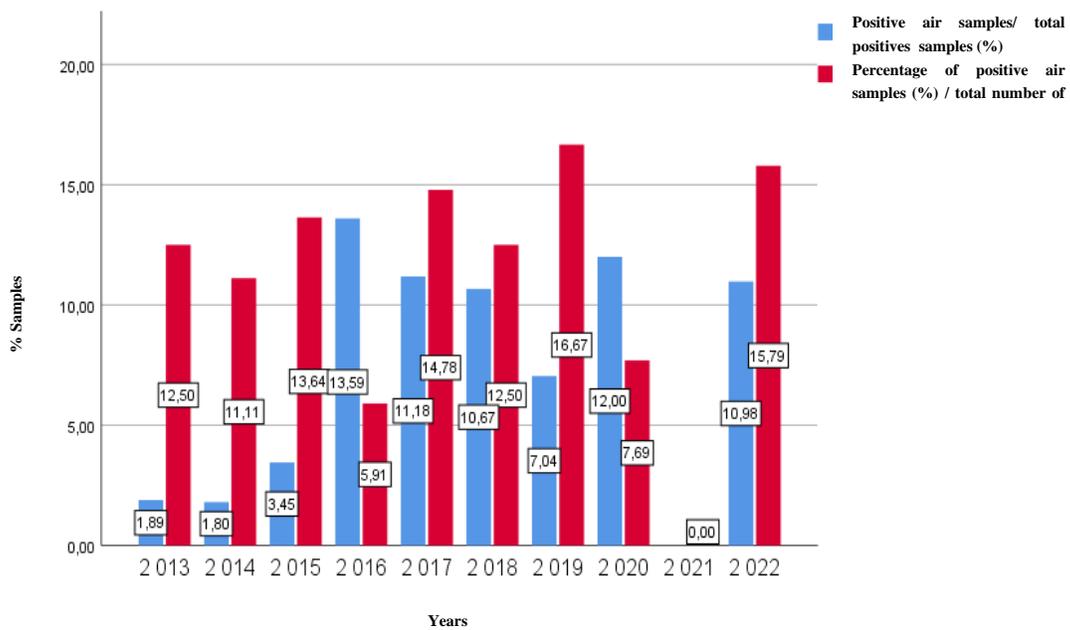


Fig. 5. Relative share of positive air samples compared to the total number of positive samples and compared to all air samples taken for the period 2013–2022.

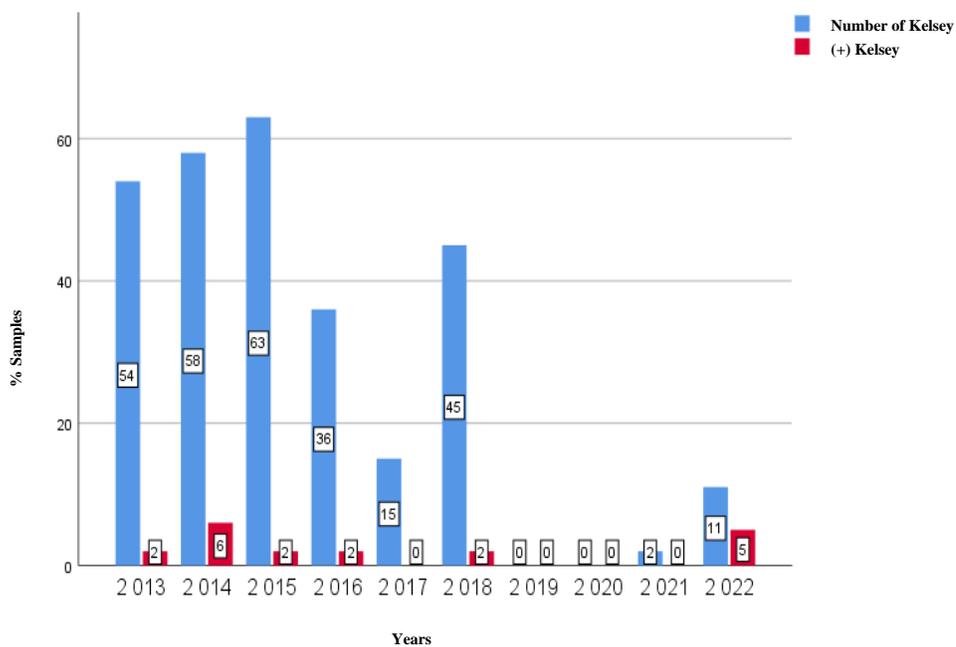
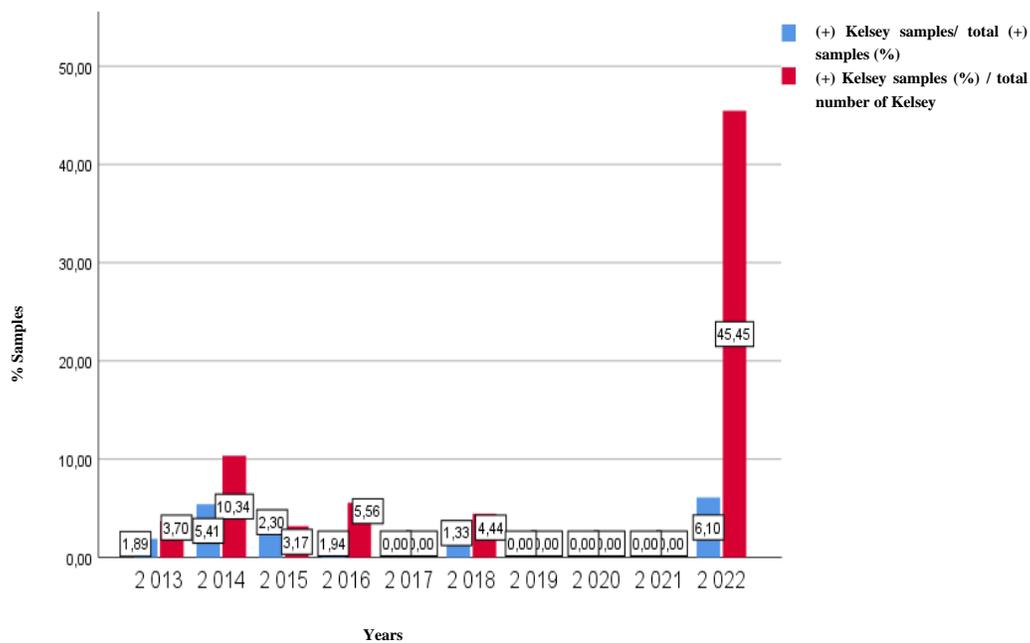


Fig. 6. Dynamics of the number of Kelsey tests performed and positive results in microbiological control of disinfection (2013–2022)

Within the ten-year study period, samples collected using the Kelsey method accounted for a limited proportion of the total number of microbiological investigations, as their application was inconsistent. In 2019 and 2020, this method was practically not used, resulting in a zero share for these years. In 2022, Kelsey sampling was reintroduced into routine control; however, the number of samples did not reach the levels observed during the initial years of the study period (Fig. 6).

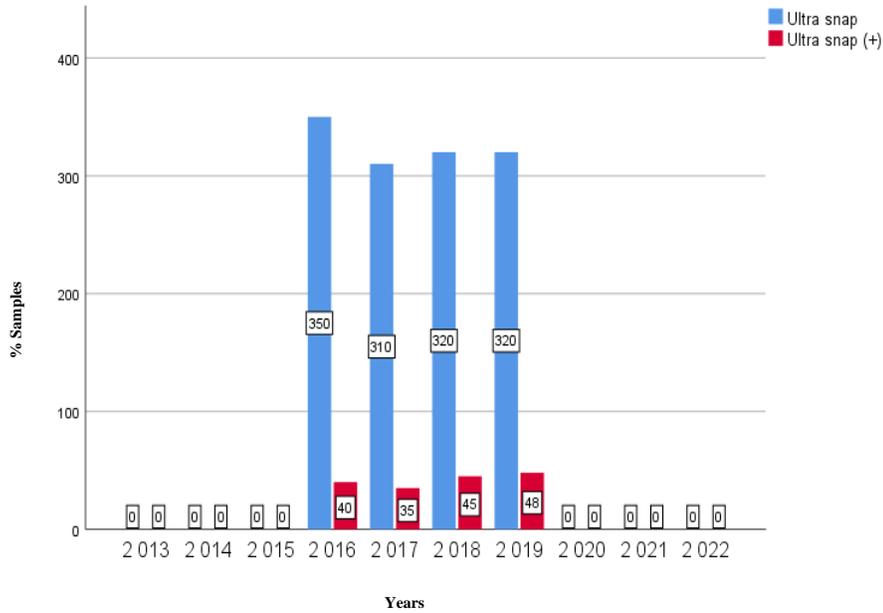
The proportion of positive samples obtained using the Kelsey method relative to the total number of positive samples remained low throughout the entire period, varying within narrow limits between 1.3% in 2018 and 6.1% in 2022. In contrast, the proportion of positive results among Kelsey samples showed considerable variability. During the initial years, positivity rates ranged between 3.17% and 10.3%, with the lowest value recorded in 2015 and the highest in 2014. The highest positivity rate for the entire study period was observed in 2022 (45.5%), representing a sharp increase compared with all previous years (Fig. 7).



*Fig. 7. Relative share of positive Kelsey samples compared to the total number of positive samples and to all Kelsey samples performed for the period 2013–2022.*

UltraSnap tests were introduced in 2016, when 350 tests were performed, of which 40 yielded positive results. Over the subsequent three years, the number of tests remained high, ranging from 310 to 320 annually, while the number of positive results varied between 35 and 48. In the period 2020–2022, no UltraSnap testing was conducted; therefore, no results were reported. These data indicate a limited and time-bound application of the method, concentrated primarily in the period 2016–2019 (Fig. 8).

The proportion of positive UltraSnap results relative to the total number of positive samples increased from 38.8% in 2016 to 67.6% in 2019, indicating a substantial contribution of this method to the overall structure of positive findings. The proportion of positive UltraSnap results relative to the total number of UltraSnap tests performed varied within a narrower range, between 11.3% and 15% (Fig. 9).



*Fig. 8. Dynamics of the number of Ultra samples performed snap and positive results in cleaning control (2013–2022)*

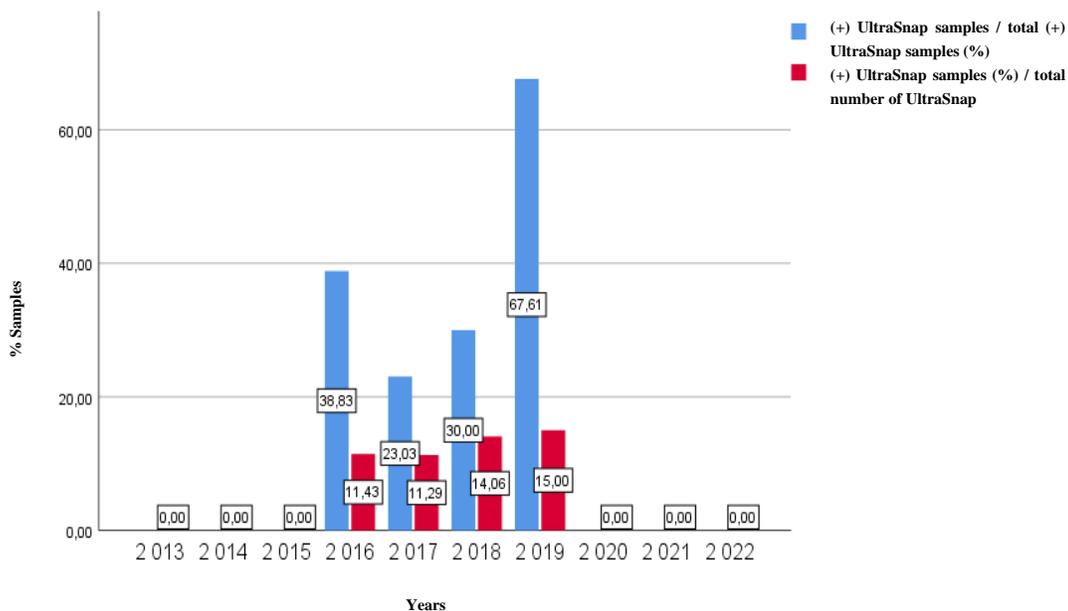


Fig. 9. Relative proportion of positive Ultra samples snap to the total number of positive samples and to all Ultra samples performed snap for the period 2013-2022.

## Discussion

The analysis of internal disinfection control results over the ten-year period (2013–2022) reveals significant differences in the application and effectiveness of the individual methods used—surface swabs, air sampling, UltraSnap ATP testing, and the Kelsey method. Each method contributes specific information to in-hospital risk assessment and demonstrates a distinct diagnostic value.

Surface swabs represent the leading approach in routine hospital practice, accounting for approximately 40–60% of all positive samples in most years. The proportion of positive results relative to all collected swabs generally ranged between 10% and 15%, indicating a stable level of effectiveness of the applied disinfection regimens. These values are comparable with data reported in European studies, where the proportion of positive surface samples typically varies between 5% and 20% (Egert et al., 2024). During the COVID-19 pandemic, both in the present analysis and in international reports, routine environmental sampling was reduced, while the relative proportion of positive results increased due to more targeted testing of high-risk objects (Kampf G et al., 2020).

Air sampling accounted for a smaller relative share of the total investigations; however, its application remained consistent and was primarily associated with departments where control of aerogenic factors is critically important, such as transplant units. The proportion of positive air samples was comparable to values reported in international literature (5–20%), confirming the adequacy of the applied methodology (Li Y et al., 2007). This underscores the role of air sampling as a reliable indicator for assessing aerogenic risks, particularly in wards caring for vulnerable patient populations.

The Kelsey method was applied episodically, which does not allow for continuous trend analysis. It was used during the period 2013–2018, discontinued for three years, and reintroduced in 2022. The final year of observation was characterized by a pronounced peak in the proportion of positive results (45.5%), substantially exceeding the values of 10–30% reported in the literature for standard disinfectant effectiveness testing (Kelsey JC et al., 1969). This finding is likely attributable to targeted sampling in environments with increased microbiological burden, as well as intensified monitoring in high-risk areas where control activities are more focused on critical points within the hospital environment. The high proportion of positive results in 2022 suggests that the Kelsey method may provide additional value under specific control conditions.

UltraSnap ATP testing, introduced in 2016, occupied a substantial position in the structure of positive findings, accounting for up to 67.6% of all positive samples in 2019. In contrast, the proportion of positive ATP results relative to all performed UltraSnap tests remained more stable, ranging between 11% and 15%, indicating good reproducibility of the method. After 2019, UltraSnap testing was discontinued, most likely due to prioritization of culture-based microbiological investigations that allow for pathogen identification and antimicrobial susceptibility testing. The discontinuation of ATP testing after 2019 limits the assessment of long-term trends using this method.

In summary, the results of the hospital environment control analysis demonstrate good comparability with international and European data. The exceptionally high positivity rates observed with the Kelsey method appear to be related to its targeted application under specific conditions. Overall, the findings support the need for a multicomponent approach to microbiological surveillance, in which different sampling methods complement each other, in accordance with recommendations issued by the WHO, CDC, and ECDC.

#### **1.4 . Analysis of the epidemic outbreaks from HAI at University Hospital “St. Marina” – Varna – Varna (2013–2022)**

Epidemic outbreaks of HAI represent an important indicator of the effectiveness of prevention and control systems, as they reflect weaknesses in anti-epidemic measures and have a substantial impact on patient safety. Table 2 presents the registered HAI outbreaks at University Hospital “St. Marina” – Varna during the period 2013–2022, stratified by clinical units. During the period 2013–2022, a total of 11 HAI outbreaks were registered at University Hospital “St. Marina” – Varna, affecting 61 patients. No outbreaks were reported in 2013–2014, while systematic annual registration began in 2015. The highest outbreak intensity was observed in 2016 and 2017, with three documented outbreaks per year. In 2018, the number decreased to two outbreaks, followed by stabilization in 2019 and 2021, with one outbreak recorded annually. In 2022, no epidemic outbreaks were identified, marking a decline in outbreak occurrence at the end of the study period (Table 2).

*Table 2. Registered epidemic outbreaks of HAI at University Hospital “St. Marina” – Varna – Varna (2013–2022)*

Year	Clinic	Number outbreaks	Clinical structure	Causative agents	Number sick
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2013		0			0
2014		0			0
2015	Hemodialysis	1	Catheter-associated bloodstream infections	<i>Enterobacter cloacae</i> ESBL	11
2016	CAIC	1	Respiratory infections	<i>Pseudomonas aeruginosa</i>	5
2016	CAIC	1	Respiratory infections	<i>Acinetobacter baumannii</i>	4
2016	Second children's clinic	1	Gastrointestinal infections	<i>Rotavirus</i>	5
2017	Hematology	1	Catheter-associated bloodstream infections	<i>Enterobacter cloacae</i> ESBL	5
2017	CAIC	1	Respiratory infections	<i>Pseudomonas aeruginosa</i>	5
2017	CAIC	1	Respiratory infections	<i>Acinetobacter baumannii</i>	9
2018	Hematology	1	Gastrointestinal infections	<i>Clostridium difficile</i>	4
2018	CAIC	1	Respiratory infections	<i>Acinetobacter baumannii</i>	5
2019	PCHO	1	Gastrointestinal infections	<i>Rotavirus</i>	3
2020		0			0
2021	Covid department	1	Respiratory infections	<i>Acinetobacter baumannii</i>	5
2022		0			0
<b>Total number</b>		11			61

Analysis of the distribution of epidemic outbreaks across clinical units indicates that the highest number was registered in the Clinic of Anesthesiology and Intensive Care (CAIC), accounting for six of the eleven documented events. The second most affected units were hematological structures, including the Hematology Clinic and the Pediatric Clinic of Hematology and Oncology (PCHO), where a total of three outbreaks were recorded. Single outbreaks were registered in the Hemodialysis Clinic, the Second Children's clinic, and the COVID-19 ward (Table 2).

#### 1.4.1. Epidemiological characteristic on registered outbreaks

The etiological spectrum of epidemic outbreaks indicates that the dominant causative agent was *A. baumannii*, isolated in 23 of the 61 affected patients (37.7%). *Enterobacter cloacae* producing extended-spectrum beta-lactamases (*E. cloacae* ESBL) ranked second, with 16 cases (26.3%), followed by *P. aeruginosa*, identified in 10 patients (16.4%). The contribution of viral and other bacterial agents was comparatively lower. Rotavirus infection was detected in 8 patients (13.2%), while *C. difficile* was identified in 4 patients (6.6%) (Fig. 10).

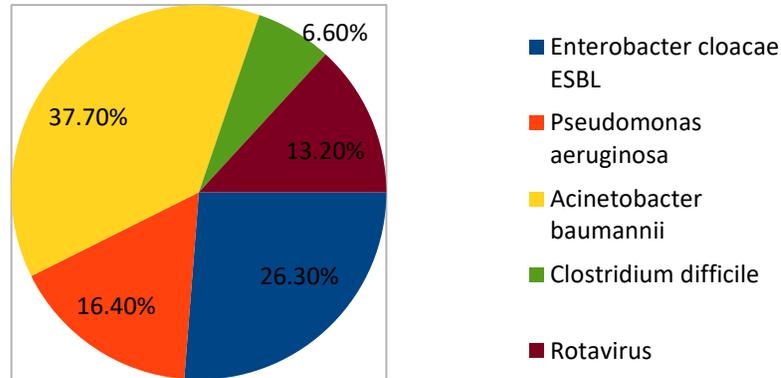


Fig. 10. Etiological structure of epidemic outbreaks of HAI (2013–2022)

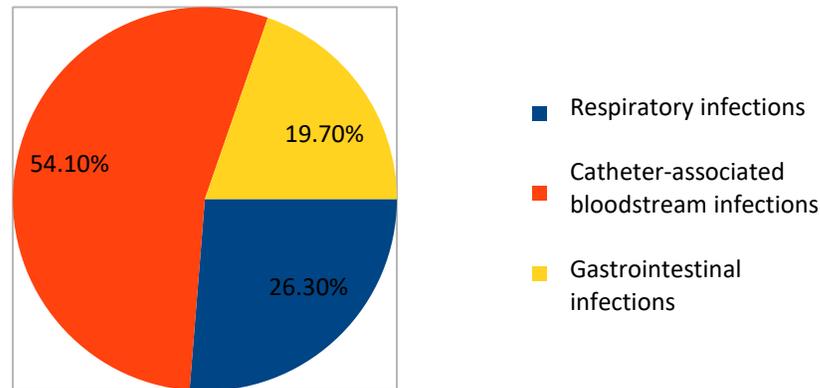


Fig. 11. Clinical structure of the epidemic outbreaks of HAI (2013–2022)

With regard to the clinical structure of epidemic outbreaks, respiratory infections accounted for the largest proportion, being registered in 33 of the 61 affected patients (54.1%). Catheter-associated bloodstream infections were identified in 16 patients (26.3%), while gastrointestinal infections accounted for 12 cases (19.7%), including rotavirus enteritis and infections caused by *C. difficile* (Fig. 11).

#### 1.4.2. Epidemiological study of a healthcare-associated infection outbreak caused by *Enterobacter cloacae* ESBL in the Hemodialysis Clinic

Among the registered HAI outbreaks at University Hospital “St. Marina” – Varna, particular attention is warranted for the outbreak that occurred in the Clinic and was caused by *Enterobacter cloacae* (*E. cloacae*) producing extended-spectrum beta-lactamases (ESBL). This event was analyzed in detail due to its clinical and epidemiological significance.

#### Epidemiological characteristics of the outbreak

In July 2015, an epidemic outbreak of HAI caused by ESBL-producing *E. cloacae* was identified in the Hemodialysis Clinic of University Hospital “St. Marina” – Varna. Within a period of ten consecutive days, clinical manifestations of HAI developed in a total of ten patients with stage IV chronic renal failure undergoing regular hemodialysis. All cases were microbiologically confirmed by positive blood cultures and were promptly registered as HAI.

### **Patient characteristics**

Among the affected patients, six were male (60%) and four were female (40%). The age ranged from 52 to 78 years, with a mean age of 66.8 years. The highest proportion of cases occurred in the 60–69-year age group (50%), followed by patients older than 70 years (30%). Only two patients (20%) were younger than 60 years.

With regard to comorbidities, nearly all patients exhibited a pronounced multimorbid profile, including combinations of chronic renal insufficiency, arterial hypertension, type 2 diabetes mellitus, and various forms of cardiovascular disease. This complex clinical background significantly increased susceptibility to infection and contributed to an unfavorable clinical course. The presence of a central vascular catheter was identified as the leading risk factor: nine patients (90%) had permanent catheters, while one patient had a temporary catheter. Microbiological analysis of catheter tips confirmed their role as the primary portal of entry for infection.

### **Clinical characteristics**

The clinical presentation of the outbreak was relatively homogeneous and clearly associated with the hemodialysis procedure. In all patients, symptoms developed approximately two hours after the initiation of hemodialysis and most commonly included chills and subfebrile or febrile temperatures ranging from 37.2°C to 38.0°C. The clinical course was acute and reproducible, facilitating rapid suspicion of an infectious etiology.

Microbiological investigation of blood cultures obtained from the arterial lumen of the catheters revealed growth of ESBL-producing *E. cloacae* in all ten patients. In six cases, follow-up blood cultures again confirmed the presence of the same microorganism, indicating persistent infection and limited effectiveness of antimicrobial therapy while the catheter remained in situ. Additional examination of catheter tips using the roll-plate method demonstrated colonization with *E. cloacae* ESBL in all removed catheters, conclusively confirming their role as the portal of entry and transmission mechanism.

Despite comprehensive microbiological control of the hemodialysis equipment, *E. cloacae* was isolated only from the inlet and outlet of a single Hemodialysis machine located in room No. 5. This isolate did not exhibit phenotypic similarity to the clinical strains, confirming that the equipment environment was not the primary source of infection. These findings further supported the central vascular catheters as the main risk factor for infection in patients with chronic renal failure and multimorbidity.

### **Clinical outcomes and therapeutic limitations**

No fatal outcomes were recorded during the outbreak. However, the clinical course was complicated by limited therapeutic options and the need for invasive interventions. ESBL production by *E. cloacae* resulted in high-level resistance to most cephalosporins and penicillins, significantly restricting effective antimicrobial therapy.

Empirical treatment was initiated with amikacin in combination with imipenem/cilastatin. In several patients, the expected clinical and microbiological response was not achieved, necessitating removal of permanent catheters in five patients and the temporary catheter in one patient. Microbiological examination of catheter tips confirmed colonization with *E. cloacae* ESBL, explaining the persistence of infection and justifying catheter removal.

Following catheter removal and continuation of carbapenem therapy, clinical stabilization was achieved in all patients. Nevertheless, the outbreak resulted in prolonged hospitalization and required transfer of seven patients to the Nephrology and Emergency Hemodialysis Clinic for further monitoring and treatment. All patients were discharged by the end of July after completion of appropriate antimicrobial therapy.

### **Dynamics of the outbreak**

The outbreak in the Hemodialysis Clinic evolved over a ten-day period, with all cases occurring within a short timeframe and exhibiting a similar clinical profile. The characteristic onset of chills and fever approximately two hours after the start of hemodialysis was promptly recognized by medical staff and raised suspicion of a common infectious source. The reproducibility of clinical manifestations facilitated rapid epidemiological linkage of cases, enabling timely microbiological investigation and identification of *Enterobacter cloacae* ESBL as the causative agent.

Phenotypic identity of the isolates was confirmed, and strain typing performed by the National Center of Infectious and Parasitic Diseases verified their epidemiological relatedness.

### **Anti-epidemic measures**

Upon detection of the outbreak, hospital management was immediately notified, and the Commission for the Control and Prevention of HAI was convened. A comprehensive set of anti-epidemic measures was implemented, aimed at eliminating potential sources of infection and preventing further transmission.

These measures included terminal disinfection of the Hemodialysis Clinic, optimization of biocidal agents used, and upgrading disinfection protocols for Hemodialysis machines in accordance with manufacturer recommendations. Extended microbiological surveillance was conducted, including sampling from healthcare workers' hands, hospital surfaces, hemodialysis solutions, and dialysates. *E. cloacae* was isolated only from the inlet and outlet of one hemodialysis machine; however, this strain was non-ESBL-producing and phenotypically distinct from clinical isolates.

These findings confirmed that central vascular catheters represented the primary portal of entry, while the Hemodialysis equipment did not play a leading role in the epidemic process. As part of the organizational and behavioral response, targeted staff training was conducted, focusing on strict adherence to hand hygiene and best practices in catheter handling, with the aim of minimizing the risk of future catheter-associated bloodstream infections.

### **1.4.3. Epidemiological study of an outbreak of HAI caused by *A. baumannii* in the CAIC**

#### **Epidemiological characteristics of the outbreak**

In February 2017, during a retrospective review of HAI in the CAIC at University Hospital “St. Marina” – Varna, an outbreak caused by a multidrug-resistant strain of *A. baumannii* was identified. During the period 15–27 February, five microbiologically confirmed cases were registered and promptly reported to the RHI. All isolates demonstrated phenotypic identity based on antibiogram analysis and were characterized by resistance to all tested antibacterial agents except colistin. This susceptibility profile classified the isolates as extremely drug-resistant and therapeutically challenging.

The isolated strains of *A. baumannii* were predominantly recovered from tracheal secretions, which defined the primary clinical diagnosis as ventilator-associated pneumonia (VAP). In two patients, the pathogen was additionally isolated from urine and wound secretions, indicating catheter-associated urinary tract infection and postoperative wound infection, respectively. This clinical presentation reflects the typical multidrug-resistant *A. baumannii* profile in intensive care settings, characterized by VAP in combination with other invasive procedures.

#### **Patient characteristics**

The demographic characteristics of the affected patients indicate pronounced vulnerability among elderly and multimorbid individuals. Of the five patients, four were male and one was female, with a mean age of 69 years. Two patients were 60–69 years, two were older than 80 years, and one patient was younger than 50 years.

Clinical characteristics highlight the role of invasive medical procedures as key risk factors. All patients had undergone major surgical interventions or prolonged mechanical ventilation. Sources of pathogen isolation included tracheal secretions in all patients and urine and wound secretions in two cases, confirming the ventilator- and catheter-associated nature of the infections.

#### **Clinical outcomes**

The outcome of the infections was unfavorable in three of the five cases, corresponding to a case fatality rate of 60%. This value is comparable to data from international studies reporting mortality rates between 40% and 70% in infections caused by multidrug-resistant *A. baumannii*, particularly in intensive care units. The two surviving patients also experienced complicated clinical courses and prolonged hospital stays, underscoring the substantial clinical and economic burden associated with such outbreaks.

## **Dynamics of the outbreak**

The epidemiological analysis demonstrates a typical pattern of nosocomial outbreak dynamics. The first two cases were identified on 15 February, followed by two additional cases on 23 February and one case on 27 February. Within a 12-day period, five etiologically identical cases were identified, indicating nosocomial transmission under conditions of high exposure and suboptimal initial preventive measures.

## **Implemented anti-epidemic measures**

In response to the outbreak, a series of anti-epidemic measures was implemented in accordance with national and international recommendations. Patients were isolated and cohorting measures were applied. On 24 and 28 February, mechanical sterilization of air and surfaces was performed in the affected wards.

Enhanced microbiological surveillance of the hospital environment and sterilization processes was conducted, along with intensified monitoring of hand hygiene compliance. Medical staff participated in targeted workshops and training sessions focusing on HAI definitions and criteria, reporting procedures, and high-risk moments in routine clinical practice within the CAIC. Additional training emphasized hand hygiene and prevention of catheter-associated infections. The outbreak was officially reported to the RHI on 28 February and remained under epidemiological surveillance. No new cases were registered following the implementation of these measures.

## **Discussion**

The findings of this study present a comprehensive overview of HAI outbreaks at University Hospital “St. Marina” – Varna during the period 2013–2022. The temporal distribution reveals a distinct peak in outbreak activity in 2016–2017, with three outbreaks documented annually, followed by a gradual decline in frequency. This pattern may reflect both actual epidemiological fluctuations and improvements in infection control practices and antimicrobial stewardship implemented in recent years.

The absence of reported outbreaks in 2013–2014 and again in 2020 and 2022 is likely attributable to enhanced surveillance and accumulated experience of the ICT, although the possibility of under- or overestimation of sporadic cases cannot be excluded.

The distribution of outbreaks by clinical units clearly highlights intensive care settings as high-risk environments. More than half of all outbreaks (54.5%) occurred in the CAIC, which is consistent with international data identifying intensive care units as particularly vulnerable to HAI due to patient severity, mechanical ventilation, and the frequent use of invasive procedures. Hematology units accounted for 27.3% of outbreaks, where immunosuppression and frequent central venous access represent major risk factors. Single outbreaks were recorded in the Hemodialysis Clinic, the Second Children’s Clinic, and the COVID-19 ward (9.1% each), confirming that the risk of HAI extends beyond intensive care units to other hospital departments caring for vulnerable patient populations.

Respiratory infections predominated in the clinical structure of outbreaks, accounting for 54.1% of cases, followed by catheter-associated bloodstream infections (26.3%) and gastrointestinal infections

(19.7%). This distribution mirrors international patterns, where VAP and catheter-associated infections are recognized as leading forms of HAI.

The etiological profile of outbreaks was dominated by multidrug-resistant Gram-negative bacteria, accounting for over 80% of cases. *A. baumannii* represented the largest proportion (37.7%), followed by ESBL-producing *E. cloacae* (26.3%) and *P. aeruginosa* (16.4%). Viral agents and other bacterial pathogens played a more limited role, with rotavirus detected in 13.2% of patients and *C. difficile* in 6.6%. This distribution aligns with European and global data identifying multidrug-resistant Gram-negative pathogens as leading causes of outbreaks in intensive care settings.

University Hospital “St. Marina” – Varna was the only healthcare facility in the region Varna that reported epidemic HAI outbreaks during the study period, according to RHI. This likely reflects higher surveillance sensitivity rather than lower risk elsewhere, as outbreaks caused by multidrug-resistant organisms are more commonly detected in large University Hospitals with established infection control systems.

The *E. cloacae* ESBL outbreak in the Hemodialysis clinic illustrates the high risk of catheter-associated bloodstream infections in hemodialysis patients. The short outbreak duration, uniform clinical presentation, and identical microbiological findings confirm epidemiological linkage through a common risk factor—central vascular catheters. These findings are fully consistent with international data demonstrating that vascular catheters are the primary risk factor for bacteremia in chronic hemodialysis patients.

Similarly, the *A. baumannii* outbreak in February 2017 highlights the growing challenges posed by multidrug resistance in intensive care units. The observed 60% case fatality rate corresponds to published data on extensively drug-resistant *A. baumannii* infections. While timely reporting and comprehensive control measures were implemented, the delay in outbreak recognition until five cases had accumulated underscores the need for early warning systems and predefined alert thresholds.

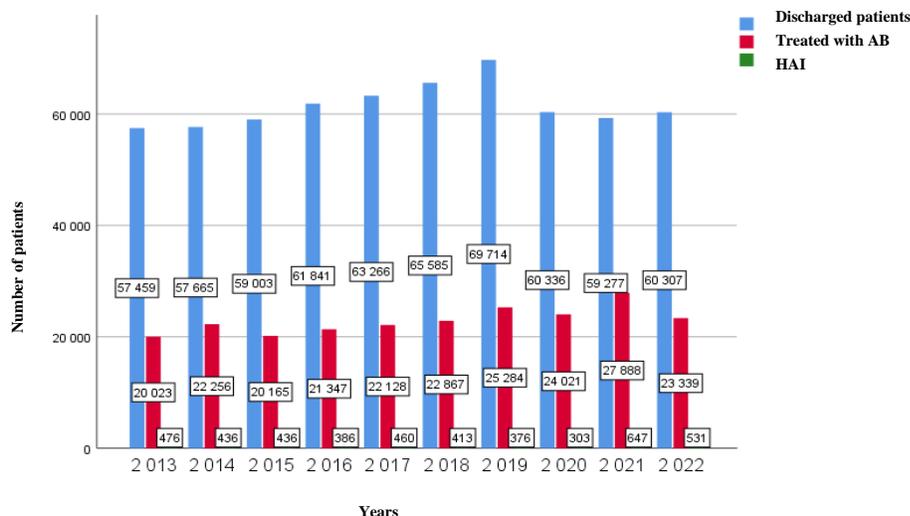
## **2. Analysis of the epidemiological characteristics of HAI at University Hospital “St. Marina” – Varna for the period 2013–2022.**

### **2. 1. Analysis of the incidence of HAI at University Hospital “St. Marina” – Varna, for the period 2013–2022.**

When identifying cases of HAI, the definitions of the CDC, Atlanta, USA, were applied, along with the criteria set out in the Medical Standard for the Prevention and control of nosocomial infections. This regulation entered into force on 11 May 2013 and was issued by the Ministry of Health and published in the State Gazette, No. 43 of 14 May 2013. The analyzed HAI cover a ten-year period, from 1 January 2013 to 31 December 2022.

Figures 12 and 13 present trends in antibiotic use and HAI, analyzed in the context of the total number of discharged patients at University Hospital “St. Marina” – Varna during the period 2013–2022. For the period 2013–2022, the total number of discharged patients at the hospital was 614,453, with a mean

annual number of 61,445 patients. Annual values ranged from 57,459 to 69,714, and three distinct subperiods can be identified. During 2013–2015, relative stability was observed, with annual discharges fluctuating between 57,000 and 59,000 patients. In the period 2016–2019, a marked increase was recorded, reaching a peak of 69,714 discharged patients in 2019, representing an increase of approximately 21% compared with 2013. In 2020, the number of discharged patients decreased substantially compared with 2019 (–13.5%), remained at a lower level in 2021, and showed a slight recovery in 2022 (+1.7%), without returning to pre-pandemic levels (Fig. 12).



*Fig. 12. Number of discharged patients treated with antibiotics and registered HAI in University Hospital “St. Marina” – Varna for the period 20 13 -20 22*

During the study period 2013–2022, the total number of patients who received antibiotic therapy at the hospital amounted to 229,318, corresponding to a mean annual value of 22,932 patients. Annual values ranged between 20,023 and 27,888 patients.

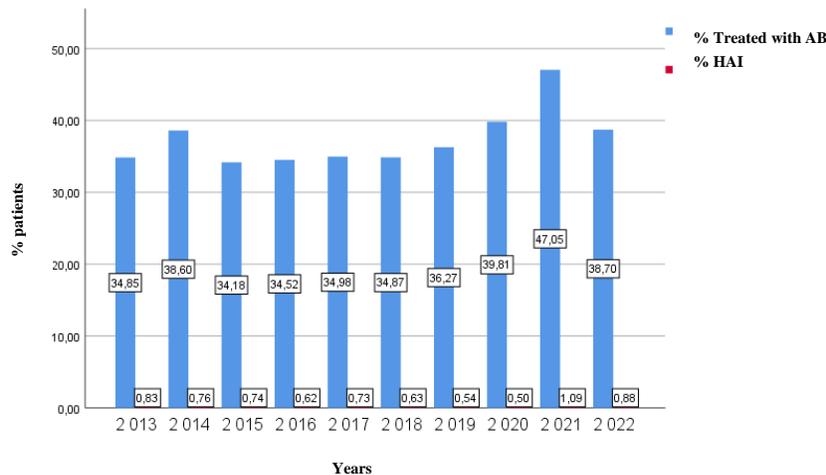
In the first subperiod (2013–2015), a marked increase was observed in 2014 compared with the baseline year 2013 (+11.2%), followed by a partial decrease in 2015, when the number of patients treated with antibiotics approached baseline levels. During the period 2016–2018, a sustained upward trend was recorded, culminating in a peak of 22,867 patients in 2018 (+14.2% compared with 2013). In the final subperiod (2019–2022), the indicator remained consistently higher than in the initial years, with a mean annual value of 25,133 patients. The maximum number of patients receiving antibiotic therapy was recorded in 2021 (27,888; +39.3% compared with 2013). In 2022, a decline to 23,339 patients was observed; however, this value remained above baseline levels and below the peak values recorded during the pandemic period (Fig. 12).

For the period 2013–2022, a total of 4,464 HAI were registered at the hospital, corresponding to a mean annual number of approximately 446 cases. In the initial years of the analysis, the number of HAI ranged between 436 and 476 cases, followed by a decrease to 386 cases in 2016 and a subsequent increase

in 2017 (460 cases). During the period 2018–2020, a downward trend was again observed, reaching a minimum of 303 cases in 2020. A pronounced peak occurred in 2021, with 647 registered HAI, representing the highest value for the entire study period. In the final year of analysis (2022), the number of HAI decreased to 531 cases, but remained substantially higher than levels observed during the initial years (Fig. 12).

Figure 13 illustrates the relative proportion of patients treated with antibiotics who developed HAI during the period 2013–2022. The indicators were calculated based on the total number of discharged patients. The proportion of patients receiving antibiotic therapy ranged from 34.18% in 2015 to 47.05% in 2021, with a mean annual value of 37.4%. At the beginning of the study period, a notable increase was observed in 2014 (38.60%) compared with 2013 (34.85%), followed by a decline in 2015 to the lowest recorded value for the decade (34.18%). During the subperiod 2016–2019, the indicator showed relative stability with a moderate upward trend (34.52–36.27%). The most substantial change was recorded during 2020–2021, when the proportion increased sharply, reaching a maximum of 47.05% in 2021—approximately a 38% increase compared with the lowest value observed in 2015. In 2022, the proportion declined to 38.7%, approaching the mean values for the entire study period.

*Fig. 13. The relative share of patients treated with antibiotics and cases of HAI for the period 2013–2022.*



### **Incidence of HAI among discharged patients**

For the period 2013–2022, the relative proportion of HAI among discharged patients ranged from 0.50% (2020) to 1.09% (2021), with a mean annual value of approximately 0.73%. During the initial stage (2013–2015), the incidence of HAI remained relatively stable, ranging between 0.74% and 0.83%. In the period 2016–2019, a persistent downward trend was observed (from 0.62% in 2016 to 0.54% in 2019), reaching a minimum of 0.50% in 2020—the lowest value recorded for the entire study period. In 2021, a sharp increase to 1.09% was registered, representing more than a twofold rise compared with 2020 and the

highest level observed during the period under review. In 2022, the indicator declined to 0.88%, representing an intermediate value—higher than the overall mean but lower than the 2021 peak (Fig. 13).

## **Discussion**

### **Discharged patients**

The dynamics of the number of discharged patients during the period 2013–2022 reveal clearly distinguishable stages reflecting both organizational aspects of hospital activity and external socio-epidemiological influences. Three subperiods with distinct characteristics can be identified. During the first subperiod (2013–2015), relative stability was observed, which may be considered a baseline for comparison. The second subperiod (2016–2019) was characterized by a steady increase, culminating in a peak in 2019, when the number of discharged patients was approximately 21% higher than in 2013. This trend corresponds to the increasing hospitalization activity reported in several European countries in the years preceding the COVID-19 pandemic.

The final subperiod (2020–2022) was marked by a sharp decline, coinciding with the COVID-19 pandemic and the implementation of restrictive measures, which substantially limited planned hospital activity. Similar trends have been reported internationally. According to data from the Organisation for Economic Co-operation and Development and the WHO, hospital admissions in most European countries decreased by 10–20% in 2020 due to postponed elective procedures and the reallocation of resources to COVID-19 care. The partial recovery observed in 2022 suggests system adaptation and gradual normalization of hospital activity, although pre-pandemic levels were not fully restored.

### **Antibiotic use**

The present study shows that, during the period 2013–2022, a total of 229,318 patients at University Hospital “St. Marina” – Varna received antibiotic therapy, corresponding to a mean annual value of 22,932 patients. The absolute number varied between 20,023 (2015) and 27,888 (2021), while the relative proportion among all discharged patients ranged from 34.18% (2015) to 47.05% (2021).

During the initial subperiod (2013–2015), the proportion of patients receiving antibiotics ranged between 34% and 39%, reflecting relative stability and comparability with average European levels. According to the ECDC Point Prevalence Survey II (2016–2017), an average of 30.5% of hospitalized patients in the European Union and European Economic Area (EU/EEA) received antibiotics, with wide inter-country variation (15.9%–55.6%). Data from the ECDC Point Prevalence Survey III (2022–2023) indicate an average antibiotic use of 35.5% in the EU/EEA, while Bulgaria reported a substantially higher value of 47.9%, placing the country among those with the highest antibiotic consumption.

Particularly notable are the results for 2020–2021, when, despite a reduction in the overall number of discharged patients, the absolute number of patients receiving antibiotics peaked at 27,888 in 2021, and the relative proportion reached 47.05%, markedly exceeding European averages. This pattern is consistent with international observations indicating widespread empirical antibiotic prescribing during the COVID-19 pandemic, often in the absence of confirmed bacterial co-infection. Although a reduction was observed

in 2022 (23,339 patients; 38.7%), antibiotic use remained above baseline levels from the beginning of the study period, suggesting the establishment of a persistently higher level of antibiotic utilization.

These findings are consistent with national reports indicating an approximately 27% increase in antibiotic consumption in Bulgaria over the past decade, in contrast to stabilization or reduction trends observed in several European countries. Furthermore, WHO and ECDC data indicate that Bulgaria ranks among countries with the highest use of broad-spectrum “Watch” group antibiotics, representing an additional risk factor for the development and spread of antimicrobial resistance.

Throughout the study period, antibiotic use at University Hospital “St. Marina” – Varna remained higher than regional values for Varna and close to or slightly above national averages. In the pre-pandemic years (2018–2019), antibiotic use ranged from 34.9% to 36.3% (compared with 28.6%–29.6% for Varna and approximately 36.5% nationally). During the pandemic, a pronounced peak was observed in 2021 (47.1%), compared with 40.43% for Varna and 42.0% nationally. In the post-pandemic year 2022, antibiotic use declined to 38.7%, remaining above regional levels (34.62%) and closely approximating national values (38.29%). These dynamics highlight the more pronounced increase in antibiotic use in the University Hospital setting, likely related to the higher concentration of severe cases and the application of more complex therapeutic approaches.

### **Healthcare-associated infections**

The incidence of HAI at University Hospital “St. Marina” – Varna during the period 2013–2022 ranged between 0.50% and 1.09%, with a mean annual value of approximately 0.73%, encompassing all hospital wards (high-, medium-, and low-risk units). These values are substantially lower than those reported in recent European point prevalence surveys, which indicate an HAI prevalence of 7.1% among patients in acute care hospitals, reaching 6.3%–8.0% after adjustment and extrapolation.

In the early years of the study (2013–2015), relative stability was observed (0.74%–0.83%), followed by a downward trend during 2016–2019, reaching a minimum in 2020 (0.50%). From an epidemiological perspective, this decline is more likely attributable to reporting artifacts rather than a true reduction in morbidity. International data suggest that the COVID-19 pandemic led to staff overload, resource reallocation to COVID-19 care, and reduced capacity for systematic HAI surveillance.

In 2021, a substantial change was observed, with a simultaneous increase in HAI incidence (1.09%) and antibiotic use (47.05%). This pattern is consistent with the expected increased risk associated with pandemic-related workload, widespread use of invasive procedures, extensive empirical antibiotic therapy, and the overall burden of COVID-19 on hospital systems. In 2022, both indicators stabilized (HAI  $\approx$ 0.88%; antibiotic use  $\approx$ 38.7%) but remained at the upper range of nationally reported levels.

Compared with published national data, the results of the present study demonstrate good comparability. The observed HAI rates align with publicly available annual reports from Regional Health Inspectorates, which report values ranging from 0.2% to 0.7% for recent years. Data from Bulgaria’s automated HAI registration system indicate an average incidence of approximately 1.27% for the period 2003–2014.

The discrepancy between routine national reporting, the present findings, and results from standardized European surveys likely reflects systematic underreporting, a phenomenon well documented in national publications and expert analyses. An additional factor influencing the relatively low reported HAI incidence at the University Hospital is its institutional profile, which includes numerous low-risk wards that reduce the overall HAI proportion when calculated at the hospital level. Furthermore, the presence of clinical pathways with very short lengths of stay (1–3 days) limits the likelihood of developing and diagnosing HAI during hospitalization, while infections manifesting after discharge often remain outside hospital reporting systems. The high frequency of empirical antibiotic therapy may also suppress clinical manifestations of infection, contributing to lower reported HAI rates.

Throughout the study period, the HAI incidence at University Hospital “St. Marina” – Varna remained higher than regional values for Varna (0.42%–0.72%) and close to or slightly above national averages (0.7%–0.8%). This difference was most pronounced during the pandemic, when the HAI rate at the University Hospital reached 1.09%, compared with 0.72% for Varna and 0.8% nationally, and persisted in 2022 (0.88% versus 0.58% for Varna and 0.8% nationally).

## 2.2. Analysis of HAI incidence and antibiotic use by clinical units grouped according to risk level

Tables 3, 4, and 5 present the frequency of HAI, antibiotic use, and statistical indicators (arithmetic mean and measures of variability) by clinical units, grouped according to the degree of risk for HAI occurrence. The normality of distributions was assessed using the Kolmogorov–Smirnov test for the ten-year period 2013–2022.

*Table 3. Statistical indicators, AB use and HAI in low-risk clinics of University Hospital “St. Marina” – Varna for the period 2013–2022.*

Low-risk clinics	Statistical indicators	Average number of discharged patients	Average number of AB received	Average number of HAI	% received AB/ discharged patients	% HAI/ discharged patients	% HAI/ received AB
<b>Oncology</b>	Arithmetic mean	4629.70	392.40	,40	8.4453	,0098	,1429
	Variation	615,850	81,383	1,265	2.41138	,03090	,45175
<b>Propedeutics of Internal Medicine</b>	Arithmetic mean	2130.60	1482.20	,40	69.1883	,0170	,0261
	Variation	677,286	500,075	,843	7.74422	,03581	,05509
<b>Cardiology - I</b>	Arithmetic mean	3192.80	440.40	,40	14.4932	,0118	,1049
	Variation	807,261	91,945	,843	4.10342	,02493	,22123
<b>Invasive cardiology</b>	Arithmetic mean	2226.20	216.70	,00	9.7772	,0000	,0000
	Variation	219,664	261,476	,000	11.06015	,00000	,00000
<b>Non-invasive cardiology</b>	Arithmetic mean	2088.20	385.80	3.00	19,1839	,1395	,7778

	Variation	456,691	70,104	3,055	4.53383	,14865	,88260
<b>Rheumatology</b>	Arithmetic mean	2513.10	147.00	,00	6.3929	,0000	,0000
	Variation	433,988	102,385	,000	5.35755	,00000	,00000
<b>Nephrology</b>	Arithmetic mean	1596.20	1023.80	1.60	58.4518	,1044	,2429
	Variation	421,570	711,670	2,066	28.08010	,15297	,46415
<b>Hematology</b>	Arithmetic mean	3709.90	1403.60	25.40	38.1044	,7260	2.0803
	Variation	346,190	452,685	25,687	12.64576	,75859	2.41328
<b>Endocrinology</b>	Arithmetic mean	1466.80	122.50	,10	9.3185	,0063	,0862
	Variation	252,508	77,207	,316	7.37296	,01981	,27261
<b>Gastroenterology</b>	Arithmetic mean	2548.40	1701.30	,00	66.3713	,0000	,0000
	Variation	430,459	609,804	,000	21.87557	,00000	,00000
<b>Nervous Clinic diseases - I</b>	Arithmetic mean	2095.00	103.90	,20	5.1188	,0099	,1667
	Variation	222,326	90,977	,632	4.70192	,03123	,52705
<b>Nervous Clinic diseases – II</b>	Arithmetic mean	1084.40	174.00	,50	19.5909	,0403	,2742
	Variation	616,372	47,579	,972	8.32763	,07511	,54740
<b>First children's</b>	Arithmetic mean	2410.00	814.80	2.30	33.7577	,0941	,2984
	Variation	273,538	215,594	1,889	7.29784	,07245	,26787
<b>Second children's</b>	Arithmetic mean	1851.10	984.50	,60	55.1019	,0280	,0539
	Variation	405,518	166,955	1,265	13.83794	,05947	,11558
<b>PCHO</b>	Arithmetic mean	1192.00	495.70	21.70	42.0097	1.8131	4.9159
	Variation	229,099	191,841	8,538	13.92675	,64623	2.46963
<b>Psychiatric clinics</b>	Arithmetic mean	3453.50	127.90	,00	3.8265	,0000	,0000
	Variation	358,445	67,872	,000	2.19458	,00000	,00000
<b>Infectious clinic - I</b>	Arithmetic mean	1488.70	874.10	2.60	57.8203	,1637	,2896
	Variation	420,808	343,987	3,062	10.55937	,19024	,31419
<b>Infectious clinic - II</b>	Arithmetic mean	898.70	,90	449.20	49.8316	,1056	,2487
	Variation	165,256	1,370	184,493	17.28508	,16395	,40894
<b>Dermatology clinic</b>	Arithmetic mean	351.40	330.20	,00	94.9451	,0000	,0000
	Variation	155,970	148,789	,000	8.68330	,00000	,00000

<b>Hemodialysis</b>	Arithmetic mean	641.60	32.40	12.70	4.8930	1.9328	47.2627
	Variation	60,694	25,691	9,889	3.85817	1.45766	36.91243

*Table 4 . Statistical indicators, AB use and HAI in medium-risk clinics of " University Hospital "St. Marina" – Varna for the period 2013–2022.*

<b>Medium- risk clinics</b>	<b>Total patients discharged</b>	<b>Statistical indicators</b>	<b>Average number of discharged patients</b>	<b>Average number of AB received</b>	<b>Average number of HAI</b>	<b>% received AB/ discharged patients</b>	<b>% HAI/ discharged patients</b>	<b>% HAI/ received AB</b>
<b>Surgery - I</b>	15817	Arithmetic mean	1581.70	635.00	,90	40.7007	,0435	,1096
		Variation	304,524	114,670	2,846	6.57877	,13742	,34666
<b>One- day surgery</b>	5656	Arithmetic mean	565.60	185.90	,00	27.3004	,0000	,0000
		Variation	461,542	178,305	,000	9.60237	,00000	,00000
<b>Surgery - II</b>	12239	Arithmetic mean	1223.90	654.00	48.90	53.4924	3.9801	6.8846
		Variation	152,318	120,791	45,747	7.99879	3.58329	5.19488
<b>Thoracic Surgery</b>	7079	Arithmetic mean	707.90	383.40	1.50	54.6608	,2158	,4358
		Variation	99,758	54,347	1,958	7.66438	,26916	,58798
<b>Urology</b>	18476	Arithmetic mean	1847.60	1473.30	14.90	79.8367	,7847	1.0801
		Variation	190,863	411,758	7,965	21.38153	,36848	,55503
<b>Vascular surgery</b>	10573	Arithmetic mean	1057.30	362.90	6.90	35.0916	,6173	2.1404
		Variation	135,351	45,686	7,385	8.01836	,66310	2.43624
<b>Neurosurgery</b>	9374	Arithmetic mean	937.40	572.70	,50	61.8693	,0515	,0857
		Variation	86,858	73,339	1,269	12.48192	,12728	,22120
<b>Maxillofacial surgery</b>	8971	Arithmetic mean	897.10	721.20	,10	80.0717	,0104	,0120
		Variation	110,384	139,292	,316	9.83698	,03277	,03801

<b>Orthopedics</b>	14992	Arithmetic mean	1499.20	565.40	,40	37.8120	,0269	,0789
		Variation	175,509	94,549	,843	5.75317	,05708	,17194
<b>Cardiac surgery</b>	6801	Arithmetic mean	680.10	426.80	5.90	63.4292	,8533	1.1882
		Variation	200,779	129,472	8,020	15.37839	1.18375	1.44141
<b>ENT</b>	8663	Arithmetic mean	866.30	620.30	,30	70.6506	,0323	,0449
		Variation	139,692	172,988	,483	11.98797	,05214	,07266

*Table 5. Statistical indicators, AB use and HAI in high-risk clinics of University Hospital “St. Marina” – Varna for the period 2013–2022*

<b>High-risk clinics</b>	<b>Total patients discharged</b>	<b>Statistical indicators</b>	<b>Average number of discharged patients</b>	<b>Average number of AB received</b>	<b>Average number of HAI</b>	<b>% received AB/ discharged patients</b>	<b>% HAI/ discharged patients</b>	<b>% HAI/ received AB</b>
<b>ICU non-invasive ventilation</b>	4138	Arithmetic mean	413.80	358.60	5.00	90.5088	1.8427	1.9346
		Variation	214,480	167,381	8,667	11.89641	4.07801	4.15831
<b>ICU – neurological diseases</b>	8468	Arithmetic mean	846.80	297.70	19.90	37.2586	2.5966	6.4652
		Variation	217,431	62,637	13,461	13.59306	2.18205	3.70849
<b>ICU – pediatric</b>	2824	Arithmetic mean	282.40	250.30	43.90	87.7506	18.2979	21.3511
		Variation	86,067	87,168	21,794	3.99230	12.04060	14.51886
<b>CAIC</b>	9338	Arithmetic mean	933.80	933.30	149.80	99.9461	17.5056	17.5129
		Variation	252,506	252,524	26,208	,17038	7.15693	7.15239
<b>ICU – cardiac surgical patients</b>	4397	Arithmetic mean	439.70	420.70	41.10	95.0813	9.2836	9.9092
		Variation	110,514	120,987	12,922	8.38782	1.68611	2.54910

A statistical test for normality of the empirical distributions was performed using the Kolmogorov–Smirnov criterion. The results are presented separately for each group of clinics according to their assigned

risk level. The dissertation adopts a significance level ( $\alpha$ ) of 0.05. Accordingly, values of  $p < 0.05$  indicate empirical distributions that differ significantly from a normal distribution, whereas values of  $p > 0.05$  indicate that the empirical distributions do not deviate significantly from normality.

Determining the type of distribution and its proximity to a normal distribution is essential for the appropriate formulation and interpretation of statistical analyses, as it allows assessment of whether the values are symmetrically distributed around the mean in an ordered statistical sequence (Tables 6, 7, and 8).

*Table 6. Indicators of AB use, frequency of HAI and results of the Kolmogorov – Smirnov test in low-risk clinics of the University Hospital “St. Marina” for the period 2013–2022.*

Low-risk clinics	Statistical indicators	Average number of discharged patients	Average number of AB received	Average number of HAI	p / K – S test / discharged patients	p /KS test/ received AB	p /KS test/ number of HAI
<b>Oncology</b>	Arithmetic mean	4629.70	392.40	,40	0.193	0.200	0.000
	Variation	615,850	81,383	1,265			
<b>Propedeutics of Internal Medicine</b>	Arithmetic mean	2130.60	1482.20	,40	0.018	0.014	0.000
	Variation	677,286	500,075	,843			
<b>Cardiology – I</b>	Arithmetic mean	3192.80	440.40	,40	0.200	0.020	0.000
	Variation	807,261	91,945	,843			
<b>Invasive cardiology</b>	Arithmetic mean	2226.20	216.70	,00	0.200	0.003	-
	Variation	219,664	261,476	,000			
<b>Non-invasive cardiology</b>	Arithmetic mean	2088.20	385.80	3.00	0.200	0.200	0.200
	Variation	456,691	70,104	3,055			
<b>Rheumatology</b>	Arithmetic mean	2513.10	147.00	,00	0.200	0.008	-
	Variation	433,988	102,385	,000			
<b>Nephrology</b>	Arithmetic mean	1596.20	1023.80	1.60	0.092	0.200	0.006
	Variation	421,570	711,670	2,066			
<b>Hematology</b>	Arithmetic mean	3709.90	1403.60	25.40	0.200	0.200	0.031
	Variation	346,190	452,685	25,687			
<b>Endocrinology</b>	Arithmetic mean	1466.80	122.50	,10	0.027	0.200	0.000
	Variation	252,508	77,207	,316			
<b>Gastroenterology</b>	Arithmetic mean	2548.40	1701.30	,00	0.200	0.200	-
	Variation	430,459	609,804	,000			
	Arithmetic mean	2095.00	103.90	,20	0.200	0.013	0.000

<b>Nervous Clinic diseases – I</b>	Variation	222,326	90,977	,632			
<b>Nervous Clinic diseases – II</b>	Arithmetic mean	1084.40	174.00	,50	0.019	0.200	0.000
	Variation	616,372	47,579	,972			
<b>First children’s</b>	Arithmetic mean	2410.00	814.80	2.30	0.200	0.200	0.200
	Variation	273,538	215,594	1,889			
<b>Second children’s</b>	Arithmetic mean	1851.10	984.50	,60	0.002	0.200	0.000
	Variation	405,518	166,955	1,265			
<b>PCHO</b>	Arithmetic mean	1192.00	495.70	21.70	0.101	0.023	0.200
	Variation	229,099	191,841	8,538			
<b>Psychiatric clinics</b>	Arithmetic mean	3453.50	127.90	,00	0.200	0.200	-
	Variation	358,445	67,872	,000			
<b>Infectious clinic – I</b>	Arithmetic mean	1488.70	874.10	2.60	0.200	0.200	0.200
	Variation	420,808	343,987	3,062			
<b>Infectious clinic – II</b>	Arithmetic mean	898.70	,90	449.20	0.182	0.104	0.001
	Variation	165,256	1,370	184,493			
<b>Dermatology clinic</b>	Arithmetic mean	351.40	330.20	,00	0.180	0.200	-
	Variation	155,970	148,789	,000			
<b>Hemodialysis</b>	Arithmetic mean	641.60	32.40	12.70	0.200	0.104	0.040
	Variation	60,694	25,691	9,889			

*Table 7. Indicators of AB use, frequency of HAI and results of the Kolmogorov – Smirnov test in medium-risk clinics of the University Hospital “St. Marina” for the period 2013–2022.*

<b>Medium-risk clinics</b>	<b>Statistical indicators</b>	<b>Average number of discharged patients</b>	<b>Average number of AB received</b>	<b>Average number of HAI</b>	<b>p / K – S test / discharged patients</b>	<b>p / K – S test / received AB</b>	<b>p / K – S test / number of HAI</b>
<b>Surgery – I</b>	Arithmetic mean	1581.70	635.00	,90	0.061	0.200	0.000
	Variation	304,524	114,670	2,846			
<b>One-day surgery</b>	Arithmetic mean	565.60	185.90	,00	0.200	0.074	-

	Variation	461,542	178,305	,000			
<b>Surgery – II</b>	Arithmetic mean	1223.90	654.00	48.90	0.200	0.200	0.003
	Variation	152,318	120,791	45,747			
<b>Thoracic Surgery</b>	Arithmetic mean	707.90	383.40	1.50	0.158	0.200	0.011
	Variation	99,758	54,347	1,958			
<b>Urology</b>	Arithmetic mean	1847.60	1473.30	14.90	0.200	0.200	0.200
	Variation	190,863	411,758	7,965			
<b>Vascular surgery</b>	Arithmetic mean	1057.30	362.90	6.90	0.030	0.171	0.019
	Variation	135,351	45,686	7,385			
<b>Neurosurgery</b>	Arithmetic mean	937.40	572.70	,50	0.200	0.200	0.000
	Variation	86,858	73,339	1,269			
<b>Maxillofacial surgery</b>	Arithmetic mean	897.10	721.20	,10	0.058	0.200	0.000
	Variation	110,384	139,292	,316			
<b>Orthopedics</b>	Arithmetic mean	1499.20	565.40	,40	0.200	0.009	0.000
	Variation	175,509	94,549	,843			
<b>Cardiac surgery</b>	Arithmetic mean	680.10	426.80	5.90	0.200	0.024	0.015
	Variation	200,779	129,472	8,020			
<b>ENT</b>	Arithmetic mean	866.30	620.30	,30	0.200	0.200	0.000
	Variation	139,692	172,988	,483			

*Table 8. Indicators of AB use, frequency of HAI and results of the Kolmogorov – Smirnov test in high-risk clinics of University Hospital “St. Marina” – Varna for the period 2013–2022.*

<b>High-risk clinics</b>	<b>Statistical indicators</b>	<b>Average number of discharged patients</b>	<b>Average number of AB received</b>	<b>Average number of HAI</b>	<b>p / K – S test / discharged patients</b>	<b>p /KS test/ received AB</b>	<b>p /KS test/ number of HAI</b>
<b>ICU non-invasive ventilation</b>	Arithmetic mean	413.80	358.60	5.00	0.200	0.200	0.001
	Variation	214,480	167,381	8,667			
<b>ICU – neurological diseases</b>	Arithmetic mean	846.80	297.70	19.90	0.200	0.200	0.062
	Variation	217,431	62,637	13,461			
<b>ICU – pediatric</b>	Arithmetic mean	282.40	250.30	43.90	0.099	0.027	0.200

	Variation	86,067	87,168	21,794			
<b>CAIC</b>	Arithmetic mean	933.80	933.30	149.80	0.200	0.200	0.200
	Variation	252,506	252,524	26,208			
<b>ICU – cardiac surgical patients</b>	Arithmetic mean	439.70	420.70	41.10	0.200	0.200	0.200
	Variation	110,514	120,987	12,922			

## Results

### Low-risk clinical units

In the low-risk group, the incidence of HAI was minimal, usually below 0.05% of discharged patients. In several units within this group, no HAI were registered, including Gastroenterology, Dermatology, Psychiatric Clinics, Rheumatology, and Invasive Cardiology. Despite the low or absent HAI incidence, antibiotic exposure was substantial, reaching 66.4% in Gastroenterology ( $p = 0.200$ ) and 94.9% in Dermatology ( $p = 0.200$ ).

A similar pattern was observed in the Department of Propaedeutics of Internal Medicine, where 69.2% of patients received antibiotics ( $p = 0.014$ ), while HAI were recorded in only 0.017% of hospitalized patients ( $p < 0.05$ ). Slightly higher HAI rates were observed in Non-invasive Cardiology (0.14% incidence rate ratio [HAI],  $p = 0.200$ ) and Nephrology (0.10% HAI,  $p = 0.006$ ), with the latter demonstrating a deviation from normal distribution.

Within this group, three units exhibited a clearly increased risk. In Hematology, the HAI incidence reached 0.73% of discharged patients ( $p = 0.031$ ) and 2.08% of patients receiving antibiotics, indicating a statistically significant deviation from normality. In the Pediatric Clinic of Hematology and Oncology, HAI occurred in 1.8% of all patients and 4.9% of those treated with antibiotics ( $p = 0.200$ ), without significant deviation from normal distribution. The highest values in this group were observed in the Hemodialysis clinic, where HAI affected 1.9% of all patients and nearly 47% of those receiving antibiotics ( $p = 0.040$ ), demonstrating a statistically significant deviation from normality (Tables 3 and 6).

### Medium-risk clinical units

In the medium-risk group, antibiotic exposure was high, ranging between 40% and 80% of patients, while the incidence of HAI varied substantially between units. Department of Day Surgery (27.3% antibiotic use;  $p = 0.074$ ) and Maxillofacial Surgery (80.1% antibiotic use;  $p = 0.200$ ) reported no significant number of HAI. A similar trend was observed in First Surgery clinic, where 40.7% of patients received antibiotics, but the HAI incidence was only 0.04% ( $p < 0.05$ ). Orthopaedics (37.8% antibiotic use; 0.03% HAI) and Otorhinolaryngology (ENT) (70.6% antibiotic use; 0.03% HAI) also demonstrated very low infection rates, with  $p < 0.05$  indicating deviation from normality due to the small number of cases. Higher risk was

identified in Second Surgery, where HAI affected 3.98% of all patients and 6.88% of those receiving antibiotic therapy ( $p = 0.003$ ), confirming a statistically significant deviation from normal distribution.

In Urology, 79.8% of patients received antibiotic therapy, with HAI detected in 0.78% of all patients and 1.08% of those treated; all indicators demonstrated normal distribution ( $p > 0.05$ ). In Vascular Surgery, antibiotic exposure was 35.1%, and HAI occurred in 0.62% of all patients and 2.14% of those receiving antibiotics, with  $p < 0.05$  for the number of infections, indicating deviation from normal distribution. Cardiac Surgery also demonstrated increased risk, with 63.4% of patients receiving antibiotics and HAI recorded in 0.85% of all patients and 1.19% of those treated ( $p = 0.015$ ).

Thoracic Surgery (0.22% HAI incidence,  $p = 0.011$ ) and Neurosurgery (0.05% HAI incidence,  $p < 0.05$ ) exhibited the lowest infection rates; however, distributions were non-normal due to the small number of cases (Tables 4 and 7).

### **High-risk clinical units**

High-risk units concentrated the highest HAI frequencies, with near-universal antibiotic exposure (90–100%). In the Intensive Care Unit with Non-invasive Ventilation, 90.5% of patients received antibiotics, and HAI were identified in 1.84% of discharged patients ( $p = 0.001$ ). In the Intensive Care Unit for Neurological Diseases, antibiotic exposure was 37.3%, while HAI occurred in 2.6% of all patients and 6.5% of those treated ( $p = 0.062$ ).

In the Pediatric Intensive Care Unit, nearly 88% of patients received antibiotics, and HAI were recorded in 18.3% of all patients and 21.4% of those treated. In this unit,  $p = 0.027$  for antibiotic exposure indicated a statistically significant deviation from normal distribution, whereas no such deviation was observed for HAI incidence ( $p = 0.200$ ). In the CAIC, almost all patients (99.9%) received antibiotics, and HAI were identified in 17.5% of discharged patients, with  $p > 0.05$  for all indicators, indicating normal distributions. In the Department of Anesthesiology and Intensive Care for Cardiac Surgical Patients, antibiotic exposure covered 95% of patients, while HAI were detected in 9.3% of all patients and 9.9% of those treated; all indicators demonstrated normal distributions ( $p > 0.05$ ) (Tables 5 and 8).

### **Discussion**

The results demonstrate a clear differentiation between clinical units with respect to HAI incidence and antibiotic exposure. In low-risk units, the incidence of HAI was minimal—typically below 0.05%—and in several units no cases were registered. Despite this, antibiotic use was disproportionately high, reaching 60–95% of patients in some departments. This combination of extensive antibiotic exposure and minimal or absent reported HAI is a concerning finding, suggesting potential underreporting and highlighting an imbalance between therapeutic practice and documented infection burden. Such patterns create favorable conditions for the development and spread of antimicrobial resistance.

Medium-risk units exhibited greater heterogeneity, ranging from complete absence of HAI (e.g., Day Surgery and Maxillofacial Surgery) to infection rates approaching those observed in high-risk units (e.g., Second Surgery, 3.98% of discharged patients), against a background of widespread antibiotic use.

High-risk units concentrated the highest infection frequencies, with intensive care units and resuscitation wards reporting HAI in 17–18% of patients, and in the Hemodialysis clinic nearly half of patients receiving antibiotics developed an HAI. These values substantially exceed those observed in low- and medium-risk units and confirm the central role of intensive care settings as primary environments for HAI occurrence. The findings are fully comparable with data from the ECDC Point Prevalence Survey II (2016–2017), which reported an average HAI prevalence of approximately 19.5% in intensive care units.

### **Conclusions from the Kolmogorov–Smirnov test**

1. In most low-risk clinics, the indicators “patients receiving antibiotics” and “discharged patients” followed normal distributions. Exceptions included the Internal Medicine Clinic, Endocrinology, Neurology, and the Pediatric Clinic, where distributions deviated from normality. For the indicator “number of patients with HAI,” most clinics showed significant deviations from normal distribution, except for Non-invasive cardiology, the First Pediatric Clinic, the Pediatric Clinic of Hematology and Oncology, and the First Infectious Diseases Clinic.
2. In medium-risk clinics, a high degree of conformity with normal distribution was observed. Exceptions included the indicator “discharged patients” in Vascular Surgery and “patients receiving antibiotics” in Orthopedics and Cardiac Surgery, where significant deviations were detected. The indicator “number of HAI” showed normal distribution only in Urology.
3. High-risk clinics demonstrated the largest number of units with normally distributed values for the indicator “number of HAI,” including the Intensive Care Unit for Neurological Diseases, the Pediatric Intensive Care Unit, the Clinic of Anesthesiology and Intensive Care, and the Department of Anesthesiology and Intensive Care for Cardiac Surgical Patients. The only exception was the indicator “patients receiving antibiotics” in the Pediatric Intensive Care Unit, which deviated significantly from normal distribution.

### **2.3. Analysis of the etiological structure of HAI at University Hospital “St. Marina” – Varna for the period 2013-2022.**

The analysis of the etiological structure of HAI represents a key stage of the study, as it allows the identification of leading causative agents and the assessment of trends in their distribution over time. This analysis has not only descriptive but also evaluative value, as it reflects the effectiveness of the HAI surveillance and control system.

In 2013, the leading causative agent of HAI was *A. baumannii*, with a relative share of 29.7%, confirming its role as a major pathogen in the hospital environment. The second most frequently isolated microorganism was *K. pneumoniae* (16.3%), followed by *P. aeruginosa* (15.7%) and *E. cloacae* (11.1%). *E. coli* accounted for 8.3% of isolates, further confirming the dominance of Gram-negative pathogens, which together comprised more than 80% of all identified microorganisms. Among Gram-positive bacteria, *Staphylococcus aureus* (*S. aureus*) had the most notable contribution (8.6%), while *E. faecalis* played a more limited role (4.6%). Fungal infections caused by *Candida* spp. Accounted for 4.9% of cases, and HAI caused by *C. difficile* were not registered during the study year (Fig. 14).

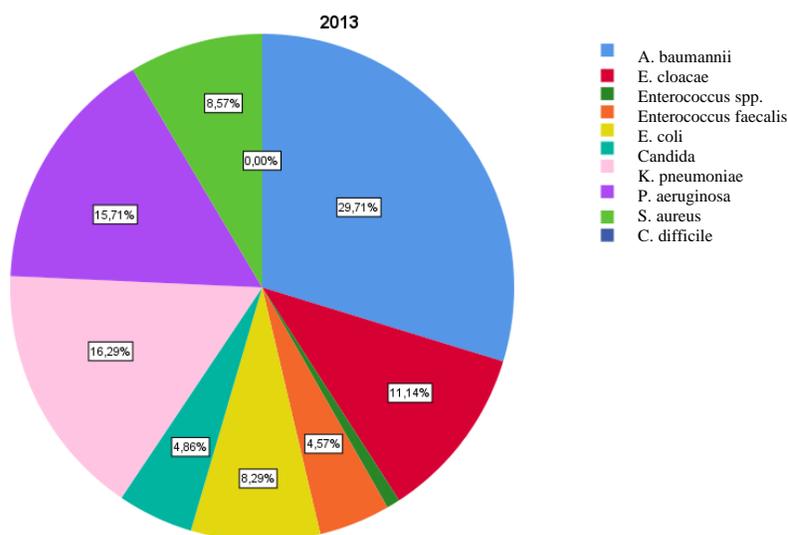


Fig. 14. Etiological structure of HAI at University Hospital “St. Marina” – Varna for 2013.

The leading causative agent of HAI in 2014 was again *A. baumannii*, with a relative share of 26.4%. Although this value was lower compared with the previous year, it confirms the persistent dominant role of this pathogen as a major nosocomial microorganism. *K. pneumoniae* ranked second (21.5%), and its increasing proportion reflects the growing clinical significance of this multidrug-resistant pathogen. *P. aeruginosa* (13.7%) and *E. cloacae* (12.2%) also occupied an important position in the etiological structure, further confirming the predominance of Gram-negative bacteria. Among the remaining pathogens, *E. coli* (8.1%) and *Candida* spp. (4.1%) showed a notable contribution to the overall spectrum of HAI. Among Gram-positive microorganisms, *E. faecalis* accounted for 5.8% and *S. aureus* for 6.98%, indicating a more pronounced presence compared with the previous year. For the first time, isolates of *C. difficile* were also reported (1.2%), which may be attributed both to the actual emergence of clinical cases and to improvements in diagnostic practices (Fig. 15).

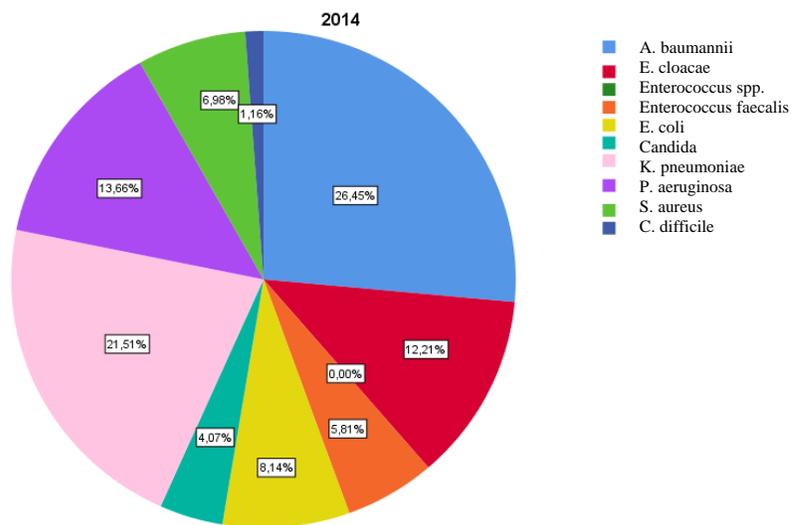


Fig. 15. Etiological structure of HAI at University Hospital “St. Marina” – Varna for 2014.

The leading causative agent of HAI in 2014 was again *A. baumannii*, with a relative share of 26.4%. Although this value was lower compared with the previous year, it confirms the persistent dominant role of this pathogen as a major nosocomial microorganism. *K. pneumoniae* ranked second (21.5%), and its increasing proportion reflects the growing clinical significance of this multidrug-resistant pathogen. *P. aeruginosa* (13.7%) and *E. cloacae* (12.2%) also occupied an important position in the etiological structure, further confirming the predominance of Gram-negative bacteria. Among the remaining pathogens, *E. coli* (8.1%) and *Candida* spp. (4.1%) showed a notable contribution to the overall spectrum of HAI. Among Gram-positive microorganisms, *E. faecalis* accounted for 5.8% and *S. aureus* for 6.98%, indicating a more pronounced presence compared with the previous year. For the first time, isolates of *C. difficile* were also reported (1.2%), which may be attributed both to the actual emergence of clinical cases and to improvements in diagnostic practices (Fig. 15).

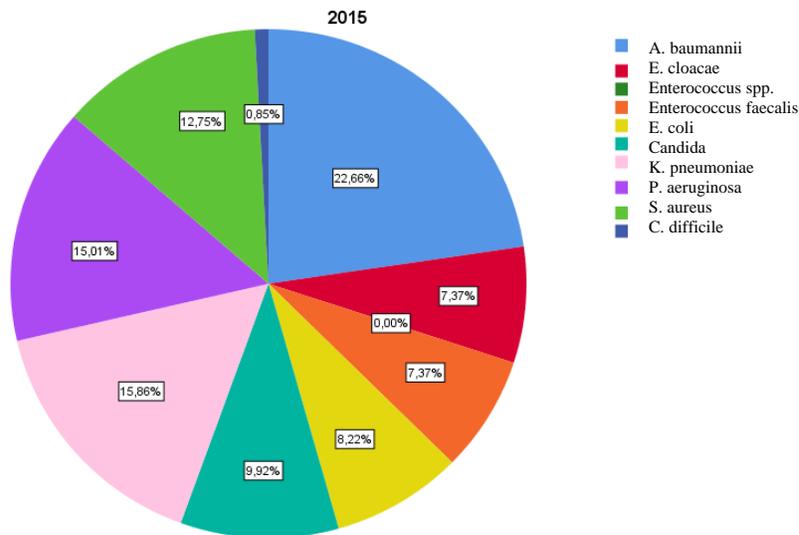


Fig. 16. Etiological structure of HAI at University Hospital “St. Marina” – Varna for 2015.

In 2016, the leading causative agent of HAI remained *A. baumannii* (23.0%), continuing to occupy the first position in the etiological structure. A notable change was observed for *P. aeruginosa*, which reached a relative share of 20.9%, displacing *K. pneumoniae* (16.6%) and ranking second among the predominant nosocomial pathogens. Next in frequency were *E. coli* (10.6%) and *E. cloacae* (10.6%), which, together with other Gram-negative microorganisms, again confirmed their dominant role in the etiology of HAI. Among Gram-positive bacteria, *E. faecalis* accounted for 6.0% of isolates, while *S. aureus* showed a limited contribution (4.6%), marking a significant decrease compared with previous years. Fungal infections caused by *Candida* spp. Represented 5.7% of cases, and in 2.2% of cases the etiological agent of HAI was identified as *C. difficile* (Fig. 17).

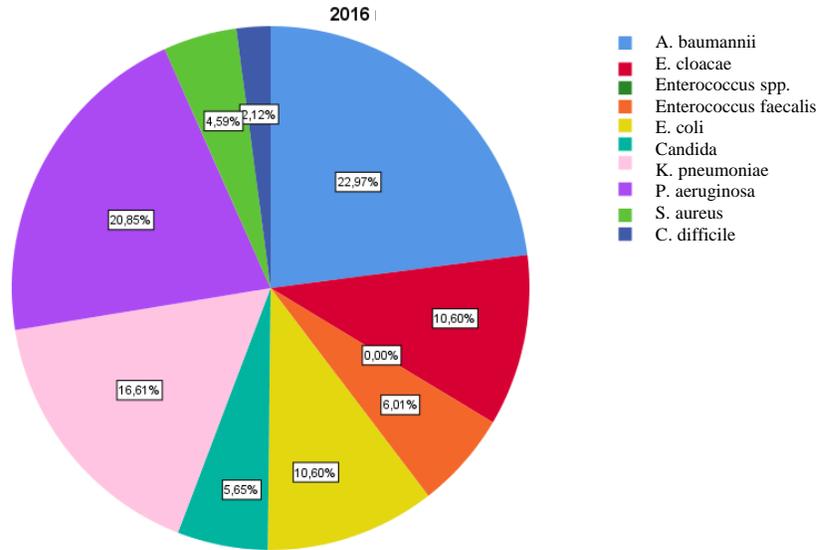


Fig. 17. Etiological structure of HAI at University Hospital “St. Marina” – Varna for 2016.

In 2017, the leading etiological agent of HAI continued to be *A. baumannii* (29.2%), followed by *K. pneumoniae* (15.7%) and *P. aeruginosa* (13.0%). *E. coli* also made a significant contribution (9.9%), as did *E. cloacae* (9.0%), further confirming the dominant role of Gram-negative pathogens. Among Gram-positive microorganisms, *E. faecalis* (9.3%) and *S. aureus* (8.4%) were most frequently isolated. *Candida* spp. Accounted for 4.5% of cases, while *C. difficile* showed marginal prevalence (0.6%) (Fig. 18).

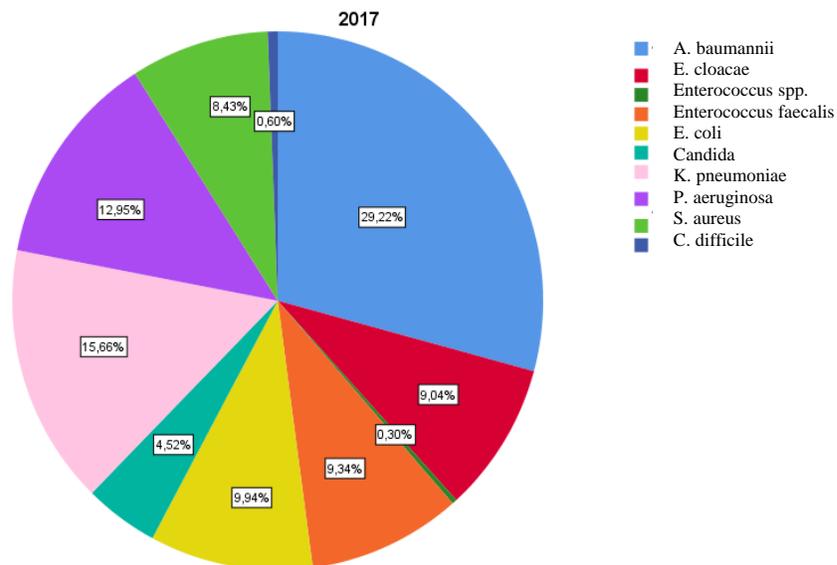


Fig. 18. Etiological structure of HAI at University Hospital “St. Marina” – Varna for 2017.

Data for 2018 indicate that *K. pneumoniae* assumed the leading position in the etiological structure of HAI (21.6%), overtaking the previously dominant *A. baumannii* (18.2%) and establishing itself as the principal Gram-negative causative agent. With a relative share of 19.2%, *P. aeruginosa* ranked second in the etiological structure for 2018. Together with *K. pneumoniae* and *A. baumannii*, it formed a triad of the most clinically significant multidrug-resistant microorganisms. Additional contributions were observed for *E. coli* (11.8%) and *E. cloacae* (6.7%), further emphasizing the persistent predominance of Gram-negative bacteria. Among Gram-positive microorganisms, *E. faecalis* accounted for the largest share (6.7%), while *S. aureus* showed a lower contribution (5.5%). *Candida* spp. constituted 6.4% of cases, and *C. difficile* was identified in 4.0% of the registered HAI (Fig. 19).

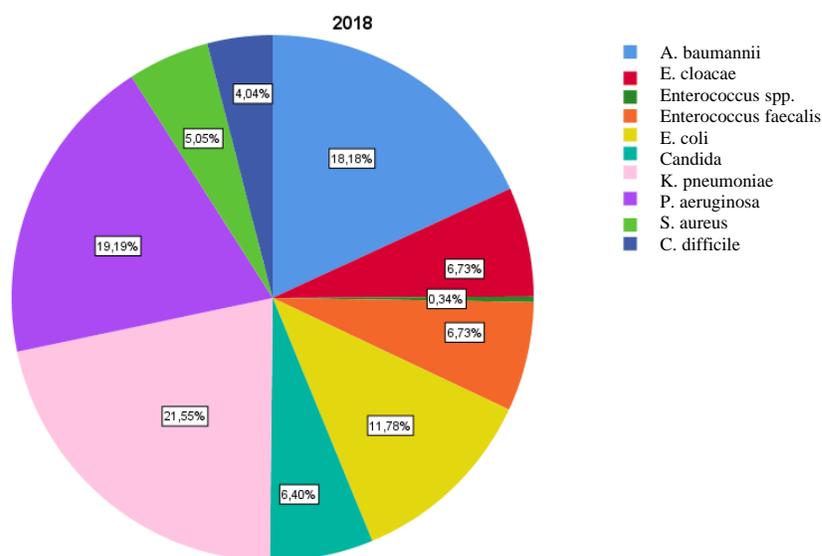


Fig. 19. Etiological structure of HAI at University Hospital “St. Marina” – Varna for 2018.

In 2019, a marked change in the etiological structure of HAIs was observed. *A. baumannii* regained the leading position with a relative share of 22.9%, displacing *K. pneumoniae*, which had been the dominant causative agent in the previous year and was identified in 13.0% of isolates. Particular attention is warranted for *Candida* spp., which, with a share of 16.0%, emerged as the second most frequent etiological agent, indicating an increasing role of fungal infections in nosocomial pathology. *P. aeruginosa* (14.9%) and *K. pneumoniae* (13.0%) also ranked among the leading pathogens. Among Gram-positive microorganisms, *E. faecalis* had the greatest contribution (11.6%), while *S. aureus* accounted for approximately 5% of isolates. *E. coli* (9.0%) and *E. cloacae* (5.0%) maintained a stable presence in the etiological structure, albeit with lower relative shares. *C. difficile* was identified in only 0.7% of HAI cases (Fig. 20).

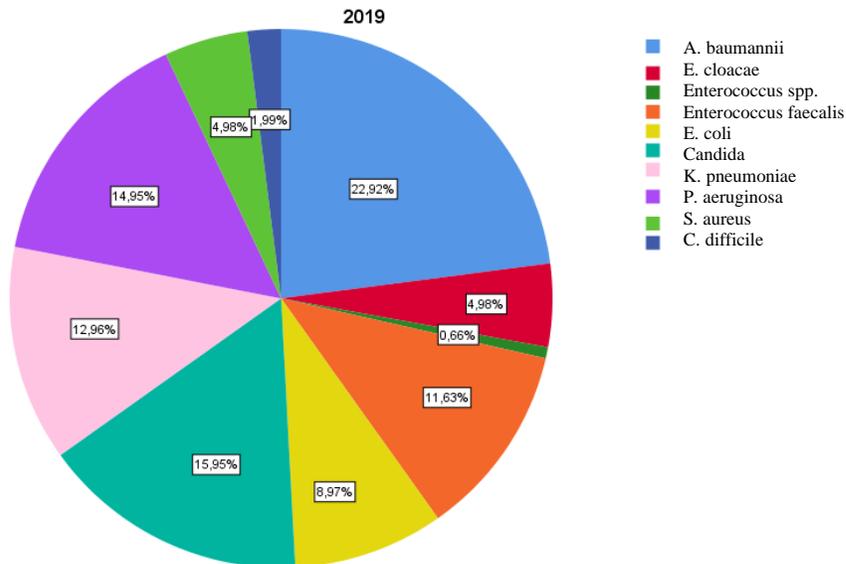


Fig. 20. Etiological structure of HAI at University Hospital “St. Marina” – Varna for 2019.

The etiological structure of HAIs in 2020 was characterized by a clear predominance of multidrug-resistant Gram-negative microorganisms. The most frequently isolated pathogen was *A. baumannii* (23.67%), followed by *E. coli* (15.51%) and *P. aeruginosa* (13.47%). A substantial contribution was also observed for *K. pneumoniae* (10.61%) and *Candida* spp. (8.57%), highlighting both the ongoing challenge posed by Enterobacterales and the increasing role of fungal infections among severely ill patients. Among Gram-positive pathogens, *E. faecalis* (9.39%) and *S. aureus* (7.35%) were most prominent. Lower frequencies were recorded for *E. cloacae* (8.98%), *Enterococcus* spp. (1.63%), and *C. difficile* (0.82%), which together further completed the etiological profile of HAIs for the year (Fig. 21).

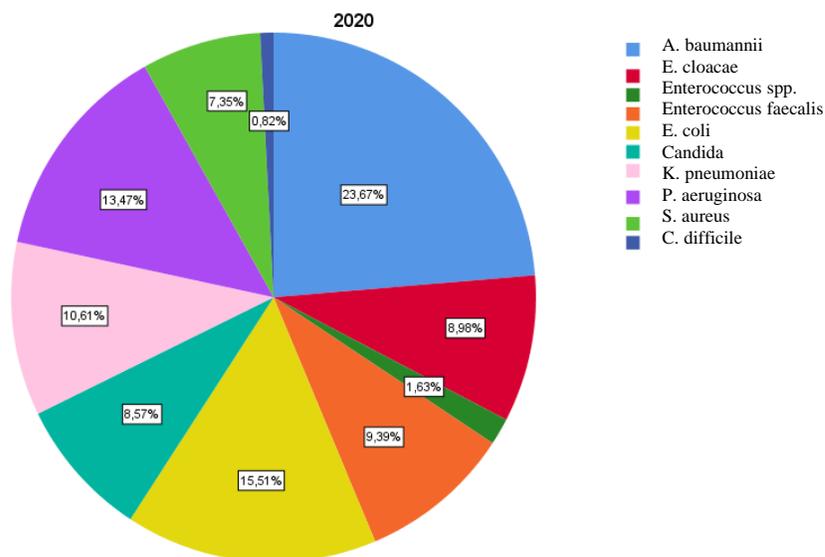


Fig. 21. Etiological structure of HAI at University Hospital “St. Marina” – Varna for 2020.

The distribution of isolates in HAI in 2021 demonstrated a clear predominance of *A. baumannii* (28.63%), followed by *Candida* spp. (20.89%) and *E. coli* (15.1%). Together, these three pathogens accounted for nearly two-thirds of all isolates and defined the main etiological profile of HAI for the year. The remaining microorganisms—*K. pneumoniae* (9.09%), *P. aeruginosa* (7.93%), *E. cloacae* (7.54%), *S. aureus* (4.84%), *E. faecalis* (4.64%), *Enterococcus* spp. (0.77%), and *C. difficile* (0.58%)—were detected with lower frequencies but remained clinically relevant (Fig. 22).

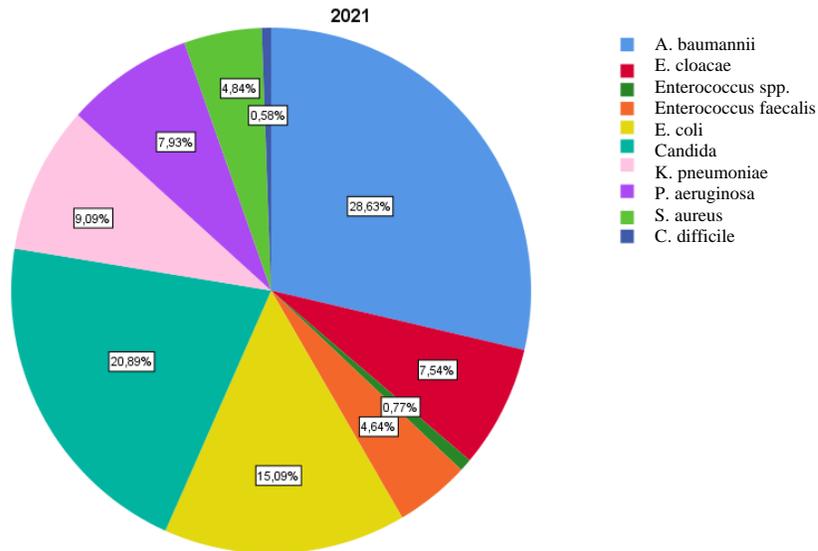


Fig. 22. Etiological structure of HAI at University Hospital “St. Marina” – Varna for 2021.

The structure of isolated nosocomial pathogens in 2022 demonstrated a relatively balanced distribution, without a clearly dominant microorganism. The leading etiological agent was *E. coli* (21.47%), which assumed a key role in the etiological profile of HAI. *A. baumannii* ranked second (16.42%), with a lower relative share compared with the previous year. A substantial contribution was observed for *K. pneumoniae* (13.05%), a typical representative of multidrug-resistant Gram-negative pathogens, as well as for *Candida* spp. (10.74%), whose occurrence is commonly associated with severely ill patients and prolonged antibiotic therapy. *P. aeruginosa* accounted for 10.53% of isolates, underscoring the continued importance of this pathogen, particularly in intensive care settings. The remaining microorganisms—*E. cloacae*, *S. aureus*, *E. faecalis*, *Enterococcus* spp., and *C. difficile*—although detected at lower frequencies, contributed to the overall microbial diversity of nosocomial infections in 2022 (Fig. 23).

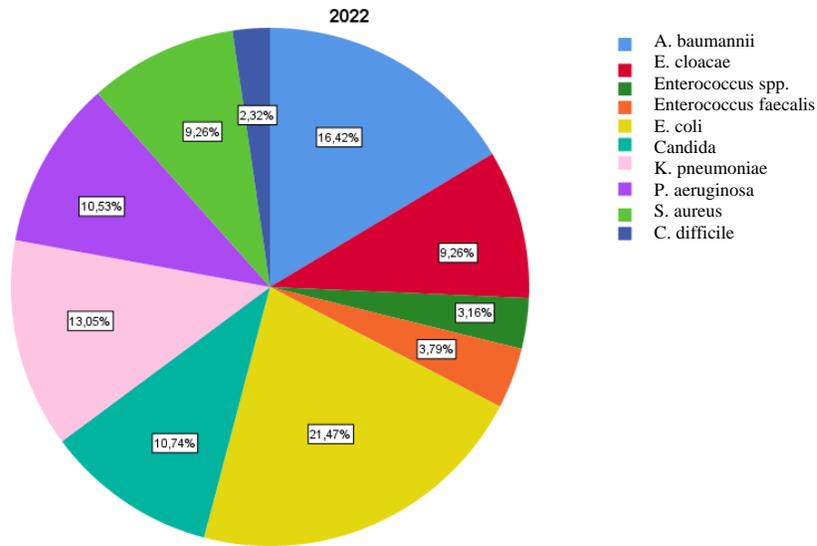


Fig. 23. Etiological structure of HAI at University Hospital "St. Marina" – Varna for 2022.

Table 9 presents the main statistical indicators, including the arithmetic mean, standard deviation, and the minimum and maximum annual values. These data allow assessment of both the average prevalence of individual pathogens and the extent of their variability over time.

Table 9. Summary statistical indicators for the frequency of the main etiological causes of HAI for University Hospital "St. Marina" – Varna (2013–2022)

Causative agent	Medium arithmetic quantity / number of occurrences/	Standard deviation /variation/ number of occurrences	Smallest value manifestations	The biggest value manifestations
<i>A. baumannii</i>	84.4	27.74	54	148
<i>E. cloacae</i>	30.70	10.01	15	44
<i>Enterococcus spp.</i>	3.00	4.50	0	15
<i>Enterococcus faecalis</i>	23.00	6.20	16	35
<i>E. coli</i>	42.90	25.68	27	102
<i>Candida spp.</i>	34.40	29.30	14	108
<i>K. pneumoniae</i>	52.40	13.60	26	74
<i>P. aeruginosa</i>	48.30	8.08	33	59
<i>S. aureus</i>	25.70	11.47	13	45
<i>C. difficile</i>	4.90	3.93	0	12

The etiological profile of HAI at University Hospital "St. Marina" – Varna during the period 2013–2022 is persistently dominated by Gram-negative microorganisms, which accounted for more than 80% of all isolates from the beginning of the study period. A central role within this profile is occupied by *A. baumannii*, which was the leading causative agent in eight of the ten analyzed years (2013–2017 and 2019–2021). In 2018, *K. pneumoniae* ranked first (21.6%), whereas in 2022 *E. coli* was the most frequently isolated pathogen (21.47%). These findings confirm *A. baumannii* as the "backbone" of

nosocomial etiology in the hospital. During the period 2013–2015, *A. baumannii* demonstrated its highest relative proportions (29.7%→22.7%), accompanied by stable involvement of *K. pneumoniae*, *P. aeruginosa*, and *E. cloacae*. *E. coli* maintained a relatively constant share (~8–10%), while among Gram-positive pathogens *S. aureus* and *E. faecalis* showed moderate variation (e.g., in 2015: *S. aureus* – 12.8%; *E. faecalis* – 7.4%). In 2016, a notable shift was observed, with *P. aeruginosa* increasing to 20.9% and occupying second place, accompanied by a marked decrease in *S. aureus* (2.1%). In the same year, *C. difficile* reached 2.2%. In 2017, *A. baumannii* re-established its dominance (29.2%). The subsequent year, 2018, was characterized by a temporary shift in leadership to *K. pneumoniae* (21.6%), forming a triad of multidrug-resistant pathogens (*K. pneumoniae* – *P. aeruginosa* – *A. baumannii*). During this period, *C. difficile* reached its highest proportion (4.0%), while *E. faecalis* and *S. aureus* remained at moderate levels. In 2019, a pronounced increase in the fungal component was observed (*Candida* spp. – 16.0%), alongside the leading role of *A. baumannii* (22.9%) and a substantial share of *E. faecalis* (11.6%). The pandemic period (2020–2021) further reinforced the dominance of *A. baumannii* (23.67%→28.63%), combined with a marked rise in *Candida* spp. (8.57%→20.89%) and persistently high proportions of *E. coli* (~15%). This trend can be explained by increased use of invasive procedures, prolonged hospital stays, and intensified antibiotic pressure—factors widely reported during the COVID-19 pandemic [Hoenigl M et al., 2022]. In 2022, signs of partial “ecological” normalization emerged: *E. coli* became the leading pathogen (21.47%), while the proportions of *A. baumannii* and *Candida* spp. Decreased (16.42% and 10.74%, respectively). At the same time, *K. pneumoniae* and *P. aeruginosa* maintained double-digit values (13.05% and 10.53%). Among Gram-positive microorganisms, *Enterococcus* spp. And *S. aureus* demonstrated a stable presence, albeit at lower proportions compared to Gram-negative pathogens. Notably, enterococci accounted for 50–70% of all Gram-positive isolates in most years, reaching 74% in 2016 and 85% in 2019, thereby confirming their role as the leading Gram-positive nosocomial pathogens in the hospital. Although the incidence of *C. difficile* infection remained relatively low (0.3–4%), its clinical relevance should not be underestimated, as it represents one of the leading causes of HAI in Europe and the United States [Davies KA et al., 2014].

Comparison with data from the Varna region reveals similar trends, albeit with more moderate amplitudes: a peak of *A. baumannii* in 2021 (23.3%) and *Candida* spp. (10.7%), followed by a decline in 2022; *E. coli* reached 14.8%, *P. aeruginosa* 11.1%, while *K. pneumoniae* ranged between 8.2% and 13.9%. At the national level (2022), the distribution appears more balanced, with comparable proportions of *E. coli* (9.3%), *K. pneumoniae* (9.3%), *A. baumannii* (7.9%), *P. aeruginosa* (7.1%), and *S. aureus* [Ministry of Health, 2022]. These findings confirm that the University Hospital exhibits a more pronounced Gram-negative profile, particularly during the pandemic period, consistent with observations reported from European intensive care units [Delbove A et al., 2024].

#### **2.4. Analysis of the clinical structure of HAI at University Hospital “St. Marina” for the period 2013–2022**

Analysis of the clinical structure of HAI is of direct importance for evaluating the effectiveness of surveillance and control systems, as the frequency and distribution of clinical manifestations reflect the quality of preventive measures, the degree of invasiveness of medical procedures, and the organization of hospital care.

In 2013, pneumonia accounted for the largest proportion of HAI at University Hospital “St. Marina” (26.91%), followed by (SSI) (19.28%). Lower respiratory tract infections also represented a substantial share (13.90%), which together with pneumonia comprised over 40% of all cases. Catheter-associated infections (8.52%) and urinary tract infections (8.30%) ranked next in frequency. Bloodstream infections (6.05%), cardiovascular system infections (4.04%), and systemic infections (3.59%) were less common. All remaining categories accounted for less than 2% each, and no cases were recorded involving bones and joints, the central nervous system, or the genital system (Fig. 24).

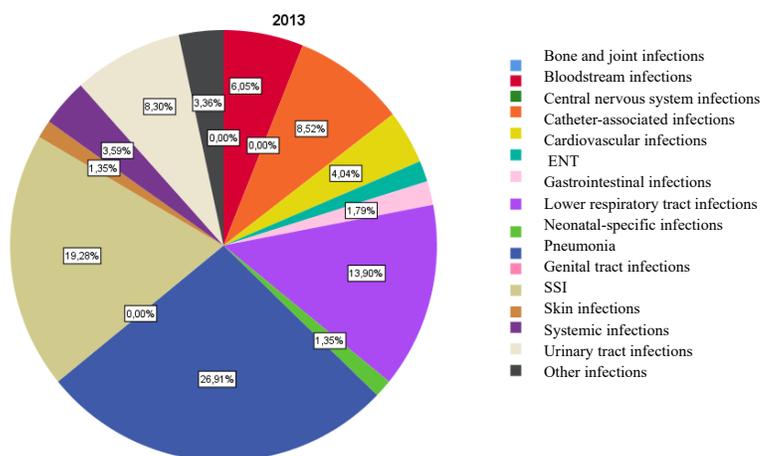


Fig. 24. Clinical structure of HAI at University Hospital “St. Marina” – Varna for 2013.

In 2014, pneumonias occupied the leading position in the clinical structure of HAI, accounting for 35.93% of all cases. This represents an increase of approximately 9 percentage points compared to 2013 (26.91%), corresponding to a relative growth of about 33.5%. SSI ranked second (20.8%), followed by bloodstream infections (7.8%). Lower respiratory tract infections (7.57%) and catheter-associated infections (7.09%) occupied the next positions in frequency. Urinary tract infections accounted for a smaller share (4.49%), as did systemic infections (1.89%). Gastrointestinal infections (1.65%) and neonatal-specific infections (3.31%) were also relatively infrequent. The lowest proportion was observed for genital infections (0.24%), while no cases were registered involving bone and joint infections, central nervous system infections, or skin infections (Fig. 25).

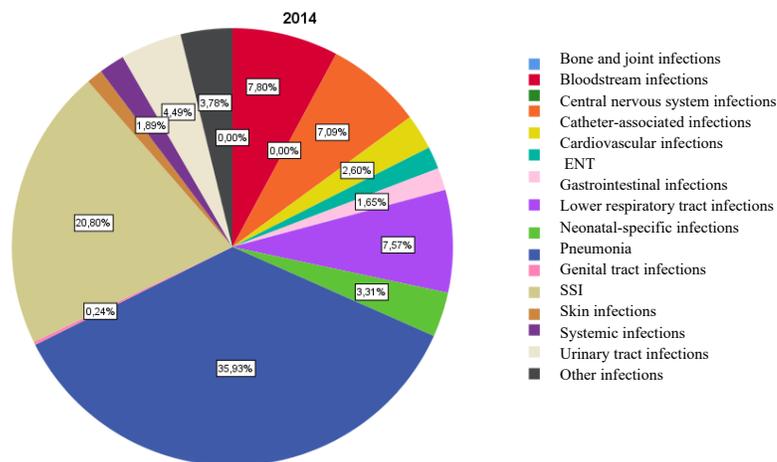


Fig. 25. Clinical structure of HAI at University Hospital “St. Marina” – Varna for 2014.

In 2015, the clinical structure of HAI was dominated by lower respiratory tract infections (LRTI), which accounted for 34.17% of all cases. By displacing pneumonias, LRTI emerged as the leading nosological group. In contrast, pneumonias represented only 5.05%, reflecting a sharp decline compared with previous key indicating changes in diagnostic criteria and reporting practices. SSI ranked second (11.01%), maintaining their epidemiological relevance, although with a lower relative share compared to 2014. Catheter-associated infections (9.17%) and eye and ENT infections (8.72%) also contributed substantially and showed a marked increase compared with the preceding period. Intermediate positions were occupied by bloodstream infections (6.65%) and urinary tract infections (6.88%), while gastrointestinal infections (5.73%) and skin infections (4.36%) also showed a noticeable presence. Lower proportions were observed for genital infections (2.98%), central nervous system infections (1.38%), systemic infections (1.61%), and neonatal-specific infections (1.38%). Minimal contributions were recorded for other infections (0.69%) and cardiovascular system infections (0.23%), while no cases of bone and joint infections were detected (Fig. 26).

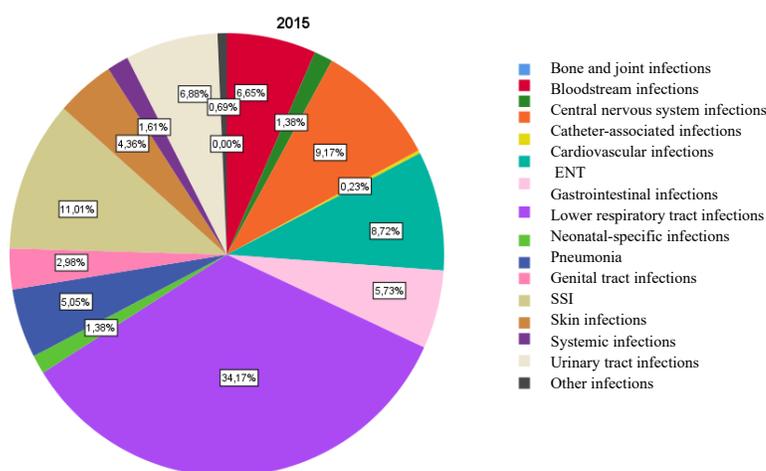


Fig. 26. Clinical structure of HAI at University hospital “St. Marina” – Varna for 2015.

In 2016, the clinical structure of HAI was characterized by a leading share of lower respiratory tract infections, which accounted for 18.91% of all registered cases. SSI ranked second (16.32%), maintaining their stable importance within the HAI spectrum. A substantial contribution was also observed for bloodstream infections (12.69%) and urinary tract infections (11.92%), both exceeding the 10% threshold and occupying a consistent position in the structure. Catheter-associated infections accounted for 10.36%, and together with bloodstream and urinary tract infections, these categories comprised more than two-thirds of all HAI cases during the year. Pneumonia (6.99%), eye and ENT infections (6.48%), and gastrointestinal infections (8.03%) contributed to a lesser, yet clinically relevant extent. The remaining categories were represented by relatively low proportions, including skin infections (1.81%), systemic infections (2.59%), central nervous system infections (1.55%), and neonatal-specific infections (1.30%). Minimal contributions were observed for genital infections (0.26%) and other infections (0.78%), while no cases of bone and joint infections or cardiovascular system infections were reported (Fig. 27).

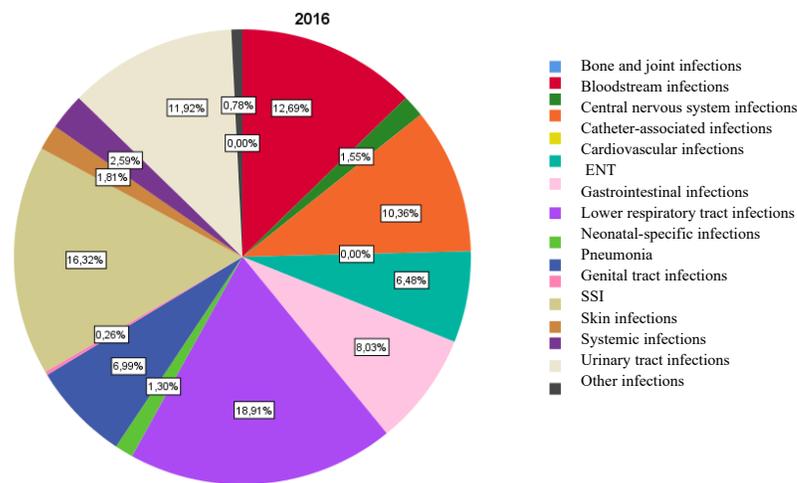


Fig. 27. Clinical structure of HAI at University Hospital “St. Marina” – Varna for 2016.

In 2017, the clinical structure of HAI was dominated by lower respiratory tract infections, which accounted for 28.04% of all registered cases and represented more than one quarter of the total, confirming their position as the leading nosological category. SSI ranked second (20.0%), constituting a significant component of hospital-associated pathology. A substantial proportion was also attributable to bloodstream infections (13.7%) and catheter-associated infections (10.0%), reflecting the elevated risk associated with invasive medical procedures and intensive care. Urinary tract infections maintained a stable position within the clinical structure (8.7%). More limited contributions were observed for pneumonia (5.87%), eye and ENT infections (4.57%), and gastrointestinal infections (3.16%). Low-frequency categories included skin infections (1.52%), central nervous system infections (1.09%), neonatal-specific infections (1.09%), and other infections (0.87%). No cases of bone and joint infections, cardiovascular system infections, or genital infections were identified, and systemic infections were not reported (Fig. 28).

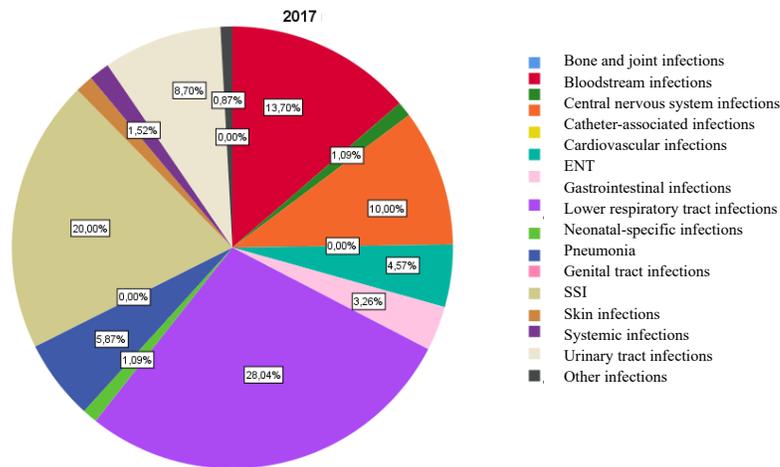


Fig. 28. Clinical structure of HAI at University Hospital “St. Marina” – Varna for 2017.

In 2018, the epidemiological profile of HAI was dominated by lower respiratory tract infections, which accounted for 28.04% of all registered cases. SSI ranked second (20.0%), followed by bloodstream infections (13.7%), which were frequently associated with catheter-associated infections (10.0%). Urinary tract infections also represented a relatively high proportion (8.7%), while pneumonia (5.87%), eye and ENT) infections (4.57%), and gastrointestinal infections (3.26%) occupied intermediate positions in the clinical structure. Low-frequency categories included skin infections (1.52%), central nervous system infections (1.09%), neonatal-specific infections (1.09%), and other infections (0.87%). No cases of bone and joint infections, cardiovascular system infections, genital infections, or systemic infections were reported (Fig. 29).

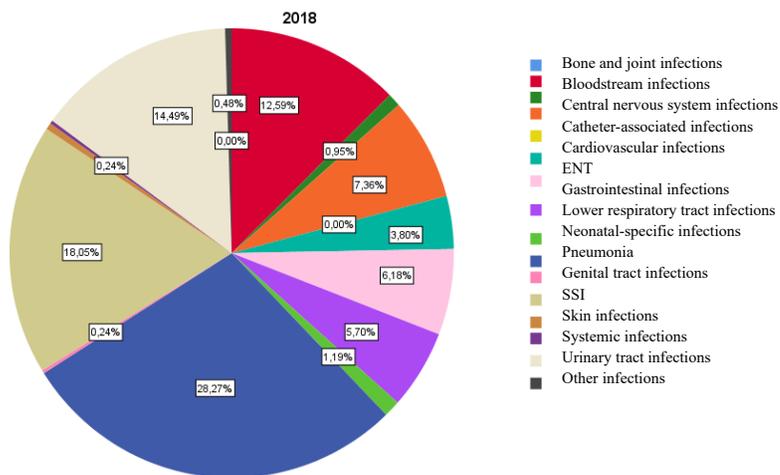


Fig. 29. Clinical structure of HAI at University Hospital “St. Marina” – Varna for 2018.

In 2019, the leading nosological group within the clinical structure of HAI was pneumonia, accounting for 22.07% of all registered cases. Gastrointestinal tract infections ranked second (15.16%), followed by SSI (12.5%). Lower respiratory tract infections (12.23%) and urinary tract infections (11.97%) occupied subsequent positions. Bloodstream infections (9.84%) and catheter-associated infections (8.78%)

also represented a substantial share of overall in-hospital morbidity. Intermediate categories included eye and ENT infections (2.66%), neonatal-specific infections (1.60%), and systemic infections (1.30%). Low-frequency categories comprised central nervous system infections (0.53%), genital infections (0.53%), and other infections (0.27%). No cases of bone and joint infections, cardiovascular system infections, or skin infections were reported during this year (Fig. 30).

In 2020, the clinical structure of HAI was dominated by SSI, which accounted for 29.18% of all cases. Pneumonia also had a high prevalence (24.17%), ranking immediately after SSI. Urinary tract infections represented the next most significant category (13.25%), while catheter-associated infections (11.26%) formed another substantial segment of in-hospital morbidity. Categories with moderate prevalence included bloodstream infections (7.28%), gastrointestinal infections (6.95%), as well as eye and ENT infections and lower respiratory tract infections, each accounting for 4.64%. Neonatal-specific infections accounted for 1.32%, and systemic infections for 0.66%. The lowest incidence was observed for central nervous system infections (0.99%) and cardiovascular system infections (0.33%). No cases of bone and joint infections, skin infections, genital infections, or other infections were registered during the study period, excluding these categories from the clinical structure for 2020 (Fig. 31).

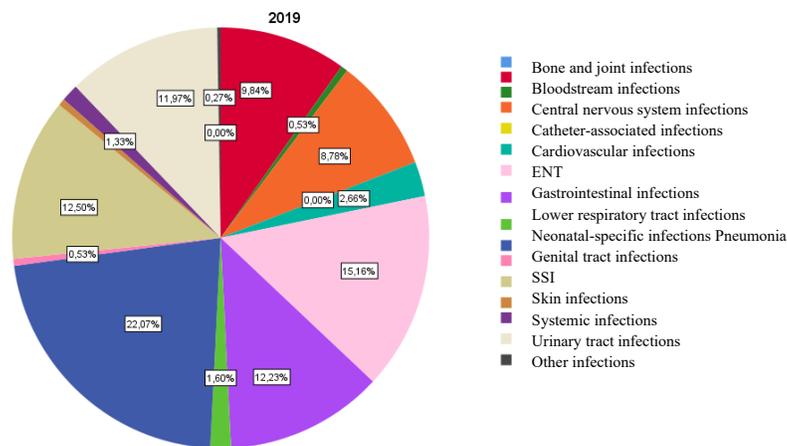
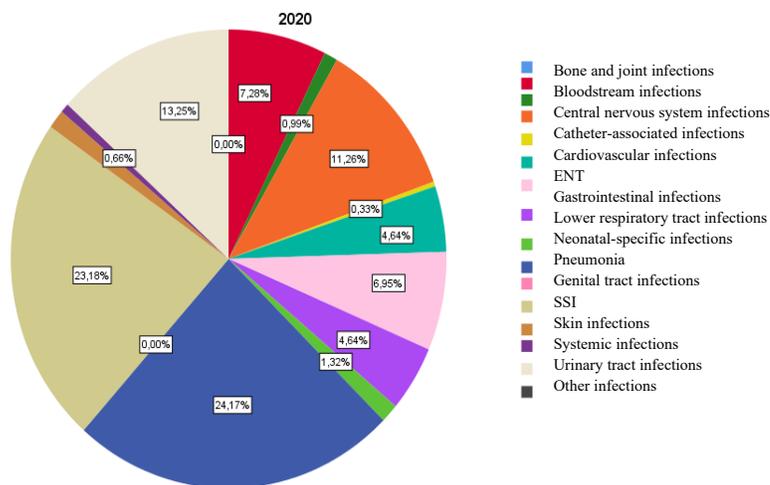
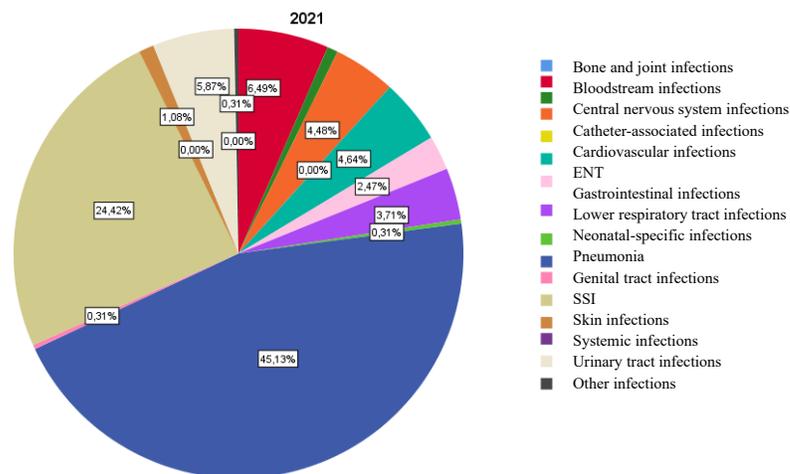


Fig. 30. Clinical structure of HAI at University hospital “St. Marina” – Varna for 2019.



*Fig. 31. Clinical structure of HAI at University Hospital “St. Marina” – Varna for 2020.*

In 2021, the leading nosological group in the clinical structure of HAI was pneumonia, accounting for 45.13% of all registered cases and representing nearly half of the total burden. SSI also occupied a substantial share (24.42%), followed by bloodstream infections (6.49%). Urinary tract infections accounted for 5.87%, while catheter-associated infections (4.48%) and eye ENT infections (4.64%) also contributed significantly. Categories with intermediate prevalence included lower respiratory tract infections (3.71%) and gastrointestinal infections (2.47%). More limited participation was observed for skin infections (1.08%), neonatal-specific infections (0.31%), genital infections (0.31%), and other infections (0.31%). During the study period, no cases of systemic infections, bone and joint infections, or cardiovascular system infections were identified (Fig. 32).



*Fig. 32. Clinical structure of HAI at University Hospital “St. Marina” – Varna for 2021.*

In 2022, the largest relative share of HAI was attributed to SSI, which accounted for 29.38% of all cases. Pneumonias followed closely with a frequency of 26.93%, ranking second in the clinical structure. Gastrointestinal infections represented the third most frequent category (9.23%). Eye and ENT infections (7.53%), bloodstream infections (7.16%), and urinary tract infections (7.16%) occupied subsequent positions, while catheter-associated infections also showed a notable presence (6.03%). Lower respiratory tract infections accounted for 4.52%, and neonatal-specific infections for 1.32%. Skin infections were recorded with a limited prevalence (0.56%). No cases of bone and joint infections, central nervous system infections, cardiovascular system infections, genital infections, or systemic infections were identified during the study period (Fig. 33).

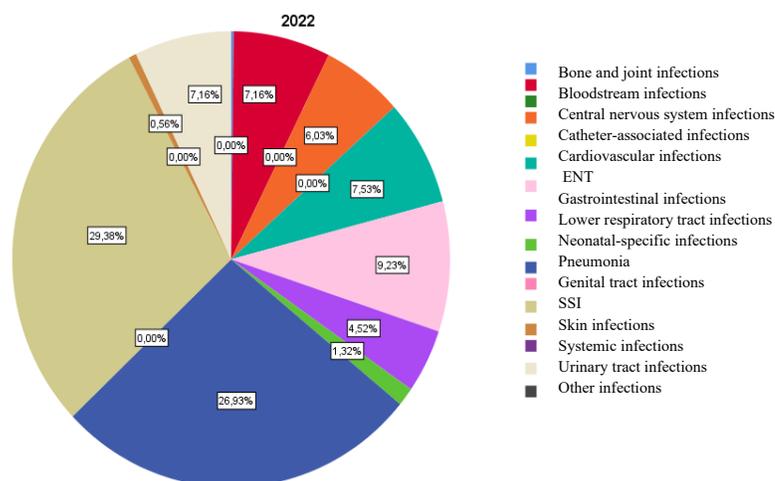


Fig. 33. Clinical structure of HAI at University Hospital “St. Marina” – Varna for 2022.

To provide a more comprehensive characterization of the clinical structure of HAI, the frequency of individual clinical forms was analyzed over the entire ten-year period (2013–2022). Table 10 presents the main statistical indicators describing the clinical structure of HAI, including mean annual values, standard deviation, minimum and maximum occurrences, and 95% confidence intervals (CI). These data allow assessment not only of the average distribution of the various clinical forms, but also of the extent of their variability and the statistical reliability of the observed trends over time.

Table 10. Statistical indicators of the clinical structure of the HAI (2013–2022)

Types of infections	Medium arithmetic quantity /number of manifestations/	Standard deviation /variation/ number manifestations	Smallest value manifestations	Biggest value manifestations	Confidence interval at 5% risk of error	
					Lower border number manifestations	Upper border number manifestations
<b>Bone and joint infections</b>	0.10	0.32	0	1	0	1
<b>Bloodstream infections</b>	39.30	12.71	22	63	30	48
<b>Central nervous system infections</b>	3.10	2.47	0	6	1	5
<b>Catheter – associated infections</b>	35.30	5.48	29	46	31	39
<b>Cardiovasc. Infections</b>	3.10	6.24	0	18	0	8

<b>ENT</b>	20.80	12.17	7	40	12	30
<b>Gastrointest. Infections tract</b>	25.50	16.48	7	57	14	37
<b>Lower respiratory tract infections</b>	57.70	46.89	14	139	24	91
<b>Neonatal-specific infections</b>	6.00	3.13	2	14	4	8
<b>Pneumonia</b>	105.80	81.38	22	292	48	164
<b>Genital tract infections</b>	2.00	3.94	0	13	0	5
<b>SSI</b>	88.40	39.32	47	158	60	117
<b>Skin infections</b>	6.10	4.91	2	19	3	10
<b>Systemic infections</b>	5.60	5.10	0	16	2	9
<b>Urinary tract infections</b>	39.40	10.83	19	61	32	47
<b>Others infections</b>	4.60	5.89	0	16	0	9

The mean frequency of HAI over the study period demonstrated a clear predominance of pneumonia, with an average of 105.8 cases per year (95% CI: 48–164), followed by SSI with a mean of 88.4 cases (95% CI: 60–117) and lower respiratory tract infections with 57.7 cases (95% CI: 24–91). A group with intermediate annual frequencies (approximately 30–40 cases) included bloodstream infections (39.3; 95% CI: 30–48), catheter-associated infections (35.3; 95% CI: 31–39), and urinary tract infections (39.4; 95% CI: 32–47). Gastrointestinal infections and eye and ENT infections showed moderate mean values of 25.5 (95% CI: 14–37) and 20.8 (95% CI: 12–30), respectively.

Lower mean frequencies were observed for neonatal-specific infections (6.0; 95% CI: 4–8), skin infections (6.1; 95% CI: 3–10), and systemic infections (5.6; 95% CI: 2–9). More limited distributions were recorded for central nervous system infections (3.1; 95% CI: 1–5), cardiovascular system infections (3.1; 95% CI: 0–8), the category “other infections” (4.6; 95% CI: 0–9), and genital infections (2.0; 95% CI: 0–5). The lowest mean frequency was observed for bone and joint infections (0.1; 95% CI: 0–1) (Table 10).

## Discussion

The analysis of the clinical structure of HAI for the period 2013–2022 at University Hospital “St. Marina” – Varna demonstrates that pneumonia represents the leading clinical form of HAI. In the peak year 2021, pneumonias accounted for 45.1% of all cases, a value that substantially exceeds commonly reported levels. According to the second ECDC point prevalence survey (2016–2017), pneumonia is the most frequent HAI in intensive care units in Europe, accounting for approximately 35–40% of ICU-associated infections. In Bulgaria, the proportion is even higher, which is likely attributable to the COVID-19 pandemic, during which the extensive use of mechanical ventilation led to a marked increase in VAP. Similar dynamics were observed in the Varna region, where pneumonias associated with intubation reached 43% in the same year. National data also demonstrate an increase, from 9% in 2016 to 14.3% in 2021, although with a more moderate growth rate. Comparison with international trends indicates that Bulgaria experienced a particularly strong pandemic-related impact in this category. According to CDC and WHO recommendations, the most effective strategy for reducing this risk is strict implementation of ventilator-associated pneumonia prevention bundles, including appropriate patient positioning, daily assessment for extubation, minimization of sedation, and adequate oral hygiene [Klompas M et al., 2016].

SSI represent the second most frequent group of HAI. In the studied hospital, their share ranged between 11% and 24%, with a clear upward trend. In the Varna region, SSI rates were even higher, reaching approximately 28% at the beginning of the period and peaking at 31.8% in 2022. At the national level, SSI account for approximately 18–20% of all HAI. According to WHO data, surgical site infections are the second most common HAI worldwide, with an average prevalence between 11% and 20% [WHO, 2020]. This indicates that regional values in Bulgaria approach or exceed the upper limits of global estimates, highlighting the need for focused interventions targeting perioperative infection prevention.

Urinary tract infections occupied a relatively stable position in the present study, ranging from 4.5% to 14.5%, with a peak in 2018. Comparable values were observed in the Varna region (6–14%), while national data indicate a prevalence of approximately 14–16%. According to ECDC data (2016–2017), Urinary tract infections account for 20–25% of all HAI in Europe, placing the observed values slightly below the EU average. This may reflect differences in diagnostic coding practices, as well as genuine improvements in catheter management and reduced catheter utilization.

Catheter-associated infections also showed relatively stable frequencies in the hospital (4.5–11.3%). The peak observed in 2020 coincided with national trends (12–14%) and is likely related to the increased use of central venous catheters in patients with severe respiratory complications during the COVID-19 pandemic. In the Varna region, similar proportions were reported (5.5–9.8%). According to ECDC data, catheter-associated infections typically account for around 10% of all HAI, placing the present findings within the expected international range.

Bloodstream infections were less frequent but of considerable clinical significance. In the studied hospital, their average share was approximately 9%, with an increase until 2017 followed by a subsequent decline. ECDC data (2016–2017) indicate that bloodstream infections account for approximately 10% of all HAI in Europe, confirming full comparability of the present results with international observations.

Rarer forms of HAI—such as central nervous system infections, skin infections, and neonatal-specific infections—occurred infrequently but are associated with high clinical impact. These infections are often considered sentinel events, requiring detailed individual analysis, as they typically affect highly vulnerable patient groups. Although they represent a small proportion of all HAI, such infections are frequently associated with severe outcomes, long-term disability, or permanent impairment, underscoring their disproportionate clinical and public health importance.

## **2.5. Analysis the impact of the COVID – 19 pandemic on the incidence and structure of HAI**

### **Pre-pandemic period (2018–2019)**

In the years preceding the COVID-19 pandemic, hospital activity was relatively stable, with the number of discharged patients exceeding 65,000 annually and reaching a maximum of 69,714 in 2019. The proportion of patients receiving antibiotic therapy ranged between 34.9% and 36.3%, while the incidence of HAI remained within the range of 0.54–0.63%. These indicators reflect a balanced system of antibiotic use and infection control and can be considered a reference baseline for comparison with subsequent periods.

During this period, the etiological structure of HAI was characterized by a stable dominance of multidrug-resistant Gram-negative pathogens. *A. baumannii* occupied a leading position (29.2% in 2017 and 22.9% in 2019), while *K. pneumoniae* and *P. aeruginosa*, together with *A. baumannii*, formed the core Gram-negative triad. *E. coli* and *Enterobacter cloacae* also made a substantial contribution, highlighting the important role of Enterobacterales. Among Gram-positive pathogens, *Enterococcus faecalis* and *S. aureus* maintained a supportive but consistent presence. *Candida* spp. Accounted for a limited proportion (4.5–6.4%), while *C. difficile* remained a marginal etiological agent. This period outlines the “baseline” etiological profile of HAI in the absence of pandemic-related influences. In 2018, *K. pneumoniae* temporarily became the leading pathogen (21.6%), followed by *A. baumannii* (18.2%) and *P. aeruginosa* (19.2%). In 2019, leadership reverted to *A. baumannii* (22.9%), while *Candida* spp. Showed a marked increase to 16.0%, suggesting a growing role of fungal infections in hospital pathology. *E. coli* and *Enterobacter cloacae* maintained stable participation, and *Enterococcus faecalis* remained the predominant Gram-positive pathogen. Clinically, the structure of HAI in 2018 was dominated by lower respiratory tract infections (28.0%), followed by surgical site infections (SSI) (20.0%) and bloodstream infections (13.7%), often associated with catheter use. This profile reflects the classical HAI distribution in large tertiary hospitals with intensive surgical and critical care activity. In 2019, a rearrangement was observed: pneumonia became the leading clinical form (22.1%), while gastrointestinal infections increased to 15.2%, likely associated with a higher incidence of *C. difficile* infection and antibiotic-related complications. Overall, the pre-pandemic period was characterized by relative balance and diversity in the clinical HAI profile.

### **Pandemic period (2020–2021)**

With the onset of the COVID-19 pandemic, a sharp decline in the number of discharged patients was observed—60,336 in 2020 and 59,277 in 2021—representing a reduction of approximately 13–15% compared to the 2019 peak. This decrease was directly related to restrictions on elective hospitalizations

and the reallocation of resources to COVID-19 care. At the same time, the proportion of patients receiving antibiotic therapy increased markedly, reaching a maximum of 47.1% in 2021, indicative of widespread empirical antibiotic use in COVID-19 patients. The incidence of HAI also peaked in 2021 (1.09%), nearly doubling pre-pandemic levels, reflecting increased pressure on intensive care units and a high prevalence of invasive procedures. A clear shift in the etiological profile accompanied the pandemic. *A. baumannii* reached its highest proportions during the study period (23.7% in 2020 and 28.6% in 2021), associated with frequent use of invasive devices and prolonged mechanical ventilation in COVID-19 patients. Simultaneously, *Candida* spp. increased substantially, reaching 20.9% in 2021, reflecting the high incidence of fungal infections under conditions of immunosuppression and intensive antibiotic exposure. *E. coli* and *P. aeruginosa* retained clinical significance, while Gram-positive pathogens continued to have a lower relative share. Overall, this period was marked by the dominance of multidrug-resistant Gram-negative pathogens and a pronounced rise in fungal infections, posing major challenges to antibiotic stewardship. The pandemic also profoundly altered the clinical structure of HAI. In 2020, SSI (29.2%) and pneumonia (24.2%) were the leading clinical forms. The high proportion of surgical infections can be explained by the concentration of hospital activity in emergency and oncological surgery, while the increase in pneumonia reflects the heavy burden on intensive care units. In 2021, the clinical profile changed dramatically: pneumonia accounted for 45.1% of all HAI, assuming an unprecedented dominant role. This was a direct consequence of frequent and prolonged mechanical ventilation in COVID-19 patients. Although SSI remained significant (24.4%), they lost their leading position, while other categories—bloodstream infections, urinary tract infections, and catheter-associated infections—declined in relative terms. Thus, the pandemic period was characterized by a concentration of infectious pathology in the respiratory system and a marked deviation from the traditional HAI structure.

### **Post-pandemic period (2022)**

In 2022, a gradual recovery of hospital activity was observed. The number of discharged patients increased to 60,307, approaching the values of the previous year but remaining below pre-pandemic levels. The proportion of patients receiving antibiotic therapy decreased to 38.7%, and the incidence of HAI declined to 0.88%. Despite this trend toward normalization, infection rates remained higher than in the pre-pandemic period, suggesting persistent effects of pandemic-related pressure on hospital microbiological ecology and antimicrobial resistance. In the post-pandemic period, partial rebalancing of the etiological structure was observed, with some restoration of the pre-pandemic profile. *E. coli* emerged as the leading pathogen (21.5%), while the proportion of *A. baumannii* declined to 16.4%. *K. pneumoniae* and *P. aeruginosa* retained their importance, and *Candida* spp. decreased to 10.7%. This distribution suggests gradual normalization of hospital microbiological ecology, although multidrug-resistant pathogens continued to occupy a central position. Clinically, the HAI structure in 2022 showed signs of normalization. SSI again ranked first (29.4%), followed by pneumonia (26.9%). Gastrointestinal infections regained importance (9.2%), while bloodstream infections, urinary tract infections, and catheter-associated infections clustered around similar proportions (6–7%). Although pneumonia remained relatively frequent, its extreme dominance observed in 2021 was reduced, indicating a transition toward a more balanced clinical profile.

### **Discussion**

The COVID-19 pandemic had an unprecedented impact on healthcare systems and profoundly influenced the dynamics of antibiotic use and HAI. In the pre-pandemic period (2018–2019) at University Hospital “St. Marina” – Varna, antibiotic use ranged from 34.9% to 36.3%, and HAI incidence from 0.54% to 0.63%. These values were comparable to national indicators and higher than regional levels, yet substantially lower than those reported in European point-prevalence surveys, where HAI prevalence averages approximately 5.5%. Such discrepancies reflect differences in methodology, surveillance sensitivity, and case definitions. During the pandemic (2020–2021), a sharp increase in antibiotic exposure and HAI incidence was observed, consistent with national, regional, and international data describing widespread empirical antibiotic use and increased infection risk associated with invasive procedures in COVID-19 patients. In the post-pandemic period (2022), partial normalization occurred, but antibiotic use and HAI incidence remained above baseline levels. Overall, comparison of data from University Hospital “St. Marina” – Varna with regional, national, and international sources demonstrates highly comparable dynamics: relative stability before the pandemic, significant deterioration during 2020–2021, and partial recovery in 2022. Despite lower absolute values compared with European averages, these findings confirm a global pattern—pandemic-driven increases in antibiotic use and HAI, followed by delayed recovery. This underscores the need for sustainable antibiotic stewardship programs, continuous microbiological surveillance, and systematic implementation of preventive bundles targeting device-associated infections, accompanied by rigorous monitoring of compliance.

## 2.6 . Correlation analysis between types of infections (clinical structure) and etiological agents

To investigate the relationships between different HAI localizations and their etiological agents, a correlation analysis was performed. The correlation coefficient (r) was used to assess the strength and direction of the associations, while the p-value indicated their statistical significance. A level of statistical significance of  $p < 0.05$  was adopted (Table 11).

Table 11. Correlation between localization of infection and etiological agents

No.	Dependent variable	Factor variable	Correlation coefficient (r)	Statistical significance (p)
1.	Bone and joint infections	<i>Enterococcus spp.</i>	0.938	0.000
2.	Bone and joint infections	<i>E. coli</i>	0.809	0.005
3.	ENT	<i>E. coli</i>	0.641	0.046
4.	ENT	<i>S. aureus</i>	0.643	0.045
5.	Neonatal-specific infections	<i>K. pneumoniae</i>	0.656	0.039
6.	Pneumonia	<i>A. baumannii</i>	0.685	0.029
7.	Pneumonia	<i>E. coli</i>	0.597	0.048
8.	Pneumonia	<i>Candida spp.</i>	0.745	0.013
9.	SSI	<i>A. baumannii</i>	0.627	0.042
10.	SSI	<i>E. cloacae</i>	0.737	0.016
11.	SSI	<i>Enterococcus spp.</i>	0.704	0.023

12.	SSI	<i>E. coli</i>	0.900	0.000
13.	SSI	<i>Candida spp.</i>	0.631	0.005

The table above presents only the statistically significant correlation coefficients derived from the validated models included in the dissertation. Among the etiological variables, *E.coli* stands out as a key factor, demonstrating a very strong association with bone and joint infections, SSI, ENT infections, and pneumonia. The *Enterococcus spp.* Also emerges as a prominent factor variable, showing a very strong correlation with bone and joint infections ( $r = 0.938$ ) and a strong association with SSI ( $r = 0.704$ ). Neonatal-specific infections demonstrated a statistically significant correlation with *K. pneumoniae* ( $r = 0.656$ ;  $p = 0.039$ ), confirming the key role of this pathogen in neonatal pathology. Pneumonia was significantly associated with *A. baumannii* ( $r = 0.685$ ;  $p = 0.029$ ), and also showed meaningful relationships with *E. coli* ( $r = 0.597$ ;  $p = 0.048$ ) and *Candida spp.* ( $r = 0.745$ ;  $p = 0.013$ ). SSI exhibited the richest correlation profile among all clinical forms. The strongest association was observed with *Escherichia coli* ( $r = 0.900$ ;  $p < 0.001$ ). In addition, statistically significant correlations were identified with *A. baumannii*, *Enterobacter cloacae*, *Enterococcus spp.* And *Candida spp.*, reflecting the etiological diversity and clinical complexity of this infection group.

## Discussion

The results of the correlation analysis reveal clear and clinically meaningful relationships between specific HAI localizations and their etiological agents. The very strong correlation between bone and joint infections and *Enterococcus spp.* ( $r = 0.938$ ;  $p < 0.001$ ), as well as the strong association with *Escherichia coli* ( $r = 0.809$ ;  $p = 0.005$ ), is consistent with published data identifying enterococci as significant pathogens in orthopedic and prosthetic infections, with substantial implications for treatment outcomes [Martin A. et al., 2023]. ENT infections showed significant associations with *Escherichia coli* ( $r = 0.641$ ;  $p = 0.046$ ) and *Staphylococcus aureus* ( $r = 0.643$ ;  $p = 0.045$ ). While *S. aureus* is a well-established causative agent in such infections, the association with *E. coli* likely reflects local microbiological characteristics and specific hospital environmental factors. Neonatal infections correlated significantly with *Klebsiella pneumoniae* ( $r = 0.656$ ;  $p = 0.039$ ), supporting evidence from other studies identifying this microorganism as a leading cause of neonatal infections and outbreaks in neonatal intensive care units [Hu Y. et al., 2023].

Pneumonia demonstrated significant associations with *A. baumannii*, *E. coli*, and *Candida spp.*, pathogens frequently reported in mechanically ventilated patients and intensive care settings. The role of *A. baumannii* and *Candida spp.* In ventilator-associated pneumonia is well documented, particularly in patients with prolonged hospitalization and extensive antimicrobial exposure [Luchian N. et al., 2025].

SSI showed the most complex etiological pattern, with *E. coli* demonstrating the strongest correlation ( $r = 0.900$ ;  $p < 0.001$ ). Additional associations with multidrug-resistant Gram-negative bacteria and opportunistic pathogens highlight the polymicrobial nature of surgical infections. Similar findings are reported in international studies, where *E. coli* and resistant Gram-negative organisms play a dominant role in SSI etiology [Owens CD et al., 2008]. Overall, the findings align with international epidemiological trends and underscore the importance of continuous microbiological surveillance, strict antibiotic

stewardship, and targeted prevention strategies tailored to infection localization and dominant etiological agents.

## **Conclusion on the research hypotheses**

Based on the analysis of the collected data and the applied statistical methods, the following conclusions can be drawn regarding the research hypotheses:

### **1. Incidence of HAI and antibiotic use (2013–2022)**

The dynamic analysis demonstrated a clear increasing trend in both the incidence of hospital-acquired infections (HAI) and overall antibiotic use over the study period. This finding confirms the first research hypothesis.

### **2. Etiological structure of HAI**

The results of microbiological surveillance revealed a clear dominance of Gram-negative microorganisms in the etiological structure of HAI, most notably *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*. These findings confirm the hypothesis and are consistent with European and national epidemiological data.

### **3. Clinical structure of HAI**

The analysis of nosological forms showed that pneumonia, urinary tract infections, and surgical site infections (SSI) occupy the leading positions in the clinical structure of HAI. The obtained results confirm the third hypothesis.

### **4. Impact of the COVID-19 pandemic**

The comparison between the pre-pandemic period (2013–2019) and the pandemic period (2020–2022) demonstrated a statistically significant increase in the number of registered HAI during the COVID-19 pandemic. This confirms the fourth research hypothesis.

### **5. Incidence of in-hospital outbreaks in high-risk departments**

The data indicate a higher incidence of in-hospital outbreaks in departments caring for patients with compromised immune status, particularly intensive care and oncohematology units. This finding confirms the hypothesis and highlights the need for enhanced prevention and control measures in these high-risk settings.

### **6. Effectiveness of the HAI surveillance and control system**

The analysis of organizational documentation and the activities of the ICT confirms that the presence of a well-structured team, integrated across all clinical units and actively supported by

hospital leadership, is a key prerequisite for effective HAI surveillance and control. This hypothesis is confirmed.

In conclusion, all six research hypotheses formulated in the dissertation were confirmed through empirical data, statistical analysis, and documentary review. These findings emphasize the importance of systematic epidemiological surveillance, rational antibiotic use, and sustained organizational support for the effective prevention and control of hospital-acquired infections.

### III. CONCLUSIONS, RECOMMENDATIONS AND CONTRIBUTIONS

#### 1. Conclusions

**1.1.** The system for prevention and control of HAI at University Hospital “St. Marina” is structured in accordance with international standards (WHO, ECDC, CDC) and demonstrates effective coordination between the ICT, clinical units, the microbiology laboratory and hospital management. The main challenges remain insufficient staffing and the lack of an integrated electronic surveillance system that would enable automated data collection, analysis and visualization, as well as national benchmarking and evaluation of the effectiveness of control measures;

**1.2.** The dynamics of hospitalizations, HAI incidence and antibiotic use at University Hospital “St. Marina” – Varna reflect the main trends in hospital practice during the period 2013–2022, characterized by relative stability until 2019, followed by a sharp increase in infectious morbidity and antibiotic exposure during the COVID-19 pandemic and partial normalization thereafter. Despite the demonstrated adaptability of the system, the indicators have not returned to pre-pandemic levels, confirming the continued pressure on the HAI control system and the need for sustainable measures for rational antibiotic use and more effective epidemiological surveillance;

**1.3.** Antibiotic therapy covers a substantial proportion of hospitalized patients (34–47%), exceeding the European average but corresponding to national trends. During the pandemic, a peak was observed (47.1% in 2021), consistent with extensive empirical antibiotic prescribing for COVID-19. Even after partial normalization in 2022, antibiotic use remains higher than baseline levels, suggesting the establishment of a new, persistently elevated level of antibiotic consumption and a potential increase in antimicrobial resistance;

**1.4.** The incidence of HAI at University Hospital “St. Marina” – Varna (0.5–1.09%) remains significantly lower than average European levels, while being comparable to national and higher than regional values. The pandemic exerted a dual effect: an apparent decline in 2020, likely related to resource diversion and reduced surveillance sensitivity, followed by a peak in 2021 parallel to increased antibiotic use. This pattern is consistent with international evidence of compromised HAI control under conditions of system overload. HAI incidence varies according to the risk profile of clinical units, being lowest in low-risk wards, fluctuating in medium-risk units and highest in high-risk settings, particularly intensive care units, which are established as the main epicenters of infection and a priority for epidemiological control;

**1.5.** The analysis of DDD activities at University Hospital “St. Marina” – Varna for the period 2013–2022 demonstrates a clear upward trend in both volume and frequency, especially after 2019, when disinfection became a key tool for limiting the spread of SARS-CoV-2 during the COVID-19 pandemic. The parallel increase in disinsection and deratization, albeit to a lesser extent, reflects systematic efforts to control environmental factors contributing to HAI emergence and transmission. These local trends correspond to regional and European data on increased disinfectant consumption and emphasize the importance of DDD activities as a core component of HAI prevention and control;

**1.6.** The multi-component approach to disinfection control, including surface swabs, air sampling, ATP testing and the Kelsey method, provides a reliable assessment of disinfection effectiveness and contributes to robust HAI prevention. The average proportion of positive samples (12.3%) reported for the period 2013–2022 is comparable to European data (5–20%) and confirms the effectiveness of the applied disinfection regimes. The increased values observed during the COVID-19 pandemic (24.7%) reflect selective monitoring of high-risk objects;

**1.7.** Epidemic outbreaks of HAI at University Hospital “St. Marina” – Varna during 2013–2022 were concentrated predominantly in intensive care and hematology units, where the specific patient population determines a high infection risk. Respiratory infections and catheter-associated bloodstream infections predominated, mainly caused by multidrug-resistant Gram-negative microorganisms, outlining the key epidemiological risk factors such as critical illness, immunosuppression and invasive devices. Observed delays in early detection highlight the need to improve surveillance sensitivity and introduce early warning alarm systems for timely outbreak containment;

**1.8.** The etiological structure of HAI at University Hospital “St. Marina” – Varna during 2013–2022 was consistently dominated by Gram-negative microorganisms, accounting for more than 80% of all isolates. *A. baumannii* emerged as the leading pathogen, particularly in intensive care units and during the COVID-19 pandemic, followed by *K. pneumoniae*, *E. coli* and *P. aeruginosa*, which in certain years displaced the leading position. Among Gram-positive pathogens, *Enterococcus spp.* and *S. aureus* were most significant, while *Candida spp.* showed a marked increase during the pandemic period. Although *C. difficile* accounted for a small proportion, its clinical significance remains considerable;

**1.9.** The clinical structure of HAI at University Hospital “St. Marina” – Varna is characterized by the dominance of respiratory infections, with a pronounced peak of pneumonia in 2021 associated with the COVID-19 pandemic and increased use of mechanical ventilation. Surgical site infections maintain a consistently high proportion, exceeding international averages and outlining a persistent epidemiological challenge. Urinary tract infections, catheter-associated infections and bloodstream infections demonstrate relative stability and alignment with European trends. Overall dynamics mirror global patterns but with more pronounced peaks and variability, typical of a university hospital with a high concentration of critically ill patients;

**1.10.** Correlation analysis revealed specific associations between HAI localization and etiological agents, outlining characteristic microbiological profiles for different clinical forms. These findings have substantial practical significance for optimizing empirical antibiotic therapy, improving HAI control strategies and identifying high-risk units.

## **2. Recommendations**

### **2.1. Improvement of HAI surveillance through integrated electronic systems**

It is recommended to enhance HAI surveillance by implementing a fully integrated electronic system for registration, analysis and monitoring in order to reduce underreporting. The development of an electronic register for automated monitoring of HAI and antibiotic exposure, integrated with electronic

health records, microbiology laboratory data and the hospital pharmacy system, is strongly advised. The system should include predefined alarm thresholds to automatically signal abrupt increases in HAI incidence in specific wards, detection of identical multidrug-resistant strains, unusually high infection rates and excessive antibiotic use.

## **2.2. Optimization of antibiotic policy**

The existing antibiotic stewardship program should be further strengthened through electronic monitoring of antibiotic use and resistance patterns and its full integration into routine clinical practice.

## **2.3. Strengthening ICT staffing**

Sustainable expansion of the ICT to meet WHO-recommended staffing levels (at least one infection control specialist per 250 beds) is essential for improving surveillance sensitivity, staff training and timely outbreak response.

## **2.4. Integration of modern environmental monitoring methods**

Routine microbiological environmental monitoring should be supplemented with modern diagnostic techniques such as PCR and MALDI-TOF, as well as the reintroduction of systematic ATP testing for rapid assessment of surface cleanliness.

## **2.5. Sustainable development of DDD activities**

The intensified DDD activities implemented during the pandemic should be institutionalized as a permanent standard of hospital safety through continued investment in modern equipment and specialized personnel.

## **2.6. Promotion of non-invasive diagnostics and therapy**

Priority should be given to non-invasive diagnostic and therapeutic approaches where feasible, reducing the need for invasive procedures and associated infection risks.

## **2.7. Telemedicine and remote monitoring**

The expansion of telemedicine and remote patient monitoring should be encouraged to reduce unnecessary hospitalizations and invasive interventions.

## **2.8. Use of antimicrobial materials and surfaces**

The introduction of antimicrobial materials, such as copper or silver-coated surfaces in high-touch areas, is recommended to reduce environmental microbial burden.

## **2.9. Sustainable implementation of care bundles**

Strict and complete implementation of evidence-based care bundles should be ensured, particularly in high-risk units, supported by regular staff training, standardized protocols and adequate resources.

### **2.10. Continuous staff training and smart hygiene technologies**

Ongoing training programs focusing on hand hygiene and infection prevention should be maintained. The introduction of smart disinfectant dispensers integrated with staff identification systems is recommended to enable personalized monitoring and feedback.

## **3. Contributions**

### **3.1. Scientific contributions**

- ✓ A comprehensive ten-year epidemiological analysis (2013–2022) of hospital-acquired infections, antibiotic use and infection control practices was conducted in a university hospital of national importance, representing the largest study of this type in Bulgaria.
- ✓ The relationship between the COVID-19 pandemic, increased antibiotic exposure and changes in the incidence and structure of HAI was systematically analyzed and interpreted in comparison with international trends.
- ✓ Distinct stages of change in the etiological and clinical structure of HAI were identified, demonstrating a persistent dominance of multidrug-resistant Gram-negative pathogens and a marked increase in fungal infections during the pandemic period.
- ✓ A comparative analysis with European indicators and ECDC data was performed, confirming the reliability of the results and highlighting specific characteristics of hospital microbiological ecology in Bulgaria.
- ✓ For the first time in Bulgaria, a systematic correlation analysis was carried out, establishing statistically significant associations between specific clinical localizations of HAI and their etiological agents.

### **3.2. Practical contributions**

- ✓ High-risk clinical structures (intensive care units, hemodialysis and hematology clinics) were identified as priority targets for focused epidemiological surveillance and preventive interventions due to the highest concentration of HAI and multidrug-resistant microorganisms.
- ✓ The effectiveness of a multi-component approach to hospital environment disinfection control (surface swabs, air sampling, ATP testing and the Kelsey method) was demonstrated and validated as a practical model applicable in other healthcare facilities.
- ✓ An integrated organizational model for HAI surveillance and control was developed, combining epidemiological monitoring, digital technologies, antimicrobial stewardship, staff training and environmental control into a unified framework.
- ✓ The potential implementation of intelligent disinfectant dispensers integrated with staff identification systems was proposed as an innovative tool for personalized monitoring and improvement of hand hygiene compliance.

- ✓ The identified microbiological profiles associated with specific clinical forms of HAI provide practical guidance for optimizing empirical antibiotic therapy and targeted prophylaxis in hospital practice.

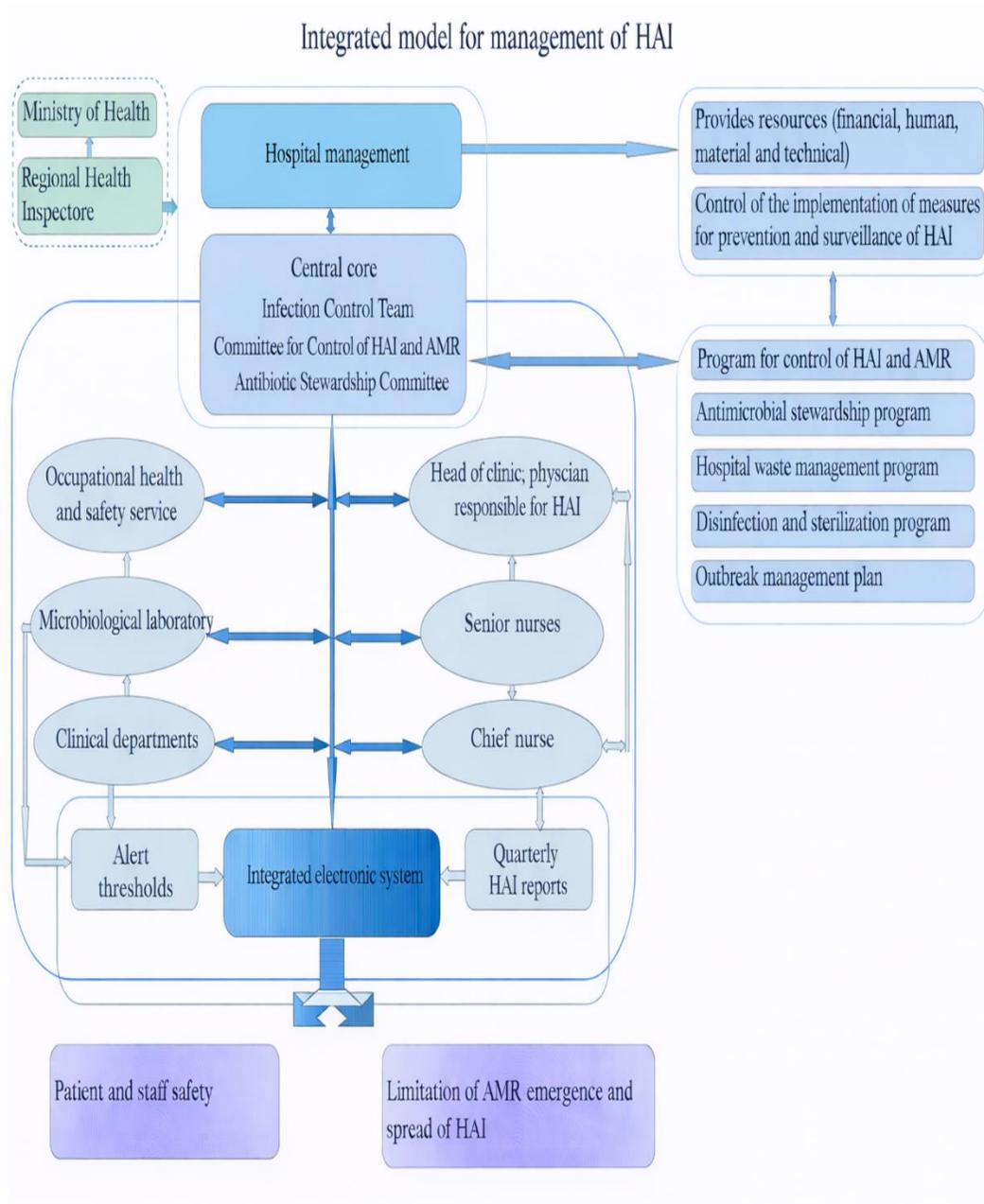
## CONCLUSION

The research conducted at University Hospital “St. Marina” – Varna for the period 2013–2022 provides a comprehensive assessment of the dynamics of hospital-acquired infections, antibiotic use and the system for their prevention and control in one of the leading university hospitals in Bulgaria. The analysis identifies clearly defined periods influenced both by internal organizational factors and by external global events, including the COVID-19 pandemic. Data on discharged patients, antibiotic consumption and HAI incidence demonstrate significant fluctuations, reflecting both the adaptability of the system and its vulnerability under conditions of increased workload and system stress. Comparison with international data from WHO, ECDC and CDC confirms that the observed trends follow global patterns, albeit with greater variability and more pronounced peaks, characteristic of highly specialized tertiary-care hospitals.

The system for surveillance and control of HAI at University Hospital “St. Marina” – Varna is structured in accordance with international standards and incorporates all essential components, including ICT coordination, microbiological surveillance, antimicrobial stewardship and control of the hospital environment. Established practices demonstrate sustainability and openness to modernization, as evidenced by the implementation of programs such as ENCOMPASS, the Gamma Code Master information system and advanced methods for disinfection monitoring. Nevertheless, ICT staffing levels remain below WHO recommendations, and the absence of a fully integrated electronic surveillance system for HAI and antimicrobial resistance represents a significant limitation. The etiological and clinical profiles of HAI highlight the dominant role of multidrug-resistant Gram-negative microorganisms, as well as infections associated with invasive procedures and intensive care. The increased incidence of fungal infections and the persistently high share of surgical site infections represent additional challenges that require a systematic and intervention-oriented approach. Moreover, the high level of antibiotic use, particularly in low-risk clinical units, indicates an imbalance between documented infection rates and therapeutic practices, underscoring the need for sustainable and effective antimicrobial stewardship programs.

The findings of this study support the need for targeted actions in several key areas: digitalization of surveillance systems and implementation of smart technologies (including smart disinfectant dispensers linked to staff identification), strengthening of human resource capacity, continuation and expansion of staff training programs, and integration of sustainable, multifaceted strategies for antimicrobial resistance control. Implementation of these measures would enhance the effectiveness of infection prevention and control, provide better protection for patients and healthcare personnel, and contribute to the establishment of University Hospital “St. Marina” – Varna as a leading model of good practice in hospital epidemiology, not only at the national level but also in an international context.

## ANNEX



## PUBLICATIONS RELATED TO THE TOPIC OF THE DISSERTATION

- ✓ **Ilieva, D.** , Vankova , D., Paunov , Ts., The COVID-crisis and the consumption of alcohol-based disinfectants — data and key measures in a critical period. *Social Medicine*. 2022;1:8–12. Available from: <https://journals.mu-varna.bg/index.php/sm/article/view/9385>.
- ✓ **Ilieva, D.** , Vankova , D., Paunov , Ts., Consumption of alcohol-based hand rubs – 2018-2022 epidemiological trends and empirical lessons from Bulgaria, *Journal of IMAB* , 2023, 29 (2-15)

DOI: [10.5272/jimab.2023v29Supplement1](https://doi.org/10.5272/jimab.2023v29Supplement1)