UNIVERSITY FOR DEVELOPMENT STUDIES

PREVALENCE AND RESISTANCE PROFILE OF BACTERIAL INFECTIONS AND FACTORS ASSOCIATED WITH MULTIDRUG RESISTANCE IN THE NORTHERN REGION OF GHANA

JEAN-PIERRE GNIMATIN

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BY

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APRIL, 2023

DECLARATION

Student

I hereby declare that this thesis is the result of my original work and that no part of it has been presented for another degree in this University or elsewhere:

Candidate's signature: ……  …… Date: 04/04/2023

Name: **Jean-Pierre Gnimatin**

Supervisor

I hereby declare that the preparation and presentation of the thesis were supervised following the guidelines on supervision of the thesis laid down by the University for Development Studies.

Supervisor`s signature  Date: 05/04/2023

Name: **Prof. Martin Nyaaba Adokiya**

DEDICATION

I wish to dedicate this work to my mother, Amévi Camille Monique Adjovi. Thank you for your prayers, your blessings, and for checking on me in the morning at sunrise and in the evening at sunset, every single day during all these years spent far from my native land.

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ABSTRACT

Problem statement: Bacterial infections caused by multidrug resistant organisms are a major global threat; however, there remains a knowledge gap on this situation in Ghana, especially in its northern Region. The objective of this study was therefore to determine the prevalence and resistance profile of bacterial infections. It also identified factors associated with multidrug resistance in the study area.

Methodology: The study employed a quantitative approach with a retrospective analytic design. Data from specimens obtained at Zonal Public Health Laboratory located in Tamale from June 2018 to May 2022 were collected and retrospectively analysed. The samples included all specimen types possible. The specimens were collected for the purpose of clinical bacteriology diagnostics. R Software, was used to perform the statistical analysis. Binary logistic regression analyses were used to determine factors associated with multidrug resistance.

Main findings: Altogether, 1222 non-duplicated isolates were collected. The three (3) main bacteria responsible for infections were: *Klebsiella spp*., *Moraxella spp*., and *Escherichia spp*. respectively with respectively 27%, 22%, and 16%. High resistance levels were found against the tested antibiotics and about 41.60% of the bacterial strains isolated were multidrug resistant. The study's results uncovered determinants of multidrug resistance within the region. Hospitalization was associated with multidrug resistance in the univariate analysis (Crude OR: 1.96; 95% with CI 1.43–2.71; $P < 0.001$) and also in the multivariable analysis (Adjusted OR: 1.78; 95% with CI 1.28–2.49; $P < 0.001$).

Conclusion and recommendations: There is a need for further research on the epidemiology of antibiotic resistance genes in the study area to effectively control the spread of multidrug resistant pathogens. In addition, efforts to build the capacity of health professionals on infection prevention and control as well as diagnostic and antimicrobial stewardship needs urgent attention.

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LIST OF ABBREVIATION

AOR	Adjusted odds ratio
AMR	Antimicrobial resistance
CI	Confidence interval
COR	Crude odds ratio
ESBLs	Extended-spectrum β-lactamases
GHS	Ghana Health Service
GNB	Gram-negative bacteria
MDR	Multidrug resistance
MDRO	Multidrug resistant organism
TTH	Tamale Teaching Hospital
TZPHRL	Tamale Zonal Public Health Reference Laboratory
WHO	World Health Organization

CHAPTER ONE

1.0 INTRODUCTION

1.1 Background

Antimicrobial resistance (AMR) represents a threat at the global level. Infections caused by multidrug resistant organisms (MDROs), which result in significantly fewer treatment options, are ranked among the top global public health concerns (Laxminarayan et al., 2020; Tangcharoensathien et al., 2017).

In hospitals, antibiotics are frequently prescribed and used to treat patients. In these environments, bacteria are exposed to antibiotics more frequently, and in order to survive, these organisms resort to developing mechanisms that could allow them to escape the effects of antimicrobial compounds. Consequently, bacteria may become resistant to one or many of these antibiotics (Aslam et al., 2018). This has had as consequence the emergence and rapid spread of strains called Multidrug Resistant which can withstand the action of a minimum of one antibiotic agent from three (03) or more antibacterial categories (Magiorakos et al., 2012). In both communities and hospitals, these resistant pathogenic organisms regularly cause serious infections. They may be involved in infections of the respiratory system, urinary system, bloodstream (sepsis), post-operative wounds, and pneumonia (Lanks et al., 2019; Liu & Dickter, 2020; Markwart et al., 2020).

High frequencies of multidrug resistant pathogens have been reported in hospital settings, according to several research conducted in various African nations, including Ghana (Agyepong et al., 2018; Asante et al., 2021; Feglo & Adu-Sarkodie, 2016; Kayode et al., 2020; Million et al., 2020; Moges et al., 2021; Odoi et al., 2022; Zachariah et al., 2021). A 2015 nationwide laboratory

surveillance in Ghana revealed that the country had high levels of pathogenic organisms which were able to resist the effect of most antibiotics (Opintan et al., 2015).

Additionally, findings from an investigation of prescription of antibiotics at the Tamale Teaching Hospital (TTH), the sole tertiary-level referral hospital in the northern Ghana, found a high rate of antibiotic abuse along with incomplete treatment, off-label prescription, and probable interactions. There were approximately 385 instances of antibiotic abuse, including 335 prescription mistakes and 50 unfinished treatments, with treatment length being the most frequently mis-prescribed element (29.6%) (García-Vello et al., 2020).

However, limited knowledge is available at the regional level regarding the prevalence of bacterial pathogens responsible for infections and the factors associated with their multidrug resistance. Multidrug resistant bacterial infections in this region must therefore be investigated by analysing the most recent data available and to provide stakeholders and public health leaders with meaningful information to aid in decision-makings and the implementation of control measures.

1.2.Problem statement

On an agar plate, Alexander Fleming observed in 1928 a region where the bacteria did not proliferate around an invading fungus. The author was able to isolate and identify penicillin as the mod's active agent. With regard to staphylococci and other gram-positive pathogens, that agent exhibited antibacterial capabilities. Nevertheless, the author was unable to remove the unstable chemical from the extract despite his best efforts (Gaynes, 2017). It took until 1941 for an Oxford University team to purify enough penicillin to start evaluating its therapeutic efficacy. The researchers made the decision to publish their clinical outcomes in the end after seeing significant success with the patients who received the drug (Abraham et al., 1941).

Since then, antibiotics have been widely employed in the medical field. Antibiotics are not just used to cure serious infections; they have also made it feasible to treat cancer, transplant organs, and perform open-heart surgery, among other advanced medical procedures (Bae et al., 2022; Chan et al., 2020; Gao et al., 2020). Perhaps the most significant medical achievement of the 20th century was the development of antibiotics for use in clinical settings (Katz & Baltz, 2016).

This epoch of medical enlightenment, unfortunately, was quickly interrupted. Microorganisms have acquired and are still developing sophisticated defense mechanisms against the effects of antimicrobial agents as a consequence of inappropriate and widespread usage of antibiotic compounds. The major resistance mechanisms include reduced drug absorption, altered drug targets, drug inactivation, as well as active drug efflux. These processes can be innate to the microorganisms or acquired through conjugation from other microbes (Reygaert, 2018; Uddin et al., 2021).

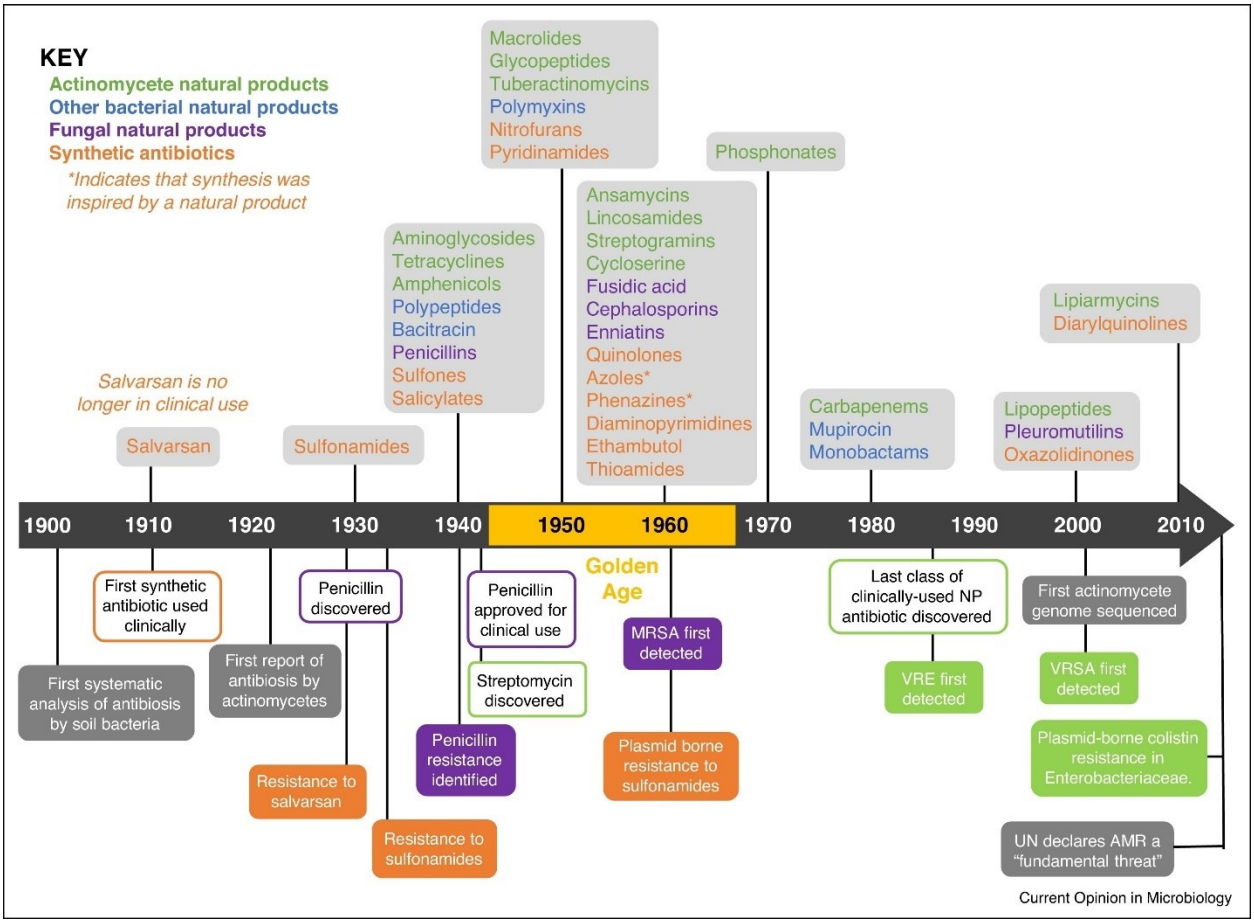

Figure 1: Chronology of the decades during which (Hutchings et al., 2019)

Chronology of the decades during which new classes of antibiotics were introduced into clinical practice

Numerous bacterial infections linked to human disease epidemics have developed into multidrug resistant (MDR) types. For instance, MDR *Mycobacterium tuberculosis* is a redoubtable form of the pathogen that is present in many low-and-middle-income countries (LMICs) as well as some high-income countries, where it is involved in severe and difficult-to-treat forms of tuberculosis (Seung et al., 2015). Other harmful infections are from nosocomial sources (hospital-related) (Davies & Davies, 2010; Reynolds et al., 2022).

The World Health Organization previously unveiled an exhaustive list on priority microorganisms highlighting gram-negative bacteria with "critical priority" drug-resistance which constitute serious health challenges worldwide (Tacconelli et al., 2018), and many of the pathogens previously mentioned were on this list. Statistics from 204 nations and territories were used in a study, which found 1.27 million of the total of 4.95 million lives lost related to AMR in the year 2019 were caused by drug-resistant illnesses. Additionally, AMR was found to be more lethal compared to the other two significant infectious diseases such as HIV/AIDS and malaria (Murray et al., 2022). In Ghana, numerous studies in the southern part of the country have documented the presence of multidrug resistant pathogens in patients, and in hospital environment and they have even been implicated in the contamination of raw meat for sale (Agyepong et al., 2018; Baah et al., 2022; Duedu et al., 2017; Labi et al., 2020). Nevertheless, in the northern region, the scientific literature on this public health threat is very poor. This poses a serious problem as effective interventions to tackle this problem will be limited or even non-existent.

1.3.Study significance

This study holds critical importance within the global public health landscape as it narrows its focus onto the previously underexplored Northern Region of Ghana. It delves into the pressing issue of bacterial infections and multidrug resistance, which poses a substantial threat worldwide by significantly limiting treatment options and causing adverse health outcomes. By examining the prevalence and resistance patterns unique to this region, our research contributes indispensable data to the ongoing global battle against antimicrobial resistance (AMR). Furthermore, this study

addresses an existing void in current academic literature. While numerous studies have documented multidrug-resistant pathogens in various African countries, including Ghana, the Northern Region has remained conspicuously understudied. This research endeavors to bridge this gap by providing insights tailored specifically to this region, which are crucial for tailoring interventions and policies that can effectively address the specific challenges faced within this area.

Understanding the underlying factors associated with multidrug resistance is pivotal for the optimization of healthcare services. The identification of a high rate of antibiotic misuse and prescription errors at the Tamale Teaching Hospital underscores the need for targeted interventions aimed at improving prescribing practices. This study aims to enlighten healthcare providers and policymakers with evidence-based strategies for antibiotic stewardship and infection control measures. Ultimately, findings of this research will guide the implementation of practical control measures, including focused surveillance, well-planned antibiotic stewardship programs, and effective infection prevention strategies. By providing stakeholders and public health leaders with such invaluable information, our study empowers them to make informed decisions and effectively combat the proliferation of multidrug-resistant pathogens within the Northern Region of Ghana.

1.4. Research questions

- What pathogens were involved in bacterial infections from June 2018 to May 2022 in the northern region of Ghana?

- What are the antibiotic resistance levels of bacterial isolates isolated at the Tamale Zonal Public Health Reference laboratory during the study period?

-What is the current prevalence of multidrug resistance in the study area?

-What are the risk factors of multidrug resistant infections in Ghana's northern region?

1.5. Study objectives

1.5.1.General objective

The general objective was to determine the epidemiology of bacteria-caused infections and risk factors for multidrug resistance covering June 2018 to May 2022 in the northern region of Ghana.

1.5.2.Specific objectives

- To retrospectively determine the distribution of bacterial pathogens isolated from the Tamale Zonal Public Health Reference Laboratory between June 2018 and May 2022.

-To estimate antibiotic resistance levels and multidrug resistance profiles of bacteria responsible for infections in the Northern region.

-To measure the prevalence of multidrug resistant infections in the study area

-To ascertain risk factors of infections caused by multidrug resistant organisms (MDRO) in Ghana' Northern region.

1.6. Conceptual framework

The conceptual framework of this study describes how contaminations with bacterial pathogens could lead to infections especially those difficult-to-treat or drug resistant. It also describes factors influencing occurrence of multidrug resistance. The microbial world is large and diverse. Bacteria are a type of microorganism frequently involved in human infections. Both gram-negative and Gram-positive bacteria could lead to serious conditions such as pneumoniae, sepsis, Urinary tract infections, skin infections, etc.

When people are infected and develop signs and symptoms of potential infections, clinicians must first of all determine the type of bacteria causing this infection to prescribe the most appropriate antibiotics for treatment. In cases where the bacterial strain shows non-sensitivity to the effect of an antibiotic, that bacteria is said to be resistant to the antibiotic. In other case, there are some bacterial strains that can withstand the action of a minimum of one antibiotic agent from three (03) or more antibacterial categories and they are called multidrug resistant bacteria (Magiorakos et al., 2012).

The rapid emergence and quick spread of multidrug resistant organisms are caused by a number of factors. At the population level, factors such as age, sex, hospitalization status, antibiotic consumption etc. are some factors associated with multidrug resistance. At the same time, some factors related to healthcare facilities such as their infection control and prevention policies as well as their diagnostic and antimicrobial resistance (AMR) stewardship programs could probably influence the outcome of treatments and also the development of multidrug resistance. Socio-cultural factors, Cultural perceptions or Stigmatization of certain illnesses (infections) may lead individuals to self-medicate or seek alternative treatments, potentially influencing antibiotic use. Perceptions of infection severity, contagiousness, and societal attitudes towards specific conditions may impact antibiotic demand. Understanding of antibiotics, their appropriate use, and potential risks of resistance is influenced by educational levels and exposure to healthcare information. Misconceptions and misinformation can lead to inappropriate antibiotic use. All these points perfectly align with "previous antibiotic use/consumptions" which is one of the potential risk factors for resistant or multidrug resistant infections.

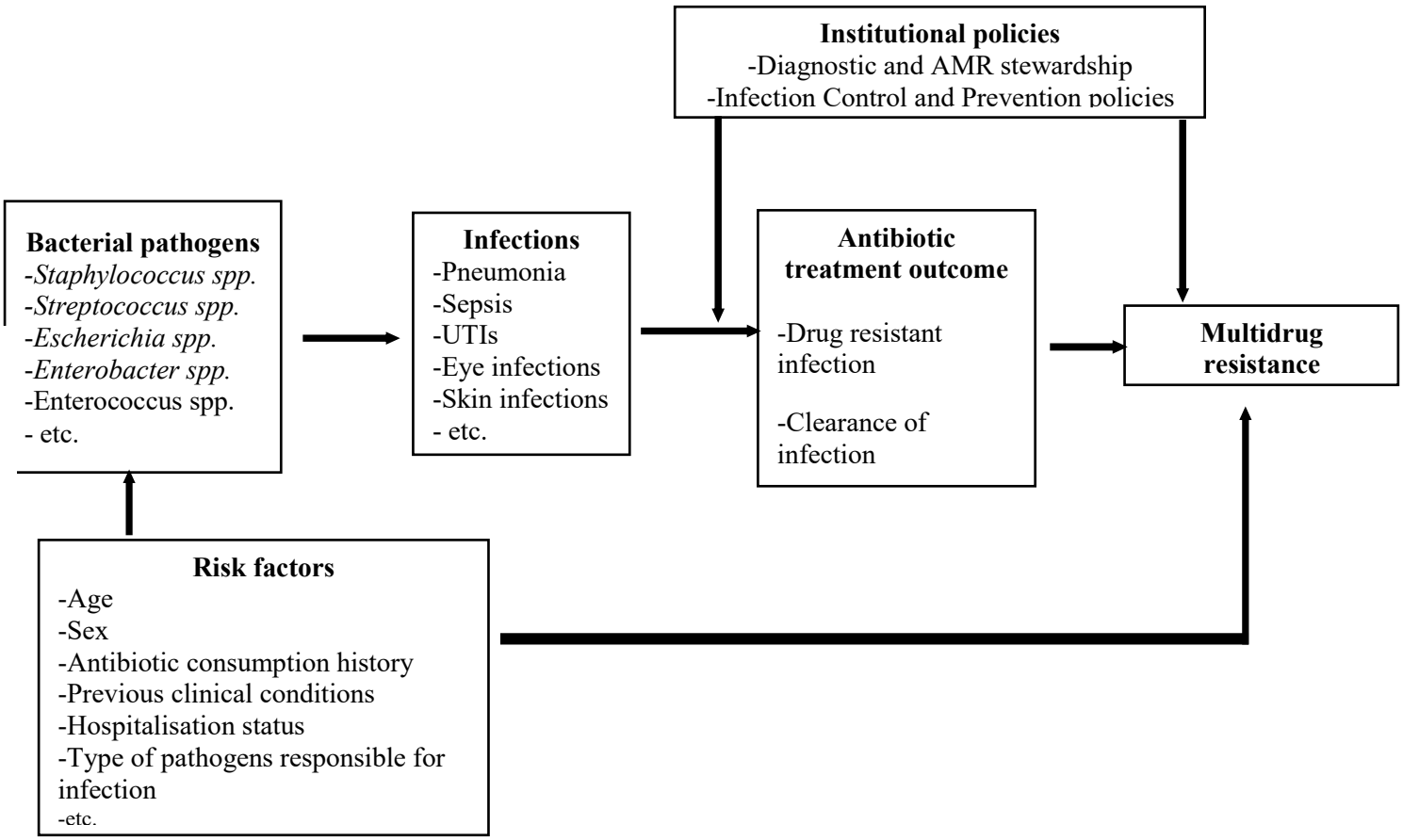

Figure 2: Conceptual framework of drug resistant infections and risk factors of multidrug resistance

1.7. Organization of the thesis

This one includes six (6) chapters. The first chapter (Introduction) describes the background, the problem statement, research questions and objectives and the conceptual framework. Chapter two provides a detailed literature review of the subject. Chapter three gives a thorough and succinct overview of the methodology used in the present study. Chapter four presents the results obtained from the data analysis and these results are discussed in chapter five. The sixth chapter of this thesis is the summary, conclusion and recommendations.

CHAPTER TWO

2.0 LITTERATURE REVIEW

2.1. Introduction

The second chapter of this study shows the literature review performed to achieve the aims of the study. The literature is broken down into many sections, but its overarching goal is to give the reader a complete picture of the research done in this field. The literature search was performed using PubMed, Google Scholar, Embase, and Medline. Keywords such as "bacteria multidrug reistant", “associated factors drug resistance”, "risk factors MDR", "MDRO infections", etc. were used.

2.2. Multidrug resistant bacteria

2.2.1.Multidrug resistant bacteria infections

Multidrug resistant bacteria were initially thought to only occur in healthcare facilities. The prevalence of multidrug resistant bacteria has risen to become the most common reason for illnesses in the general public. Incidences of illness, death, medical costs, and antibiotic use have all increased because germs resistant to many antimicrobials have proliferated. (van Duin & Paterson, 2016). Outcomes are often worse for persons infected by multidrug resistant germs than for those who are afflicted with susceptible pathogens (Vardakas et al., 2013). Intensified antibiotic treatment has raised new worries about the rise of drug-resistant bacteria known as "superbugs" (Adegoke et al., 2016). This would have devastating consequences for cancer treatment, organ transplants, and other medical procedures. Certain multidrug resistant (MDR) bacterial strains are thought to be strongly correlated with the administration of wide-ranging antibiotics both for prophylactic and curative purposes (Bharadwaj et al., 2022).

2.2.2.Community acquired infections by MDROs

This overexploitation is largely responsible for the rise in MDR, which in turn increases the expansion of a continuous cycle. An infection is a disease that can be split into two categories: those spread in the general population and those spread in healthcare settings. Infections picked up outside of a hospital setting (known as community-acquired illnesses, or CAIs) and those picked up in hospitals (HAIs) are distinguished by when symptoms first appeared: in the patient's home or at the hospital (nosocomial type). Infections in the community might be further classified as either healthcare-associated or community-acquired (Henderson et al., 2013) reflecting the work begun by (Friedman, 2002; Morin & Hadler, 2001).

2.2.3. Nosocomial and health-care associated MDR infections

For an infection to be considered healthcare-associated, the patient must meet several criteria (Cardoso et al., 2014): They must have:

- been administered to them within the last month; wound care, IV antibiotics, or chemotherapy;
- been in a hospital's intensive care unit for at least 48 hours;
- spent significant amount of time hospitalized or under constant care;
- received critical care; and
- spent time in the ICU unit.

All patients who do not meet the aforementioned criteria or who contract their infection in the community are included in the category of "community-acquired infections" (healthcare-associated infection). The proliferation of MDR microorganisms in society can be solved and accessed using these criteria, however they are insufficient on their own. Patients tend to contract

infections from the same organisms they were colonized with previously. Hence, when considering the source of MDR bacteria, the time of colonization is more important than the time of infection diagnosis (Kaspar et al., 2015).

Once predominantly linked with healthcare environments, they have now emerged as a significant public health issue affecting the wider population. The surge in multidrug resistance has resulted in a rise in instances of sickness, heightened mortality rates, increased healthcare costs, and amplified consumption of antibiotics.

Moreover, the gravity of infections instigated by multidrug resistant microorganisms surpasses that caused by susceptible pathogens, underscoring the pressing necessity for efficient intervention approaches. The emergence of antibiotic-resistant "superbugs" due to intensified antibiotic therapies poses notable risks to vital medical procedures, potentially compromising patient outcomes. The utilization of wide-ranging antibiotics plays a pivotal role in the development of specific strains of multidrug resistant bacteria.

2.3. Antibiotics and drug resistance: History, Benefits and major causes

2.3.1. History of antibiotics

Ancient Egyptian, Greek, and Chinese medical texts have significantly detailed the management of bacterial illnesses. Modern antibiotic therapy took shape with Alexander Fleming's 1928 discovery of penicillin (Sengupta et al., 2013). Antibiotics, discovered soon after, would go on to save millions of lives and revolutionize modern medicine (Gould & Bal, 2013). In the 1940s, doctors began using antibiotics to treat life-threatening infections. Penicillin was able to effectively manage combat the spread of bacterial illnesses among soldiers during the 2nd World War (Sengupta et al., 2013). But by the 1950s, many of the gains made in the previous decade were in

jeopardy due to penicillin resistance, which emerged as a major clinical problem not long after (Spellberg & Gilbert, 2014). In this context, new β-lactam antibiotics have been found, produced, and introduced, which has restored patients' trust in medical science. Nonetheless, Throughout the identical decade, the methicillin-resistant *Staphylococcus aureus* (MRSA) has been reported for the first time in both the UK and US respectively in 1962 and 1968 (Gould, 2016; Sengupta et al., 2013). Despite the success of antibiotics, resistant bacteria have emerged against almost all of them. With its initiation to medical care in 1972, vancomycin was first used to treat MRSA and coagulase-negative Staphylococcus (Becker et al., 2014; Tasneem et al., 2022). Inducing resistance to vancomycin had proven so difficult that its occurrence in a clinical setting was thought to be highly improbable (Srinivasan et al., 2002). However, coagulase-negative staphylococci were found to be resistant to vancomycin in 1979 and 1983 (Becker et al., 2014; Sengupta et al., 2013). During the years of the late 1960s and the early 1980s, drug manufacturing firms released a plethora of novel antibiotics in an effort to combat antibiotic resistance, but after that, innovation slowed, and the pipeline for antibiotics dried up. Therefore, bacterial infections have become a problem once again in 2015, lengthy after the initial antibiotic-treated individuals (Spellberg & Gilbert, 2014).

2.3.2. Benefits of Antibiotics

Innumerable lives have been saved thanks to antibiotics, which have played a crucial role in the advancement of contemporary surgical and medical procedures (Gould & Bal, 2013). Among patients receiving chemotherapy, infections have been prevented or effectively treated in patients experiencing hypertension, end-stage renal disease, rheumatoid, and individuals who have undergone major surgical operations such as organ transplants, joint replacement, or heart surgery.

(Rossolini et al., 2014; Wright, 2014).

Along with influencing the course of illnesses, antibiotics have helped to increase life expectancy (Piddock, 2012; Rossolini et al., 2014). Beneficial effects of antibiotics are consistent across regions. Antibiotics decrease sickness and death from bacterial and viral diseases spread by contaminated food and water in third-world nations where sanitation and hygiene are inadequate (Rossolini et al., 2014).

2.3.3. Antibiotic resistance phenomenon: Major causes

2.3.3.1. Overuse

There is no doubt that antibiotics over prescription and misuse represent one of the primary factors contributing to the emergence of resistance (Llor & Bjerrum, 2014). Studies on the epidemiology of antibiotic resistance have connected the misuse of these drugs to the rise and dissemination of antibiotic-resistant microorganisms: either from a close relative, or from an unrelated source, on mobile genetic elements called plasmids (Speck, 2013). Due to horizontal gene transfer (HGT), antibiotic resistance can spread between bacterial species. Furthermore, resistance might arise spontaneously as a consequence of a mutated gene (Read & Woods, 2014). Antibiotic overuse raises the odds that drug-resistant bacteria will survive and multiply, as opposed to their drug-sensitive counterparts (Michael et al., 2014). Antibiotics are overprescribed all over the world despite warnings about this practice (Speck, 2013). Antibiotics have less stringent regulations and are supplied with no medical prescription in numerous developing nations (Michael et al., 2014; Speck, 2013). Due to a lack of oversight, antibiotics are readily available and inexpensive, all of which contribute to their misuse. Even in nations where antibiotics are strictly controlled, consumers can now buy these goods online (Michael et al., 2014).

2.3.3.2. Inappropriate Prescribing

Antibiotics promoted antibiotic-resistant bacteria in part because they were inappropriately prescribed (Llor & Bjerrum, 2014). Studies have shown that between 30 and 50 percent of the time, antimicrobial therapy was not administered for the proper period, was not given to the correct patients, or was not given the correct therapeutic indication (Ventola, 2015). Another study found that anywhere from 30-60% of antibiotics given in intensive care units are inappropriate or unneeded (Luyt et al., 2014).

Patients who receive antibiotics that were inappropriately prescribed are at risk for experiencing unwanted side effects (Lushniak, 2014). Concentrations of antibiotics below that needed to limit growth or those needed to treat an infection can promote antibiotic resistance through the promotion of genetic alterations including changes in gene expression, horizontal gene transfer (HGT), and mutagenesis (Viswanathan, 2014)Mutagenesis and HGT both contribute to the spread of antibiotic-resistant bacteria, and alterations in gene expression induced by antibiotic may increase the the degree of pathogenicity of certain strains (Ventola, 2015; Viswanathan, 2014).

2.3.3.3. Extensive agricultural use

Animals throughout both the industrialized and emerging nations often get antibiotics to assist in their development (Bartlett et al., 2013; Speck, 2013). Antibiotics are used extensively in animal agriculture, with the majority of sales going toward the treatment of diseases and the promotion of growth (Gross, 2013; Spellberg & Gilbert, 2014). Animal husbandry practices involving the use

of antimicrobials have been shown help achieving higher yields while simultaneously enhancing the quality of the product by reducing disease and improving animal welfare (Michael et al., 2014).

Antibiotic residues in animals are consumed by humans through their food supply (Ghimpețeanu et al., 2022). Over than thirty-five (35) years ago, it was discovered that both farm livestock and humans have unusually high levels of resistant bacteria in their gut flora (Bartlett et al., 2013). Recent advances in molecular detection have provided further evidence that meat products from livestock harbor resistant bacteria (Bartlett et al., 2013). The following chain of causes and effects leads to this result: 1)Antibiotic use in livestock results in the death or suppression of susceptible bacteria, fostering the growth of antibiotic-resistant bacteria; 2) Transmission of antibiotic-resistant microorganisms from animals to humans through food systems; and 3) Humans are susceptible to infection from these germs, with potentially harmful effects on their health (Ventola, 2015).

Consequences on the natural world's microbiome have been linked to the widespread use of antibiotics in agriculture (Ghimpețeanu et al., 2022). Medications administered to animals can end up in the environment through various pathways, including fertilizer, groundwater , and surface runoff, with a potential excretion rate of up to 90% (Bartlett et al., 2013). Fruit trees in the west and south of the USA sometimes utilize tetracyclines and streptomycin as insecticides. While only a small fraction of antibiotics is used in this manner, the resulting geographic spread can be significant (Ghimpețeanu et al., 2022). Moreover, environmental microbes are subjected to growth-inhibiting chemicals as a result of this practice, which changes ecological systems by increasing the ratio of resistant to susceptible microorganisms (Ghimpețeanu et al., 2022).

The building up of an immune system among both children and adults against environmental antigens may be affected by the use of products designed to kill germs and bacteria that may be used for cleaning and hygiene. Because of this, the immune system may be less adaptable, which could make people more susceptible to infections that would otherwise be mild (Michael et al., 2014; Ventola, 2015).

2.3.3.4. Availability of few new antibiotics

The pharmaceutical industry's ability to synthesize novel antibacterial chemicals, a tactic that had been successful in the past in combating resistant germs, has effectively halted because of financial and regulatory barriers (Bartlett et al., 2013). Drug companies no longer believe that antibiotic research is a good financial bet. Antibiotics have lower profit margins than medications for treating long-term diseases such as diabetes, mental illness, asthma, or GERD because they are used for shorter periods and are often curative (Piddock, 2012; Wright, 2014). Pharmaceutical companies prefer to put their money into treatments for long-term illnesses because of the higher potential return (Gould & Bal, 2013). The low price of antibiotics is another reason why research into new antibiotics isn't a good financial bet. When compared to the tens of thousands of dollars required for cancer chemotherapy, the cost of modern antibiotics is typically between $1,000 and $3,000 (Piddock, 2012; Wright, 2014). Because of antibiotics' broad availability, simplicity of using it, and typically inexpensive cost, they are often viewed as having little value by insurers and the public at large. Antibiotic overuse has also been urged against by microbiologists and infectious disease experts (Piddock, 2012). As a result, when a new antibiotic becomes available on the market, doctors often save it for "the worst cases" and stick to prescribing tried-and-true treatments like older antibiotics that have shown similar efficacy for fear of encouraging drug resistance

(Golkar et al., 2014; Gould & Bal, 2013). That's why 'last-line' drugs are typically new antibiotics, used only when all other options have been exhausted in the fight against deadly infections (Gould & Bal, 2013). The value of investments in new antibiotics declines as a result of this practice (Piddock, 2012). Even if new agents are used in a long-term perspective, the emergence of resistance is almost certain to occur at some point. The timing of resistance development is obscured, however, by the unpredictability of bacterial evolution. If a company spends a lot of money researching and developing an antibiotic, it may find that its profits are suddenly cut if antibiotic resistance emerges (Ventola, 2015). Consumers' demand for antibiotics has been dampened by the Great Recession's lingering economic uncertainty. Another complication is that generic drug companies now supply most antibiotics that are off-patent. The public benefits from widespread availability of low-cost, high-quality medications, but the practice has led many insurers to demand uniform pricing for antibiotics of all types, including novel agents used to combat MDR pathogens (Wright, 2014).

2.4. Priority pathogens implicated in drug-resistant infections

In 2017, the World Health Organization (WHO) produced a list of global priority diseases which thus highlighted the urgent need for antibiotic research and development. This list brought to light the danger posed by Gram-negative bacteria, which can express resistance to a wide variety of medications (Govindaraj Vaithinathan & Vanitha, 2018). The World Health Organization classified the worldwide pathogens into the following three categories: Patients who are immunocompromised and need ventilators and the insertion of blood catheters are more likely to be vulnerable to infection from the critical priority group, which is why this group is regarded to be a danger in healthcare settings. This group has the potential to include microorganisms that are

not susceptible to antibiotics, as well as the majority of GNBs (Tacconelli et al., 2018). Antibiotic-resistant bacteria that are Gram-positive as well as Gram-negative that are linked to the most prevalent illnesses make up the other categories that have been given the high and medium antibiotic priorities, respectively. In 2019, the CDC unveiled a revised list of infections that are resistant to antibiotics. The list is organized into three categories: urgent, severe, and worrying (Kadri, 2020). Documenting the morbidity and financial effects of pathogens, as well as pathogens' ease of spread, how easy or difficult it is to get hold of good antibiotics, and obstacles to prevention are all essential considerations when synthetizing new antibiotics. Both CDC and WHO lists represent a pressing demand for more focused investigation and synthesis of new antibiotics. They take into account the prevalence of resistance that is currently present. This investigation and synthesis has to be carried out while keeping in mind the already existing prevalence of resistance, monitoring the clinical and financial repercussions of infections, and more (Iskandar et al., 2022).

Antibiotics have assumed a vital role within modern medicine, ushering in a new era of healthcare marked by life-saving interventions. Nevertheless, the unsettling rise of antibiotic resistance, fueled by factors such as excessive usage, improper prescription practices, widespread agricultural application, and a noticeable scarcity of novel antibiotics, presents an undeniable and substantial peril to the realm of public health. The prioritization of pathogens by esteemed global health entities serves as a stark reminder, underscoring the imperative nature of research and development efforts geared toward crafting precision-targeted antibiotics.

Table 1: Priority pathogens list identified by CDC and WHO (Iskandar et al., 2022)

	WHO		CDC	
Org	**Pathogens**	**Level of Priority**	**Pathogens**	**Level of Threat**
Acin ba	*Acinetobacter baumannii*, carbapenem-resistant	Critical		Urgent *
Pseu aer	*Pseudomonas aeruginosa*, carbapenem-resistant	Critical	Multidrug-resistant *Pseudomonas aeruginosa* [1]	Serious **
Enterol *eae*	*Enterobacteriaceae*, carbapenem-resistant, ESBL-producing	Critical	*Enterobacteriacea*, Carbapenem-resistant [2 3]	Urgent
	Enterobacteriaceae, ESBL-producing	Critical	Extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae [4]	Serious
Enteroc *ium*	*Enterococcus faecium*, vancomycin-resistant	High	Vancomycin-resistant Enterococci (VRE)	Serious
Staphylo *reus*	*Staphylococcus aureus*, methicillin-resistant	High	Methicillin-resistant *Staphylococcus aureus* (MRSA) [5]	Serious
Staphylo *reus*	*Staphylococcus aureus*, vancomycin-intermediate and resistant	High		
Helicob *ori*	*Helicobacter pylori*, clarithromycin-resistant	High		
Campyl pp.	*Campylobacter* spp., fluoroquinolone-resistant	High	Drug-resistant *Campylobacter*	Serious
Salı	*Salmonellae*, fluoroquinolone-resistant	High	Drug-resistant nontyphoidal *Salmonella* Drug-resistant *Salmonella* serotype Typhi	Serious
Neisseria *oeae*	*Neisseria gonorrhoeae*, cephalosporin-resistant, fluoroquinolone-resistant	High	Drug-resistant *Neisseria gonorrhoeae*	Urgent
Strep pne	*Streptococcus pneumoniae*, penicillin-non-susceptible	Medium	Drug-resistant *Streptococcus pneumoniae*	Serious
			Erythromycin-Resistant Group A *Streptococcus* Clindamycin-resistant Group B *Streptococcus*	Concerning ***
Hae inf	*Haemophilus influenzae*, ampicillin-resistant	Medium		
Shig	*Shigella* spp., fluoroquinolone-resistant	Medium	Drug-resistant *Shigella*	Serious
Clostridi *ficile*				Urgent
Mycobacterium tuberculosis	Not listed in the 2017 high priority pathogens because it is previously established as high priority		Drug-resistant tuberculosis	Serious
Bordetella pertusis			Drug-resistant *Bordetella pertusis*	Watch

2.4.1. ESKAPE pathogens

Nosocomial pathogens, whose multidrug resistance and virulence are on the rise, are referred to by the acronym ESKAPE. They are very costly to patients, healthcare systems, and economies. Gram-positive bacteria include *Enterococcus faecium* and *Staphylococcus aureus*, while Gram-negative bacteria include *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and Enterobacter species, hence the acronym ESKAPE (de Oliveira et al., 2020). In critically ill and immunocompromised patients, hospital-acquired infections caused by these pathogens are frequently fatal. They share a common characteristic of having high levels of multidrug resistance (Mulani et al., 2019). All ESKAPE pathogens were included in the WHO's list of 12 bacterial species for which new chemotherapeutics are urgently needed (Tacconelli et al., 2018).

2.4.1.1. *Enterobacter faecium*

Enterobacter. faecium, a Gram-positive commensal, is not particularly dangerous, it is also not easily eliminated from a healthcare facility. Nosocomial infections and outbreaks are a major concern in the healthcare system because of this (García-Solache & Rice, 2019). Vancomycin-resistant Enterococci (VRE) infections have reached 14.9% in the European Union (EU) in 2017 (ECDC, 2018) and 30% in the United States (USA) over the past few decades (CDC, 2019). Nosocomial VRE infections are notoriously difficult to treat, if not impossible, due to the resistance that often accompanies them (García-Solache & Rice, 2019).

2.4.1.2. *Staphylococcus aureus*

S. aureus, a Gram-positive bacterium, is a common resident of the nose and other parts of the normal skin microbiota. *S. aureus* is a major contributor to bacteremia, skin and soft tissue

infections, osteomyelitis, and infective endocarditis. When *S. aureus* bacteremia was first discovered, mortality rates were over 80%. This dramatically decreased once antibiotics became widely available (Skinner & Keefer, 1941). The patients' prognosis drastically improved after the discovery of penicillin in the 1940s. Although penicillin was initially used to treat *S. aureus* infections, its widespread application accelerated the development of strains that produced resistance mechanisms called lactamases. In 1948, penicillin G resistance was already present in more than 80% of clinical isolates (Huemer et al., 2020). In 1962, just one year after the introduction of semi-synthetic penicillins, *MRSA* strains were isolated, and there is evidence that *S. aureus* developed methicillin resistance even before its clinical use (Harkins et al., 2017; Turner et al., 2019). Before methicillin was developed, first-generation -lactams were widely used, and this led to the selection of strains that carry the mecA determinant, which confers resistance to methicillin (Harkins et al., 2017). The propagation of the mecA gene, which causes methicillin resistance, is caused by the staphylococcal cassette chromosome mec (SCCmec), a mobile genetic element (Uehara, 2022).

2.4.1.3. *Klebsiella pneumoniae*

Nosocomial infections frequently involve *K. pneumoniae*, a Gram-negative rod-shaped pathogen. Many strains of *K. pneumoniae* have developed resistance to penicillin, cephalosporins, and carbapenems due to the acquisition of lactamases (Pitout et al., 2015). Infections caused by Gram-negative bacteria are typically treated with carbapenems, but the spread of *K. pneumoniae* strains that produce carbapenamases (KPC) and harbor the bla KPC gene has made these infections increasingly challenging to treat (Reyes et al., 2019). In addition, the metallolactamase NDM1, which is encoded by bla NDM1, is expressed by some *K. pneumoniae strains* . Because of NDM1,

more and more strains of *K. pneumoniae* are resistant to the antibiotic carbapenem, necessitating the use of alternative treatments like aminoglycosides and fluoroquinolones (Robilotti & Deresinski, 2014).

2.4.1.4. *Acinetobacter baumannii*

Nosocomial infections caused by *Acinetobacter baumannii* typically affect patients who have been hospitalized for more than 90 days and who have compromised immune systems(Montefour et al., 2008). Infections of the respiratory system and urinary tract are just two of the many that *A. baumannii* can bring on. Since many antibiotics are no longer effective against it, *A. baumannii* is a major health risk, especially for those in intensive care. Their resistance to most common antibiotics is due to a combination of resistance genes (Lin & Lan, 2014). Due to the worldwide spread of *Acinetobacter baumannii* strains that are resistant to multiple antibiotics, the World Health Organization has designated *A. baumannii* as a priority 1 pathogen in need of urgent attention in the form of novel antimicrobials (Tacconelli et al., 2018).

2.4.1.5. *Pseudomonas aeruginosa*

Inherent low susceptibility to many antimicrobial drugs and a high propensity to develop resistance characterize the Gram-negative bacterium *P. aeruginosa*, which is also included in the WHO priority group 1 of pathogens that urgently require new treatment options (Tacconelli et al., 2018). Enhanced carbapenem resistance in *P. aeruginosa* is due to decreased porin permeability and increased production of AmpC (Meletis et al., 2012). High-level resistance to carbapenem antibiotics is another side effect of *P. aeruginosa*'s ability to express KPCs, ESBLs, and imipenem metallolactamases (Pang et al., 2019). Although the last-resort antibiotic colistin is effective in

most cases, resistance has already been reported due to its widespread use in pig and poultry farming, which compounds the difficulty of treating the increasingly common multidrug resistant isolates (Hameed et al., 2019; Pedersen et al., 2018).

2.4.1.6. Enterobacter Species

Enterobacter spp. are widespread Gram-negative pathogens that are notorious for harboring many antibiotic resistance genes like ESBLs and carbapenemases, and are typically responsible for infections in immunocompromised, hospitalized patients (Davin-Regli et al., 2019). Intense production of the AmpC -lactamase, which can hydrolyze broad-spectrum penicillins and cephalosporins, is characteristic of Enterobacter species (Schwaber et al., 2003). An increase in mortality has been linked to this overproduction, which is induced by beta-lactams and carbapenems and results in resistance during treatment (Huh et al., 2014; Schwaber et al., 2003). The rapid evolution of resistance means that many strains of *Enterobacter spp.* are now resistant to all but a handful of antibiotics, including colistin and tigecycline (Pendleton et al., 2013).

2.5. Economic burden of multidrug resistance

MDR-organism-caused infections are notoriously difficult to cure and as a direct consequence, they may contribute to increased morbidity and mortality. It has been found, however, that there are monetary and social costs associated with these infections. Costs associated with AMR in the US are evaluated at $55 billion annually, according to the Centers for Disease Control and Prevention, with an additional $35 billion in societal costs due to lost productivity (CDC, 2013).

Hospital costs increased by $42,203 and $35,556, respectively, for MDR-*Acinetobacter baumannii* (MDR-AB) and MDR-*Pseudomonas aeruginosa* (MDR-PA) pneumonia patients, according to a

study conducted in South Korea. It was estimated that there were 1,309,248 cases of MDRAB-P and 339,644 cases of MDRPA-P in South Korea during the past year. Estimates placed the annual death toll from MDRAB-P at 485-920, and that from MDRPA-P at 133-253. The financial cost of MDRAB-P was $64,549,723-22,533,585, while MDRPA-P cost $15,241,883-28,994,008. Hospital costs for MDRAB-P and MDRPA-P (multidrug resistant-group) cases were found to be 1.80 and 1.42 times higher than for cases involving infections caused by susceptible organisms (Susceptible-group) and 6.14 and 5.57 times higher than for cases involving no infection (No infection-group), respectively (Kim et al., 2022).

Another meta-analysis and systematic review of English-language literature published between 1980 and 2019 found that MDR HAI are associated with higher rates of fatality rates, resource consumption, and direct costs compared to what is observed for infections caused by susceptible microorganisms (Serra-Burriel et al., 2020). They also included two papers (Kopp et al., 2004; Mauldin et al., 2010) showing that the cost estimates for MDR HAIs can vary widely depending on the context in which they are examined, with average increases ranging from $3,000 to $40,000.

Nosocomial infections have been shown to be a cost-effective target for multifaceted prevention programs, as reported by (Dick et al., 2015). This is significant because secondary infections, particularly those caused by multidrug resistant organisms, need extra medical care, prolong hospital stays, and inflict an economic and social loss.

2.6. Multidrug resistance in Ghana

In several investigations carried in Ghana, researchers have documented the existence of MDR-organisms. In 2015, researchers at the Komfo Anokye Teaching Hospital (KATH) in Ghana's

Ashanti region found that 89.5% of clinically-relevant Gram-negative bacteria tested were resistant to three or more classes of antimicrobials (Agyepong et al., 2018).

Extremely high rates of MDR organisms were also found in a study conducted in the region of the Upper East. Antimicrobial testing results from January 2018 through July 2020 were retrospectively analyzed, and 796 of 800 (99.6%) isolates were found to be multidrug resistant (Inusah et al., 2021). Multidrug resistant bacteria were isolated from patients, but they were also found in sewage from hospitals, tap water in homes, and contaminated raw meat. Hospital wastewater isolates showed a 55.4% prevalence of multidrug resistance (Maternity Unit = 53.4%; Child Health Unit = 46.2%). In 2022, researchers at Accra's Korle Bu Teaching Hospital looked into this (Addae-Nuku et al., 2022). Multidrug resistance was reported in 48.7% of Escherichia coli isolates from rural household drinking water samples in the Talensi District of the Upper East Region (Kichana et al., 2022).

This literature review provides a crucial underpinning for studying the epidemiology and risk elements associated with multidrug resistance. Its value lies in guiding the formulation of specific research inquiries regarding multidrug resistance (MDR) grounded in established insights on antibiotic resistance. Furthermore, it aids in recognizing less-explored aspects within the field of antibiotic resistance epidemiology, offering potential for novel contributions. Additionally, the review influences choices regarding research design, data gathering techniques, and statistical methodologies, drawing from successful approaches in analogous studies.

CHAPTER THREE

3.0 STUDY METHODOLOGY

3.1. Introduction

The study's methodology is the section that describes in detail where the research was conducted, how the study's approach and design were formulated, what data collection and acquisition procedures were used, and what statistical analyses were performed on the collected data.

3.2. Study site

The data collection site for this study was the Tamale Zonal Public Health Reference Laboratory (TZPHRL), located in Tamale, the capital city of the Northern Region of Ghana. It is a pertinent part of the public health system in Ghana and hence a part of the Ghana Health Service. The laboratory can detect potential threats from infectious agents early, collect data to help in epidemic investigations, and determine illness causes to better treat and prevent them, the Zonal Public Health Laboratory offers the science and investigations needed to promote and protect the national population. The TZPHL is geographically located at the Tamale Teaching Hospital but operates under the mandate and authority of the Ghana Health Services (GHS). As the zonal reference microbiology laboratory, it plays an overarching role to the Regional and District Health Laboratories.

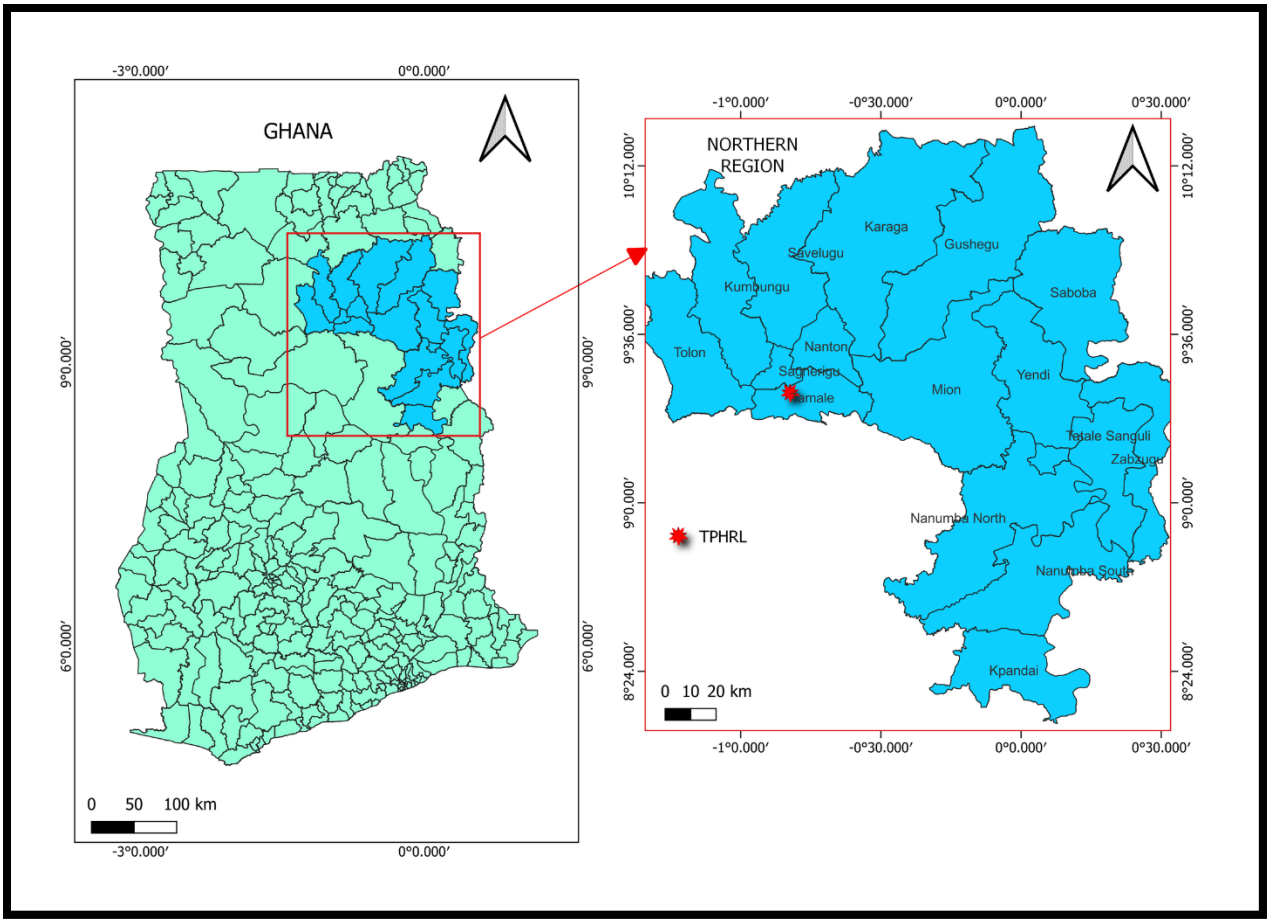

Figure 3: Geographical map of the study area

3.3. Study approach and design

The study used a quantitative approach and a retrospective analytic design. A quantitative approach entails gathering and analyzing numerical data. It is imperative for obtaining precise information regarding the distribution of bacterial pathogens. This method enables precise counting and classification of isolated pathogens within the specified timeframe. Analyzing data from past years necessitates an analytic approach. A retrospective design permits the scrutiny of historical records and patterns, empowering researchers to draw significant conclusions about the distribution of bacterial pathogens. These methodologies are apt for attaining the outlined research

goals concerning the distribution of bacterial pathogens, antibiotic resistance, multidrug resistance, and factors influencing MDRO infections in the Northern region of Ghana.

Data were analyzed retrospectively from samples submitted to the Tamale Zonal Public Health Laboratory for isolation and identification, and antimicrobial susceptibility testing. for a period of 48 months, or four years, from June 2018 to May 2022. (Year 1: June 2018 - May 2019, Year 2: June 2019 - May 2020, Year 3: June 2020 - May 2021, Year 4: June 2021 - May 2022). The period was selected because it would yield a sizable amount of recent data for the analysis.

3.4. Pre-study realization: Bacteria isolation, identification, and antibiotic susceptibility testing

All clinical specimens obtained by the TZPHL were subjected to routine microbiological tests following standard operating protocols in order to identify infectious microorganisms. The Gram stain and other common biochemical assays were then used to properly identify the isolated bacteria (catalase testing, oxidase testing, urease and substrate utilization tests), and sometimes the API 20E system. The disk diffusion technique was used to assess susceptibility. (Bauer et al., 1966).

In addition, inhibition zone sizes were measured and reported in millimeters according to the guidelines of the Clinical and Laboratory Standards Institute (CLSI) (CLSI, 2021). Antimicrobial disks targeting either gram-negative or gram-positive bacteria were chosen for the respective isolates. The microgram concentrations of the tested disks were as follows: Amikacin (30), Amoxicillin (30), Azithromycin (15), Cefotaxime (30), Cefoxitin (30), Ceftazidime (30), Ceftriaxone (30), Chloramphenicol (30), Ciprofloxacin (05), Erythromycin (15), Gentamicin (10), Meropenem (10), Penicillin V (10), Tetracycline (30), and Trimethoprim/Sulfamethoxazole (1.2). Once the bacterial culture, isolation, identification and antibiotic susceptibility tests were done and

the results were entered into the Microbiology electronic database of the Laboratory. The entered data were verified by the Chief laboratory technician and the Chief data manager of the TZPHRL.

3.5. Sampling and data extraction

There was no predefined or calculated sample size for this study. The study included all samples of suspected bacterial infections received at the TZPHRL for microbiological testing including bacterial culture, isolation, identification and susceptibility testing received from June 2018 to May 2022. For data extraction, the microbiology electronic records of the TZPHRL were used. Apart from the records with no bacterial growth, information about all cultured samples of patients such as age, sex, specimen type, hospitalization status, bacterial isolates, year of isolation and antibiotic susceptibility patterns were collected. In total, 1,222 positive bacterial culture were recorded over the study period.

3.6. Inclusion and exclusion criteria

This study included clinical records from patients whose samples have been received for bacterial culture and antibiotic susceptibility testing at the Microbiology section of the TZPHRL from June 2018 to May 2022. Records from patients whose samples culture resulted in no bacterial growth and records on fungi elements were excluded.

3.7. Definitions

From the antimicrobial susceptibility tests, different resistance patterns are observed for each bacterial strain. When an antibiotic agent had the expected inhibition effect on a bacterium, it is said to be sensitive or susceptible to that antibiotic agent. A bacterium is identified as resistant to

a given antibiotic agent when it thwarts the effect that is supposed to kill the organism and continues to grow in its presence. Bacterial pathogens which can withstand the action of a minimum of one antibiotic agent from three (03) or more antibacterial categories are identified as being multidrug resistants (Magiorakos et al., 2012).

3.8. Study variables

The list of all study variables study variable is presented in table 2.

Table 2: List of the study variables

Variables	Definition	Indicator	Variable type	Source of data
Dependent variables				
Multidrug resistance	Multidrug resistance status of the isolated bacteria	Positive or negative	Categorical	Electronic records
Independent variables				
Year	Year of bacteria isolation	Year	Categorical	Electronic records
Age	Age of patient in years	Age	Continuous	Electronic records
Age group	Age group of the patient	Under 5, 5-14, 15-44, 45-59, 60+	Categorical	Electronic records
Sex	Biological sex of patient	Male or female	Categorical	Electronic records
Specimen type	Type of specimen from which the bacteria has been isolated	Puss, urine, blood, seminal fluid, and swabs	Categorical	Electronic records
Bacterial pathogen	Bacteria isolated from the sample's culture as the cause of the infection	Type of bacteria isolated from the sample	Categorical	Electronic records
Hospitalization status	Location of the patient regarding to the hospital	In-patient or out-patient	Categorical	Electronic records
Antibiotic resistance	Antibiotic resistance profile of the isolated bacteria	Resistant or susceptible	Categorical	Electronic records

3.9. Statistical analysis

The data was extracted, cleaned and made ready for analysis using Microsoft Excel 2019. The formal analysis was conducted using the R software version 4.2.0. The age of the patients was presented as descriptive statistics such as mean, median, range, and quantiles. The distribution of age has been tested using the Shapiro-Wilk normality test. The gtsummary (Sjoberg et al., 2021) package version 1.6.1 was used to create publication-ready analytical and summary tables where comparisons were done for continuous and categorical data. Non-normally distributed quantitative variables were compared using the Kruskal-Wallis-rank-sum test. The Pearson Chi-squared test was used to compare categorical data. Predictors of multidrug resistant (MDR) infections were identified using univariate and multivariate logistic regression (binary) models. Logistic regression proves highly valuable when the response variable is binary, indicating two potential outcomes (e.g., yes/no, positive/negative). It finds application in cases where the dependent variable is categorical, not continuous. This approach enables the assessment of the importance of individual predictor variables, aiding in the identification of statistically significant factors for outcome prediction. Cases with missing values were excluded from the regression analyses. All variables associated with MDR at a P-value < 0.200 in the univariate model were included in the initial multivariable model. The "stepAIC" function was then applied to the initial multivariable model using a stepwise method with both forward and backward selection to get the final multivariable logistic regression model. All analyses were performed with a P-value of 0.05 considered " statistically significant, and the results were reported as odds ratios (ORs) with 95% confidence intervals (CIs).

3.10. Ethical considerations

This research work has been approved by the Committee of Human Research and Publication Ethics of the Kwame Nkrumah University of Science and Technology (KNUST) (Ref: CHRPE/AR/060/22; Date 15/02/2022). The protocol amendment has also been approved by the same Committee (Ref: CHRPE/AP/163/22; Date 05/05/2022). We also received permission from the Northern Regional Health Directorate.

CHAPTER FOUR

4.0 PRESENTATION OF RESULTS

4.1 Introduction

The current chapter outlines results from the data analysis. It also provides a comprehensive overview of the testing that was done because of the goals that needed to be met. From June 2018 to May 2022, the TZPHRL recorded a total of 1222 specimen records.

4.2. Patients' characteristics

Table 3 presents the baseline characteristics of the patients recorded from June 2018 to May 2022 at Tamale Zonal Public Health Reference Laboratory (TZPHRL). A total of 1,222 positive bacterial cultures including 593 (48.5%) females were recorded. The age of the patients of the samples received ranged between 0 and 105 years with the median age being 41 years (28, 60). In the first, second, third and fourth years, 149 (55.0%), 150 (50.0%), 147 (49.0%) and 147 (47.0%) of the samples were from females respectively. A statistically significant difference was observed for the distribution of age groups over the years (P-value = 0.010). The majority of specimens were obtained from patients in the 24-44 age group (39.0%) and 60+ age group (28%). Patients under 5 years of age represented only 2.40% of the samples. On the patient's hospitalization status, we found that 81.0% of the samples were from hospitalized patients.

Table 3: Baseline characteristics of patients recorded during the study period

Characteristic	Year 1 N = 284[1]	Year 2 N = 309[1]	Year 3 N = 308[1]	Year 4 N = 321[1]	Overall N = 1,222[1]	p-value[2]
Sex						0.300
Female	149 (55%)	150 (50%)	147 (49%)	147 (47%)	593 (50%)	
Male	123 (45%)	149 (50%)	151 (51%)	167 (53%)	590 (50%)	
Median age	39 (27, 60)	41 (28, 58)	42 (29, 60)	42 (28, 60)	41 (28, 60)	0.800
Age group						0.010
Under 5	14 (5.4%)	8 (2.8%)	4 (1.3%)	1 (0.3%)	27 (2.4%)	
5 - 14	15 (5.8%)	9 (3.1%)	17 (5.7%)	8 (2.6%)	49 (4.3%)	
15 - 24	16 (6.2%)	23 (8.0%)	28 (9.4%)	30 (9.9%)	97 (8.5%)	
25 - 44	102 (40%)	120 (42%)	106 (36%)	114 (38%)	442 (39%)	
45 - 59	39 (15%)	54 (19%)	55 (19%)	63 (21%)	211 (18%)	
60 +	69 (28%)	66 (25%)	78 (29%)	79 (29%)	292 (28%)	
Hospitalization status						0.200
Inpatient	236 (83%)	258 (83%)	238 (77%)	255 (79%)	987 (81%)	
Outpatient	48 (17%)	51 (17%)	70 (23%)	66 (21%)	235 (19%)	

[1] n (%); Median (IQR); [2] Pearson's Chi-squared test; Kruskal-Wallis rank sum test

4.3. Distribution of specimens

Table 4 shows the samples received at the TZPHRL between June 2018 and May 2022. We found that sputum was the most common sample with a percentage of 68.0%, followed by urine (11.0%), high vaginal swab (6.4%), wound swab (6.1%) and blood (5.1%).

Table 4: Samples received at the TZPHRL between June 2018 and May 2022

Sample	**N = 1,222**[1]
Sputum	827 (68%)
Urine	133 (11%)
High vaginal swab	78 (6.4%)
Wound Swab	74 (6.1%)
Blood	62 (5.1%)
Aspirates	18 (1.5%)
Gastric lavage	4 (0.3%)
Stool	4 (0.3%)
Pus	3 (0.2%)
Throat Swab	3 (0.2%)
Semen	2 (0.2%)
Tissue	2 (0.2%)
Urethral Swab	2 (0.2%)
Abdominal Abscess	1 (<0.1%)
Bone Scrub	1 (<0.1%)
Cerebrospinal Fluid	1 (<0.1%)
Nails	1 (<0.1%)
Scrotal Swab	1 (<0.1%)

[1] n (%)

4.4. Epidemiology of bacterial infections

Table 5 shows bacterial pathogens isolated during the study period. The results revealed the five (5) main bacterial genus responsible for the infections isolated from the TZPHRL. These were: :

Klebsiella spp., *Moraxella spp*., and *Escherichia spp*. respectively with respectively 27%, 22%, and 16% followed by *Pseudomonas spp.* (13.0%), and *Staphylococcus spp.* (7.7%). *Sphingomonas spp*., *Shewanella spp*., *Providencia spp*., *Photobacterium spp.* and *Gandnerella spp.* were rarely isolated (n=1) during the study period. Each of these bacterial genus had a prevalence of less than 0.1% in total.

Table 5: Bacteria isolated from the TZPHRL during the study period

Isolated bacteria	**Year 1** N = 284[1]	**Year 2** N = 309[1]	**Year 3** N = 308[1]	**Year 4** N = 321[1]	**Overall** N = 1,222[1]	**p-value**[2]
						<0.001
Klebsiella spp.	50 (18%)	151 (49%)	116 (38%)	17 (5.3%)	334 (27%)	
Moraxella spp.	4 (1.4%)	52 (17%)	113 (37%)	95 (30%)	264 (22%)	
Escherichia spp.	107 (38%)	77 (25%)	16 (5.2%)	1 (0.3%)	201 (16%)	
Pseudomonas spp.	4 (1.4%)	7 (2.3%)	39 (13%)	104 (32%)	154 (13%)	
Staphylococcus spp.	5 (1.8%)	8 (2.6%)	10 (3.2%)	71 (22%)	94 (7.7%)	
Enterobacter spp.	56 (20%)	9 (2.9%)	1 (0.3%)	1 (0.3%)	67 (5.5%)	
Acinetobacter spp.	46 (16%)	2 (0.6%)	1 (0.3%)	0 (0%)	49 (4.0%)	
Proteus spp.	1 (0.4%)	0 (0%)	8 (2.6%)	5 (1.6%)	14 (1.1%)	
Raoultella spp.	1 (0.4%)	0 (0%)	1 (0.3%)	9 (2.8%)	11 (0.9%)	
Streptococcus spp.	0 (0%)	2 (0.6%)	1 (0.3%)	6 (1.9%)	9 (0.7%)	
Salmonella spp.	2 (0.7%)	0 (0%)	1 (0.3%)	2 (0.6%)	5 (0.4%)	
Serratia spp.	0 (0%)	0 (0%)	0 (0%)	4 (1.2%)	4 (0.3%)	
Corynebacterium spp.	3 (1.1%)	0 (0%)	0 (0%)	0 (0%)	3 (0.2%)	
Citrobacter spp.	2 (0.7%)	0 (0%)	0 (0%)	0 (0%)	2 (0.2%)	
Enterococcus spp.	2 (0.7%)	0 (0%)	0 (0%)	0 (0%)	2 (0.2%)	
Micrococcus spp.	0 (0%)	0 (0%)	1 (0.3%)	1 (0.3%)	2 (0.2%)	

Isolated bacteria	Year 1 N = 284[1]	Year 2 N = 309[1]	Year 3 N = 308[1]	Year 4 N = 321[1]	Overall N = 1,222[1]	p-value[2]
Pantoea spp.	0 (0%)	0 (0%)	0 (0%)	2 (0.6%)	2 (0.2%)	
Gardnerella spp.	1 (0.4%)	0 (0%)	0 (0%)	0 (0%)	1 (<0.1%)	
Photobacterium spp.	0 (0%)	0 (0%)	0 (0%)	1 (0.3%)	1 (<0.1%)	
Providencia spp.	0 (0%)	1 (0.3%)	0 (0%)	0 (0%)	1 (<0.1%)	
Shewanella spp.	0 (0%)	0 (0%)	0 (0%)	1 (0.3%)	1 (<0.1%)	
Sphingomonas spp.	0 (0%)	0 (0%)	0 (0%)	1 (0.3%)	1 (<0.1%)	

[1] n (%); [2] Pearson's Chi-squared test

Table 6 reports the sex distribution of bacteria isolated at the TZPHRL. Bacteria such as *Klebsiella spp.*, *Escherichia spp.*, *Staphylococcus spp.* and *Enterobacter spp.* were more common in women than men, with percentages of 51.0%, 62.0%, 56.0% and 53.0%, respectively. In contrast, bacteria such as *Moraxella spp.* (56.0%) *Pseudomonas spp.* (59.0%) and *Acinetobacter spp.* (54.0%), were isolated more frequently in men than women.

Table 6: Sex-based distribution of the isolated bacteria

Isolated bacteria	Female N = 593[1]	Male N = 590[1]	Overall N = 1,183[1]	p-value[2]
				0.018
Klebsiella spp.	162 (51%)	158 (49%)	320 (100%)	
Moraxella spp.	115 (44%)	146 (56%)	261 (100%)	
Escherichia spp.	120 (62%)	75 (38%)	195 (100%)	
Pseudomonas spp.	62 (41%)	90 (59%)	152 (100%)	
Staphylococcus spp.	49 (56%)	39 (44%)	88 (100%)	
Enterobacter spp.	33 (53%)	29 (47%)	62 (100%)	

Isolated bacteria	Female N = 593[1]	Male N = 590[1]	Overall N = 1,183[1]	p-value[2]
Acinetobacter spp.	22 (46%)	26 (54%)	48 (100%)	
Proteus spp.	5 (38%)	8 (62%)	13 (100%)	
Raoultella spp.	7 (64%)	4 (36%)	11 (100%)	
Streptococcus spp.	8 (89%)	1 (11%)	9 (100%)	
Salmonella spp.	2 (40%)	3 (60%)	5 (100%)	
Serratia spp.	1 (25%)	3 (75%)	4 (100%)	
Corynebacterium spp.	2 (67%)	1 (33%)	3 (100%)	
Citrobacter spp.	0 (0%)	2 (100%)	2 (100%)	
Enterococcus spp.	1 (50%)	1 (50%)	2 (100%)	
Micrococcus spp.	1 (50%)	1 (50%)	2 (100%)	
Pantoea spp.	1 (50%)	1 (50%)	2 (100%)	
Gardnerella spp.	1 (100%)	0 (0%)	1 (100%)	
Photobacterium spp.	0 (0%)	1 (100%)	1 (100%)	
Providencia spp.	0 (0%)	1 (100%)	1 (100%)	
Sphingomonas spp.	1 (100%)	0 (0%)	1 (100%)	

[1] n (%); [2] Pearson's Chi-squared test

Table 7 presents the distribution of bacteria isolated according to age group. *Staphylococcus spp.* was the most common bacterium among patients under-5 age group, accounting for 48%. *Moraxella spp.* was the most common bacterial genus (22.0%) in the 5-14 age group. The two most isolated bacterial genus in the 45-59 age group were *Klebsiella spp.* and *Moraxella spp.* (each accounting for 26.0%). Among people aged 15-24, *Escherichia spp.* was the most isolated bacteria (29.0%). *Klebsiella spp.* was the most commonly isolated bacteria in the 25-44 and 60+ age groups, accounting for 29.0% and 30.0% respectively.

Table 7: Distribution of the isolated bacteria by patient age group

Characteristic	Under 5 N = 27[1] (2.36%)	5 – 14 N = 49[1] (4.28%)	15 – 24 N = 97[1] (8.47%)	25 – 44 N = 442[1] (38.60%)	45 – 59 N = 211[1] (18.43%)	60 + N = 319[1] (27.86%)	p-value[2]
Bacteria							<0.001
Klebsiella spp.	3 (11%)	7 (14%)	24 (25%)	126 (29%)	54 (26%)	96 (30%)	
Moraxella spp.	4 (15%)	11 (22%)	11 (11%)	104 (24%)	55 (26%)	72 (23%)	
Escherichia spp.	0 (0%)	7 (14%)	28 (29%)	73 (17%)	33 (16%)	47 (15%)	
Pseudomonas spp.	2 (7.4%)	4 (8.2%)	8 (8.2%)	53 (12%)	29 (14%)	49 (15%)	
Staphylococcus spp.	13 (48%)	5 (10%)	9 (9.3%)	32 (7.2%)	9 (4.3%)	11 (3.4%)	
Enterobacter spp.	0 (0%)	3 (6.1%)	8 (8.2%)	17 (3.8%)	12 (5.7%)	23 (7.2%)	
Acinetobacter spp.	2 (7.4%)	5 (10%)	4 (4.1%)	14 (3.2%)	8 (3.8%)	14 (4.4%)	
Proteus spp.	0 (0%)	2 (4.1%)	0 (0%)	5 (1.1%)	6 (2.8%)	1 (0.3%)	
Raoultella spp.	0 (0%)	0 (0%)	2 (2.1%)	5 (1.1%)	1 (0.5%)	3 (0.9%)	
Streptococcus spp.	1 (3.7%)	0 (0%)	1 (1.0%)	5 (1.1%)	2 (0.9%)	0 (0%)	
Salmonella spp.	2 (7.4%)	2 (4.1%)	0 (0%)	0 (0%)	0 (0%)	1 (0.3%)	
Corynebacterium spp.	0 (0%)	1 (2.0%)	0 (0%)	2 (0.5%)	0 (0%)	0 (0%)	
Serratia spp.	0 (0%)	0 (0%)	1 (1.0%)	2 (0.5%)	0 (0%)	0 (0%)	
Citrobacter spp.	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)	1 (0.3%)	
Micrococcus spp.	0 (0%)	0 (0%)	1 (1.0%)	0 (0%)	1 (0.5%)	0 (0%)	
Pantoea spp.	0 (0%)	0 (0%)	0 (0%)	2 (0.5%)	0 (0%)	0 (0%)	
Enterococcus spp.	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.3%)	
Gardnerella spp.	0 (0%)	1 (2.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Photobacterium spp.	0 (0%)	0 (0%)	0 (0%)	1 (0.2%)	0 (0%)	0 (0%)	
Providencia spp.	0 (0%)	1 (2.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Sphingomonas spp.	0 (0%)	0 (0%)	0 (0%)	1 (0.2%)	0 (0%)	0 (0%)	

[1] n (%), [2] Pearson's Chi-squared test

4.5. Antibiotic resistance profile of the isolated bacteria

In general, high rates of resistance were recorded against the different antibiotics tested. As it is shown in Table 8, the highest resistance rates were found with Penicillin V. against which 95.2% (n=40) of the tested bacteria showed non-sensitivity. It is followed by Amoxicillin against which 77.4% of the tested bacteria were resistant. The other antibiotics with a high rate of resistance were: Cefoxitin (74.4%), Tetracycline (71.3%), Trimethoprim/Sulfamethoxazole (68.2%), Ceftriaxone (66.7%), Cefotaxime (62.4%), Chloramphenicol (54.8%) and Erythromycin (51.3%). Low rates of resistance were recorded against other antibiotics such as Amikacin (15.4%), Meropenem (24.0%), Gentamicin (30.6%), and Ceftazidime (38.5%).

Table 8 shows the bacterial resistance profile for the tested antibiotics at TZPHRL between June 2018 and May 2022. *Klebsiella spp*. strains showed high resistance to Amoxicillin (74.0%), Tetracycline (71.0%), Trimethoprim/Sulfamethoxazole (68.0%), Ceftriaxone (64.0%) and Cefotaxime (63.0%). *Klebsiella spp.* strains showed high sensitivity to Amikacin with only 5.1% of resistance. The highest rate of resistance among *Moraxella spp.* strains were observed against Ciprofloxacin (69.0%). Strains of *Escherichia spp*., *Pseudomonas spp*., *Enterobacter spp*. and *Acinetobacter spp*. were highly resistant to Amoxicillin (81.0%, 87.0%, 84.0%, and 87.0% respectively) and to Ceftriaxone with resistance rates of 63.0%, 93.0%, 68.0%, and 88.0% respectively. These same bacteria showed resistance levels of 60.0%, 93.0%, 64.0%, and 90.0% to Cefotaxime, respectively. It was found that the strains of *Staphylococcus spp.* showed the highest levels of resistance to Penicillin V (95.0%), Tetracycline (70.0%) and Cefoxitin (71.0%).

Table 8: Antibiotic resistance profile of bacteria isolated at the TZPHRL

	AMX	PNV	AZM	ERY	CHL	CIP	CAZ	CRO	CTX	FOX	GEN	MEM	SXT	TCY
Klebsiella spp.	223(74%)	-	128(42%)	-	2(50%)	118(42%)	143(46%)	118(64%)	91(63%)	3(100%)	69(33%)	11(22%)	77(68%)	5(71%)
Moraxella spp.	2(29%)	-	4(36%)	-	-	152(69%)	70(28%)	1(100%)	2(67%)	-	50(28%)	67(27%)	2(67%)	1(50%)
Escherichia spp.	147(81%)	-	88(48%)	-	0(0%)	82(52%)	90(48%)	78(63%)	70(60%)	-	53(38%)	4(18%)	35(76%)	5(71%)
Pseudomonas spp.	20(87%)	-	13(57%)	-	-	29(21%)	33(23%)	14(93%)	14(93%)	-	26(21%)	26(21%)	6(75%)	1(100%)
Enterobacter spp.	51(84%)	-	22(35%)	-	2(67%)	29(48%)	25(42%)	23(68%)	21(64%)	-	14(36%)	1(20%)	15(68%)	2(100%)
Acinetobacter spp.	39(87%)	-	11(24%)	-	-	15(35%)	23(51%)	22(88%)	18(90%)	-	13(37%)	1(20%)	10(67%)	0(0%)
Proteus spp.	4(40%)	-	9(82%)	-	2(100%)	3(25%)	3(30%)	4(57%)	1(17%)	-	2(25%)	0(0%)	4(80%)	-
Raoultella spp.	7(78%)	-	1(11%)	-	-	5(83%)	3(33%)	6(67%)	4(50%)	-	1(17%)	-	4(100%)	-
Salmonella spp.	4(100%)	-	0(0%)	-	-	2(50%)	2(40%)	-	0(0%)	-	0(0%)	-	4(100%)	-
Serratia spp.	4(100%)	-	1(25%)	-	-	1(25%)	1(25%)	1(33%)	0(0%)	-	0(0%)	-	-	-
Staphylococcus spp.	1(100%)	40(95%)	33(42%)	33(49%)	31(52%)	23(42%)	0(0%)	1(100%)	2(67%)	27(71%)	19(36%)	0(0%)	31(55.36%)	51(70%)
Citrobacter spp.	1(50%)	-	0(0%)	-	-	0(0%)	0(0%)	-	-	-	0(0%)	-	-	-
Pantoea spp.	1(50%)	-	1(50%)	-	-	2(100%)	2(100%)	2(100%)	1(100%)	1(100%)	0(0%)	-	1(100%)	-
Photobacterium spp.	0(0%)	-	1(100%)	-	-	1(100%)	0(0%)	1(100%)	0(0%)	-	0(0%)	-	-	-
Providencia spp.	1(100%)	-	1(100%)	-	-	0(0%)	0(0%)	-	-	-	0(0%)	-	-	-
shewanella spp.	-	-	-	-	-	-	1(100%)	-	-	-	0(0%)	1(100%)	-	-
Sphingomonas spp.	1(100%)	-	1(100%)	-	-	0(0%)	0(0%)	1(100%)	1(100%)	-	-	-	1(100%)	-
Streptococcus spp.	-	-	5(71%)	5(83%)	5(62%)	0(0%)	-	-	1(14%)	-	1(100%)	-	-	5(71%)
Corynebacterium spp.	-	-	0(0%)	1(33%)	1(50%)	0(0%)	-	-	-	1(100%)	0(0%)	-	0(0%)	3(100%)
Enterococcus spp.	-	-	2(100%)	-	2(100%)	1(50%)	-	-	1(100%)	-	0(0%)	-	1(100%)	2(100%)
Micrococcus spp.	-	-	2(100%)	-	1(100%)	1(50%)	-	-	-	-	0(0%)	-	2(100%)	1(50%)
Gardnerella spp.	-	-	0(0%)	-	0(0%)	1(100%)	-	-	-	-	1(100%)	-	-	1(100%)
Total	**147/956 (15.40%)**	**506/654 (77.37%)**	**40/42 (95.24%)**	**323/758 (42.61%)**	**39/76 (51.32%)**	**46/84 (54.76%)**	**465/995 (46.73%)**	**396/1029 (38.48%)**	**272/408 (66.67%)**	**227/364 (62.36%)**	**32/43 (74.42%)**	**249/815 (30.55%)**	**111/462 (24.03%)**	**193/283 (68.20%)**	**77/108 (71.30%)**

AMK: Amikacin, AMX: Amoxicillin, AZM: Azithromycin, CAZ: Ceftazidime, CHL: Chloramphenicol, CIP: Ciprofloxacin, CRO: Ceftriaxone, CTX: Cefotaxime, ERY: Erythromycin, FOX: Cefoxitin, GEN: Gentamicin, MEM: Meropenem, PNV: Penicillin V, SXT: Trimethoprim/Sulfamethoxazole, TCY: Tetracyclin

4.6. Prevalence of the multidrug resistance

Results indicate a significant prevalence of multidrug resistant bacteria. Generally, 41.6% of the bacteria strains isolated from the TZPHRL were multidrug resistant. Among the females, 45.0% were infected by multidrug resistant organisms (MDROs) compared to 38.0% among males. From Table 9, which shows the bivariate distribution of patient characteristics according to their multidrug resistance status, it revealed that 45.0% of hospitalized patients were infected with multidrug resistant bacteria compared to 28.0% of non-hospitalized patients. We also found that patients among the under-5 age group had a high prevalence of infection with multidrug resistance (56.0%). Among the most prevalent isolated bacteria, the highest rates of multidrug resistance were found among *Staphylococcus spp.* (56.0%), *Escherichia spp.* (56.0%) and *Enterobacter spp.* (54.0%) and those with the lowest multidrug resistance rates were *Pseudomonas spp.* (19.0%) and *Moraxella spp.* (25.0%).

Table 9: Bivariate distribution of patient characteristics according to their multidrug resistance status

Characteristic	MDR- N = 714[1] (58.40%)	MDR+ N = 508[1] (41.60%)	Overall N = 1,222[1] (100%)	P-value[2]
Sex				0.019
Female	328 (55%)	265 (45%)	593 (100%)	
Male	366 (62%)	224 (38%)	590 (100%)	
Age	40 (28,58)	41 (28,62)	41 (28,60)	0.300

Characteristic	MDR- N = 714[1] (58.40%)	MDR+ N = 508[1] (41.60%)	Overall N = 1,222[1] (100%)	P-value[2]
Age group				0.031
Under 5	12 (44%)	15 (56%)	27 (100%)	
5 - 14	33 (67%)	16 (33%)	49 (100%)	
15 - 24	49 (51%)	48 (49%)	97 (100%)	
25 - 44	280 (63%)	162 (37%)	442 (100%)	
45 - 59	128 (61%)	83 (39%)	211 (100%)	
60 +	176 (55%)	143 (45%)	319 (100%)	
Hospitalization status				<0.001
Inpatient	544 (55%)	443 (45%)	987 (100%)	
Outpatient	170 (72%)	65 (28%)	235 (100%)	
Isolated bacteria				
Acinetobacter spp.	27 (55%)	22 (45%)	49 (100%)	
Citrobacter spp.	2 (100%)	0 (0%)	2 (100%)	
Corynebacterium spp.	2 (67%)	1 (33%)	3 (100%)	
Enterococcus spp.	0 (0%)	2 (100%)	2 (100%)	
Enterobacter spp.	31 (46%)	36 (54%)	67 (100%)	
Escherichia spp.	89 (44%)	112 (56%)	201 (100%)	
Gardnerella spp.	0 (0%)	1 (100%)	1 (100%)	
Klebsiella spp.	171 (51%)	163 (49%)	334 (100%)	
Micrococcus spp.	0 (0%)	2 (100%)	2 (100%)	
Moraxella spp.	198 (75%)	66 (25%)	264 (100%)	
Pantoea spp.	1 (50%)	1 (50%)	2 (100%)	
Photobacterium spp.	0 (0%)	1 (100%)	1 (100%)	
Proteus spp.	8 (57%)	6 (43%)	14 (100%)	

Characteristic	MDR- N = 714[1] (58.40%)	MDR+ N = 508[1] (41.60%)	Overall N = 1,222[1] (100%)	P-value[2]
Providencia spp.	1 (100%)	0 (0%)	1 (100%)	
Pseudomonas spp.	125 (81%)	29 (19%)	154 (100%)	
Raoultella spp.	6 (55%)	5 (45%)	11 (100%)	
Salmonella spp.	3 (60%)	2 (40%)	5 (100%)	
Serratia spp.	3 (75%)	1 (25%)	4 (100%)	
shewanella spp.	1 (100%)	0 (0%)	1 (100%)	
Sphingomonas spp.	0 (0%)	1 (100%)	1 (100%)	
Staphylococcus spp.	41 (44%)	53 (56%)	94 (100%)	
Streptococcus spp.	5 (56%)	4 (44%)	9 (100%)	

[1] n (%); Median (IQR); [2] Pearson's Chi-squared test; Kruskal-Wallis rank sum test

4.7. Factors associated with the multidrug resistance

Tables 10 and 11 respectively show the univariate and the multivariable logistic regression analyses. From the univariate analysis, we found that the odds of infection by MDROs were 1.33 times higher in females than males (COR: 1.33; 95% CI: 1.05 – 1.69; P 0.018). Patients of the under 5 age group (COR: 2.35; 95% CI: 1.06 – 5.37; P 0.037) and those who were 60 and more years of age (COR: 1.41; 95% CI: 1.05 – 1.89; P 0.023) had 2.35 times and 1.41 times more odds of MDROs infections respectively compared to those aged from 25 to 44 years. Hospitalized patients were 1.96 times more likely to have been infected by multidrug resistant bacteria than those who were not (COR: 1.96; 95% CI: 1.43 – 2.71; P<0.001).

Table 10: Univariate logistic regression of factors associated with multidrug resistance

Characteristic	COR[1,2]	95% CI[2]	p-value
Sex			
Male	—	—	
Female	1.33*	1.05, 1.69	0.018
Age group			
25 - 44	—	—	
Under 5	2.35*	1.06, 5.37	0.037
5 - 14	0.86	0.45, 1.60	0.600
15 - 24	1.55	0.98, 2.43	0.057
45 - 59	1.11	0.79, 1.56	0.500
60 +	1.41*	1.05, 1.89	0.023
Hospitalization status			
Outpatient	—	—	
Inpatient	1.96***	1.43, 2.71	<0.001
Isolated bacteria			
Klebsiella spp.	—	—	
Moraxella spp.	0.35***	0.24, 0.51	<0.001
Staphylococcus spp.	1.43	0.87, 2.39	0.200
Acinetobacter spp.	0.90	0.48, 1.68	0.700
Enterobacter spp.	1.11	0.64, 1.93	0.700
Escherichia spp.	1.32	0.92, 1.92	0.130
Pseudomonas spp.	0.24***	0.15, 0.38	<0.001
Others	0.90	0.50, 1.59	0.700

[1] *p<0.05; **p<0.01; ***p<0.001; [2] COR = Crude Odds Ratio, CI = Confidence Interval

The multivariable regression analysis revealed that only the inpatient status was positively associated with multidrug resistance. Generally, it increased by 1.78 times the odds of infections by MDROs in comparison to non-hospitalized patients (AOR: 1.78; 95% CI: 1.28 – 2.49; P<0.001). Other factors such as infections by *Moraxella spp.* and *Pseudomonas spp.* were found to lower the odds of multidrug resistance with statistical significance in both univariate and multivariable regression analyses.

Table 11: Multivariable logistic regression of factors associated with multidrug resistance

Characteristic	AOR[1,2]	95% CI[2]	P-value
Hospitalization status			
Outpatient	—	—	
Inpatient	1.78***	1.28, 2.49	<0.001
Isolated bacteria			
Klebsiella spp.	—	—	
Moraxella spp.	0.38***	0.26, 0.54	<0.001
Staphylococcus spp.	1.40	0.85, 2.34	0.200
Acinetobacter spp.	0.86	0.46, 1.60	0.600
Enterobacter spp.	1.15	0.66, 2.00	0.600
Escherichia spp.	1.32	0.91, 1.91	0.150
Pseudomonas spp.	0.23***	0.14, 0.37	<0.001
Others	0.89	0.50, 1.59	0.700

[1] *p<0.05; **p<0.01; ***p<0.001; [2] AOR = Adjusted Odds Ratio, CI = Confidence Interval

CHAPTER FIVE

5.0 DISCUSION OF RESULTS

5.1. Introduction

This chapter focuses on the discussion of the study results. It also compares our results with those of other studies, as well as possible explanations.

This discussion will be centered on the following areas;

- Bacterial pathogens implicated in recorded infections
- Antibiotic resistance levels
- Prevalence of multidrug resistance
- Risk factors associated with multidrug resistance
- Limitations and strengths of the study

5.2. Bacterial pathogens detected in recorded infections

Diagnostic stewardship is essential for health facilities at the local level. It contributes to the promotion of timely and adequate laboratory diagnostic testing. This involves the collection of samples, the identification of disease-causing agents and the accurate as well as prompt reporting of results to guide the treatment of patients (Global AMR Surveillance System (GLASS), 2016). This is lacking in many hospitals in sub-Saharan Africa, with little or no monitoring of whether or not a newly admitted patient is a carrier of multidrug resistant germs, whose infections frequently lead to increased morbidity and mortality (Haque et al., 2018; Zowawi et al., 2015). The present study had to fill the knowledge gap on the organisms involved in bacterial infections, their resistance profile and the prevalence of multidrug resistance as well as the associated risk factors in the northern region of Ghana.

The results of this study's data analysis revealed that *Klebsiella spp.* was the most prevalent bacteria and had shown a very significant resistance to Amoxicillin and to many other antibiotics including Tetracycline, Trimethoprim/Sulfamethoxazole, Ceftriaxone, and Cefotaxime. Similar results were found in a study to map the regional distribution of *Klebsiella spp*. strains in health facilities that act as referral centers in Ghana's northern, central, and southern parts. More than 70.0% of resistance has been found against Cephalosporins of the third generation (ceftazidime, cefotaxime, and ceftriaxone) among *Klebsiella spp.* strains, with a greater resistance to ampicillin (Quansah et al., 2019). There have been more than 100 acquired resistance genes identified in *Klebsiella* strains conferring them the capacity to neutralize the damaging effects of several different antibiotic types, notably polymyxins, beta-lactams, aminoglycosides, quinolones, and tigecycline (Long et al., 2022; Navon-Venezia et al., 2017; Wyres & Holt, 2016) which could consequently explain these high resistance levels. The existence of resistance genes has been documented among *Klebsiella spp*. strains in different parts of Ghana (Agyekum et al., 2016; Oduro-Mensah et al., 2016; Pankok et al., 2022) and in other countries of the West African sub-region (Afolayan et al., 2021; Ayobola et al., 2021; Kpoda et al., 2018; Müller-Schulte et al., 2020; Salah et al., 2019; Sanou et al., 2021; Shitta et al., 2021). This demonstrates the need to conduct molecular epidemiology studies to assess the resistance genotypes of these circulating strains and their spatial distribution.

Among the five (5) most prevalent bacteria, three (3) of them (*Staphylococcus spp*., *Klebsiella spp*., and *Pseudomonas spp*.) had strains classified as pathogens belonging to ESKAPE group (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa,* and *Enterobacter species*) (de Oliveira et al., 2020). These

strains are well known in clinical settings and have the ability to resist the bactericidal or bacteriostatic actions of many antimicrobial agents by developing resistance mechanisms either by gene or plasmid acquisition or by genetic mutations (Pandey et al., 2021; Pérez-Lazo et al., 2021). In hospitals and nursing homes, these ESKAPE bacteria pose a particularly high risk because they can lead to pneumonia and bloodstream infections, both of which can be deadly (Tacconelli et al., 2018). In our study, blood was the 5th most prevalent specimen and multiple studies have reported the involvement of ESKAPE pathogens in bloodstream infections where they had significant degrees of resistance when tested (de Angelis et al., 2018; Deku et al., 2019; de Socio et al., 2019; Velázquez-Acosta et al., 2018; Wei et al., 2020). In a study conducted in the United States, these pathogens were even associated with higher costs ($5500 more) and mortality (2.10% absolute increase) (Marturano & Lowery, 2019). This shows that it is of major importance for countries such as Ghana to engage in research focused on exploring traditional African pharmacopeia for new antimicrobial molecules to help in the development of new antibiotics that can effectively combat these pathogens to minimize undesirable consequences.

The most representative specimen in our study was sputum (68.0%). This differs from a study on multidrug resistant bacteria conducted at the Komfo Anokye Teaching Hospital (KATH) located in Kumasi (Agyepong et al., 2018) where the most representative specimen was urine (47.0%). This difference may be due to geographical location of the studies in Ghana. Whereas the KATH research was performed in the Ashanti area in the south of Ghana, we did ours in the country's northern region. This geographical difference may explain the differences in the types of infections to which people in these regions are prone.

5.3. Antibiotic resistance levels

High resistance levels have been found in our study against Cefoxitin (74.0%), Tetracycline (71.0%), Trimethoprim/Sulfamethoxazole (68.0%), Ceftriaxone (68.0%), Cefotaxime (62.0%), Chloramphenicol (54.8%) and Erythromycin (51.0%) in Northern Ghana. These results are similar to those reported from the Greater Accra region (Variations in the percentage of resistant organisms were found to be between 37.1 and 69.1) (Mohammed et al., 2018) but also in Uganda (cefotaxime (74.2%) and cefoxitin (92.1%)) (Obakiro et al., 2021). One possible explanation for such high resistance rates is that these drugs have become increasingly widely used in medical settings (Ghana Ministry of Health, 2017). In addition, these antibiotics are easily accessible in pharmacies and drugstores over the counter. Therefore, self-medication practiced by the population in Ghana (Jimah et al., 2020; Kretchy et al., 2021) could be a contributing factor. It has already been reported that at the referral hospital in Northern Region (the Tamale Teaching Hospital); there is a high proportion of antibiotic abuse coupled with a high prevalence of incomplete treatment, off-label prescriptions, and potential interactions (García-Vello et al., 2020). This may explain the particular case of these high proportions of resistance against the tested antibiotics in this study. This, therefore, demonstrates the urgent need for strengthening hospital-based antibiotic stewardship programs and extending its interventions to community levels. In sub-Saharan African countries, services for clinical bacteriology testing are usually reserved for higher levels of care and are therefore under-utilized (Nkengasong et al., 2018). As bacteriological diagnostics are performed in a very restrictive manner, this could result in patients with recurrent, difficult-to-treat and often resistant infections not receiving early and appropriate treatment because they have not had the opportunity to visit these institutions for accurate diagnosis and

treatment. This leads to the selection of more resistant isolates and thus to high estimations of resistance levels, which may also explain the rates recorded in the current research.

5.4. Prevalence of multidrug resistance

A proportion of 41.6% was found for multidrug resistance of the strains isolated from TZPHRL. These results are lower than those found in northwest Nigeria (88.9%) (Olowo-okere et al., 2020) and Ethiopia (85.8%) (Moges et al., 2021) where significantly higher rates were reported. This difference could be explained by two factors. The first is related to the sample sizes used to determine the prevalence of MDR which were respectively 397 and 141 for Nigeria and Ethiopia while our study had a total of 1,222. The second is that in their studies, they took into account only Gram-negative bacteria. However, both Gram-positive and Gram-negative bacteria were present in the current investigation.. It is well known that Antimicrobial resistance is typically higher in Gram-negative bacteria (GNB) than in Gram-positive bacteria (Breijyeh et al., 2020). This is due to the fact that their outer membrane gives them extra protection by preventing antibiotic molecules from penetrating the bacterial cell. In addition, carbapenemases (CBPs) and Extended-spectrum beta-lactamases (ESBLs) are produced at extremely high rates by GNBs, which allows them to resist more antibiotics and thus express a greater multidrug resistance phenotype (Rodríguez-Baño et al., 2018; Wilson & Török, 2018). This could explain why the total prevalence of multidrug resistant strains is higher in these studies than in our current study. Magiorakos et al. reported various classes of antibiotics in their paper (Magiorakos et al., 2012). However, some of these classes were not tested in our study. Thus, some bacteria that would normally be multidrug resistant would have been missed. This could also explain the relatively low proportion we found in our study compared to the previous studies.

5.5. Risk factors associated with multidrug resistance

About 28.00% of non-hospitalized patients were infected by multidrug resistant bacteria. This rate, although relatively low, it shows that these strains are circulating even in community settings where they could be transmitted either by Human-to-Human transmission or by the Human-Animal-Environment system. Typically, animal farming practices that employ excessive amounts of antibiotics can contaminate the agroecosystem through applying infected manure as fertilizer and irrigating crops with wastewater (Larsson & Flach, 2022; Polianciuc et al., 2020). This is supported by results of earlier research in the Northern Ghana (Adzitey et al., 2020; Egyir et al., 2022) the rest of the country as well (Dsani et al., 2020; García-Vello, González-Zorn, et al., 2020) where there was evidence of resistance genes in environmental, dietary, and animal samples.

The current study found the female sex to be independently associated with multidrug resistance. These results corroborate those found in studies conducted in India and Saudi Arabia (al Hamdan et al., 2022; Kalluru et al., 2018). One possible explanation for these re is the estimated 27.0% exposure rate of women to antibiotic usage (Schröder et al., 2016) higher than men's. This is because they often use antibiotic treatment regimens in several phases of their lives, including but not limited to preconception, labour and delivery, and postpartum. Moreover, young women, especially those who are sexually active, are at greater risk for vaginal infections, urinary tract infections, gonorrhea, and other diseases that may also lead to increased antibiotic prescriptions.

Out of the hospitalized patients from whom samples were taken for bacteriological diagnostics, 44.0% of the isolates were multidrug resistant and being hospitalized was also strongly associated with multidrug resistance in both univariate and multivariable analyses. This association has been found in previous investigations in other different parts of Ghana (Bediako-Bowan et al., 2020;

Labi et al., 2020). This demonstrates that there is an urgent need to initiate interventions that will help to control this situation. An immediate action should be taken to reduce the circulation of MDROs in hospital settings by conducting observational studies on the practice of hygiene among health professionals working in hospitals within the study setting. In addition, there is the need to assess the state of knowledge regarding MDROs, their consequences and the means by which these strains can be transmitted in a health care facility. This allows for the creation of training content and adapt to the existing needs in the sector to effectively reinforce the capacities of healthcare professionals. Several studies have shown that capacity-building programs for healthcare professionals, particularly on the topic of hands hygiene, have been effective in controlling outbreaks of nosocomial infections involving multidrug resistant strains (Meißner et al., 2017; Mody et al., 2021; Ruiz et al., 2017).

5.6. Limitations and strengths of the study

Our study's limitations include the inability to record additional potential risk factors like the time spent in the medical facility, past antibiotic use, and history of clinical conditions. Previous research in both developed and developing nations identified them as risk factors for the presence of multidrug resistant pathogenic organisms (Elduma et al., 2019; Fernández-Martínez et al., 2022; Ramos-Castaneda et al., 2019). Nevertheless, we were unable to conduct these investigations in our specific situation because such data were not available.This study has a number of strengths. Among others, we have a large number of samples that were analyzed at the TZPHRL, which is an integral part of Ghana's health services within the public health system. This study also covers a 48-month period and therefore provides a snapshot of the situation in the Northern Region, as the samples were brought from different parts of the region.

CHAPTER SIX

6.0. CONCLUSION AND RECOMMENDATION

6.1. Summary

In summary, a total of 1,222 positive bacterial cultures were recorded including 593 (48.5%) females were recorded. The age of the patients of the samples received ranged from 0 to 105 years. We found that sputum was the most common sample with a percentage of 68.0%, followed by urine (11.0%), high vaginal swab (6.4%), wound swab (6.1%) and blood (5.1%). The results revealed the five (5) main bacterial genus responsible for the infections isolated from the TZPHRL. These were: : *Klebsiella spp*., *Moraxella spp*., and *Escherichia spp*. respectively with respectively 27%, 22%, and 16% followed by *Pseudomonas spp.* (13.0%), and *Staphylococcus spp.* (7.7%).

High rates of resistance were recorded against the different antibiotics tested. The highest resistance rates were found with Penicillin V. against which 95.2% (n=40) of the tested bacteria showed non-sensitivity. It is followed by Amoxicillin against which 77.4% of the tested bacteria were resistant.

Results indicate a significant prevalence of multidrug resistant bacteria. Generally, 41.6% of the bacteria strains isolated from the TZPHRL were multidrug resistant. Among the females, 45.0% were infected by multidrug resistant organisms (MDRO) compared to 38.0% among males. 45.0% of hospitalized patients were infected with multidrug resistant bacteria compared to 28.0% of non-hospitalized patients. Hospitalization was associated with multidrug resistance in the univariate analysis (Crude OR: 1.96; 95% with CI 1.43–2.71; $P < 0.001$) and also in the multivariable analysis (Adjusted OR: 1.78; 95% with CI 1.28–2.49; $P < 0.001$).

6.2. Conclusion

This study analyzed data from specimens collected from several types of infections. We found high resistance rates against the tested antibiotics in Ghana's northern region and it is coupled with a relatively high prevalence of multidrug resistance. Hospitalization was a risk factor of infections with multidrug resistance. Thus, it is crucial to strengthen antibiotic stewardship programs while giving refresher training to healthcare professionals regarding this topic. Further studies using molecular epidemiology and mathematical modeling are also required to formulate recommendations for decision-makers at different levels of the health system in Ghana. This will contribute to strengthening the different initiatives that are taken to tackle the progression of antimicrobial resistance at the national level.

6.3. Recommendations

- Reinforce awareness programme on water, sanitation and hygiene (WASH) in communities to promote effective ways of preventing infections.
- There is a need for health authorities to reinforce data capturing systems for routine data collection on antibiotic susceptibility testing results in order to create a nationwide database (with a one health approach) that could be used to monitor antibiotic/multidrug resistance levels.
- Hospital facilities need to regularly provide their staff with refreshing and high-quality training on hygiene and its importance in infection prevention and control.
- The management of hospitals need investigate infections by multidrug resistance pathogens among hospitalized patients at the facility level to consequently reinforce their diagnostic and antimicrobial stewardship policies.
- Educate the general populations on the role of self-medication habits as well as inappropriate use of antibiotics in occurrence of drug resistance and associated consequences.

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APPENDIX

Data extraction sheet

Year	Sex	Ag	talization	sample	Bacteria	Gram	AMK	AMX	PNV	AZM	ERY	CHL	CIP	CAZ	CRO	CTX	FOX	GEN	MEM	NOV	SXT	TCY	MDR_Status

BACTERIAL INFECTIONS EPIDEMIOLOGY AND FACTORS ASSOCIATED WITH MULTIDRUG RESISTANCE IN THE NORTHERN REGION OF GHANA

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