An-Najah National University

Faculty of Graduate Studies

TRENDS IN ANTIBIOTICS RESISTANCE OF BACTERIAL PATHOGENS IN A TERTIARY CARE HOSPITAL: A RETROSPECTIVE STUDY FROM PALESTINE

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Dedication

To my wonderful family (father, mother, brothers and sisters).

To my new family

My wife and God's new gifts, "Sameer and Hana"

To anyone with a life goal

Every student, researcher, and teacher

Acknowledgments

I am sincerely grateful to Allah Subhanah Watalla for all of his blessings and grace, which made this effort possible.

My sincere gratitude goes to my dear family for their encouragement and support during my education.

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Finally, I'd like to thank everyone at An-Najah National University Hospital, especially those in the laboratory, for their contributions to my study.

Declaration

I, the undersigned, declare that I submitted the thesis entitled:

TRENDS IN ANTIBIOTICS RESISTANCE OF BACTERIAL PATHOGENS IN A TERTIARY CARE HOSPITAL: A RETROSPECTIVE STUDY FROM PALESTINE

I declare that the work provided in this thesis, unless otherwise referenced, is the researcher's own work, and has not been submitted elsewhere for any other degree or qualification.

Student's Name: Ayman Dawoud

Signature:

Date: 22.6.2023

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TRENDS IN ANTIBIOTICS RESISTANCE OF BACTERIAL PATHOGENS IN A TERTIARY CARE HOSPITAL: A RETROSPECTIVE STUDY FROM PALESTINE

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Abstract

Antibiotic resistance has become a major public health problem worldwide, resulting in more severe infections and longer hospital stays. The goal of this study is to detect changes in resistance rates to first-line and last-resort antibiotics in Nablus, Palestine.

A retrospective assessment of data gathered from a tertiary care hospital's microbiology department between January 2018 and December 2021. The resistance rate of the bacterial isolates was the outcome of interest. Microsoft Excel 2019 was used to depict trends from 2018 to 2021, and statistical analysis was performed using the Statistical Package for Social Science (SPSS) version 26.

A total of 4659 isolates, of six highly virulent and antibiotic resistant bacterial pathogens were included in our study. The most common source for these organisms was urine (34.6%) followed by swabs from different parts of the body (30.7%), (13%) from respiratory samples, (10.1%) from blood culture samples, (7.6%) from body fluid samples, and (4%) from tissue samples. The most commonly isolated organism of the ESKAPE family was *Escherichia coli* (27%), followed by *Klebsiella pneumoniae* (15.5%), *Enterococcus faecalis* (14.6%), *P. aeruginosa* (13.0%), *S. aureus* (10.6%), *Enterococcus faecium* (10.2%), and *Acinetobacter baumannii* (9.0%)

Over the four years period of study, ampicillin and penicillin showed the highest rates of resistance ranging from 55-75. Resistance of *E. coli* to amoxicillin/clavulanic acid decreased significantly while carbapenem-resistant *E. coli* and *K. pneumoniae* increased. For *K. pneumoniae* there is a significant increase in resistance to trimethoprim-sulfamethoxazole and a significant decrease in resistance to norfloxacin. *Enterococcus*

Spp. showed an increase to last-resort antibiotics i.e., linezolid and vancomycin. *P. aeruginosa* demonstrated a significant decrease in resistance.

Our study showed that antibiotic resistance is a major concern in Palestine because our country has limited resources. Policy-makers in the country should take the proper measures to slow down the development of resistance. Among the steps that should be taken into consideration is instituting antibiotic stewardships in all hospitals, putting forward legislation to stop dispensing antibiotics without prescriptions and increasing the public awareness of antibiotic resistance.

Keywords: Antimicrobial Resistance; First-Line; Last-Resort Antibiotics; Nablus; Palestine; Stewardship Programs; Surveillance.

Chapter One

Introduction and Literature Review

1.1 Introduction

Bacterial infections that do not respond to antibiotics are an increasing cause for concern in recent years. One of the significant causes behind this trend is antibiotic misuse and overuse, which has led to the emergence of resistant bacterial strains. Evidence from several studies shows a worrisome level of resistance among various bacterial illnesses. (1)

Antibiotic resistance poses a significant challenge in Palestine as well as in other countries, with numerous bacterial pathogens demonstrating high levels of resistance. The risk for the emergence and spread of antibiotic-resistant bacteria is particularly high in tertiary care hospitals because choosing a successful therapy becomes much more difficult due to their various patterns of resistance. In addition to the frequent antibiotic use and the concentration of severely ill patients. Several studies have shown this concerning trend. (2–4)

Infectious diseases were a major cause of death in the past. However, the discovery of antibiotics during the last 50 years has been a remarkable achievement in combating infections. In particular, penicillin, discovered in the late 1920s, has saved countless lives by curing previously fatal illnesses. (5) Furthermore, antibiotics have proven to be effective in preventing surgical site infections when used prophylactically. (6) Despite their success stories and millions of lives being spared globally from bacterial harms, the antibiotic resistance is becoming increasingly common with time. (7) This emerging crisis could render these miracle drugs ineffective against bacterial infections posing an alarming threat to humanity's health security. (8)

Bacteria's immunity towards antibiotics can arise in two ways innate and acquired. (9) Innate resistance is found only in certain strains of bacterial species and is natural to them. (10) In contrast, acquired resistance occurs when bacteria become less vulnerable to antibiotics that were previously effective against them because of overusing such drugs. This type of resistance affects many different bacterial species. (7)

In 1928, Alexander Fleming found penicillin, the primary anti-microbial agent. Since that point, other anti-microbials such as quinolones, tetracyclines, macrolides, and sulfonamides have been created. These anti-microbials have all been utilized to treat bacterial sicknesses like pneumonia, throat infection, and urinary tract diseases. Since of their wide utilization in therapeutic areas, anti-microbials have spared the lives of incalculable individuals. Anti-microbial mishandle has driven microbes to evolve resistance, coming about within the rise of antibiotic-resistant superbugs. Misuse of antibiotics could be the main reason that may contribute to the increase in antibiotic resistance. The misuse of antibiotics can occur in the form of self-medication, insufficient dosage, missing doses, reusing extra medication from a previous prescription, and using antibiotics based on family and friend recipes, and personal experiences. Additionally, a contributing factor in the emergence of antibiotic resistance is healthcare professionals' noncompliance with infection control procedures and professionals nonscientific based prescription. (11) As a result, it is basic to utilize anti-microbials cautiously and to follow to doctor's proposals.

Various antimicrobial agents act by interfering with cell wall synthesis, plasma membrane integrity, nucleic acid synthesis, ribosomal function, and folate synthesis. (12) Bacterial cell wall synthesis is hindered by beta-lactam anti-microbials. Penicillins, cephalosporins, monobactams, and carbapenems are all members of this group. B-lactam anti-microbials incorporate amoxicillin, ampicillin, and cefazolin. Aminoglycosides antibiotics anticipate microorganisms from creating proteins. Off note, among aminoglycoside antibiotics; streptomycin, gentamicin, and tobramycin, are frequently managed intramuscularly or intravenously. For specific bacterial infections, supplementary antibiotic varieties are utilized alongside the primary types. Antibiotics serve various purposes, including prophylaxis against bacterial infections, empirical treatment before final culture and susceptibility results are obtained, and definitive treatment following microbiology findings. To select the appropriate antibiotic, different factors must be considered. A few variables are taken into consideration when selecting an anti-microbial: patient's age, therapeutic history, pharmacokinetic, fetched, mode of activity, recurrence of dosing, and course of organization. (13)

Antibiotic resistance is a growing concern worldwide. The development of bacterial resistance is influenced by various factors such as the extensive use of antibiotics in clinical practice and agriculture activities by utilizing antimicrobials as growth promoters in animal breeding as well as to prevent (prophylaxis in high risk animals) and treat animal illnesses. Additionally, they are employed as additives in plant agriculture (fruits, vegetables, orchids, etc.), particularly when applying antibiotic-containing fertilizers to fields and spraying fruit trees to prevent disease. (14) Bacteria have evolved diverse mechanisms to resist antibiotics including weakened membrane barriers, destruction by enzymes, and changes in target molecules. (15,16) Mechanisms of resistance include reduced permeability due to the development of efflux pumps or actual alteration in the cell wall itself which prevents antibiotics from entering the cell. (17) Antibiotics can lose their effectiveness due to various enzymes produced by bacteria. For instance, beta lactam antibiotics can be inactivated by the production of beta lactamases while quinolone and aminoglycoside antibiotics can be rendered ineffective through the action of quinolone-modifying and aminoglycoside-modifying enzymes respectively. (18) Some bacteria may also alter their cell membrane proteins or DNA gyrase to avoid antibiotic binding. Additionally, some produce biofilms that protect against antibiotics. (19)

To overcome resistance mechanisms, scientists are exploring a range of approaches. These include developing new antibiotics, targeting resistance pathways with inhibitors and creating vaccines. The goal is to find effective solutions that can combat the rise of resistant infections. (20)

Antimicrobial resistance occurs naturally. However, it can worsen due to misuse of antimicrobial medications, the absence of proper regulation in their use, lack of laboratory facilities, and inadequate surveillance to track the spread of pathogens. In addition, issues such as poor medicines and inefficiency in infection prevention and control methods also contribute towards this problem. (21)

To effectively combat antibiotic resistance and ease the financial burden on both patients and authorities, it's crucial to determine its prevalence in a given area. A reliable antibiotic resistance survey that can be regularly conducted is needed for an accurate understanding of the situation. (22)

The Center for Disease Dynamics, Economics, and Policy (CDDEP) in the United States has reported a concerning increase in bacterial resistance to first-line antibiotics i.e., the initial, or first antibiotics recommended for a disease or illness. (23) This raises significant threats for fatal illnesses worldwide as bacteria resistant to specific antibiotics can spread globally depending on their usage in different countries. To address this issue, both the US Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) have taken measures such as producing lists of antibiotic-resistant pathogens based on priorities. The CDC list was updated in 2019 while the WHO developed theirs back in 2017. These organisms, which include *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Enterobacteriaceae* (*Klebsiella Spp*. and *E. coli*), are the most threatening and have shown great resistance to antibiotics such as carbapenems and third-generation cephalosporins, (24) they were categorized into threat tiers of urgent, serious, and concerning depending on the harm they represent to human health and the urgency of the need for new and efficient methods of treatment and prevention.(25)

Researchers worldwide have conducted extensive studies in this field, with the retrospective approach being most commonly used. Consequently, the global community recognized antimicrobial resistance (AMR) as a serious public health concern and endorsed the Worldwide Action Plan on AMR during the 2017 World Health Assembly. They also stated that antimicrobial abuse and misuse is a major contributor to the spread of resistance, emphasizing the need of optimizing antimicrobial usage. (26)

Globally documented research has established that bacterial disorders such as urinary tract infections, sepsis, sexually transmitted infections, and various forms of diarrhea are becoming increasingly resistant to traditional antibiotic therapies. This concerning phenomenon suggests that effective antibiotics may soon become inaccessible. The Global Antimicrobial Resistance and Use Surveillance System (GLASS) report provides additional insights into the topic with recorded ciprofloxacin resistance rates varying between 8.4% to 92.9% in *E. coli* and from 4.1% to 79.4% in *K. pneumoniae* populations. (27)

Carbapenem-resistant *Enterobacteriaceae* infections caused by bacteria such as *E. coli* and *Klebsiella* are potentially life-threatening, with colistin being the only available treatment option at present. However, there have been instances of colistin resistant bacteria documented in several countries and regions. Such resistance poses a challenge as appropriate antibiotic therapies are unavailable for treating these conditions. (27)

This retrospective study aims to investigate the trends in antibiotic resistance of bacterial pathogens in a tertiary care hospital in Nablus city in Palestine. Antibiotic-resistant strains will be determined by analyzing clinical isolates of bacterial pathogens collected over four years in this study. In Palestine, this study discoveries will hold immense significance for both clinical practice and public health policies. It's imperative to comprehend the contemporary behaviors and facets that aid in antibiotic resistance within a tertiary care hospital atmosphere to construct efficient approaches for tackling this international public health predicament.

1.2 Problem statement

Antimicrobial resistance is currently regarded as the most severe threat to human health. Every year, it kills 700,000 people, and experts predict that by 2050, it will kill more than 10 million people. In addition, the world economy is predicted to lose $100 trillion in productivity. (28,29) Furthermore, 28 million bacterial infections resistant to several antibiotics are recorded in the United States alone each year, resulting in at least 35,000 fatalities and $20 billion in medical expenses. (29) As a result, present therapies for illnesses are becoming less effective, and diseases are getting more complex, costly to manage, and difficult to limit. (30,31) Diseases have gotten increasingly complicated, costly to control, and outbreaks difficult to contain as the efficiency of conventional antimicrobials has declined. Furthermore, first-line antibiotics are becoming less effective, necessitating the use of more expensive second and third-line antibiotics in high-income nations. (31) Unfortunately, the situation is worse in developing countries where there is a heavy burden of infectious diseases and resistant pathogens. (32)

The consequences of incorrect and excessive antibiotic usage are thought to be the primary cause of the rising resistance trend. Antibiotic use increased by 39% globally between 2000 and 2015. This rise was mostly driven by low- and middle-income nations. (33) Furthermore, both high-income and low- and middle-income countries expanded their usage of last-resort antibiotics such as Glycylcyclines, Oxazolidinones, Carbapenems, and Polymyxins. (34)

The COVID-19 pandemic is causing an increase in AMR. According to research from five countries, bacterial infections have been linked to 6.9 percent of COVID-19 cases, with a higher incidence among individuals in need of immediate medical intervention. A multi-center research conducted in the United States discovered that 72 percent of COVID-19 patients were administered antibiotics even when they were not clinically essential, potentially leading to an increase in AMR. (35)

As bacterial antibiotic resistance increases, the prevalence of resistance shifts from country to country and changes over time. Countries with modern medical systems have built surveillance systems that measure resistance levels to keep track of these changes.

The data produced by these systems is used by healthcare professionals to improve their protocols for treating infectious diseases. (36)

1.3 Significance of the Study

According to the WHO antimicrobial resistance worldwide report from 2014, there is an antibiotic resistance knowledge gap in many underdeveloped countries, including Palestine. The report made no mention of the outcomes of this problem returned from the West Bank or the Gaza Strip. (37)

It is critical to monitor antibiotic resistance in Palestinian areas since only a few research on infection patterns and/or antibiotic resistance have been done. Furthermore, the majority of these studies focused on specific pathogens and their antibacterial resistance, (38) while others concerned specific infectious diseases, their causative pathogens, and antibacterial resistance, (39–41) or study the prevalence bacterial and fungal resistance patterns in one hospital. (42)

A review of literature from 2002 to 2021 was conducted in April 2021 to investigate the incidence rate of antibiotic-resistant bacteria among patients and hospital settings in Gaza/Palestine. The results showed a high prevalence of multidrug-resistant gram-negative bacteria such as *Klebsiella Spp*., *E. coli*, *Enterobacter Spp.*, *P. aeruginosa*, and *Acinetobacter Spp.* Gram-positive bacteria, including Methicillin-Resistant *Staphylococcus aureus (MRSA)* and vancomycin-resistant *Enterococci*, were commonly observed. (43) However, it is important to understand that infection patterns and antibiotics resistance can change over time, stressing the need for further research on the current status.

1.4 Aim and Objectives

1.4.1 Aim

This study aims to analyze the development of antimicrobial resistance amongst pathogenic bacteria of serious concern and determine the impact of drug resistance to antibiotics of last resort. Additionally, the research will investigate the causes of the existing trends and give useful recommendations to medical professionals and decision makers.

1.4.2 Objectives

1.4.2.1 Primary Objectives

The primary goal of the study is to look at the antibiotic resistance trends in bacterial pathogens in a tertiary care hospital.

1.4.2.2 Secondary Objectives

1.) To determine the resistance patterns for *E. coli*.
2.) To determine the resistance patterns for *K. pneumoniae*.
3.) To determine the resistance patterns for *P. aeruginosa*.
4.) To determine the resistance patterns for *A. baumannii.*
5.) To determine the resistance patterns for *Staphylococcus aureus (Staph aureus).*
6.) To determine the resistance patterns for *Enterococcus faecium (E. faecium).*
7.) To determine the resistance patterns for *Enterococcus faecalis (E. faecalis).*

Over 4 years (2018, 2019, 2020, 2021) in a Tertiary Care Hospital.

1.5 Literature Review

The risk of antibiotic resistance has become a serious issue for public health globally because of misuse and overuse of antibiotics in addition to the natural evolution among bacteria resulting in resistant mechanisms. Moreover, the current shortage of new antibiotic development has led to a decrease in the effectiveness of existing antibiotics against bacterial diseases. (44) This literature review aims to investigate current studies on antibiotic resistance patterns in bacterial pathogens as well as the variables that contribute to its emergence and dissemination.

The issue regarding antibiotic resistance is getting worse due to a variety of factors which includes poor usage or administration of antibiotics among both human and animal patients during medical treatments alongside weak measures for controlling infections and rapid spread or transmission across borders by resistant bacteria. (45) Inappropriate use of antibiotics for animal feeds, such usage can include their employment as growth promoters or preventive measures have caused an increase in antibiotic-resistant microbes. (46) The underuse and overuse of antibiotics in humans can lead to the development and spread of antibiotic-resistant infections. (47)

Treating bacterial illnesses with antibiotics becomes less effective due to antibiotic resistance which is a major cause for concern among healthcare practitioners. As a result, the WHO has designated some bacterial pathogens as priority pathogens for antibiotic research and development due to their high levels of resistance. (48) Some examples of these bacteria *P. aeruginosa, Enterobacteriaceae*, including *E. coli* and *K. pneumonia,* and *A. baumannii*. Existing research shows that these pathogens are difficult to treat because of the presence of multiple resistant mechanisms against current antibiotics. (49)

To combat antibiotic resistance, several measures have been proposed, including reducing antibiotic usage in both human and animal healthcare settings, developing novel medicines, improving infection-control strategies and antibiotic combination treatment, which takes use of synergies, old-drug rejuvenation, and resistance reduction. (50) However, in recent years, the primary focus of research has been on the development of new antibiotics. In recent years, the primary focus of research has been on the development of new antibiotics. (51) Because of complicated antibiotic resistance mechanisms and high development costs, progress remains difficult. In addition to this method, other scientists have proposed alternative tactics such as using bacteriophages and antimicrobial peptides in conjunction with producing vaccinations to prevent bacterial infections. (44)

Several studies conducted throughout the world revealed an alarming rise in antibiotic resistance among bacterial infections. (52–55) For example, a study done by Mhondoro et al. on 23,432 bacterial pathogen isolates from Harare, Macdonia between 2012 and 2017 demonstrated a worrying increase in antibiotic resistance. The most prevalent pathogens were *E. coli* (43.2 %) and *Staph aureus* (15.8 %), with *Neisseria gonorrhoeae* (0.2 %) among the least frequent reported. Ampicillin and penicillin had the highest resistance rates, which ranged from 70 to 100 percent. Furthermore, there was a significant increase in resistance to antibiotics such as amoxicillin-resistant *Streptococcus pneumonia*e, *E. coli* and third-generation cephalosporin-resistant *E. coli,* as well as last-line antibiotics such as fluoroquinolone-resistant *Salmonella Spp.*, carbapenem-resistant *A. baumannii,* and *P. aeruginosa*. On the other hand, there was a decreasing trend in resistance to MRSA. (56)

Recent retrospective research in Ethiopia between 2010 and 2019 investigated bacterial isolates and antibiotic resistance changes in urinary tract infection patients. The most commonly reported infections were *E. coli* (37.7 %) and *K. pneumoniae* (11.4 %), whereas *Morganella morganii* (0.18 %) was among the least frequently reported. Antibiotics such as ampicillin, amoxicillin-clavulanate, trimethoprim-sulfamethoxazole, cefuroxime, tetracycline, and penicillin were shown to be resistant in a large proportion of Gram-negative (more than 75 %) and Gram-positive isolates (more than 70 %). (53–55)

Evidence from the United States confirmed a significant increase in antibiotic resistance (AR), particularly among Gram-negative bacilli such as *P. aeruginosa*, *A. baumannii*, *Proteus mirabilis*, *E. coli*, *Serratia marcescens*, *Klebsiella species*., *Citrobacter species*, *Haemophilus species*, *Shigella species*, *Enterobacter species*, and *Salmonella species*, as well as Gram-positive bacteria. (53–55) However, some studies reported variation in AR by patient type and age. (57) For example, Siva Sankar et al. did a recent retrospective analysis in the United States to evaluate the trends of antibiotic resistance from 2012 to 2017. The studies indicate that antibiotic resistance rates differed by age group and hospital environment. Ertapenem-resistant *Enterobacter cloacae* isolates, for example, were more prevalent in children than in adults. (57)

On the other hand, a review study conducted by Canton et al. found that the increased rates of antimicrobial resistance in intensive care units (ICUs) were due to the spread of high-risk clones of ESKAPE Gram-negative microorganisms. The COVID-19 outbreak has had a negative impact on the rising rates of antimicrobial resistance and it is therefore important to monitor this through surveillance studies and programs. (58)

The prevalence of multidrug-resistant (MDR) infections has significantly increased all over the world in recent years, especially among Gram-negative bacteria (GNB). *P. aeruginosa* is a common cause of health care-associated illnesses and MDR *P. aeruginosa* is a major contributor to morbidity and mortality. In the Middle East and North Africa (MENA) region, there is a wide variation in the reported prevalence of MDR *P. aeruginosa* from general medical samples. Egypt has the highest prevalence of 75.6% while Morocco has the lowest, with 0%. Saudi Arabia and Qatar have modest prevalence with 7.3% and 8.1%, respectively. The Levant countries (Jordan, Palestine, Lebanon, Israel, and Iraq) present a similarly varied picture, with Lebanon having the highest resistance of 64.5%, followed by Jordan (52.5%), Palestine (47.6%), and Israel (30%), while Iraq has the lowest at 12.4%. (59)

As far as Palestine is concerned, the results of various studies indicated high resistance rates of several types of bacterial pathogens against antibiotic drugs. (60–62) For example, a recent Master's thesis conducted by Algharabli to retrospectively determines bacterial infection patterns and antibiotic susceptibility in Gaza between 2014 and 2015. She reported that higher resistance rates were found against amoxicillin and clavulanic acid (91.67%), ampicillin (89.64%), amoxicillin (86.87%), penicillin G (82.46%), and cefaclor (83.72%). Conversely, lower resistance rates were found against other antibiotics including amikacin (6.84%), tazobactam (20%), streptomycin (20%), vancomycin (20.07%), rifampicin (21.74%), and meropenem (21.94%). Furthermore, she found that *E. coli* was the predominant pathogen (30.5%) among all isolates and was highly resistant to all penicillin, ceftazidime, ceftriaxone, and cefotaxime. This was followed by *P. aeruginosa* (14.6%), and *K. pneumoniae* (12.8%) such that they were extremely resistant to ampicillin, amoxicillin, cefuroxime, and cephalexin. (62)

Chapter Two

Methodology

2.1 Study design and Setting

This retrospective chart review was conducted at a teaching care hospital with 130 beds that had emergency, internal medicine, surgery, cardiology, oncology, pediatric, and nephrology wards. The data was collected over a four-year period from January 2018 to December 2021.

The outcome of interest was the antibiotic resistance rate of the isolates. For statistical analysis, isolates divided into two categories: resistant or susceptible to an antimicrobial. Any isolates with intermediate reactions were classified as resistant. Required data were collected from microbiological laboratories and medical archives.

A Chi-square test was used to see whether there were any statistically significant changes in antibiotic resistance over time. A statistically significant result was defined as a P-value of less than 0.05.

2.2 Study Period

The study investigated antibiotic resistance patterns during January of 2018 and ending in December of 2021.

2.3 Study population

All patients admitted to An-Najah National University Hospital (NNUH) in the study period from both genders, all ages, and in any department.

2.4 Sampling

4659 cases constituted the sample of the study. This included all inpatients who were admitted to the hospital during the study period and who were given a culture sensitivity test order and met the inclusion criteria.

2.4.1 Inclusion Criteria

For this analysis, seven species of bacteria were selected based on their clinical relevance and growing resistance issues. To ensure statistical validity, only bacterial species with susceptibility data for at least 30 isolates were chosen. (4) These species include *A.*

baumannii, P. aeruginosa, K. pneumoniae, E. coli, E. faecalis, E. faecium, and *Staph aureus*. The bacteria were identified by growing and incubating different specimens on the suitable medium at 35.5°C. The Vitek 2 Compact System was used to identify the isolated microorganisms (BioMerieux, USA). The same system was used to assess antibiotic sensitivity. Before sensitivity testing, a saline solution of an isolate was standardized using the Dens check plus equipment (BioMerieux, USA) to achieve an inoculum density comparable with the McFarlane standard.

Only antibiotics used for infections from anybody sites analyzed, such as piperacillin-tazobactam, cefepime, ciprofloxacin, ceftazidime, levofloxacin, moxifloxacin, gentamicin, ertapenem, amikacin, meropenem, imipenem, trimethoprim-sulfamethoxazole, ticarcillin, ticarcillin-clavulanic acid, norfloxacin penicillin, ampicillin, oxacillin, clindamycin, erythromycin, tetracycline, nitrofurantoin, and vancomycin. To avoid duplication, only the susceptibility profiles from the initial isolate of each bacterial species per patient and reporting period were included in the antibiograms. Only susceptibility profiles from bacteria isolated from diagnostic samples were included in these antibiograms.

2.4.2 Exclusion Criteria

All isolates not indicated above were excluded. Susceptibility profiles from bacteria detected from surveillance samples were not included in the antibiograms. The cephalosporins were not tested for extended spectrum beta-lactamase (ESBL) producing *K. pneumoniae* and *E. coli* since these antibiotics were immediately reported as resistant if these isolates tested positive for the ESBL enzyme.

2.5 Antibiotic Resistance Data

Data from medical records and microbiological laboratory reports were collected using the retrospective chart review approach. Data on antibiotic resistance were gathered from hospital antibiograms, which are generated annually according the Clinical and Laboratory Standards Institute guidelines. Data from cumulative antimicrobial susceptibility tests were analyzed and presented. (63) These antibiograms include the aggregate percent susceptibility (%S) for certain bacteria species during a particular time period. Every year, the antibiograms are compiled to include the susceptibility profiles of bacteria detected from January to December for the years 2018-2021.

2.6 2.6 Antibiotic Sensitivity Testing Methods

Bacterial identification and antibiotic susceptibility tests were carried out using the VITEK 2 Compact automated system (bioMérieux, France), as previously described. (64) The VITEK 2 Gram-Negative (GN) and Gram-Positive (GP) cards were used to identify bacteria, while the AST-N222 and AST-N204 cards were utilized to test for antimicrobial agents against aerobic Gram-negative bacilli, including piperacillin ticarcillin-clavulanic acid, ticarcillin, piperacillin-tazobactam, amikacin, imipenem, tobramycin, meropenem, ceftazidime, gentamycin, nitrofurantoin, tobramycin, cefepime, ceftriaxone, cefotaxime, sulfamethoxazole–trimethoprim, ampicillin, and ciprofloxacin. The VITEK 2 AST-GP67 Card was used to test antimicrobial agents for Gram-positive cocci (*Enterococcus species* and *Staphylococcus species*) including ampicillin, penicillin, oxacillin, gentamycin, clindamycin, erythromycin, ciprofloxacin, levofloxacin, moxifloxacin, vancomycin, tigecycline, linezolid, rifampicin, and nitrofurantoin. The MIC of each antibiotic was determined and evaluated using the Clinical and Laboratory Institute (CLSI) M100-S30 document's breakpoints. (63)

2.7 Outcome measures

2.7.1 Primary Outcome Measures

- **Antimicrobial Resistance Rates**
  - **The Overall Antimicrobial Resistance Rates**

    The percentage of resistant isolates for each antibiotic was calculated by dividing the number of resistant isolates by the total number of tested cases of that antibiotic and multiplying the result by 100.
  - **Certain antimicrobial resistance rates against specific pathogen**

    The percentage of resistant isolates of this pathogen against that antibiotic calculated by multiplying the number of resistant isolates divided by the total number of tested isolates of the pathogen against the antibiotic by 100.

2.7.2 Secondary outcome measures

  - **Prevalence of different types of specimens**

    The percentage of specimen A calculated by dividing the number of cases of specimen A by the total number of cases, then multiplying the result by 100.

- **Prevalence of different types of pathogens**

  The percentage of pathogen A was calculated by dividing the number of its isolates by the total number of isolates and then multiplying by 100.
- **Prevalence of different types of pathogens in specific specimen type:**

  The percentage of pathogen A present in a sample was calculated by dividing the number of isolates of pathogen A by the total number of isolates from the sample, then multiplying the result by 100.

2.8 Data entry and statistical analysis

Data entry process was done by giving a serial number for each patient's data, coding variables and finally, using the Statistical Package of Social Science (SPSS) version 26 to enter data.

At first, data analysis was done to identify the pathogens present in each type of specimens. This goal was achieved by splitting the overall data according to the specimen type into 6 groups (blood, respiratory samples, body fluids, swabs, tissue, and urine).

In order to identify the resistance pattern of each pathogen, the data was divided according to the pathogen and the resistance prevalence for each antibiotic was calculated.

Descriptive statistics were carried out for all variables. Categorical data were summarized as frequencies and percentage. Chi-square test was used to identify if there is a significant difference of resistance rates during the study period. Results were considered significant if P-values were ≤ 0.05.

The following terms were considered during data analysis:

Isolates: a pure microbial strain.

Specimen: a small sample or part taken to show the nature of the whole, such as a small quantity of urine for urinalysis.

Urine sample: urine specimens collected normally, by urine catheter or suprapubic aspiration method, and given to the microbiological laboratory in sterile cup or bag.

Body fluid sample: specimen collected from sterile body fluids.

Swab sample: specimen collected from wounds, injuries, abscesses, burns, surgical operations, ear, eye, throats, and central line swabs. In this study, swab samples were not specified.

2.9 Ethical considerations

The researcher ensured that all ethical considerations necessary for conducting the research were adhered to, and approval from the Institutional Review Boards (IRB) of An-Najah National University and the clinical research center of NNUH was obtained. Ref: Mas. May 2022/11 see appendix A.

Chapter Three

Results

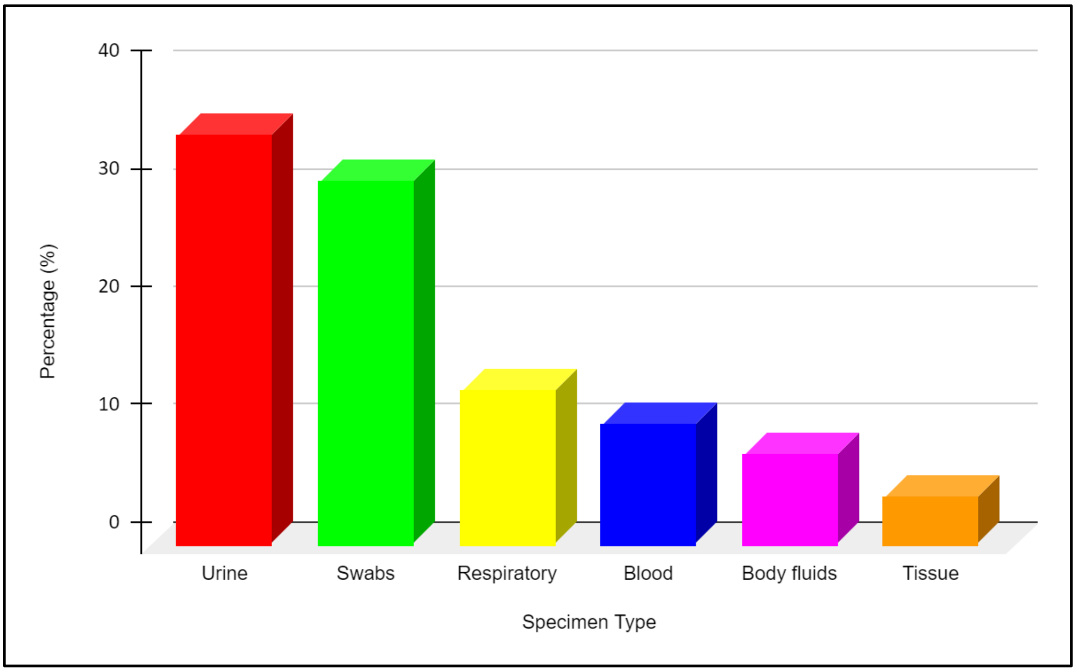
In this chapter, the results of the study are detailed in accordance with the objectives of the study. First, the distribution of specimens and bacterial isolates throughout the study period is presented. Afterward, the patterns of antibiotic resistance to various pathogens are outlined.

3.1 Distribution of specimens and bacterial isolates during the study period

Out of the analyzed variables, 100% of the records were complete. Urine specimens accounted for 34.6% (1613) of the total, making it the most common specimen type, followed by swabs, respiratory, blood, and body fluids samples at 30.7% (1433) and 13% (605), 10.1% (471), and 7.6% (352) respectively. Tissue samples were the least frequent, making up only 4% (185) Of the specimens, *E. coli* was the most common isolate at 27% (1258), followed by *K. pneumoniae*, *E. faecalis*, *P. aeruginosa*, *Staph aureus*, and *E. faecium* at 15.5% (723), 14.6% (682), 13% (606), 10.6% (495), and 10.2% (477) respectively, while *A. baumannii* was the least frequent at 9% (418) (see figure 1 and table 1).

Figure 1

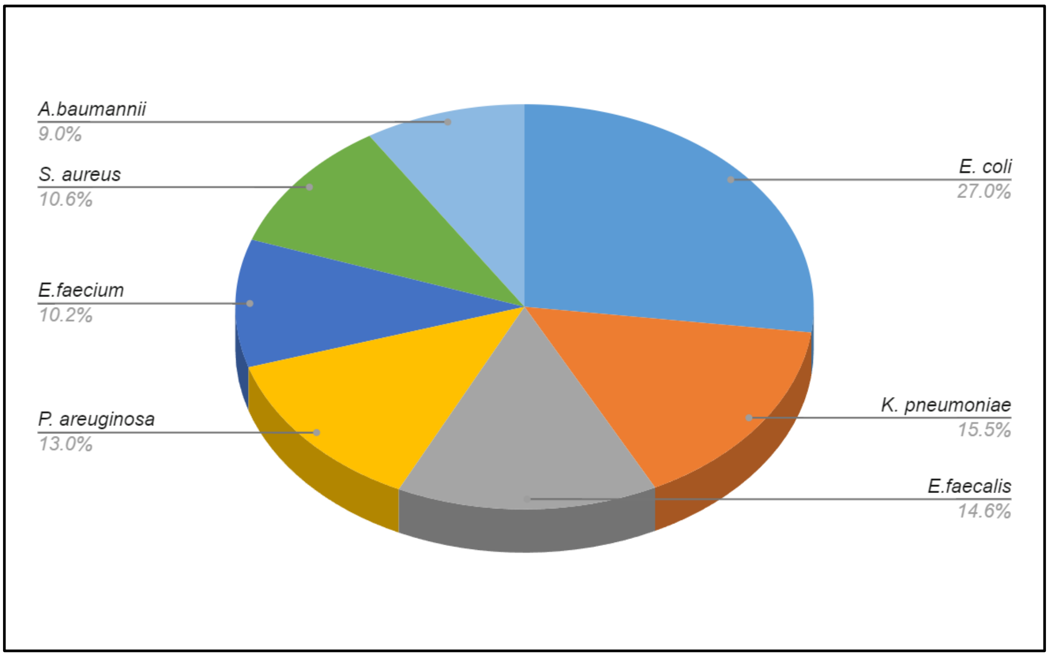
Distribution of specimen analyzed



NNUH 2018–2021

Figure 2

Distribution of bacterial isolates



NNUH 2018–2021

Table 1

Distribution of specimen and bacterial isolates analyzed

Variable	Category	Frequency (*n* = 4659)	Percentage (%)
Specimen type	Urine	1613	34.6
	Swabs	1433	30.7
	Respiratory	605	13
	Blood	471	10.1
	Body fluids	352	7.6
	Tissue	185	4
Bacteria species	*E. coli*	1258	27
	K. pneumoniae	723	15.5
	E. faecalis	682	14.6
	P. aeruginosa	606	13
	S. aureus	495	10.6
	E. faecium	477	10.2
	A. baumanii	418	9

NNUH 2018–2021

The most prevalent gram-negative bacterial pathogen identified in the urine samples was *E. coli*, followed by *K. pneumoniae*. For the gram-positive bacteria, *E. faecalis* was the most common uropathogen, followed by *E. faecium*. The least commonly identified uropathogen was *Staph aureus* as seen in (Table B.1) in appendix B.

The swab culture samples yielded *E. coli* as the most frequent gram-negative bacteria, followed by *P. aeruginosa*, *Staph aureus*, and *E. faecalis* comprised the two most prevalent gram-positive bacterial pathogens. *E. faecium* was the least common bacterial pathogen isolated from the swab culture specimens during the study period see (Table B.1) in appendix B.

From respiratory samples *A. baumannii* was the most common gram negative bacteria identified followed by *K. pneumoniae* during the first year (2018) of the study. In the following year (2019) *P. aeruginosa* replaced *A. baumannii* as the most common gram negative bacteria isolated. In 2020, 2021 *K. pneumoniae* was the most common gram negative bacteria identified. Among gram positive bacteria *E. faecium* followed by *Enterococcus faecalis* respectively were the most common bacterial pathogen isolated during the first three years (2018, 2019, and 2020) of the study. But in the last year (2021) *Staph aureus* was the second most common gram positive bacteria isolated after *E. faecium* see (Table B.1) in appendix B.

From blood samples *E. coli* was the most common gram-negative bacteria isolated followed by *A. baumannii* and *P. aeruginosa* during the first year (2018) of the study, during the second year (2019) *P. aeruginosa* was the most common gram-negative bacteria isolated followed by *K. pneumoniae* and *E. coli*, during the followed years 2020, 2021 of the study *E. coli* was the most common gram-negative bacteria isolated followed by *K. pneumoniae*. Among gram positive bacteria *Staph aureus* followed by *E. faecalis* respectively were the most common bacterial pathogen isolated during the first three years (2018, 2019, and 2020) of the study then *E. faecium* was the second most common gram-positive bacteria isolated after *Staph aureus* during the last year of the study see (Table B.1) in appendix B.

From body fluid samples *E. coli* was the most common gram negative bacteria isolated followed by both of *A. baumannii* and *P. aeruginosa* during the first year (2018) of the study, during the next three years (2019, 2020, and 2021) *K. pneumoniae* was the second most common gram negative bacteria isolated after *E. coli*. Among gram positive bacteria

E. faecalis followed by *E. faecium* respectively were the most common bacterial pathogen isolated during the first year (2018) of the study and during the second year (2019) both of *E. faecalis* and *Staph aureus* were the most common gram positive bacteria isolated, during the third year (2020) *E. faecium* become most common gram positive bacteria isolated followed by *E. faecalis* and then during the last year (2021) *Staph aureus* become most common gram positive bacteria isolated followed by both of *E. faecium* and *E. faecalis* see (Table B.1) in appendix B.

From tissue samples *P. aeruginosa* was the most common gram negative bacteria isolated followed by *E. coli* during the first year (2018) of the study, during the second year (2019) *P. aeruginosa* was the second most common gram negative bacteria isolated after *E. coli* after that during the third year (2020) *E. coli* was the most common gram negative bacteria isolated followed by *K. pneumoniae*, while *E. coli* was the most common gram negative bacteria isolated followed by *P. aeruginosa* during the last year (2021) of the study. Among gram positive bacteria *E. faecalis* followed by *E. faecium* respectively were the most common bacterial pathogen isolated during the first year of the study (2018) and during the second year (2019) *Staph aureus* was the most common gram positive bacteria isolated followed by *E. faecalis,* during the third year (2020) *E. faecium* become most common gram positive bacteria isolated followed by *E. faecalis* and then during the last year (2021) *Staph aureus* become most common gram positive bacteria isolated followed by *E. faecium see* (Table B.1) in appendix B.

Among medical department samples: *A. baumannii* was the most widely-occurring gram-negative bacterial pathogen in the first year (2018), while in the second year (2019) *E. coli* was the most prevalent followed by *P. aeruginosa*. During the last two years (2020, 2021) *E. coli* was the most commonly identified gram-negative bacterial pathogen, with *K. pneumoniae* following close behind. For gram-positive bacterial pathogens, *E. faecium* and *E. faecalis* were the two most frequent in the first year (2018). In the second year (2019) *E. faecium* was the most frequently isolated, followed by *E. faecalis*. For the last two years (2020,2021) *E. faecium* was the most commonly identified gram-positive bacterial pathogen, with *E. faecalis* coming in second see (Table B.2) in appendix B.

Among surgical department samples: For the samples taken from the surgical department, *E. coli* was the predominant gram-negative bacteria identified in the first year (2018) of the study. Over the following three years (2019, 2020, and 2021) *K. pneumoniae* was the second most common gram-negative bacterium found after *E. coli*. As for the gram-positive bacteria, *E. faecalis* and *E. faecium* were the two most common pathogens in the initial two years (2018, 2019) of the study, while in the third year (2020) *E. faecium* was the most frequently observed species followed by *E. faecalis*. The fourth year (2021) saw *E. faecalis* as the leading gram-positive bacteria with *E. faecium* in second place see (Table B.2) in appendix B.

Among pediatric department samples: for the duration of the study, *K. pneumoniae* was the most commonly isolated gram-negative bacteria among pediatric department samples. Subsequently, *E. coli* and *P. aeruginosa* were the two next most frequently seen gram-negative bacterial pathogens in the first (2018) and second (2019) years, respectively. However, *P. aeruginosa* was the predominant gram-negative bacteria found in the last year. When looking at gram-positive bacteria, *Staph aureus* emerged as the most common bacterial pathogen, with *E. faecalis* coming in second. In the second (2019) and fourth year (2021), both of *E. faecalis* and *E. faecium* were the second most common gram-positive bacteria after *Staph aureus* see (Table B.2) in appendix B.

Among Emergency department specimens: The analysis of Emergency department specimens revealed that *E. coli* was the most consistently isolated gram-negative bacterial pathogen over the course of the study. *K. pneumoniae* was the second most common gram-negative bacteria isolated in the first, second, and last year (2018, 2019, and 2021). However, during the third year (2020) *P. aeruginosa* and *K. pneumoniae* were the second most common gram-negative bacteria after *E. coli*. As for the gram-positive bacteria, *E. faecalis* and *Staph aureus* were the most commonly isolated pathogens in the first two years (2018 and 2019). In the third year (2020) *E. faecalis* was the most common gram-positive bacteria isolated, while *E. faecium* was the second most common. In the last year (2021) *Staph aureus* and *E. faecalis* were the most commonly isolated gram-positive bacterial pathogens see (Table B.2) in appendix B.

Among outpatient specimens: During the first three years (2018, 2019, and 2020) of the study, the most frequently encountered gram-negative bacteria among outpatients was *E. coli*, followed by *P. aeruginosa*. In the fourth year (2021) *K. pneumoniae* was the second most common gram-negative pathogen after *E. coli*. For gram-positive bacteria, the two most common pathogens isolated during the study were *E. faecalis* and *Staph aureus* see (Table B.2) in appendix B.

Among dialysis department specimens: For the first two years of the study (2018 and 2019), the most common gram-negative bacterial pathogen isolated in the dialysis department was *E. coli*, and *K. pneumoniae* came in second. For the third year (2020), the sequence was reversed, with *K. pneumoniae* taking the lead and *E. coli* following. During the last year (2021), *E. coli* once again was the top bacterial organism isolated, with *P. aeruginosa* in the number two spot. As for gram-positive bacteria, *Staph aureus* was the most common throughout the study, followed by *E. faecalis* see (Table B.2) in appendix B.

3.2 Trends of total antimicrobial resistance by common antibiotics during the study period

Between 2018 and 2020, the percentage of total resistance to ampicillin increased from 65.5% to 74.6%, but then decreased to 71.2% in 2021 (with a statistical significance of P=0.005). Total resistance to penicillin increased from 54.9% in the first of the study (2018) reaching to 60.1% during the last year of the study. while total resistance to trimethoprim/sulphamethexazole increased from 51% in 2018 to 57.9 % 2020, but then decreased to 54% in 2021. The total resistance to amoxicillin/Clavulanic acid increased from 54.1% to 58.9% between 2019 and 2020, before decreasing to 45.1% in 2021 (with a statistical significance of P<0.001) (as shown in figure 3). However, the total resistance to piperacillin/tazobactam decreased from 39.8% to 33.8% during the study period (with a statistical significance of P=0.033).

The study found a significant rise in the overall resistance to ertapenem, increasing from 5.4% to 14% over the course of four years (P< 0.001). In contrast, there was a significant decrease in total meropenem resistance from 32.7% to 22.7% during the first three years (2018, 2019, and 2020) of the study, but it increased to 26.6% in the last year (P< 0.001).

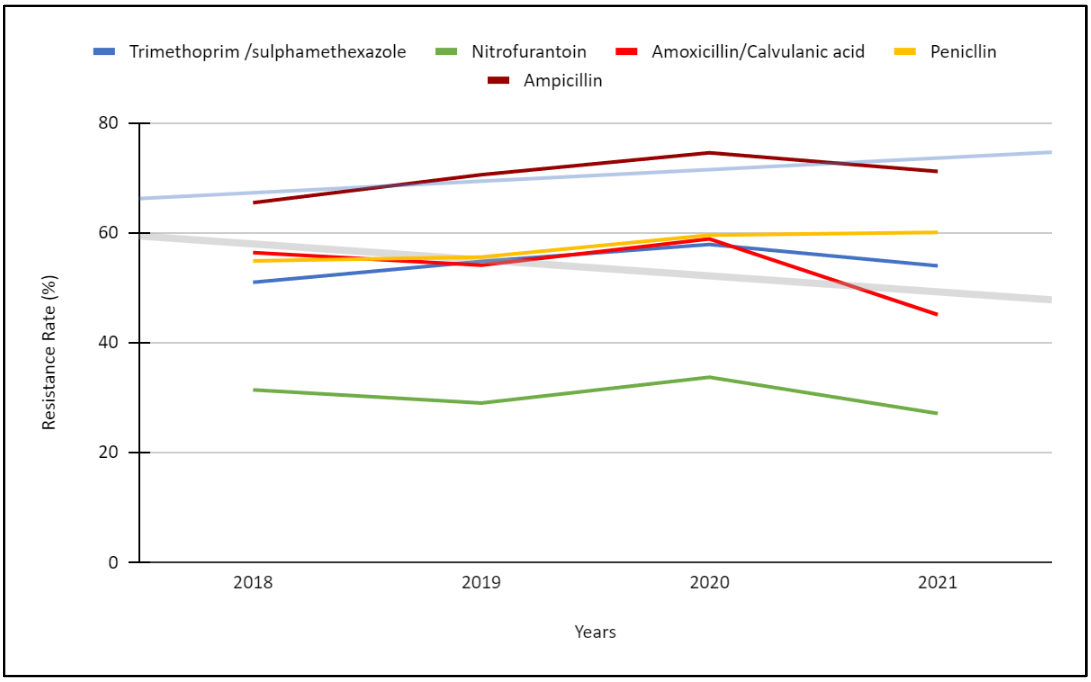
The resistance rates to aminoglycosides significantly declined during the course of the study. Amikacin and Gentamycin both saw decreases from 23.9% to 10.8% and 42.2% to 32.7%, respectively. This progression is supported statistically (P-value 0.001) and is viewed as favorable. Additionally, overall cefepime resistance declined significantly from 66.4% to 50.8% throughout the first three years (2018, 2019, and 2020) of the study period before increasing somewhat to 51.7% in the last year (2021) (P-value 0.001). Similar positive findings were shown for overall ceftazidime resistance, which decreased from baseline levels of 67.8% to just 50.5%. Although it had a small increase (52%) in the last year (2021) (P-value 0.001).

The study found a significant reduction in overall moxifloxacin resistance from 21.9% to 3.1% in the first three years (2018, 2019, and 2020), followed by a sharp increase to 31.4% in the final year, with a P-value of 0.023.

The study period showed a significant rise in total resistance to linezolid from 1.7% to 6.6%, with a P-value of 0.001, as shown in Table 2.

Figure 3

Total antimicrobial resistance by common antibiotics



NNUH 2018-2021

Table 2

Total Resistance rates during the study period

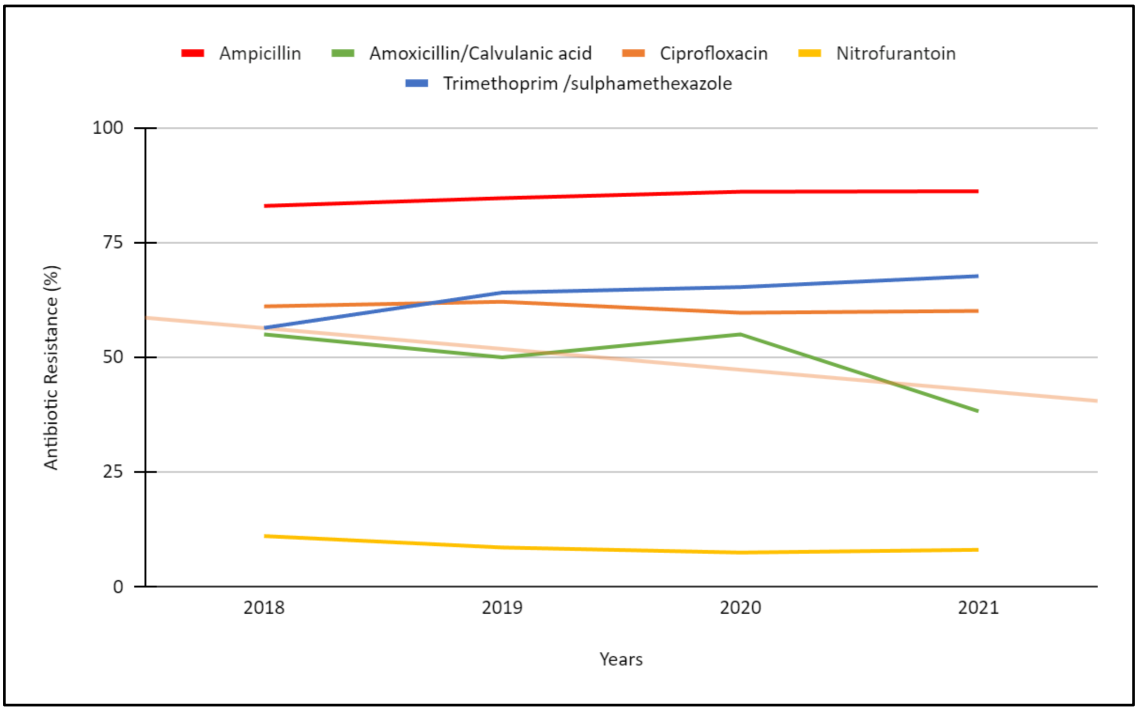
Antibiotic	Resistance %				P-value
	2018	2019	2020	2021	
Ampicillin	65.5	70.6	74.6	71.2	0.005
Penicillin	54.9	55.6	59.6	60.1	0.301
Trimethoprim /sulphamethexazole	51	54.8	57.9	54	0.155
Amoxicillin/Clavulanic acid	56.4	54.1	58.9	45.1	< 0.001
Piperacillin/Tazobactam	39.8	33.3	33.7	33.8	0.033
Ertapenem	5.4	9.3	12.8	14	< 0.001
Meropenem	32.7	24	22.7	26.6	< 0.001
Amikacin	23.9	16.4	10.7	10.8	< 0.001
Gentamycin	42.2	38.2	33.2	32.7	< 0.001
Cefepime	66.4	52.2	50.8	51.7	< 0.001
Ceftazidime	67.8	52.2	50.5	52.5	< 0.001
Moxifloxacin	21.9	14.8	3.1	31.4	0.023
Linezolid	1.7	2.8	2.8	6.6	0.001

3.3 Trends of resistance to antibiotics by *Escherichia coli* during the study period

Resistance to ampicillin showed an increase from 83% in 2018 to 86.2% in 2021. However, there was a significant decrease in resistance to amoxicillin/clavulanic acid from 55% in 2018 to 38.2% in 2021 (P-value < 0.001). There were fluctuations in resistance levels for piperacillin/tazobactam ranging from 19.2% in 2018 to 22.7% in 2020 before decreasing to 16.1% in 2021. Resistance to ertapenem increasing from 1.5% in 2018 to 5.1% in 2020 then decreased to 5% during 2021 (P=0.003). Resistance to meropenem increasing from 1.9% in 2018 to 5.1% in 2020 then decreased to 5% during 2021 (P= 0.007), as well as resistance to imipenem increasing from 1.5% in 2018 to 5.1% in 2020 then decreased to 4.8% during 2021 (P= 0.005). While *E. coli* show a significant decrease in resistance to amikacin from 16% in 2018 to 1.8% in 2021 (P-value < 0.001). There were fluctuations in resistance levels for gentamycin ranging from 29% in 2018 to 36.5% in 2021 with a dip to 28.8% in 2020. *E. coli* show high resistant rates to ciprofloxacin during the study period with highest rate of 62.1% in 2019 and lowest rate of 59.7% in 2020. Resistance to nitrofurantoin slightly decreased from 11% to less than 8% over the study period. Resistance to norfloxacin also decreased from 89.6% in 2018 to 61.5% in 2021, while resistance to trimethoprim/sulphamethoxazole increased from 56.4% in 2018 to 67.7% in 2021 (Table 3).

Figure 4

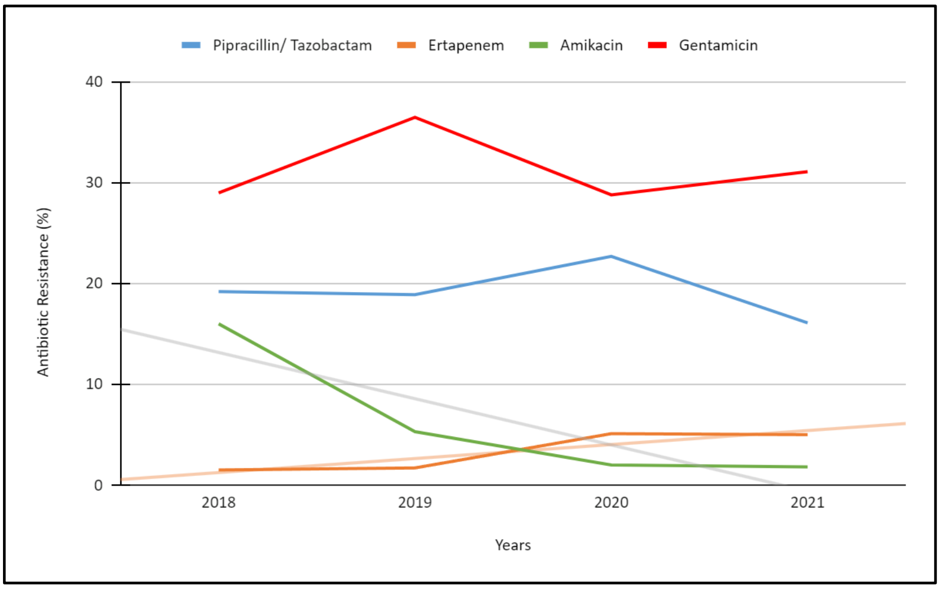
Trends of resistance to common antibiotics by E. coli



NNUH 2018-2021

Figure 5

Trends of resistance to certain antibiotics by E. coli



NNUH 2018-2021

Table 3

Resistance rates of Escherichia coli during the study period

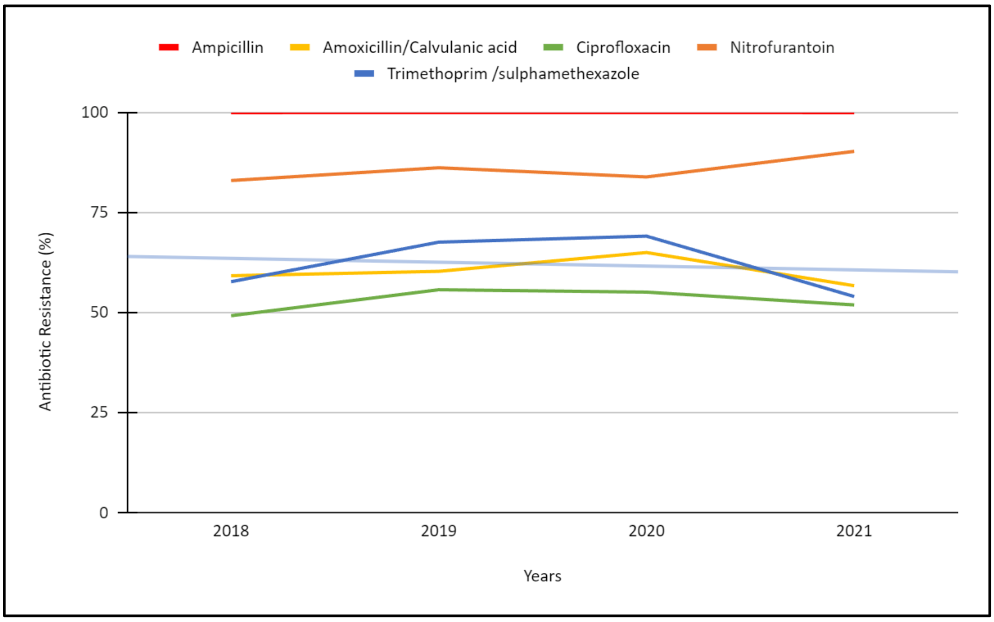
Organism/Antibiotic	Resistance %				P-value
	2018	2019	2020	2021	
Escherichia coli	n=262	n=301	n=296	n=399	
Ampicillin	83	84.7	86.1	86.2	0.674
Amoxicillin/Clavulanic acid	55	50	55	38.2	< 0.001
Piperacillin/Tazobactam	19.2	18.9	22.7	16.1	0.182
Ertapenem	1.5	1.7	5.1	5	0.003
Meropenem	1.9	1.7	5.1	5	0.007
Imipenem	1.5	1.7	5.1	4.8	0.005
Amikacin	16	5.3	2	1.8	< 0.001
Gentamycin	29	36.5	28.8	31.1	0.149
Ciprofloxacin	61.1	62.1	59.7	60.1	0.924
Nitrofurantoin	11	8.5	7.4	8	0.699
Norfloxacin	89.6	69.5	56.2	61.5	< 0.001
Trimethoprim-sulfamethoxazole	56.4	64.1	65.3	67.7	0.059

3.4 Trends of resistance to antibiotics by *Klebsiella pneumoniae* during the study period

K. pneumonia was completely resistant to ampicillin during the study period. The resistance to amoxicillin/clavulanic acid showed an increase from 59.2% in 2018 to 65% in 2020, but then decreased to 56.7% in 2021. Resistance to piperacillin/tazobactam also increased from 40% to 44.1% in 2021. Carbapenem resistance increased from less than 13% in 2018 to 29% in 2021 with a P-value < 0.007 (Figure 7). Resistance to amikacin increased from 13.8% in 2018 to 23.1% in 2019, but then decreased to 19.7% in 2021. Gentamicin resistance fluctuated from 41.9% in 2018 to 45.9% in 2019 before decreasing to 36.1% in 2021. Ciprofloxacin resistance increased from 49.2% in 2018 to 55.7% in 2019 before decreasing to 51.9% in 2020. During the study, nitrofurantoin resistance grew from 83 to 90.3 %. However, there was a significant decrease in resistance to norfloxacin from 85.1 % in 2018 to 45.5 % in 2020, but then climbed to 52.8 % in 2021 P-value of 0.001 and to trimethoprim/sulfamethoxazole from 69.1% in 2020 to 54.2% in 2021 with a P-value of 0.004 (Table 4).

Figure 6

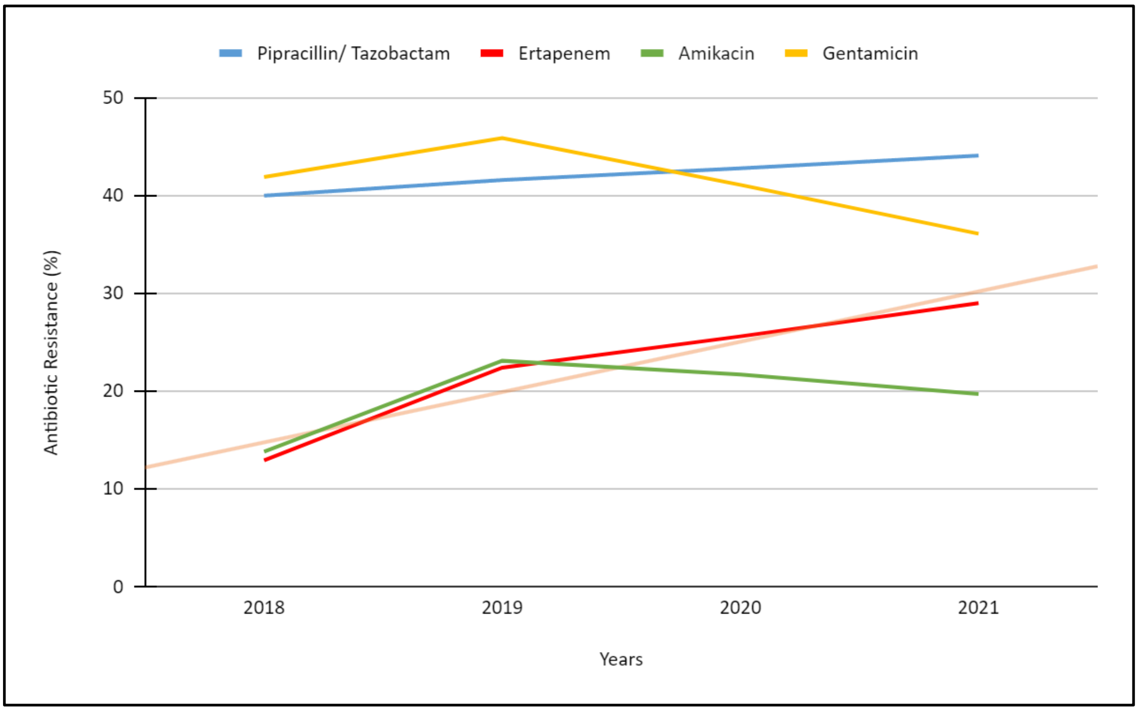
Trends of resistance to common antibiotics by K. pneumoniae



NNUH 2018-2021

Figure 7

Trends of resistance to certain antibiotics by K. pneumoniae



NNUH 2018-2021

Table 4

Resistance rates of Klebsiella pneumoniae during the study period

Organism/Antibiotic	Resistance %				P-value
	2018	2019	2020	2021	
Klebsiella pneumoniae	n=131	n=174	n=180	n=238	
Ampicillin	100	100	100	100	
Amoxicillin/Clavulanic acid	59.2	60.3	65	56.7	0.395
Piperacillin/Tazobactam	40	41.6	42.8	44.1	0.886
Ertapenem	12.9	22.4	25.6	29	0.006
Meropenem	12.2	21.8	25	29	0.003
Imipenem	12.2	21.8	25.6	29	0.003
Amikacin	13.8	23.1	21.7	19.7	0.216
Gentamicin	41.9	45.9	41.1	36.1	0.245
Ciprofloxacin	49.2	55.7	55.1	51.9	0.641
Nitrofurantoin	83	86.2	83.9	90.3	0.645
Norfloxacin	85.1	54.1	45.5	52.8	0.001
Trimethoprim-sulfamethoxazole	57.7	67.6	69.1	54	0.004

3.5 Trends of resistance to antibiotics by *Pseudomonas aeruginosa* during the study period

The study observed changes in resistance rates for various antibiotics over the years. Resistance to ticarcillin decreased from 61.2% in 2018 to 31.4% in 2020, then increased to 36.2% in 2021 with P-value less than 0.001. Also, resistance to ticarcillin/clavulanic acid decreased from 49.3% in 2018 to 31.4% in 2020, then increased to 34.5% in 2021 with P-value of 0.001. Similarly happened with piperacillin at the first year of the study resistance was 51 % then it decreased to 18.1% in 2020, then increased to 34.5% in 2021 with P-value less than 0.001. Also, resistance to piperacillin/tazobactam decreased from

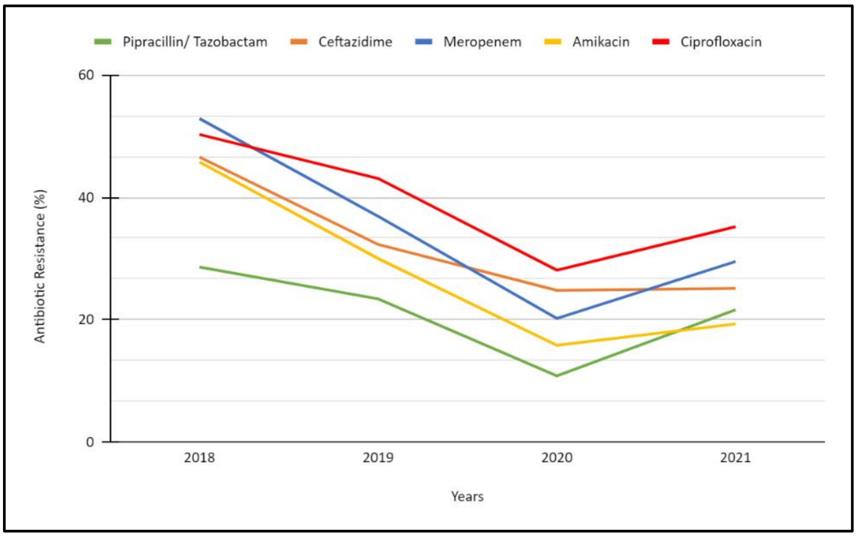
28.6% in 2018 to 10.8% in 2020, then increased to 21.6% in 2021 with P-value of 0.008. Ceftazidime resistance decreased from 46.6% in 2018 to 24.8% in 2020 with a P-value of less than 0.001, but slightly increased to 25.1% in 2021. Similarly, resistance to cefepime decreased from 45.2% in 2018 to 25.4% in 2020 with a P-value less than 0.001, before slightly increasing to 25.6% in 2021. Resistance to carbapenem decreased significantly from 52.9% in 2018 to 20.2% in 2020 for meropenem, with a P-value less than 0.001, but increased to 29.5% in 2021. However, resistance for imipenem increased from 53.9% in 2018 to 62.5% in 2019, and then decreased to 32.4% in the last year (2021) of the study with a P-value less than 0.001.

Resistance rates for aminoglycosides were high in the first year of the study, with 48.4%, 45.8%, and 43.1% for gentamicin, amikacin, and tobramycin, respectively. However, resistance for gentamicin declined to 23.7% in 2020 before increasing to 25% in 2021. Resistance for amikacin declined to 15.8% in 2020 before increasing to 19.3% in 2021 and resistance for tobramycin decreased to 17.8% in 2020 before reaching 21.4% in 2021 with a P-value less than 0.001.

Resistance rates for ciprofloxacin were high in the first year (2018) of the study at 50.3%, but significantly declined to 28.1% in 2020 before increasing to 35.2% in the last year (2021) of the study with a P-value of 0.001. Please see figure 8 and table 5 for more information.

Figure 8

Trends of resistance to certain antibiotics by P. aeruginosa



NNUH 2018-2021

Table 5

Resistance rates of Pseudomonas aeruginosa during the study period

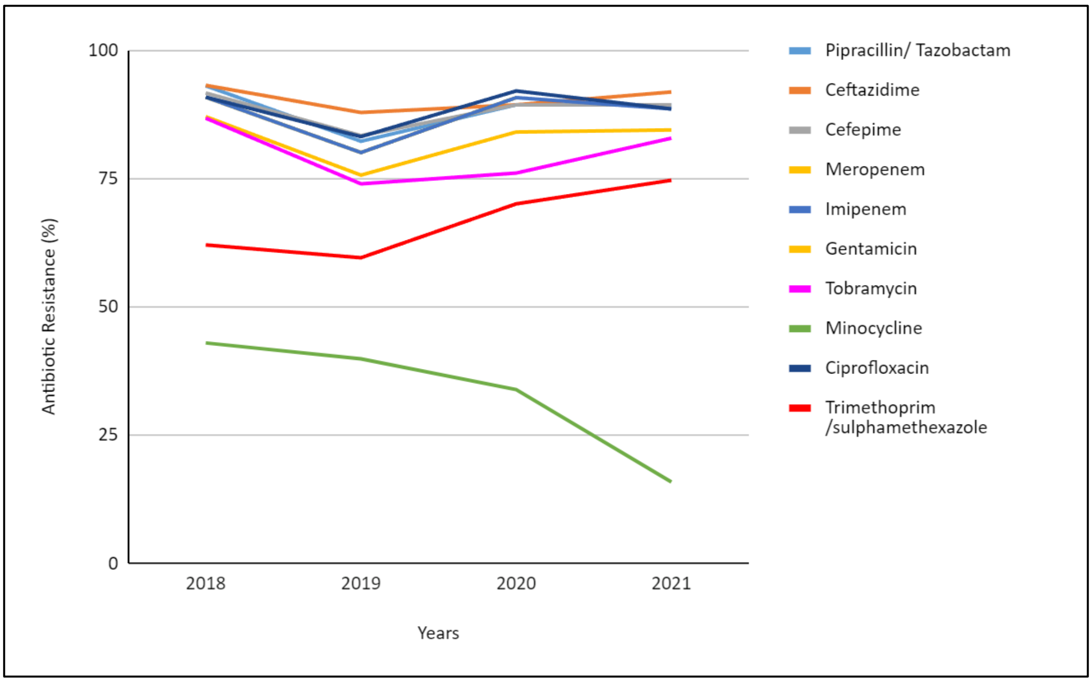
Organism/Antibiotic	Resistance %				P-value
	2018	2019	2020	2021	
Pseudomonas aeruginosa	n=155	n=161	n=114	n=176	
Ticarcillin	61.2	53.2	31.4	36.2	< 0.001
Ticarcillin/Clavulanic acid	49.3	50	31.4	34.5	0.001
Piperacillin	51	41.7	18.1	34.5	< 0.001
Piperacillin/Tazobactam	28.6	23.4	10.8	21.6	0.008
Ceftazidime	46.6	32.3	24.8	25.1	< 0.001
Cefepime	45.2	34.8	25.4	25.6	< 0.001
Meropenem	52.9	36.9	20.2	29.5	< 0.001
Imipenem	53.9	62.5	46.5	32.4	< 0.001
Amikacin	45.8	30	15.8	19.3	< 0.001
Gentamicin	48.4	36.3	23.7	25	< 0.001
Tobramycin	43.1	29.7	17.8	21.4	< 0.001
Ciprofloxacin	50.3	43	28.1	35.2	0.001

3.6 Trends of resistance to antibiotics by *Acinetobacter baumannii* during the study period

Most antibiotics used to treat *A. baumannii* exhibited high resistance rates during the initial year of the study. Please see figure 9 for more information. However, resistance rates slightly decreased during the second year. In the last two years of the study, the resistance rates almost returned to the same level as at the beginning of the study. According to table 6, the resistance to minocycline showed a statistically significant decrease from 42.9% in 2018 to 15.8% in 2021, with a P-value of less than 0.001. Conversely, resistance to trimethoprim/sulfamethoxazole increased from 62% in 2018 to 74.6% in 2021.

Figure 9

Trends of resistance to certain antibiotics by A. baumannii



NNUH 2018-2021

Table 6

Resistance rates of Acinetobacter baumannii during the study period

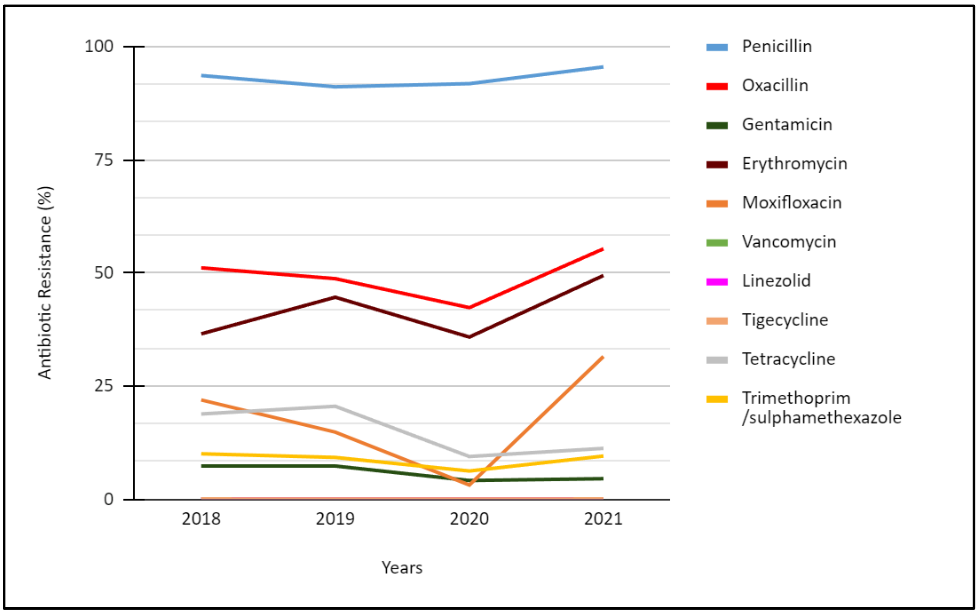
Organism/Antibiotic	Resistance %				P-value
	2018	2019	2020	2021	
Acinetobacter baumannii	n=131	n=90	n=75	n=122	
Ticarcillin	90.9	82.8	92	89.3	0.459
Ticarcillin/Clavulanic acid	90.9	93	91.7	89.3	0.576
Piperacillin	93	86.4	90.7	90.2	0.445
Piperacillin/Tazobactam	93	82.2	89.3	89.3	0.092
Ceftazidime	93.1	87.8	89.3	89.3	0.533
Cefepime	91.6	83.3	89.3	89.3	0.286
Meropenem	90.8	80	90.7	88.5	0.076
Imipenem	90.8	80	90.7	88.5	0.076
Gentamicin	87	75.6	84	84.4	0.162
Tobramycin	86	73.9	76	82.8	0.070
Minocycline	42.9	39.8	33.8	15.8	< 0.001
Ciprofloxacin	90.8	83.1	92	88.5	0.244
Trimethoprim-sulfamethoxazole	62	59.5	70	74.6	0.073

3.7 Trends of resistance to antibiotics by *Staph aureus* during the study period

The study revealed a consistently high rate of penicillin resistance from the first year (2018) ranging from 93.6% to 95.5% in the last year (2021). The resistance to oxacillin decreased from 51.1% in 2018 to 42.3% in 2020 but then increased again to 55.3% in 2021, indicating a high prevalence of methicillin-resistant Staphylococcus aureus (MRSA). On the other hand, the study showed a low rate of resistance to gentamicin, ranging from 7.3% in 2018 to 4.1% in 2020 before slightly increasing to 4.5% in 2021. The study also showed a slight increase in resistance to clindamycin from 22.9% in the first year (2018) to 26.6% in the last year (2021). Resistance to erythromycin increased from 29.2% in 2018 to 49.4% in 2021. Resistance to ciprofloxacin and levofloxacin increased from 29.2% and 25% in 2018 to 34.1% and 33.1% in 2021, respectively, before declining in 2020 (22.9% for ciprofloxacin and 24% for levofloxacin). A statistically significant decrease in resistance to moxifloxacin was observed (from 21.9% in 2018 to 3.1% in 2020) with a P-value of 0.023 before sharply increasing to 31.5% in 2021. Notably, Staphylococcus aureus showed no resistance rates for vancomycin, linezolid, and tigecycline being completely susceptible to each of them during the study period. The study revealed a statistically significant decrease in resistance to tetracycline, from 18.8% in 2018 to 9.4% in 2020 with a P-value of 0.037, before slightly increasing to 11.2% during 2021. However, there was a low rate of resistance to rifampicin, with a maximum of 1.6% during 2019 and a minimum of 1% in 2020. The same trend was observed for trimethoprim/sulfamethoxazole, with a maximum rate of 10% during the first year (2018) of the study and a minimum of 6.2% in 2020. Please see figure 10 and table 7 for more information.

Figure 10

Trends of resistance to certain antibiotics by S. aureus



NNUH 2018-2021

Table 7

Resistances rates of Staph aureus during the study period

Organism/Antibiotic	Resistance %				P-value
	2018	2019	2020	2021	
Staph aureus	n=96	n=123	n=97	n=179	
Penicillin	93.6	91.1	91.8	95.5	0.438
Oxacillin	51.1	48.7	42.3	55.3	0.218
Gentamicin	7.3	7.3	4.1	4.5	0.215
Clindamycin	22.9	25.6	24.2	26.6	0.919
Erythromycin	36.5	44.6	35.8	49.4	0.079
Ciprofloxacin	29.2	33.6	22.9	34.1	0.234
Levofloxacin	25	33.6	24	33.3	0.212
Moxifloxacin	21.9	14.8	3.1	31.5	0.023
Vancomycin	0	0	0	0	
Linezolid	0	0	0	0	
Tigecycline	0	0	0	0	
Tetracycline	18.8	20.5	9.4	11.2	0.037
Rifampicin	1.1	1.6	1	1.1	0.972
Trimethoprim-sulfamethoxazole	10	9.2	6.2	9.5	0.773

3.8 Trends of resistance to antibiotics by *Enterococcus faecalis* during the study period

Resistance to penicillin increased gradually from 6.7% in 2018 to 11% in 2021. On the other hand, since the first year (2018) of the study, there were low rates of ampicillin resistance (less than 1.4%) which continued until the last two years (2020 and 2021) of the study. Resistance to erythromycin showed a statistically significant decline from 97.5% in 2018 to 80.3% in 2020 with a P-value of 0.006, before increasing again to 91.1% in 2021. Fluoroquinolones demonstrated high rates of resistance during the first three years (2018, 2019, and 2020) of the study, with rates of more than 52%, which later in 2021 declined to 46.1% and 44.6% for ciprofloxacin and levofloxacin, respectively. *E. faecalis* showed almost no resistance rates to vancomycin and tigecycline, with susceptibility rates almost remaining unchanged during the study period. However, an increase in linezolid resistance was observed, with resistance rates increasing from 2.8% in the first year (2018) of the study to 11.8% during the last year (2021) of the study with a P-value of 0.001. High rates of resistance to tetracycline were observed during the study period, ranging from 86.1% in 2018 to 89.9% in 2021, while resistance to nitrofurantoin was very low during the study period, with the highest level of 2.1% recorded in 2020. *E. faecalis* almost completely resistant to quinupristin/dalfopristin during the study period. Also, show high resistance rate more than 50% for each of streptomycin high level and gentamycin high level during the study period. Please see figure C.1 in appendix C and table 8 for more information.

Table 8

Resistance rates of Enterococcus faecalis during the study period

Organism/Antibiotic	Resistance %				P-value
	2018	2019	2020	2021	
Enterococcus faecalis	n=152	n=171	n=141	n=218	
Penicillin	6.7	7.1	7.1	11	0.353
Ampicillin	1.4	2.3	0.7	0.6	0.205
Erythromycin	97.5	94.2	80.3	91.1	0.006
Ciprofloxacin	55.3	58.5	55.3	46.1	0.077
Levofloxacin	52	56.7	53.9	44.6	0.189
Vancomycin	0.1	0	0.1	0	0.948
Linezolid	2.8	4.8	5.2	11.8	0.001
Tigecycline	0	0	0	0.5	0.233
Tetracycline	86.1	88.9	86.3	89.9	0.639
Nitrofurantoin	0.7	0.6	2.1	0.9	0.475
Quinupristin/Dalfopristin	98.7	98.8	99.3	99.5	0.329
Streptomycin high level	54.3	58.8	54.3	52.5	0.662
Gentamycin high level	60.5	60	59.3	51.6	0.240

3.9 Trends of resistance to antibiotics by *Enterococcus faecium* during the study period

Throughout the study, there was a consistently high rate of resistance to penicillin, ranging from 87% to 95%, and a statistically significant increase in resistance to ampicillin from 79% to 95% with a P-value of 0.027 before decreasing to 89.6% in 2021. Resistance rates for erythromycin, ciprofloxacin, and levofloxacin were very high, over 97%, 91%, and 89% respectively, throughout the study period. Resistance to vancomycin was high, starting at 53.2% in the first year (2018) of the study and increasing to 62.4% in 2019 before declining to 60.4% in the final year (2021). Resistance to linezolid showed a statistically significant increase from 1.9% in 2018 to 7.1% in 2020 with a P-value of 0.042. Resistance rates for tigecycline were very low, less than 2% for the first three years (2018, 2019, and 2020) of the study, and zero in 2021. Resistance to tetracycline was also high, with rates exceeding 40% for the first three years (2018, 2019, and 2020) of the study and reaching 42% in 2021. Resistant to quinupristin/dalfopristin increased from 15.3% in 2018 to 34.7% in 2021 with P-value less than 0.001. Resistance to nitrofurantoin increased from 12.6% in 2018 to 36.4% in 2020 before decrease to 25% in 2021. *E. faecium* show high resistance rate more than 60% for each of streptomycin high level and gentamycin high level during the study period. Please see figure C.2 in appendix C and table 9 for more information.

Table 9

Resistances rates of Enterococcus faecium during the study period

Organism/Antibiotic	Resistance %				P-value
	2018	2019	2020	2021	
Enterococcus faecium	n=111	n=101	n=121	n=144	
Penicillin	87.4	94.1	95	91	0.145
Ampicillin	79	94.1	95	89.6	0.027
Erythromycin	100	99	99.1	97.6	0.124
Ciprofloxacin	91	95	95.9	92.4	0.401
Levofloxacin	89.2	93.1	94.2	91.7	0.536
Vancomycin	53.2	62.4	62	60.4	0.464
Linezolid	1.9	3	2.5	7.1	0.042
Tigecycline	1.8	1	1.7	0	0.224
Tetracycline	41.4	40.6	41.7	42	0.997
Quinupristin/Dalfopristin	15.3	18.8	10.7	34.7	< 0.001
Nitrofurantoin	12.6	22.8	36.4	25	0.155
Streptomycin high level	72.7	68.3	63	66	0.453
Gentamycin high level	64.5	70.3	67.5	77.8	0.108

Chapter Four

Discussion

This study analyzed antibiotic resistance in 7 high-priority pathogens, including *A. baumannii*, *P. aeruginosa*, *K. pneumoniae*, *E. coli*, *E. faecalis*, *E. faecium*, and *Staph aureus* in a tertiary hospital located in Palestine between 2018 and 2021. Its aim was to provide an overview of resistance trends for selected antibiotics while identifying the resistance rates for each isolated pathogen from the samples obtained during this period. This section discuss the study findings while comparing them with those of previous research studies that addressed similar concerns.

In this present study, the predominant pathogens that led to infections were *E. coli* (27%), *K. pneumoniae* (15. 5%), *E. faecalis* (14. 6%), *P. aeruginosa* (13%), *Staph aureus* (10. 6%), *E. faecium* (10. 2%), and *A. baumannii* (9%). Of all these pathogens found in this study, majority was from medical and surgical wards which is consistent with results of another systematic review conducted of the articles published on Medline PubMed between the years 2000 and 2020 in Arab countries concerning various antibiotic resistances among ESKAPE pathogens together with *E. coli* and retrieved only six articles. The review considered a total of 119,144 clinical isolates obtained in 19 Arab regions for antibiotic resistance and uncovered 74,039 isolates belonging to the ESKAPE pathogens. The most prevalent one was *E. coli* (46%), while *K. pneumoniae* (25%) ranked second followed by *P. aeruginosa* (16%), *MRSA* (6%), *A. baumannii* (5%), and *Enterobacter Spp.* (2%). (65)

In a previous study conducted on bacterial cultures obtained from the microbiology laboratory of NNUH to determine the frequency and antibiotic susceptibility of bacterial pathogens isolated in 2015 analyzed bacterial cultures from urine, pus, blood, and cerebrospinal fluid specimens. The goal was to determine the frequency and antibiotic susceptibility of bacterial pathogens isolated that year that showed *A. baumannii*, *P. aeruginosa*, *K. pneumoniae*, *E. coli*, *Enterococcus Spp.*, and *Staph aureus* were present in similar amounts. (39)

The current study found that *E. coli* was the most common pathogen isolated from urine samples. A study conducted in the West Bank Palestine over a period of 12 years revealed that *E. coli, CoNS, Streptococcus Spp., Staph aureus,* and *K. pneumoniae* were also isolated from urine samples, with frequencies of 47%, 19.6%, 18.4%, 4.9%, and 2.9%, respectively. (66) Similar findings were reported in studies conducted in Gaza strip (43), Poland, (67) Ethiopia, (64) India, (68) and Brazil. (69)

During the study period (2018, 2019, 2020, and 2021), the most commonly isolated pathogens from swab specimens were *E. coli*, *Staph aureus,* and *P. aeruginosa*. These findings are consistent with those of another study conducted in Nablus city, Palestine, which examined 30 wound swabs from patients with postoperative wound infections at Rafidia Hospital. *E. coli* and *Staph aureus* were the predominant pathogens, accounting for 56.7% and 30% of isolates, respectively. *K. pneumoniae*, *Enterobacter Spp*., and *A. baumannii* were also identified and accounted for 6.7%, 3.3%, and 3.3%, respectively. (70)

In our study, we found that *P. aeruginosa* and *K. pneumoniae* were the most frequently isolated pathogens in respiratory samples. Similar results were obtained in a cross-sectional observational study conducted in Bangladesh, where *K. pneumoniae* was the most common bacterium isolated (36.95%), followed by *P. aeruginosa* (21.73%), *Staph aureus* (15.21%), *Streptococcus pneumoniae* (10.86%), *Streptococcus pyogenes*, and *E. coli* (6.52%), as well as MRSA (2.17%). Moreover, in our study, we also isolated *A. baumannii*, *E. coli*, *E. faecium, E. faecalis,* and *Staph aureus* were isolated from respiratory samples. (71)

The current study found that *E. coli* and *Staph aureus* were the most frequently identified bacteria in blood samples, which agrees with a recent investigation conducted in Irbid-Jordan that examined the prevalence and features of bacteria detected in positive blood cultures in patients receiving treatment at King Abdullah University Hospital. The study reported that Gram-negative bacteria, including mainly *K. pneumoniae* and *E. coli,* accounted for 50.5% of the bacteria, while 49.5% were Gram-positive, with *Staphylococci Spp.* being the most common. (72)

During the period from January 2018 to December 2021, significant changes in antibiotic resistance rates were observed. Notably, there were higher rates of resistance to commonly prescribed antibiotics, and the emergence of carbapenem resistance in *K. pneumoniae* and *E. coli*. Conversely, there was a decrease in the resistance rates of *P.*

aeruginosa during this period, the establishment of an antimicrobial stewardship program (ASP) may be responsible for the decrease in antibiotic resistance.

Resistance to commonly used oral antibiotics including penicillin, ampicillin, amoxicillin-clavulanic acid, ciprofloxacin, and trimethoprim-sulfamethoxazole was observed at high levels, with an average resistance rate of 57.5%, 70.5%, 53.6%, 58.6%, and 54.4% respectively. This finding agrees with the literature, which suggests that the more frequently an antibiotic is used, the higher the likelihood of bacteria developing resistance to it. (73)

Gentamycin is available in the community pharmacies however; its total resistance rate during the study period was decrease from 42.2% in 2018 to 32.7% in 2021. Gentamycin dosage regimen (intramuscular injection twice daily) limits its use in the community to physician prescription. On the other hand, the relatively restricted use of antibiotics in hospitals may explain the lower resistance rates to hospital-only antibiotics (when compared with the antibiotics used in community pharmacies) such as amikacin 15.4%, tazobactam 35.1%, and meropenem 26.5%.

A research conducted in Gaza strip investigated the treatment of 141 individuals who had community-acquired pneumonia at the European Gaza Hospital. The study revealed that doctors prescribed 18 different antibiotic regimens and only two patients (2%) underwent microbiological testing. The findings indicated that physicians did not follow current standards of care regarding the management and severity of community-acquired pneumonia. The use of various antibiotic regimens without microbiological guidance was inappropriate and increased the risk of antibiotic resistance. (74)

At NNUH, carbapenem resistance in *E. coli* is still relatively low, but there was a significant increase observed during the study period from 1.5% to 5.1%. In contrast, a cross-sectional study conducted over seven months from September 2016 to March 2017 in three major hospitals in Gaza (Al-Shifa, Al-Naser, and the European Gaza hospitals) showed higher rates of carbapenem resistance. Among Enterobacteriaceae, carbapenem resistance was observed in 13.2% (30/226) of clinical isolates, while no resistance was found in *P. aeruginosa* (0/21). *Klebsiella Spp.* was the most resistant to carbapenems with a resistance rate of 14.4% (13/90), followed by *E. coli* with a rate of 9.8% (9/91). The resistance observed may be due to the recent introduction of carbapenem use in Gaza. (75) In the Arab world, most studies report a low prevalence of Carbapenem Resistant

Enterobacteriaceae (CRE), with the proportion of resistant isolates not exceeding 5%. (76)

Additionally, the results indicate that there is a rising tendency in the rates of resistance to ampicillin and trimethoprim-sulfamethoxazole, with ampicillin resistance being one of the highest compared to other antibiotics. This observation is in line with a review of published articles on antibiotic-resistant bacterial isolates from patients and hospital environments in Gaza strip/Palestine from 2002 to 2021. However, our study also found a decreasing trend in resistance to amoxicillin/clavulanic acid and amikacin. This decrease in antibiotic resistance might be ascribed to the introduction of ASP. Conversely, there were differences in *E. coli* resistance rates to piperacillin/tazobactam, ciprofloxacin, and gentamycin. (43)

A noteworthy and concerning rise in carbapenem resistance rates of *K. pneumoniae* was observed, which increased from 12.9% in 2018 to 29%, and this increase was statistically significant (P-value = 0.04). This finding is consistent with the results of a multicenter Point-Prevalence Survey conducted in April 2018 in seven Middle Eastern countries including Egypt, Kingdom of Saudi Arabia, United Arab Emirates, Lebanon, Oman, Kuwait, and Bahrain, where carbapenem-resistant organisms among Enterobacteriaceae ranged from 10 to 30%. (75,77)

During the study period *K. pneumoniae* was completely resistant to ampicillin which is consistent with the literature because of the natural resistance of *K. pneumoniae* to ampicillin. (63) Additionally, *K. pneumoniae* showed high rates of resistance to amoxicillin-clavulanic acid, piperacillin/tazobactam, ciprofloxacin, gentamicin, trimethoprim-sulphamethoxazole, and nitrofurantoin, but a low resistance rate to amikacin. A prior study from Palestine in 2020 using PCR technique, hypermucoviscosity (HMV) phenotype, and antibiotic resistance profile aimed to determine the frequency of virulence genes in *K. pneumoniae* isolates. Sixty-six *K. pneumoniae* isolates were collected from various clinical sources in Palestine, and the resistance rates to various antibiotics were higher than our results and were reported as follows: aztreonam (77%), amoxicillin/clavulanic acid (82%), tetracycline (71%), imipenem (59%), levofloxacin (44%), ceftriaxone (67%), ceftazidime (56%), kanamycin (58%), and trimethoprim/sulphamethoxazole (89%) but resistant rate for ciprofloxacin (40%) was lower than our result. (78)

During the first three years (2018, 2019, and 2020) of the study, a significant decrease was observed in antibiotic resistance rates for *P. aeruginosa*, especially toward carbapenem, aminoglycosides, and cephalosporins that had antipseudomonal activity with P-value < 0.001. Additionally, resistance to piperacillin/tazobactam also declined significantly with a P-value < 0.008, this decline in antibiotic resistance could be attributed to the implementation of ASP, aimed at curbing the use of broad-spectrum antimicrobials such as anti-pseudomonal agents. The program was implemented in 2019 across all wards at NNUH. However, during the final year (2021) of our study, coinciding with the COVID-19 pandemic, we noted an uptick in resistance rates for *P. aeruginosa*. Despite this concerning trend, there was no change in the overall number of clinical isolates of *P. aeruginosa*, suggesting that their efforts to control resistant strains through ASP were effective. Additionally, they were successful in reducing usage of antipseudomonal drugs without any changes made to infection control and preventive methods.

At the beginning of the study, *P. aeruginosa* showed significant resistance rates to various antibiotics, including imipenem, meropenem, ciprofloxacin, and piperacillin - ranging up to 50%. However, aminoglycosides had lower resistance rates, with tobramycin exhibiting a resistance rate of 43.1%, while gentamicin and amikacin exhibited rates of 48.4% and 45.8%, respectively. Similarly, cephalosporins showed considerable levels of antibiotic resistance with ceftazidime and cefepime displaying rates up to almost 50%. In contrast, piperacillin/tazobactam exhibited one of the lowest antibiotic resistance rates at around 28%. Comparison with another study from the Arab region that examined β-lactamase and antibiotic-resistant *P. aeruginosa* between 2011-2018 revealed similar findings during their period of investigation. (79)

During the study period, *A. baumannii* exhibited high resistance rates to all tested antibiotics. This aligns with the growing prevalence of carbapenem-resistant *A. baumannii* (CRAB) worldwide and is particularly prevalent in the Arab world, where 87.0% of *A. baumannii* isolates collected from 13 Lebanese hospitals between 2015-2016 were CRAB. Prior to COVID-19, antimicrobial resistance was a cause for concern in the region, with carbapenem resistance levels in *Acinetobacter Spp*. varying between 70 and 80% across Levant, Gulf, and Egypt. (80)

According to this study, there was a significant decrease of minocycline resistance trend during the study period, dropping from 42.9% in 2018 to 15.8% in 2021, with a P-value of less than 0.001. Minocycline has been recommended as a possible treatment for drug-resistant *A. baumannii.* However, about 20% of *A. baumannii* strains have become resistant to minocycline since its introduction, (81) combining minocycline therapy with colistin has proven to be effective in treating minocycline-resistant *A. baumannii* infections in most cases. Moreover, minocycline therapy, when combined with rifampicin, colistin, or imipenem, has a synergistic effect. (82)

The study found that *Staph aureus* had high resistance rates to penicillin G, ranging from 91.1% in 2019 to 95.5% in 2021, while resistance to oxacillin declined from 51.1% in 2018 to 42.3% in 2020, before sharply increasing in the last year (2021) to reach 55.3%. The resistance rates to gentamycin, tetracycline, rifampicin, and trimethoprim-sulphamethoxazole were less than 8%, 21%, 2%, and 10%, respectively. However, over 50% of the *Staph aureus* isolated during the study period were *MRSA*. On the other hand, all isolates were fully sensitive to vancomycin, tigecycline, and linezolid. The proportion of MRSA was higher than in a previous study that investigated the prevalence of nasal carriage of *Staphylococcus aureus* and MRSA strains among 360 healthy university students at An-Najah National University in 2013, where MRSA accounted for only 9% of *S. aureus* isolates. In that study, all strains of *S. aureus* were sensitive to vancomycin, but 98%, 93%, 33%, 23%, and 12% of the isolates were resistant to penicillin G, amoxicillin/clavulanic acid, ciprofloxacin, erythromycin, and clindamycin, respectively. (41) These findings were consistent with a systematic literature review conducted between January 2011 and June 2018, which identified observational studies on antimicrobial resistance. The review found that the overall median percentage of methicillin-resistance in *S. aureus* was 45.1%. (83)

Vancomycin resistance among *Enterococci* has been rarely reported from Palestine and the region. In the Arab world, study at a tertiary care center in Saudi Arabia reported a prevalence of 17.3%. (84) Another study in Lebanon conducted a retrospective review of surveillance data from 2010 until 2018 with a prevalence reaching 5.9%. (85) In our study, infections due to VRE have traditionally amounted to a handful of cases every year with 53.2% during 2018 reaching more than 60% during the last three years (2019, 2020, and 2021) of the study. Moreover, *E. faecalis* showed complete sensitivity to vancomycin while all VRE was restricted to *E. faecium* which is consistent with a result of a three-year prospective study conducted to evaluate the trend of vancomycin-resistant enterococci bacteremia in a tertiary care hospital of South India. The study reveals that of the total 427 Enterococcus species isolated, 63 (45.6%) were VRE. Among them, 51/63 (81%) were *E. faecium* and 5/63 (8%) were *E. faecalis.* (86)

While some trends in AMR can be explained, there is still a lot of complexity and genetic dynamism involved in the development and spread of resistance. This means that resistance can be unpredictable and difficult to control, and new resistant strains can emerge rapidly.

4.1 Limitations

Due to the retrospective nature of our study, there are several limitations that should be acknowledged. Although the health facility maintains good clinical and laboratory services with proper documentation, it cannot guarantee that retrospective data meets the highest quality standards of a well-conducted prospective study. Standard procedures were used for sample collection, microbiological analysis, and report updates, but they may have been performed by different personnel over the 4-year period, potentially introducing inter-personnel variations in laboratory procedures.

Moreover, the study was conducted in a single center, which may not be representative of the overall resistance patterns in the entire population of Palestine. Additionally, the study did not differentiate between community-acquired and hospital-acquired infections, which may have different resistance patterns and risk factors. Finally, the study did not investigate the underlying mechanisms of resistance or the genetic factors that contribute to resistance, which may have important implications for the development of new therapies and the control of antibiotic resistance.

4.2 Conclusion and recommendations

The study finds several key trends in antibiotic resistance of bacterial infections at a tertiary care hospital in Nablus, Palestine. These trends included significant rates of resistance to commonly given antibiotics and the emergence of carbapenem resistance in *K. pneumoniae*. The most prevalent pathogens observed in urine and swab samples were *E. coli* and *Staph aureus*, respectively, whereas *K. pneumoniae* and *P. aeruginosa* had the biggest contributions in respiratory specimens. The study also revealed that medical and surgical wards had the highest incidence of isolates during the study period. Furthermore, *E. coli* was the most prevalent pathogen isolate in all wards except the dialysis ward, where *Staph aureus* was the most common isolate.

Furthermore, the study found a significant level of antibiotic resistance to the most commonly used antibiotics in the health sector, as well as antibiotics of first choice as empirical therapy for life-threatening conditions including sepsis and meningitis. Resistance rates were high for amoxicillin/clavulanic acid, ampicillin, and penicillin. In compared to other studies, cefepime, ceftazidime, clindamycin, ciprofloxacin, and trimethoprim sulfamethoxazole showed alarming resistance rates. Amikacin, tazobactam, vancomycin, rifampicin, and meropenem, on the other hand, had the lowest resistance rates among the other antibiotics.

The antibiotics identified in this study as significant are prescription drugs that should only be taken as prescribed. However, a lack of information regarding optimum dose and adherence to the schedule, as well as misuse or usage for personal convenience, may be factors affecting the development of resistance. Proper hygienic measures, as well as patient treatment and care, may all have an effect on the dissemination of resistance genes in the environment. In addition, preliminary screening procedures for resistant strains must be developed in order to identify and isolate instances, preventing infection dissemination and driving future resistance.

We recommend that bigger healthcare institutions frequently monitor and evaluate emerging patterns and trends in antimicrobial resistance (AMR) in order to effectively prioritize, plan, and execute facility-level policies and recommendations for the optimal use of antimicrobial medications.

Based on these findings, additional study should be undertaken in Palestine to examine or link antibiotic prescription practices and subsequent AMR patterns. The study also suggests comparing AMR prevalence in hospital-acquired infections (HAIs) with community-acquired infections to better focus therapies. Understanding the variables that contribute to antibiotic resistance in the local environment allows public health officials and healthcare practitioners to take efforts to reduce resistance propagation and enhance patient outcomes.

List of Abbreviations

Abbreviation	**Meaning**
AMR	Antimicrobial resistance
AR	Antibiotic-Resistance
A. baumannii	*Acinetobacter baumannii*
ASP	The Antimicrobial Stewardship Program
CDC	Centers for Disease Control and Prevention
CDDEP	Center for Disease Dynamics, Economics & Policy
CLSI	Clinical and Laboratory Institute.
CoNS	*Coagulase-negative Staphylococci*
CRAB	Carbapenem Resistant *Acinetobacter baumannii*
CRE	Carbapenem Resistant Enterobacteriaceae
E. coli	*Escherichia coli*
E. faecalis	*Enterococcus faecalis*
E. faecium	*Enterococcus faecium*
ESKAPE	*Escherichia coli, Staph aureus, Klebsiella pneumonia, Acinetobacter baumannii, Pseudomonas aeurginosa, Enterococcus faecalis* and *Enterococcus faecium.*
GLASS	Global Antimicrobial Resistance and Use Surveillance System
GNB	Gram-negative Bacteria
GN	Gram-Negative
GP	Gram-Positive
HAIs	hospital-acquired Infections

HMV	Hyper-mucoviscosity
IRB	Institutional Review Boards
K. pneumoniae	*Klebsiella pneumoniae*
MDR	Multidrug-resistant
MENA	Middle East and North Africa
MIC	Minimal Inhibitory Concentration
MRSA	Methicillin Resistant *Staph aureus*
NNUH	An-Najah National University Hospital
P. aeruginosa	*Pseudomonas aeruginosa*
SPSS	Statistical Package of Social Science
Staph aureus	*Staphylococcus aureus*
UTI	Urinary Tract Infection
WHO	World Health Organization

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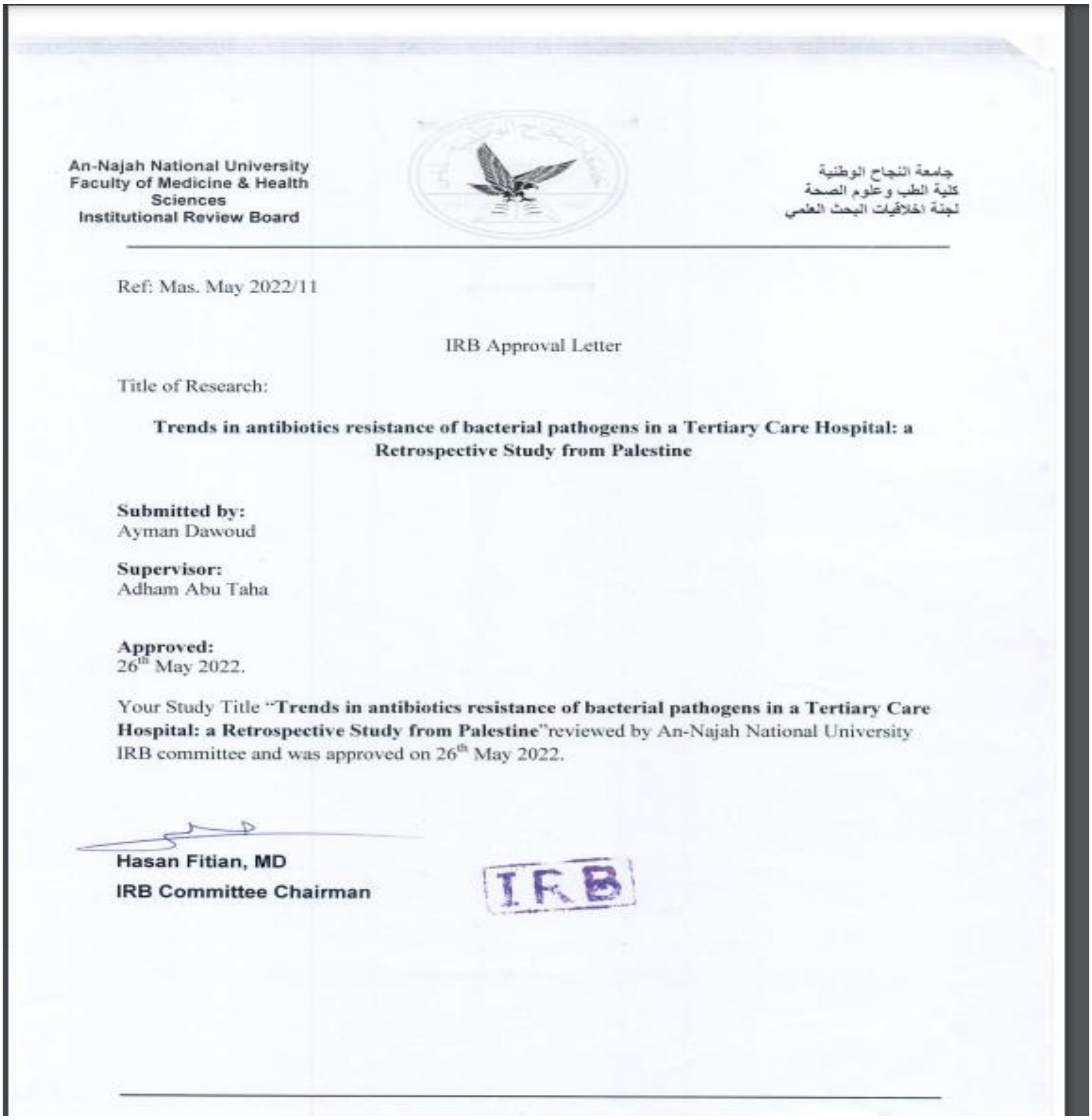
Appendix A

IRB Approval Letter



An-Najah National University
Faculty of Medicine & Health Sciences
Institutional Review Board

جامعة النجاح الوطنية
كلية الطب وعلوم الصحة
لجنة اخلاقيات البحث العلمي

Ref: Mas. May 2022/11

IRB Approval Letter

Title of Research:

Trends in antibiotics resistance of bacterial pathogens in a Tertiary Care Hospital: a Retrospective Study from Palestine

Submitted by:
Ayman Dawoud

Supervisor:
Adham Abu Taha

Approved:
26th May 2022.

Your Study Title "**Trends in antibiotics resistance of bacterial pathogens in a Tertiary Care Hospital: a Retrospective Study from Palestine**"reviewed by An-Najah National University IRB committee and was approved on 26th May 2022.

Hasan Fitian, MD
IRB Committee Chairman

IRB

Appendix B

Tables

Table B.1

Distribution of bacterial isolates in specimens analyzed during the study period

Specimen/Organism	Years				
Urine	2018	2019	2020	2021	Total
Acinetobacter baumannii	15	12	12	27	66
Pseudomonas aeruginosa	32	27	24	43	126
Escherichia coli	145	160	152	207	664
Klebsiella pneumoniae	46	65	61	73	245
Staph aureus	4	3	5	17	29
Enterococcus faecium	36	32	43	42	153
Enterococcus faecalis	62	79	63	126	330
Swabs	2018	2019	2020	2021	Total
Acinetobacter baumannii	52	35	27	39	153
Pseudomonas aeruginosa	66	64	38	70	238
Escherichia coli	67	80	48	95	290
Klebsiella pneumoniae	36	49	39	62	186
Staph aureus	47	64	54	80	245
Enterococcus faecium	39	31	31	40	141
Enterococcus faecalis	47	52	32	49	180
Respiratory	2018	2019	2020	2021	Total
Acinetobacter baumannii	34	24	17	25	100
Pseudomonas aeruginosa	21	31	24	33	109
Escherichia coli	11	14	13	13	51
Klebsiella pneumoniae	28	30	35	35	128
Staph aureus	13	17	13	18	61
Enterococcus faecium	15	20	21	32	88
Enterococcus faecalis	15	18	19	16	68
Blood	2018	2019	2020	2021	Total
Acinetobacter baumannii	15	11	11	14	51
Pseudomonas aeruginosa	15	27	16	11	69
Escherichia coli	16	19	34	35	104
Klebsiella pneumoniae	12	19	24	29	84
Staph aureus	26	22	17	37	102

Enterococcus faecium	8	6	6	7	27
Enterococcus faecalis	11	6	12	5	34
Fluids	2018	2019	2020	2021	Total
Acinetobacter baumannii	9	4	5	8	26
Pseudomonas aeruginosa	9	3	10	9	31
Escherichia coli	16	17	42	38	113
Klebsiella pneumoniae	5	8	15	31	59
Staph aureus	5	7	5	18	35
Enterococcus faecium	8	5	15	16	44
Enterococcus faecalis	10	7	11	16	44
Tissues	2018	2019	2020	2021	Total
Acinetobacter baumannii	6	4	3	9	22
Pseudomonas aeruginosa	12	9	2	10	33
Escherichia coli	7	11	7	11	36
Klebsiella pneumoniae	4	3	6	8	21
Staph aureus	1	10	3	9	23
Enterococcus faecium	5	7	5	7	24
Enterococcus faecalis	7	9	4	6	26

Table B.2

Distribution of Department and bacterial isolates analyzed, NNUH 2018–2021

Department/Organism	Years				
Medical	2018	2019	2020	2021	Total
Acinetobacter baumannii	64	30	8	37	139
Pseudomonas aeruginosa	44	60	23	35	162
Escherichia coli	62	69	62	93	286
Klebsiella pneumoniae	33	46	36	60	175
Staph aureus	28	30	11	39	108
Enterococcus faecium	45	41	42	59	187
Enterococcus faecalis	41	42	36	49	168
Surgical	2018	2019	2020	2021	Total
Acinetobacter baumannii	48	33	46	59	186
Pseudomonas aeruginosa	62	50	41	58	211
Escherichia coli	77	84	105	136	402
Klebsiella pneumoniae	*47*	*68*	*97*	*101*	*313*

Staph aureus	20	28	28	37	113
Enterococcus faecium	52	38	59	55	204
Enterococcus faecalis	63	50	54	72	239
Pediatric	2018	2019	2020	2021	Total
Acinetobacter baumannii	1	9	4	7	21
Pseudomonas aeruginosa	2	10	11	21	44
Escherichia coli	9	10	8	14	41
Klebsiella pneumoniae	10	12	12	13	47
Staph aureus	7	11	4	13	35
Enterococcus faecium	2	7	1	2	12
Enterococcus faecalis	4	7	3	2	16
Emergency	2018	2019	2020	2021	Total
Acinetobacter baumannii	3	8	8	8	27
Pseudomonas aeruginosa	9	15	18	23	65
Escherichia coli	35	40	57	55	187
Klebsiella pneumoniae	15	20	18	28	81
Staph aureus	7	14	12	35	68
Enterococcus faecium	4	6	15	16	41
Enterococcus faecalis	14	32	18	35	99
Out patient	2018	2019	2020	2021	Total
Acinetobacter baumannii	13	7	8	8	36
Pseudomonas aeruginosa	32	24	18	29	103
Escherichia coli	70	89	58	87	304
Klebsiella pneumoniae	20	21	9	31	81
Staph aureus	23	24	27	37	111
Enterococcus faecium	7	9	4	10	30
Enterococcus faecalis	25	38	28	56	147
Dialysis	2018	2019	2020	2021	Total
Acinetobacter baumannii	2	3	1	3	9
Pseudomonas aeruginosa	6	2	3	10	21
Escherichia coli	9	9	6	14	38
Klebsiella pneumoniae	6	7	8	5	26
Staph aureus	11	16	15	18	60
Enterococcus faecium	1	0	0	2	3
Enterococcus faecalis	5	2	2	4	13

Appendix C

Figures

Figure C.1

Trends of resistance to certain antibiotics by E. faecalis, NNUH 2018-202

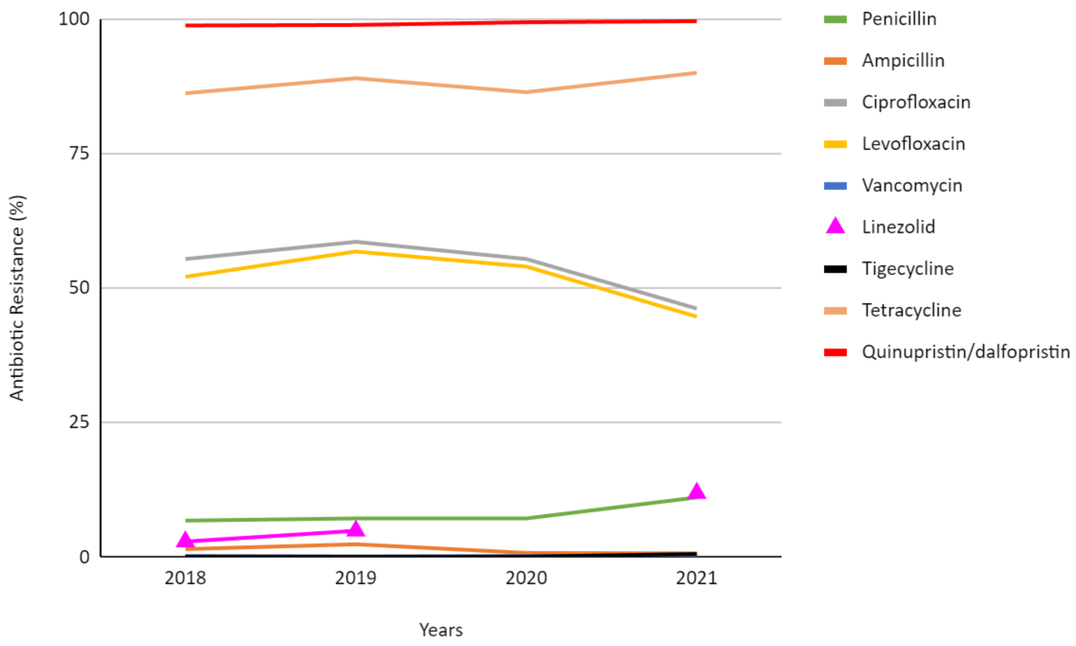
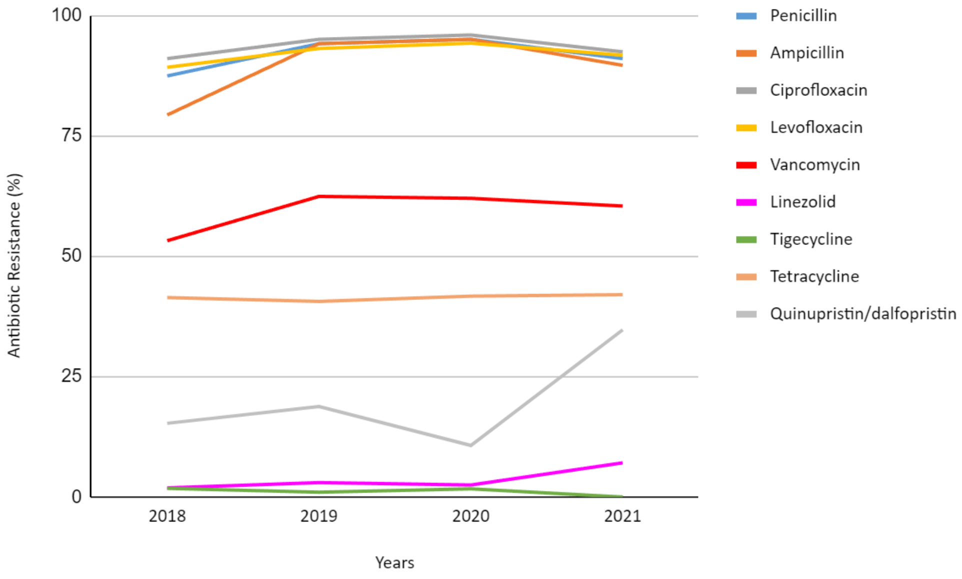


Figure C.2

Trends of resistance to certain antibiotics by E. faecium, NNUH 2018-2021



جامعة النجاح الوطنية

كلية الدراسات العليا

الاتجاهات في مقاومة المضادات الحيوية لمسببات الأمراض البكتيرية في مستشفى رعاية ثالثية: دراسة بأثر رجعي من فلسطين

إعداد

أيمن داود

إشراف

د. أدهم أبو طه

قدمت هذه الرسالة استكمالا لمتطلبات الحصول على درجة الماجستير في مكافحة ضبط والعدوى، من كلية الدراسات العليا، في جامعة النجاح الوطنية، نابلس– فلسطين.

2023

الاتجاهات في مقاومة المضادات الحيوية لمسببات الأمراض البكتيرية في مستشفى رعاية ثالثية: دراسة بأثر رجعي من فلسطين

إعداد

أيمن داود

إشراف

د. أدهم أبو طه

الملخص

أصبحت مقاومة المضادات الحيوية مشكلة صحية عامة رئيسية في جميع أنحاء العالم، مساهمة في تفاقم العدوى والإقامة في المستشفيات لفترات أطول. هدفت هذه الدراسة إلى تقييم الوضع الحالي لمقاومة المضادات الحيوية في نابلس، فلسطين، وتحديد الاتجاهات في معدلات المقاومة للمضادات الحيوية من الخط الأمامي والخط الأخير.

تم إجراء استعراض تدقيقي لسجلات سابقة للبيانات التي تم جمعها من قسم علم الأحياء الدقيقة في مستشفى رعاية تعليمية ثالثية خلال الفترة من يناير 2018 حتى ديسمبر 2021. كان موضوع اهتمام الدراسة هو معدل مقاومة العزلات البكتيرية. تم استخدام Microsoft Excel 2019 لرسم الاتجاهات من 2018 إلى 2021 وتم استخدام برنامج Statistical Package of Social Science (SPSS) الإصدار 26 للتحليل الإحصائي.

تم تحليل ما مجموعه 4659 عزلة، من 7 انواع بكتيريا مهمة طبيًا. 34.6٪ من العزلات كانت من البول و30.8٪ من المسحات و4٪ من الأنسجة. كانت الإشريكية القولونية (27٪) أكثر مسببات الأمراض شيوعًا ، يليها الكليبسيلا الرئوية (15.5٪) والأقل شيوعًا هي الراكدة البومانية (9٪). كانت المقاومة هي الأعلى للأمبيسلين يليها البنسلين، وكلاهما تراوح بين 55 و75٪ على مدى السنوات الأربع للدراسة. لوحظ انخفاض كبير إحصائيًا في مقاومة المضادات الحيوية الشائعة الاستخدام في الأموكسيسيلين/الكلافولانيك المقاوم

لحمض الإشريكية القولونية. من ناحية أخرى، لوحظت زيادات ذات دلالة إحصائية في مقاومة المضادات الحيوية في الإشريكية القولونية والكليبسيلا الرئوية المقاومة للكاربابينيم.

بالنسبة للكليبسيلا الرئوية هناك زيادات ذات دلالة إحصائية في مقاومة تريميثوبريم–سلفا – ميثوكسازول وانخفاض إحصائيًا لنورفلوكساسين.

كانت هناك زيادة في المقاومة للمضادات الحيوية من النوع الأخير مثلا لبكتيريا المعوية المقاومة لللاينزوليد، و البكتيريا المعوية البرازية المقاومة للفانكومايسين. ومع ذلك، أظهرت الزائفة الزنجارية اتجاه تناقص في مقاومة المضادات الحيوية معتد به إحصائياً.

توفّر هذه الدراسة رؤى مهمة حول الوضع الحالي لمقاومة المضادات الحيوية في نابلس، فلسطين. تشير النتائج إلى أن مقاومة المضادات الحيوية تشكّل مشكلة كبيرة في المنطقة، حيث يتم ملاحظة مستويات عالية من المقاومة للمضادات الحيوية المستخدمة عادةً، بما في ذلك الأمبيسيلين والبنسلين. وعلاوة على ذلك، كشفت الدراسة عن اتجاه مقلق لزيادة المقاومة للمضادات الحيوية الأخيرة، مثل الكاربابينيم واللينيزوليد، التي تعتبر ضرورية لعلاج العدوى البكتيرية المتعددة المقاومة للأدوية. وتسلط النتائج الضوء أيضًا على الحاجة إلى مراقبة مستمرة لأنماط مقاومة المضادات الحيوية وتطوير استراتيجيات للحد من ظهور وانتشار الأمراض البكتيرية المقاومة للمضادات الحيوية. وبشكل عام، تؤكد هذه الدراسة على الحاجة الملحة لتحسين ممارسات رعاية المضادات الحيوية ومكافحة العدوى في نابلس، فلسطين، وتؤكد أهمية الجهود العالمية لمكافحة مقاومة المضادات الحيوية.

الكلمات المفتاحية: مقاومة مضادات الميكروبات، نابلس، فلسطين، المراقبة، برامج الإشراف، الخط الأول، المضادات الحيوية الأخيرة.