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MULTIDRUG-RESISTANT BLOODSTREAM ORGANISM INFECTION AT THE NEONATAL INTENSIVE CARE UNIT IN THE GREATER ACCRA REGIONAL HOSPITAL IN GHANA

BY

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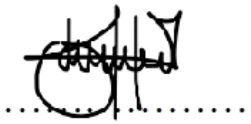
DECLARATION

I Abena Odurowaa Yeboah, hereby declare that except for the references of other people's work which have been cited, this dissertation is the result of my own original work, and that this work either in whole or part has not been presented for a degree in another institution.



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DEDICATION

This work is dedicated to God Almighty for the strength and grace given me to undertake this remarkable journey. I would also like to acknowledge my parents for the support and my mentors for the tireless encouragement given to me to be the best version of myself. Lastly, I would like to dedicate this work to my hopes and dreams and to my future self.

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LIST OF ABBREVIATION

ADR- Antimicrobial drug resistance

CLABSI - Central line-associated bloodstream infections

CoNS – Coagulase Negative Staphylococcus

ESBL - Extended spectrum beta lactamase

GARH - Greater Accra Regional Hospital

GNB - Gram Negative Bacteria

HAI – Hospital acquired infections

HGT - Horizontal gene transfer

ICU- Intensive care Unit

LMICs - Low and middle-income countries

MDR – Multidrug resistance

MDR-GNB - Multidrug resistant Gram-Negative Bacteria

MDR-TB - Multi-drug resistant Tuberculosis

MDRO- Multidrug resistant Organism

MDROI- Multidrug resistant Organism Infection

MRSA - Methicillin-resistant Staphylococcus aureus

NICU- Neonatal Intensive care Unit

RCR - Retrospective chart review

RR-TB - Rifampicin-resistant Tuberculosis

TB – Tuberculosis

VRSA - Vancomycin resistant S. aureus

ABSTRACT

Abstract

Background:

Antimicrobial drugs since their inception have improved contemporary medicine. Blood stream infections (BSIs) are a significant source of morbidity and mortality among the neonatal population in hospitalized settings with a penchant for Low and middle-income countries (LMICs). Data on newborn BSIs showing Multidrug resistance (MDR) using a mixed technique approach are few. As a result, it has become critical to identify and analyze the scope of this hidden health problem in a vulnerable and at-risk population in order to raise awareness and prompt action. The general objective was to assess the multidrug resistant-organism infections in Neonatal Intensive care unit (NICU) in Greater Accra Regional Hospital in Ghana.

Methods:

The study was conducted using a mixed method research design at a tertiary level in a neonatal intensive care unit (NICU) in Greater Accra Regional Hospital (GARH), Ghana. All blood cultures taken for newborns admitted to the NICU within the period of 1st June 2020 to 31st May 2021were included. Multidrug resistance (MDR) in BSI rates were analysed, and the effect of antimicrobial resistance (AMR) on outcomes and duration of hospitalization were analysed. Participants in the qualitative study were Neonatal ICU nurses, Microbiologists, and Laboratory technicians. The sampling approach used for interviewing health workers was convenience sampling in view of the tight work scheduled of many of the qualified respondents. All interviews were conducted in the facility with prior notice to the participants. Data was analyzed into proportions as per total sample size. Analyzed data, together with interview findings, together forming quantitative and qualitative data, were compared with the

secondary data extracted to answer the proposed research questions. *P* values <0.05 were considered significant.

Results:

Of 1,043 blood culture samples taken from neonates in the NICU, 195 cultured Multidrug resistant organisms (MDROs). Overall incidence of MDR BSI was 18.7% (195/1043). The predominantly isolated pathogenic organism was *Klebsiella spp* 31.2% (61/195) and *Staphylococcus aureus* 20.5% (40/195). Additionally, 38 coagulase negative Staphylococci were isolates. Among the *Klebsiella spp* resistance to ampicillin, cefotaxime and gentamicin was 72.1%, 39.3% and 52.4%, respectively, while carbapenem resistance was 10.4%. Mortality among neonates with MDR BSI was 26.2% (51/195).

Results also indicated that knowledge of MDROs amongst Health care workers and control measures to curtail their development and spread were very general and lacked. Qualitative results also indicated that public education and sensitization at the community level as well as providing a framework and guidelines for antimicrobial stewardship at the facility level is a basic and urgent need in the management of MDR.

Conclusion:

This study corroborates existing literature, reiterating the urgent need for intervention. The empirical regimen in the setting of low- and middle-income countries such as Ghana is unlikely to lead to advancement substantial enough to improve outcomes associated with MDR BSI. The required improvement would require advancements in various medical fields including improvement in clinical microbiological services.

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DEFINITION OF TERMS

ANTIMICROBIALS: Medicines used to diagnose and reduce infections in people, animals, and plants are referred to as antimicrobials. Antibiotics, antivirals, antifungals, and antiparasitic are among them.

ANTIMICROBIAL DRUG RESISTANCE (ADR): Refers to the phenomenon of microbes such as bacteria, viruses and fungi changing their physiological make – up to render medications used for treatment ineffective, thus resulting in continued illness and death.

MULTIDRUG RESISTANCE (MDR): When a single bacterium is resistant to more than one antibiotic, this is referred to as multi-drug resistance. MDR is clinically defined as an isolate that is resistant to at least one antimicrobial agent from one of three groups.

NEONATE: An infant less than four (4) weeks old.

INFANT: A baby zero (0) to one (1) year old.

BACTERAEMIA: Viable bacteria that are present in the bloodstream. They could be associated with an active disease or not.

GRAM NEGATIVE BACTERIA: Refers to a wide range of bacteria found in environments that support life on earth.

MORBIDITY: The state of being afflicted with a sickness or medical condition.

MORTALITY: Refers to the state or situation of being subject to death.

NOSOCOMIAL INFECTIONS: Refers to infectious diseases acquired from contact with various transmission channels of a healthcare facility, 48 hours after admission or post admission.

CHAPTER ONE

INTRODUCTION

1.1 Background

Neonatal ICU patients require extremely critical care and around the clock assistance with the management of health their conditions (Comisso et al., 2018). This unfortunately and more often than not, results in the onset of nosocomial infections (Comisso et al., 2018).

Hospital-acquired (nosocomial) infection is a primary health problem for premature and term neonates requiring long term hospitalization due to mild to serious medical disorders with the most common being central line-associated bloodstream infections (CLABSI) and nosocomial pneumonia (Knowles, 2009). Sepsis has been found to be the most frequent infection in neonates in NICU (Zou et al., 2021), while premature birth, severe infection and suffocation have been to be the leading causes of neonatal mortality (Comisso et al., 2018). Late-onset sepsis (sepsis that occurs after 72 hours) on admission affects up to about 5% of NICU admissions (Ramirez & Cantey, 2019)

According to demographic studies conducted during the last two decades, the global estimate of the incidence of new-born sepsis was 2202 per 100,000 live births (LBs), with death ranging between 11 and 19 percent (Zou et al., 2021). Nevertheless, despite recording global reductions in paediatric mortality during the period, there hasn't been much improvement regarding neonatal mortality, currently accounting for nearly half of death of children under age five (Zou et al., 2021). Infections caused by multi-drug resistant gram-negative bacteria are linked with increased morbidity, mortality, length of stay, as well as patient healthcare costs. Zhou et al., (2013) in a study conducted at Johns Hopkins medical institution revealed that patients hospitalized for infections caused by antimicrobial-resistant organisms have significantly

higher costs ranging from approximately 6,000 to 30,000 dollars more than those with antimicrobial susceptible organisms (Cosgrove, 2006)

Appropriate treatment of severe infections, especially Sepsis, is crucial for neonatal survival and an improvement in neonatal mortality records. However, increased development of antimicrobial resistance (AMR) microorganisms continues to complicate the management of these diseases.

1.2 Problem Statement

In health care delivery pertaining to the management of microbial infections, the ultimate aim is to successfully treat patients while ensuring that no harm is caused in the process. Comisso et al. (2018) showed that, to achieve this, there are stipulated guidelines to be adhered to when attending to a patient. Rennie and Kendall (2013) explained that adhering to these guidelines ensure that there is little to no risk at all to patients when receiving the best possible healthcare that could be afforded them.

Neonates in the intensive care unit (NICU) are susceptible to Hospital acquired infections. Transmitted through consistent contact with healthcare professionals as well as contaminated objects/instrument. Asare et al., (2009) explained that high infection rates in intensive care facilities can be linked to various factors including, but not limited to effective hand hygiene practices as well as instrumentation and highly invasive procedures (Ulu-Kilic et al., 2013). Surgical and mechanical procedures such as arterial and venous catheters, tracheal cannulas, peritoneal shunts, chest drains, and other similar devices increase the chance of transmission. (Raj Bhatta et al., 2020).

S. aureus, including methicillin-resistant S. aureus (MRSA), Klebsiella species, E. coli, Pseudomonas species, Acinetobacter species, and Enterococcus species are some of the bacteria that are commonly transmitted (Raj Bhatta et al., 2020). Raj Bhatta et al., (2020) and

Inusah et al., (2021) in their studies showed that, increased antibiotic resistance and the rise of multidrug resistant (MDR) organisms such as MRSA, vancomycin resistant S. aureus (VRSA), extended spectrum beta lactamase (ESBL) generating Enterobacteriaceae and Acinetobacter species in the NICU result in significant morbidity and mortality.

Multidrug Resistance (MDR) leads to upscaling of antibiotics and the use of comparatively higher doses which perpetuates a cycle of resistance. Low and middle-income countries (LMICs) have higher antimicrobial resistance and concomitant higher mortality rates than higher-income countries (Saharman et al., 2021). Multidrug-resistant gram-negative species have been found to also play a much more significant role in LMIC's Intensive care units than in higher-income countries. Studies conducted in Africa in Northern Tanzania and Rwanda by (Kumburu et al., 2017) and (Carroll et al., 2016) respectively, revealed alarming rates of antimicrobial resistance (AMR) and exposed the need for a review in antibiotic stewardship.

Resistant microbial strains provide a challenge to paediatric healthcare practitioners because they are more likely to be passed to and cause difficult to treat illnesses in high-risk children. (Milstone et al., 2010).

Martinez and Baquero, (2009) explained that this has compelled healthcare practitioners in this field to consider combining and trying out antimicrobial drugs with impaired activity to ascertain whether their combined chemical formulations will make it possible to easily treat infections Also, the use of old antimicrobial agents have been employed. An example is re-introducing an old antibiotic, vancomycin as treatment for MRSA infections.

Unfortunately, inadequate antibiotic stewardship as well as a lack of detailed and practical treatment protocols in health care facilities in Ghana is nurturing a man-made pandemic of antibiotic resistance within the country's healthcare facilities (Newman et al., 2011) The result is an ever soaring rate of self-medication and the inappropriate as well as overuse of antibiotics

is fast depleting the level the effectives of common and even sometimes, strong antibiotics in the management of the microbial infection of the average Ghanaian patient. The country is at the brink of developing extreme drug-resistant strains of microbes as is in the case of tuberculosis. A study conducted in Ghana observed a higher prevalence of MDR-GNB among inpatients 80.5% compared to outpatients which accounted for only 19.5%. (Agyepong et al., 2018)

To make matters worse, though there is a high rate of nosocomial or hospital acquired infections (HAIs) in the country's health care facilities requiring successful antimicrobial treatment, infections caused by resistant bacteria are extremely difficult, probably almost impossible to treat (Inusah et al., 2021)

The spectrum of organisms inhabiting the NICU environment alter with time and vary from hospital to hospital, both inside and outside the nation. As a result, this study was conducted to assess the bacterial contamination of routinely handled NICU objects/instruments.

It has therefore become imperative to identify and assess the extent of this burgeoning health concern for prompt intervention. Hence, the need for a study into Multidrug Resistance that focuses on Neonatal intensive care units at the Greater Accra Regional Hospital to identify the extent of the problem there for possible intervention.

1.3 Research Questions

The study was carried out to find answers to the following research questions:

1. What is the antibiotic susceptibility profile of infections in patients admitted to the NICU with bloodstream infections at the Greater Accra Regional Hospital?
2. What is the level of prevalence of Multidrug-resistant organism Blood Stream infection in the NICU of Greater Accra Regional Hospital?

3. What are the most frequently prescribed first-line antibiotics in the NICU of Greater Accra Regional Hospital?
4. What is the rate of morbidity and mortality associated with multidrug-resistant organisms in the NICU of Greater Accra Regional Hospital?
5. What are the measures currently in place to prevent the emergence of antimicrobial resistance in Greater Accra Regional Hospital?

1.4 Objectives

1.4.1 General Objective

The General objective for the study was to assess the multidrug resistant-organism infections in Neonatal Intensive care unit (NICU) in Greater Accra Regional Hospital in Ghana.

1.4.2 Specific Objectives

Specific Objectives were as follows:

1. To determine antibiotic susceptibility profile of infections in patients admitted to the NICU with bloodstream infections at the Greater Accra Regional Hospital.
2. To determine the prevalence of Multidrug-resistant organism Blood Stream infection in the NICU
3. To determine the most frequently prescribed first-line antibiotics in the NICU to treat infection.
4. To assess morbidity and mortality associated with multidrug-resistant organisms in the NICU of the Greater Accra Regional Hospital.
5. To identify the measures that are currently in place to prevent the emergence of antimicrobial resistance in Greater Accra Regional Hospital.

1.5 Significance of the Study

Prior investigations to this study revealed that though multidrug resistance is prevalent in Ghana, and having a clearly significant negative impact on the effective treatment of infections, no study on antimicrobial resistance had yet been carried out at the NICU of the Greater Accra Regional Hospital (GARH), The UK Government commissioned a report on antimicrobial resistance, which claimed that by 2050, AMR might kill 10 million people each year (Murray et al., 2022a). According to systematic review of global AMR trends in 2019 bacterial AMR is known to be a concern in many regions; it was projected that Sub-Saharan Africa had the greatest rates of AMR burden in 2019. Six pathogens were responsible for 73.4 percent of bacterial AMR-related mortality (95 percent confidence interval: 669–788). (Murray et al., 2022a). An empirical study revealing the current status of events is important as deduced findings could help salvage the development of Multidrug resistant strains of bacteria within local communities, and the hospital environments to which children, infants and neonates are more susceptible.

Through this study, healthcare practitioners at GARH will be informed about how the hospital's antimicrobial use correlates with antimicrobial resistance data of patients in NICU data on which id currently unknown. By being privy to such empirical data, they can deduce an effective strategy for prescribing groups of antibiotics and dosage trends that could prevent resistance as well as ways of monitoring and evaluating the administration of antibiotics. To conserve the efficacy of the current antibiotics and stall the development of AMR, development of Antimicrobial Stewardship Programs (ASPs) is a very essential step (Dramowski et al., 2020). According to Dramowski et al., (2020) Neonatal units must first be enabled to measure and monitor trends in their antimicrobial usage in order to create robust and effective ASPs and to provide locally suitable treatment guidelines, institutions need data on pathogen profiles and AMR trends which are not currently known in GARH. This Study identified the most

frequently prescribed antibiotic, the AMR trends and the antibiotic organism resistance profile in the NICU. This information is invaluable and provides a robust foundation for more extensive AMR research and the development of ASPs in the facility. The findings of this study will bridge the knowledge gap about antibiotic prescription and misuse, provide data for developing antibiotics prescription protocols at the Neonatal Intensive Care Units of the Greater Accra Regional Hospital.

1.6 Theoretical Framework

Antimicrobial resistance (AMR) is becoming more common as a consequence of diverse, complicated prescription and eating behaviors. As a result, behavior modification is a crucial component of AMR response. Little is known about the most effective methods for changing antibiotic usage practices and behaviors (Lohiniva et al., 2022).

The Theoretical Domains Framework (TDF) is a theoretical framework rather than a theory; it does not provide testable correlations between aspects but rather gives a theoretical lens through which to observe the cognitive, emotional, social, and environmental impacts on behavior (Atkins et al., 2017). The employment of the TDF provides a methodical and reproducible approach to identification of the determinants of antimicrobial resistance (AMR) in low resource settings. Theoretical Domains Framework's conceptualization of the determinants and identification of behavior change utilizing the Behavior Change Wheel (BCW) method allows for specific recommendations for intervention design and future research (Lohiniva et al., 2022).

1.6.1 Domains

The TDF comprises fourteen different domains with constructs under each given domain. These domains include Knowledge, Skills, Social role, Beliefs about capabilities, Beliefs about

consequences, Motivation and goals, Memory and attention, Environmental contest and resources, social influence, emotion, Behavioral regulation and Nature of beliefs (Atkins et al., 2017).

1.6.2 Knowledge

The domains of knowledge is based on the awareness of existence of something. The constructs that underlie this are general knowledge, knowledge about condition or scientific rationale and procedural knowledge. The levels of knowledge about AMR and antibiotics misuse and its consequences, that are readily available within a community reflects a great deal in how the people manage infections and use of antibiotics. Patients tend to not complete antibiotics dosage courses due to lack of adequate knowledge base on how the antimicrobials enact their actions against bacteria.

This construct also pertains to the hospital setting where adequate knowledge of the type of infections and the appropriate antibiotic class prescribe for which type of infection as per the tentative causative organism is an important aspect of the construct of knowledge in relation to the Hospital staff.

Intervention: educating the public and hospital staff and equipping them with theoretical and practical information to prevent spread of nosocomial infections and community acquired Antimicrobial resistant infections.

1.6.3 Belief in capabilities

Acceptance of the truth, realism, or validity of a skill, talent, or aptitude that a person can put to good use. The constructs that underpin this are Self-confidence, Perceived competence, Self-efficacy, Perceived behavioral control, Beliefs, Self-esteem, Empowerment and Professional confidence. Self-confidence and perceived competence of prescribers and dispensers of antibiotics to patients without evidence of active susceptible bacterial infection is a major

contributory factor to the development and persistence of AMR. Diagnostic inefficiencies and delays have led to widespread use of empirical antibiotic therapy and as a result AMR prevails in our setting.

Intervention: Adherence to Antimicrobial prescription guidelines provided for health care workers, developing surveillance systems monitoring antibiotic use in the communities and providing checks and balances within the health care system to prevent over-prescription and under-prescription of medication as well as correct medication per weight measurements especially for pediatric and neonatal care.

1.6.4 Environmental Factors

Any aspect of a person's condition or environment that hinders or stimulates the development of skills and talents, independence, social competence, and adaptive behavior. The constructs that describe this domain are as follows - Environmental stressors, Resources/material resources, Organizational culture/climate, Salient events/critical incidents, Person and environment interaction as well as Barriers and facilitators. The environmental stressors such as polluted water bodies, lack of proper disposal of unused antibiotics, animal farms overusing antibiotics and exposing humans to low doses of antibiotics, poor sanitation and hygiene practices contribute to the overall problem of AMR. The organizational culture concerning AMR or lack thereof in communities and hospitals contributes to the spread of AMR which is a constant threat to current Antibiotics in existence

Intervention: Environmental protection and preservation is also an essential and fairly neglected aspect of AMR prevention. The maintenance of clean water, good sanitation and environmental hygiene protects humans. Interactions with the environment is an important way that human beings pick up different types of Multidrug resistant infections.

1.6.5 Belief in consequences:

Acceptance of the truth, actuality, or validity of the results of a behavior in a specific situation. The constructs such as Beliefs, Outcome expectancies, Characteristics of outcome expectancies, Anticipated regret and Consequents are fundamental to discussing the domain of Belief in consequences. This provides a cause-and-effect model for individuals. The exposure to AMR and its various causative factors as well as behavioral concepts underlying making an impact in the society is also an important way to help reduce antimicrobial resistance.

Intervention: Frequent review of AMR rates in the hospital as well as associated morbidity and mortality rates associated with the vulnerable populations such as neonates.

1.6.6 Behavioral regulation:

The domain of behavioral modification is anything that involves regulating or modifying acts that are objectively seen or measured. This is an innate quality or trait which involves with constructs such as Self-monitoring, Breaking habit and Action planning. This quality in individuals can be harnessed especially at the professional level as part of the oath in physician practice to do no harm, physicians have to be reminded that Non-maleficence can also involve withholding medication which may harm the patient and medical community in the long run

1.6.7 Reinforcement:

Increasing the likelihood of a reaction by establishing a dependent link, or contingency, between the response and a specific stimulus.

1.7 Conceptual Framework

The chart below is a representation of the Conceptual Framework of the study. It explains how factors interact leading to health complications that cause morbidity of neonates resulting in their admission NICU, with MDRO infection.

While on admission, patients are susceptible to Hospital Acquired Infections (HAIs), also known as nosocomial infections. Ideally, these infections should be treated using antimicrobial therapy. However, patients have an increased risk of aggravated morbidity and eventual mortality due to the use Antimicrobial and Multidrug Resistance.

The factors that lead to and promote the development of antibiotic resistance in our communities are represented in four major classes, known as institutional factors, environmental factors, socioeconomic factors and individual factors.

The institutional factors encompass the many factors emanating from the facilities that individuals in our communities seek health. The first point of call is the prescriber and health care workers in the facilities who have the power to prescribe medication to patients. Indiscriminate and irresponsible prescription of medication not taking into consideration the patient factors and susceptibility of the antibiotics to the prescribed drugs. Evidence-based medicine is stressed at all levels of health care delivery however not adhered to a large extent. Infection prevention and control strategies in health facilities in our subregion are ill equipped to manage the scale of Hospital acquired infections developing in our facilities. The antimicrobial stewardship frameworks in our hospitals are not extensive in nature and do not provide frameworks that adequately and realistically guide the use of antibiotics.

Environmental factors implicated in the framework include poor hygiene and sanitation practices in our communities and improper drug disposal. Indiscriminate disposal of antibiotics onto open refuse dumps leads to the development antimicrobial resistance from the fertile

ground of microbes found in the dumpsite, soil and run off seepage leading to development of 'super bugs' which are resistant to a wide range of antimicrobials.

Socioeconomic factors involved in the development of antimicrobial resistance include, educational factors, living conditions and income. These factors interact with each other to determine the extent to which individuals can afford medication, the timing of antibiotic dosing is usually indicated by prescribers or dispensers. However, patients require a level of education and understanding to promptly administer medication to themselves and their wards in a timely fashion with correct dosages.

Individual factors are arguably the most compelling factors that are leading to the development of antimicrobial resistance. The abuse and misuse of drugs and over and under dosing of prescriptions. The development of MDRO infections may originate from the community or may be Hospital acquired infections. These lead to neonatal morbidity warranting hospital admission which exposes patients further to nosocomial infections. Morbidity leads to increase in cost and length of stay in the hospitals and ultimately if not well managed mortality.

1.7 Justification

Most antimicrobial resistant (AMR) pathogens exhibit high resistance to first-line drugs recommended by the World Health Organization such as ampicillin, gentamicin, and cefotaxime. This is evident of developing a multidrug-resistant (MDR) phenotype (Zou et al., 2021), especially in Gram-negative bacteria (Folgori et al., 2017). Gram negative bacteria form much of bacteraemia affecting neonatal health and survival and are of the greatest concern, globally regarding neonatal health issues (Folgori et al., 2017)

A recent meta-analysis of Chinese literature on new-born sepsis from 2009 to 2014 indicated that more than 50% of E. coli and Klebsiella spp. were resistant to third-generation cephalosporin, and approximately. In Ghana, studies in two teaching, seven regional and two

district hospitals revealed the existence of Anti-microbial drug resistance, with over microbes such as Streptococci, Salmonella, and E. coli showing resistance levels as high as 78.7% (Newman et al., 2011b). Antibiotic resistance caused by multidrug-resistant Gram-negative bacteria has been seen in Ghanaian hospitals; however, methods to ameliorate the problem, such as surveillance studies that offer accurate data, are not in place. A study conducted by (Agyepong et al., 2018) in the Komfo Anokye Teaching hospital in the Ashanti region of Ghana revealed Multidrug resistance was found in 89.5 percent of the bacterial isolates, ranging from 53.8 percent in Enterobacter spp. to 100.0 percent in Acinetobacter spp. and Pseudomonas spp. According to the Centres for Disease Control and Prevention, more than 70% of the bacteria presently cause hospital-acquired illnesses are resistant to at least one of the medications most routinely used to treat them. (Muto, 2005)

Bacterial infections are a major cause of morbidity and mortality in neonates cared for in the NICU (Rennie & Kendall, 2013). In 1997 the paediatric prevention network was launched to assess antimicrobial resistance rates in hospitalized paediatric patients. In the late 1990s, multi-drug resistant organisms and hospital-acquired infections were found to have a low prevalence of methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant enterococci (VRE), this was done through a point prevalence study conducted in the neonatal ICU and paediatric ICU (Milstone et al., 2010). A more serious situation is the emergence of gram – negative bacteria that are resistant to almost all available ant-microbial agents.

Infections secondary to multi-drug-resistant gram-negative bacilli some of which include Klebsiella pneumoniae, Pseudomonas aeruginosa, and Acinetobacter species, have surged, particularly in intensive care units (ICUs), attributable to various factors including antimicrobial selectivity pressure, horizontal acquisition of genes that encode for antimicrobial resistance, contamination of the healthcare environment with bacteria and the subsequent

transmission to patients, and patient-to-patient spread through the handling by healthcare workers (Zhou et al., 2013)

A study was conducted by (Zhou et al., 2013) to assess the attitudes and practices of clinicians regarding infections and MDR-GNB. This study revealed that most clinicians in institutions surveyed did not have adequate knowledge about the prevalence of antibiotic resistance in their current facility, large percentages of ICU up to about 97% of staff believed antimicrobials were overused in their facility. Multidrug resistance in bacteria is induced by the accumulation of genes, each of which codes for resistance to a specific agent, on resistance (R) plasmids or transposons, and/or the activation of multidrug efflux pumps, each of which may pump out more than one drug type. (Nikaido, 2009a)

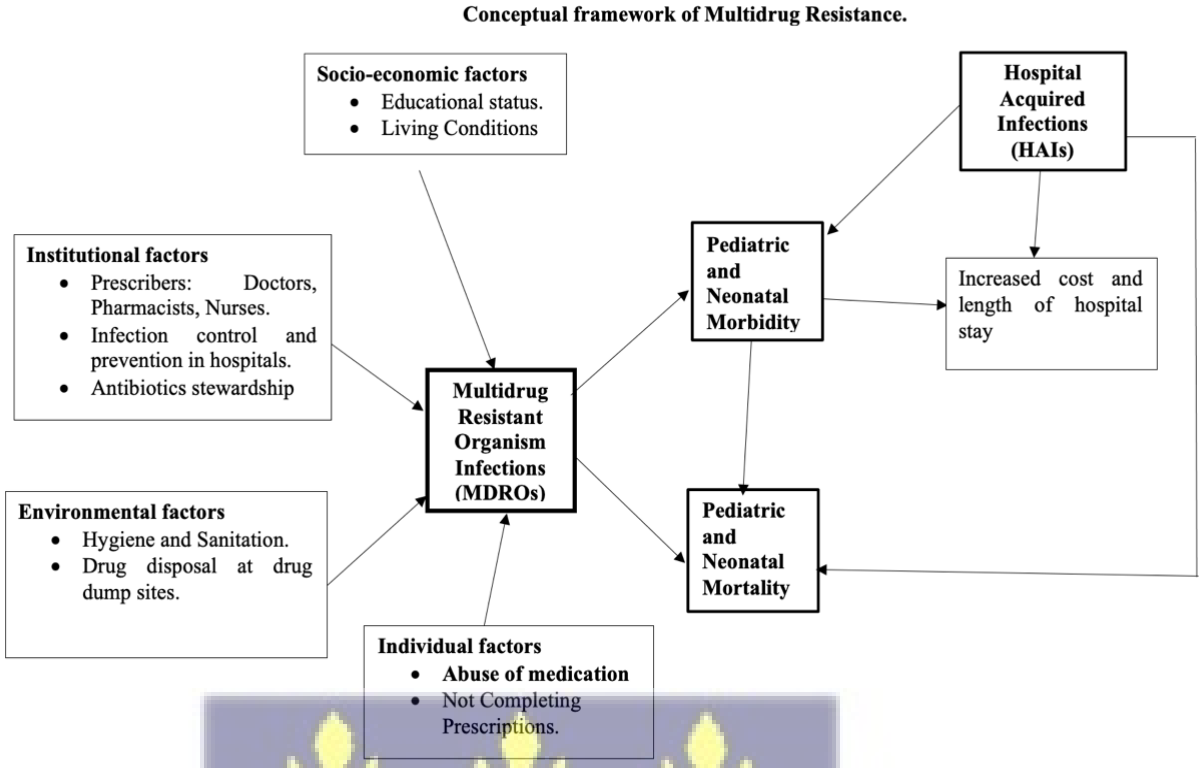


Figure 1 - Conceptual Framework

CHAPTER TWO

LITERATURE REVIEW

This chapter reviews relevant literature in the field of study. Many infectious diseases are curable by antibiotic therapy and their use, since its first discovery in 1928, antibiotics have been significant to sustaining the quality of human life on earth and maintaining the existence of the human race (Nikaido, 2009). It is estimated that annually, about 100,000 tons of Antibiotics are produced by manufacturers worldwide (Nikaido, 2009)

Antimicrobial therapy's purpose is thus to eliminate germs at the site of infection. Bacterial eradication is not often examined as a main objective within the confines of current clinical trial design guidelines (Song, 2003). This chapter reviews literature on antimicrobial resistance (AMR), risk factors of AMR, Multidrug resistant organisms (MDROs), management of MDROs and related issues to inform the study.

2.1 Antimicrobial Resistance (AMR)

Antimicrobial resistance (AMR) is an evolving global health threat such that it has caught the attention of global health agencies like the World Health Organization (WHO) for which ambitious projects have been earmarked to adequately handle it (Carroll et al., 2016) Antimicrobial resistance (AMR) has gradually emerged as one of the major public health issues of the twenty-first century, threatening the effective prevention and subsequent treatment of an ever-increasing variety of infections caused by bacteria, parasites, viruses, and fungi that are no longer susceptible to the conventional medications designed to treat them (Prestinaci et al., 2015). Antimicrobial medications have had a profound impact on humanity's fate as well as how infectious infections are treated. The great advancements in antimicrobial chemotherapy led to the unduly optimistic belief that infectious illnesses will soon be eradicated (Saga and

Yamaguchi, 2010). In actuality, though, newly and re-emerging infectious illnesses have made humans vulnerable to infections. Drug-resistant infections are still a significant and challenging issue in clinical practice (Saga & Yamaguchi, 2010).

It is now a global health and development threat and has been declared by the World Health Organization as one of the top 10 threats to global public health facing humanity. Antibiotics are over the years, becoming increasingly ineffective as medication resistance grows over the world, resulting in more difficult-to-treat diseases and death (WHO, 2014). Globally, high resistance rates against anti-biotics have been observed for pathogens that cause common infections including sepsis, urinary tract infections, sexually transmitted infections and some forms of diarrhoea (World Health Organization., 2012). This is a strong indication that the world is running out of effective anti-biotics. E.g., Resistance to fluoroquinolone antibiotics, which are used to treat urinary tract infections, is common in E. coli. In many nations across the world, this medication is unsuccessful for more than half of the population. (World Health Organization, 2012)

Widespread resistance in extremely variable strains of N. gonorrhoeae makes Gonorrhoea treatment and control challenging. Over the years, Resistance to fluoroquinolones, macrolides, sulphonamides, penicillin, tetracycline and early generation cephalosporins has been on the ascendency (World Health Organization., 2012). Unemo and Nicholas, (2012) showed that, the only remaining only remaining empiric monotherapy for gonorrhoea in most countries currently is the injectable extended-spectrum cephalosporin (ESC).

Antimicrobial Resistance has a significant impact on the economies of nations as it renders patients and their care givers less productive through prolonged hospital admissions as well as requiring for more expensive and intensive care to help save lives (World Health Organization., 2012). Without effective measures for preventing and treating drug-resistant infections, as well as enhanced access to current and future quality-assured antimicrobials, the number of

individuals who are unable to get treatment or who die as a result of infections may rise yearly. (Anderson et al., 2020)

2.2 Risk Factors of Antimicrobial Resistance (AMR)

The main cause of antimicrobial resistance is the use of antimicrobial drugs to treat a wide range of infections caused by pathogens including bacteria, viruses and fungi (Selgelid & Jamrozik, 2020). When antimicrobials are used, some pathogens die and some survive and develop resistance to the particular drug used (Choffnes et al., 2010) the more frequently a patient uses antimicrobials the higher the chances of developing resistance to them. Implying that the same microbial agent may not work for that individual when required in future. If frequency of use is decreased, their effectiveness could be restored to some extent. (Selgelid & Jamrozik, 2020)

2.2.1 Natural Occurrence

AMR occurs naturally over time, often through genetic changes. Through mutation and natural selection, bacteria can develop defence mechanisms against antibiotics (World Health Organization, 2009). Lin et al., (2015) showed that bacteria develop three fundamental mechanisms in the form of enzymatic degradation of antimicrobial agents, alteration of bacterial proteins that are targeted by antimicrobial agents such that the agents cannot function on the altered proteins, and changes the permeability of their membranes to antimicrobial agents, preventing drugs from permeating bacterial cells. E.g., some bacteria have developed biochemical secretions that can remove an antibiotic before it reaches its target, while others have developed the ability to produce enzymes to completely inactivate the antibiotic.

People, animals, food, plants, and the environment, i.e., water, soil, and air, all include antimicrobial resistant microbes. They are passed on from person to person or between humans and animals. (World Health Organization, 2012). For example, for Methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant enterococci (VRE) and other multidrug resistant Gram-negative bacteria are spread primarily from person to person by direct or indirect contact (Rao, 1998)

2.2.2 General Risk Factors for development of Antibiotic resistance.

The genesis and spread of antibiotic resistance are mostly owing to the overuse and often unneeded use of antibiotics in people and animals. Overuse, self-medication, overcrowding, and lapses in cleanliness or poor infection control management are all general risk factors for the development of resistant bacteria in hospitals and the community. (Fair & Tor, 2014)

The WHO (2012) showed that the main drivers of antimicrobial resistance include their misuse and overuse, lack of access to clean water, sanitation and hygiene (WASH) for both humans and animals, often making them susceptible to epidemic, poor infection and disease prevention and control in health-care facilities and farms, insufficient access to quality and affordable health care, often resulting in self-medication, insufficient availability of vaccines and diagnostics, a lack of awareness and knowledge, and a lack of legislative enforcement as well as the slow development and improvement of antimicrobial.

For resistant bacteria such as Methicillin-resistant Staphylococcus aureus (MRSA), risk factors for making it resistant include the use of broad-spectrum antibiotics in an attempt to effectively treat it, as well as the presence of decubitus ulcers and prosthetic devices (Rao, 1998).

Martinez and Baquero, (2009) in a study showed that factors for the spread of resistance for vancomycin-resistant enterococci (VRE) include hospitalization for an extended period of time

and treatment with glycopeptides or broad-spectrum antibiotics overcrowding, tracheostomies, and excessive use of penicillin for viral respiratory infections are all risk factors for the emergence of penicillin-resistant pneumococci (PRP).

2.2.3 Pharmaceutical Industry's Decreased Interest

A major contributing factor to the increasing occurrence of bacterial resistance is the rescinding interest of the pharmaceutical industry (Gould, 2012). Antibiotics regimens are typically administered for very limited durations making them far less profitable than drugs used to treat chronic ailments. Hence, pharmaceutical companies do not have much interest in investing in them, let alone developing new ones as existing ones become resistant (Gould, 2012). Dougherty and Pucci, (2011) showed that in 2004, only 1.6% of drugs in clinical development by the world's 15 largest drug companies were antibiotics.

Cumbersome regulatory procedures also contribute to the reducing interest of pharmaceutical companies. Regulation presents pharmaceutical companies with a paradoxical situation. In certain countries, regulatory bodies support the development of new antimicrobials and their immediate use, while simultaneously, regulatory companies in some countries enact policies supporting the reservation of newly approved antimicrobials (Dinkel et al., 1991). They further indicated that for other ailments, newly approved drugs are immediately prescribed, whereas for bacterial infections, newly approved antibiotics were reserved and only prescribed for infections that already existing antibiotics were unable to treat. Although this regulatory policy helped to delay the emergence of resistant strains, it also limited returns on investments for pharmaceutical companies. Hence, their gradual lack of business in investing in the production of newer antimicrobials.

Such policy also totally erases competition from the pharmaceutical since it results in almost every company producing generic antimicrobials. This further reduces profit, because consumers have a wide range of different brands of the same drug to choose from (Martinez & Baquero, 2009).

Requirements for approval coupled with a lack of clear trial guidelines for antibiotics, in particular, were found to be contributing factors (Dinkel et al., 1991).

2.3 Multi-Drug Resistant Organisms (MDRO)

Many pathogen strains have developed resistance to antimicrobial medicines throughout time, and some have developed resistance to a wide range of antibiotics and chemotherapeutic treatments. This is a case of multidrug resistance. (World Health Organization, 2012)

Deficiencies in infection control practices, overcrowding and a lack of antimicrobial stewardship programs in hospitals and within the health sectors of many developing countries greatly increases the risk of multidrug resistant hospital acquired infections. More often than not, healthcare workers choice of antimicrobial agents is deficient in the guidance of adequate and prompt microbiological services and inappropriately based on the availability of a given medication, the funds of the patient or guardian and the assumed severity of illness (Enweronu-Laryea & Newman, 2007).

Multi-drug resistant organism (MDRO) infection is not only medically tasking on the patient's immune system and body but it is also a financially strenuous on many families (World Health Organization., 2012). MDROs are defined as microorganisms, that are resistant to one or more classes of antimicrobial agents for example Methicillin resistant Staphylococcus aureus (MRSA) (Lederberg & Harrison, 1998). A study conducted in multiple health care facilities in Ghana on resistance to antimicrobial drugs by Newman et al., (2011) showed that generally the

prevalence of multidrug resistant organisms' isolates was high. Specifically for four antimicrobial agents namely tetracycline (82%), ampicillin (76%), chloramphenicol (75%), and cotrimoxazole (73%) the prevalence of resistance is higher in the regional hospitals than in the teaching hospitals (Anderson et al., 2020).

2.3.1 Mycobacterium tuberculosis

Tuberculosis (TB) is a potentially fatal airborne infection caused by a bacterial infection. The condition primarily affects the lungs; however, it can affect other sections of the body in certain cases. (Selgelid & Jamrozik, 2020). It is often treated with a regimen of various antimicrobial medications administered over a period of 6 months to two years, depending on the kind and degree of infection. Though curable in many cases, tuberculosis (TB) is becoming increasingly difficult to cure because to the causative bacterium, tuberculosis. Mycobacterium tuberculosis has become multidrug resistant (Selgelid & Jamrozik, 2020).

Antibiotic resistant Mycobacterium tuberculosis strains are a threat to the global efforts to combat Tuberculosis. These strains cause Multidrug Resistant TB (MDR TB). MDR-TB necessitates longer, less effective, and significantly more expensive treatment regimens than non-resistant TB. Less than 60% of those who are treated for MDR/RR-TB are effectively cured. (WHO, 2009).

In 2018, half a million new instances of rifampicin-resistant tuberculosis (RR-TB) were detected worldwide, with the majority of these cases being multi-drug resistant TB (MDR-TB). Rifampicin-resistant tuberculosis (RR-TB) is a kind of tuberculosis that is resistant to the two most potent anti-TB medications. (WHO, 2009).

2.3.2 Clostridium difficile

Clostridium difficile a major healthcare problem in the United States, causing mild to severe diarrhoea. About half a million people are infected each year, resulting in approximately 15,000 deaths. Janssen et al., (2016) showed that the infection is scarce in Sub-Saharan Africa.

C. difficile is a bacterium that infects individuals' colons after antibiotic therapy. C. difficile colonization is typically prevented and C. difficile-associated illness is suppressed by the communities of bacteria that ordinarily exist in the gut (WHO, 2009). Antibiotics such as aminoglycosides, cephalosporins, penicillin, erythromycin, lincomycin, tetracyclines, clindamycin, and fluoroquinolones, which are routinely used in the treatment of bacterial infections in clinical settings, are known to be resistant to C. difficile. (WHO, 2009)

2.3.3 Neisseria gonorrhea

Gonorrhoea is a sexually transmitted infection that can cause severe reproductive complications if left untreated. To be able to successfully manage and control the prevalence of Gonorrhoea within a particular location, diagnosis and treated of infected persons must be done promptly (Anderson et al., 2019) Ophthalmia neonatorum is a suppurative conjunctivitis in neonates in which the Gram stain of an eye swab shows at least one polymorphonuclear leukocyte per high-power field. The two most common causes of the disorder are Neisseria gonorrhoea and Chlamydia trachomatis.(Abazi et al., 2011)

Gonococcal ophthalmia neonatorum (GCON) is significant in terms of public health since it can cause blindness quickly. The prevalence of maternal gonococcal infection is what determines the frequency of GCON. In most developed nations, the prevalence of gonorrhoea in pregnant women is less than 1%; in underdeveloped countries, rates range from 3% to 15%, with penicillinase-producing Neisseria gonorrhoeae strains accounting for more than half of the cases (PPNG).(Laga et al., 1989)

Antimicrobial susceptibility patterns in gonococci are constantly changing, and they can difer significantly between and within geographic regions. Healthcare practitioners must stay on the lookout for changes to treatment recommendations in their areas. In 2003, the Gonococcal Isolate Surveillance Project found that 16.4% of gonococcal isolates tested were resistant to penicillin, tetracyclines, or both in the United States. At the moment, spectinomycin resistance is uncommon. Although a few isolates with reduced susceptibility to cefixime were discovered in 2003, there has been no evidence of ceftriaxone resistance.(Woods, 2005)

In order to prevent gonorrhoea, infected people and their sexual partners must be identified and treated as soon as possible. The CDC recently changed its treatment guidelines for gonorrhoea to limit the establishment of medication resistance as some treatments become less effective (WHO, 2009).

Gonorrhoea is a worldwide issue. Although action in the United States alone is unlikely to prevent the development of resistance, early diagnosis and good treatment of patients and their partners may help to delay the spread of resistance (Martinez and Baquero, 2009).

Widespread resistance in highly variable strains of *N. gonorrhoeae* has made the disease difficult to manage. Over the years, there has been an emergence of resistance to several antimicrobials in Neisseria gonorrhoea, making the disease difficult to treat (World Health Organization, 2009) they include sulphonamides, penicillin, tetracyclines, macrolides, fluoroquinolones, and early generation cephalosporins (Kon et al., 2016).

In many countries, the injectable extended-spectrum cephalosporin (ESC) ceftriaxone is now the sole empiric treatment for gonorrhoea (Anderson et al., 2019).

2.3.4 Methicillin-resistant Staphylococcus aureus (MRSA)

Staphylococcus aureus bacteria are found in the skin flora and are a major source of illness in both the community and health-care settings (Hemeg et al., 2019). MRSA infection is caused by a type of staphylococcus bacteria that has become resistant to many of the antibiotics used to treat common staphylococcus infections. It more often than not transmitted by contact with the skin of an infected person. RSA is not only resistant to Methicillin but also to penicillin, oxacillin, cefazolin, daptomycin amoxicillin and other common antibiotics collectively known as cephalosporins (Kon et al., 2016).

Over the past four decades, methicillin-resistant Staphylococcus aureus (MRSA), has evolved from a controllable infection within small communities of people into a serious public health concern. MRSA is one of the most common hospital-acquired infections. Unfortunately, resistant strains keep increasing within local communities, causing severe infections (Kon et al., 2016). Studies show that people with methicillin-resistant Staphylococcus aureus (MRSA) infections are 64% more likely to die than people with drug-sensitive staphylococcus infections (Hemeg et al., 2019).

2.3.5 Vancomycin-resistant Enterococci (VRE)

Enterococci are bacteria that are commonly found colonizing the human digestive tract and female genital tract. VRE infections tend to occur in people who are in hospitals or other health care facilities (World Health Organization, 2009). They also often occur in people who are susceptible to infection due to their peculiar medications or the presence of certain catheters or other devices. Health care providers commonly use the antibiotic vancomycin to treat Enterococci infections, unfortunately, VRE are resistant to the drug (Selgelid & Jamrozik, 2020)

2.3.6 Carbapenem-resistant Enterobacteriaceae (CRE)

CRE is a family of highly resistant bacteria, including Klebsiella species and Escherichia coli (E. coli). CRE primarily affect patients on admission in hospitals, especially those who have compromised immune systems (Anderson et al., 2019) The bacteria can enter the body through medical devices like ventilators or catheters (Andersen, 2019). Some CRE infections are resistant to most available antibiotics and can be life-threatening (WHO, 2009). Multiple structural adaptations and antibiotic degradation enzymes, such as expanded spectrum beta-lactamases (ESBL), AmpC cephalosporinases, and carbapenemases, have resulted in Gram-negative bacteria developing the broadest range of resistance. Carbapenemase-producing Enterobacteriaceae (CRE) are especially dangerous bacteria.(Smith & Kendall, 2021)

According to a study conducted by Birgy et al., (2012) Nosocomial outbreaks of carbapenemase-producing Entero-bacteriaceae infection have been described, notably in Greece as well as certain subspecies of this bacteria have also been isolated in water sources in New Delhi.

2.4 MDRO Infections in Neonatal ICU

The non-specific clinical appearance of neonatal illness is a major obstacle to correctly diagnosing severe bacterial infection in this population (Russell & Kumar, 2015). Distinguishing bacterial infection, viral infection or respiratory failure can be challenging bacterial infections are also known to lead to rapid deterioration and patient demise, and undue delays in diagnosis and management tend to have lethal consequences (Osvald & Prentice, 2014). Thus, patients tend to be treated routinely with first line empiric broad spectrum antibiotics (Gezmu et al., 2021).

2.4.1 Blood Stream Infections (BSI)

Bloodstream infections are infectious disease defined by the presence of bacterial or fungal microorganisms in the bloodstream that elicit or have elicited an inflammatory response characterized by alterations of clinical, laboratory and hemodynamic parameters (Viscoli, 2016). Fascinatingly the pattern of pathogens causing BSI have changed over the years with rising numbers of gram negative and fungal infections, nevertheless the last few decades have witnessed an upsurge in resistance to antibiotics especially for gram negative rods. The diagnosis of a bloodstream infection is based on obtaining one or more positive cultures, for common skin contaminants two positive cultures are required to ascribe etiology of BSI to the organism in question (Viscoli, 2016)

Bloodstream infections (BSI) are a significant cause of illness and death and require early and suitable empiric therapy. In the information age the management of BSI are complicated by antimicrobial resistant patterns that are emerging in the communities. Most especially in resource deficient countries where inadequate support for culture and antimicrobial surveillance exists makes management even more (Opintan & Newman, 2017).

Studies conducted on neonatal infections such as Zou et al., (2021) have shown that is a serious emerging challenge among hospitalized neonates. Gram-negative bacteria gradually became the main pathogenic bacteria of neonatal sepsis, with E. coli and K. pneumoniae contributing the largest proportion. Moreover, late-onset sepsis and antibiotic exposure were significantly associated with MDR infection

2.4.2 AMR in Nosocomial Infections in Infants and Neonates

Neonates by design do not have optimally functioning immune capacity. They spend the first few years developing their immunity both passively and actively through breastfeeding, infection and reinfection. Nevertheless, a study conducted with data from Eunice Kennedy

Shriver National Institute of Child health and human development found that commonly occurring infections in the NICU are becoming increasingly difficult to treat (Stoll et al., 2010). For instance, Neonatal sepsis has such substantial morbidity and mortality and is challenging to diagnose on initial presentation and as such most neonates with sepsis are subjected to empirical therapy pending culture results when sepsis can be rules out. The consequent overuse of antibiotics aids in the development of antibiotic resistant organisms (ARO) (Ballot et al., 2012). Work done by Laxminarayan et al., (2013) showed that approximately 60,000 neonates die from Antibiotic resistant neonatal infections in India.

Klebsiella pneumoniae are common intestinal bacteria that can cause life-threatening infections. Resistance in K. pneumoniae to carbapenem antibiotics, which is currently the last resort treatment for the infection is spread to many parts of the world. Colistin is the only last resort treatment for life-threatening infections caused by carbapenem resistant Enterobacteriaceae, e.g., E. coli, Klebsiella, etc. Other bacteria resistant to colistin have also been detected in several countries and regions, causing infections for which there is no effective antibiotic treatment, currently.

2.5 Management of MDROs

Antibiotics have played, and continue to play the extremely essential role of reducing morbidity and mortality from infectious diseases. However, indiscriminate use and unrestricted access, coupled with inadequate knowledge of user protocols by healthcare workers are contributing to the emergence of bacterial resistance (WHO, 2014)

Many researchers have suggested that antimicrobial cycling may slow the evolution and spread of resistant bacteria strains and even multiply them. Selgelid and Jamrozik, (2020) defined Multidrug Resistance as a system of empiric use of two or more classes of antibiotics is alternated over a time scale of months to years, Hence, in case resistance to a particular drug

reaches its peak in a hospital's ward, it would be switched scheduled classes of antibiotics, thus making most resistant bacteria strains susceptible to the new therapy.

Studies have also shown that, fluctuating patterns of antimicrobial use may reduce the rate at which drug-sensitive strains can acquire resistance to single or multiple antibiotics. In addition to the intuitive appeal of these arguments, more than two decades of experience have shown that a one-time formulary shift can effectively control a hospital epidemic of antibiotic-resistant strains in a rotation through a series of alternative drugs (Selgelid and Jamrozik, 2020)

Continued increase in AMR & MDR worldwide suggests the need for empirical therapy be guided by local susceptibility to enhance improved therapeutic outcomes. (Obeng-Nkrumah et al., 2016). Patel and Saiman, (2010) showed that management of requires a more measured approached involving multiple disciplines, judicious use of antimicrobial agents and effective hand hygiene practices.

Recent developments in the genomic mapping of many bacteria and advances in combinatorial chemistry promise to usher in a new era of antibiotic development. While this may result in our regaining some of the ground lost to resistant bacteria, there will still be a continuing need to minimise the spread of antibiotic resistance through the rational use of antibiotic agents and stringent infection control practice (Ahmad et al., 2019).

2.6 Conclusion

Antibiotics have played a pivotal role in saving the human race and achieving major milestone victories in the practice of Medicine and Surgery throughout the 18th and 19th centuries to present day. With the aid of Antibiotics, microbial infections and opportunistic infections have been treated saving countless lives even in the most delicate cases such as disseminated opportunistic infections in patients receiving chemotherapy, patients with Uncontrolled

Diabetes, End-stage renal disease and HIV-AIDS. The treatment of opportunistic infections in patients' complex cases such as patients recovering from organ transplants, major surgeries and joint replacements cannot be over emphasized. A review of existing literature in this study revealed that unfortunately, the rapid worldwide emergence of resistance in the late 19th century and its persistence through-out the 20th century into n the 21st century has gradually made microbial infections a massive threat to the future of the practice of medicine and even to the human race at large, if proper precaution is not taken is not taken. The rate of development of AMR is leading to a future that is set-up for surges in drug resistant epidemics destined to set the world back several decades.

The surge in antimicrobial resistance has through empirical studies by researchers and scientists globally, been mainly attributed to the misuse and over use of antibiotics and the lack of new drug developments by the pharmaceutical industry due to reduced interests borne out of a reduction in the economic returns as well as cumbersome industry regulations. Epidemiological studies have demonstrated a direct relationship between antimicrobial use and the emergence and dissemination of resistant bacteria strains. In many other countries, antibiotics are unregulated and available over the counter without a prescription. Hence, they are easily accessible to the lay person, plentiful, and cheap, resulting in misuse and overuse and eventually, resistance. Even in countries where antibiotics are regulated, one will find that most common antibiotics are readily available for purchase online.

In bacteria, genes can be inherited from relatives or can be acquired from nonrelatives on mobile genetic elements such as plasmids. This horizontal gene transfer (HGT) can allow antibiotic resistance to be transferred among different species of bacteria. Resistance can also occur spontaneously through mutation. Antibiotics remove drug-sensitive competitors, leaving resistant bacteria behind to reproduce as a result of natural selection. Despite warnings regarding overuse, antibiotics are overprescribed worldwide.

The effects of AMR to the economies of nations are significant. In addition to death and disability, prolonged illness results in longer hospital stays, that require more expensive medicines, posing financial challenges for those impacted and for governments as they fund their health sectors. (WHO, 2012) Without effective antimicrobials, the success of modern medicine in treating infections, including during major surgery and cancer chemotherapy, would be at an increased risk (WHO, 2012)

CHAPTER THREE

RESEARCH METHODS

3.1 Introduction

This chapter discusses the methodology employed in carrying out the study. The Chapter focuses on the Area of Study, Research Design, Population of Study, Data Collection and Data collection Techniques are discussed into detail. The chapter concludes with ethical issues considered during the study.

3.2 Study Approach

A mixed method study approach was employed for conducting this study. Quantitative and qualitative methods were applied for data collection. The approach employed involved is pragmatism as stated by Grover, (2015) which mainly focusses on what works. Grover, (2015) stated that where theories fail pragmatism begins with techniques that may be traditional or self-invented all leading to the delivery of valid results.

3.2.1 Study Design

A retrospective chart review (RCR), also known as a medical record review, is a research design for which pre-recorded, patient-centered data is used to answer one or more research questions (Matt & Matthew, 2013). The quantitative aspect of this study is a retrospective Medical Record review of blood cultures from NICU of the Greater Accra Regional Hospital over a one-year period beginning from 1st June 2020 through to 31st May 2021.

A descriptive research design allows the incorporation of a several research methods in one study to facilitate the successful investigation of more than one variable, such that information regarding the study is collected without making changes to the environment or area of study (Kothari, 2008). It is useful when not much is known yet about the topic or area of study and

it reveals an understanding of how, when and how something happens. These answers enable further studies to be carried out to determine why it happens (Kothari, 2008).

Being a mixed method study, it incorporated both qualitative and quantitative research methods which involved the collection and analysis of both qualitative and quantitative data. The justification for blending methodologies is that neither quantitative nor qualitative methods are suitable to represent the patterns and subtleties of a problem, such as the complicated issue of multidrug resistant organism infection (Ivankova, 2002). Other well-known and researched rationales or benefits for doing a mixed methods study includes the ease of which this method allows corroboration of both quantitative and qualitative data in leading to an increase in the validity of the study.

Completeness is also an added benefit which aims at combining research methodologies to bring about a more comprehensive and thorough view of the phenomenon under inquiry (Doyle et al., 2009)

3.3 Area of Study

Ghana currently has 162 district hospitals, 10 regional hospitals and five teaching hospitals in the public sector. District hospitals serve as the first referral points for other peripheral facilities whereas regional hospitals for secondary level referral points (Nsiah-Asare, 2017)

The study was conducted at the Greater Accra Regional Hospital (GARH), formerly known as the Ridge Hospital, situated at North Ridge, within the Osu Clottey Sub-Metro Municipality of the Greater Accra Region (GAR).

GARH occupies a total land area of about 15.65 acres. As the regional hospital for the GAR, its catchment area is the whole of the Greater Accra Region, with an estimated population of over 4,671,363. People living in nearby communities in adjoining regions also seek health care services from the GARH.

Data from Greater Accra Regional Hospital (GARH) records show that the NICU admits approximately 800 - 900 neonates, every year. The units is managed by the Pediatric department of the GARH. The NICU consists of 2 parts a Babies unit. Each part can accommodate 30 neonates each thus making a grand total of 60 patients when unit is at full capacity

3.4 Study Variables

The variables which formed the main focus of this study are blood stream infections and multidrug resistant organisms. Multidrug-resistance in this study was defined as isolates that were resistant to at least one agent in three or more antibiotic classes (Agyepong et al., 2018). Other factors such as age, sex, payment method, patient diagnosis, days on admission, First line antibiotics prescribed and outcome of management served as independent variables.

3.5 Population of the Study

The study population comprised of blood culture samples of patients in the Neonatal Intensive Care Units of the Greater Accra Regional Hospital.

3.6 Inclusion/Exclusion criteria

Patients admitted to the NICU with blood stream infections are eligible for this study following the criteria

- Microbiology samples taken on admission in GARH of both patients who were primarily admitted and referred from other facilities

Exclusion criteria

- Patients with Covid-19 infection.

3.7 Sample Size patient records

The sample size was calculated with reference to a study conducted by (Agyepong et al., 2018) on multidrug resistant gram-negative bacteria infection showed the prevalence within the age group <10 years was 24% in Komfo Anokye Teaching Hospital (KATH).

$\approx n = \frac{Z^2_{1-\frac{\alpha}{2}} P(1-P)}{MOE^2}$ formula sample size calculation.

n = estimated sample size,

Z = the z-score that corresponds with 95% confidence interval (1.96),

p = estimated proportion of ITN usage (24%) = 0.24

q = estimated proportion of households who do not use the ITN (1 – 0.24 = 0.76),

MOE = margin of error set at 5% (0.05).

n = 280.283

n = 281 participants

3.7.1 Selection of participants for the Qualitative study

The number of health professionals to be recruited depended on achievement of saturation, level of availability from their work schedules as well as time limitations. The expectation at the facility in question is to conduct 10 in-depth interviews with Nurses in the NICU, lab technicians, NICU nurses, NICU doctors and parents of patients on admission in NICU. There was also one focused group discussions with 6-8 lab technicians and/or neonatal nurses at GARH microbiology lab.

3.7.2 Sampling Technique

Simple random sampling technique was used to identify the month to begin with within the 12-month period of retrospective study. This affords equal chance of each month being selected and thus controlling for inherent biases that may be in the data.

Researchers can generalize their findings to the population from which the sample was drawn by using random selection to account for sampling bias (Matt & Matthew, 2013).

The sampling used for the quantitative study data was a Convenience sampling technique when selecting the individual members of the sample per month this was according to chronology of how the patient samples have been taken and recorded in these specialized neonatal units. Convenience sampling is a type of nonprobability in which members of the target population who meet certain practical criteria (Etikan et al., 2015). This method allowed the researcher to collect thorough data not leaving out any important patient data from the study start date to the study end date. The population's elements were chosen in a chronological fashion as per month, which means that each medical record has were duly collected and codded as required.

3.8 Data Collection Techniques

Based on the qualitative and quantitative aspects of the study. The quantitative study design was a medical desk-based review of laboratory data over the period of one year. The qualitative aspect involves in-depth interviews and focused group discussions (FGDs).

In the quantitative approach an electronic data extractions form, was used to extract data on blood cultures that were conducted at the GARH microbiology lab of patients on admission in the NICU over the one-year period in question. Only neonates i.e., babies aged 0-28 days of life were considered as NICU patients.

Qualitative data collection involved interviewing stakeholders of the Greater Accra Regional Hospital, comprising Doctors, Nurses at the NICU, Laboratory Technicians as well as some Parents of the patients.

Focus group discussions was carried out to gather first hand qualitative data from Laboratory Technicians. One Focused group discussion comprising 6-8 Laboratory Technicians and or neonatal nurses was conducted.

3.8.1 Extraction of Research Data from Records

This research adopted a retrospective medical records review which employed the use of research data extraction forms to gather information from the hospital's laboratory records on microbiological specimen cultures conducted during the period under study.

Microbiological specimen culture reports of all with MDR Blood stream infection in the NICU patients was retrieved from the laboratory data on all clinical cultures from the NICU. Blood culture results from neonates born in the hospital and secondarily referred was also included.

3.8.2 Data Collection Instruments

A Data Extraction form was used in collecting laboratory data. On the following demographic and health data of the study population: age, sex/gender, date of admission, diagnoses, isolated organisms, resistance profile, year of infection, date of first culture, days on admission and outcome of management.

The qualitative aspect involved the use of an interview guide whereas a semi-structured discussion guide was used for the focused group discussions.

3.9 Data Analysis

Data collected was analyzed using with descriptive statistics using STATA/SE version 16 for windows. Continuous variables such as age at diagnosis and days on admission were summarized using univariate analysis as means and standard deviations. Categorical variables such as sex, patient diagnosis, first-line antibiotics prescribed and outcome of management

were summarized in proportions. Bivariate analysis was done using cross tabulations of first line antibiotics with specific antimicrobial sensitivity. All analyses were considered statistically significant at probability value less than 0.05.

Data collected was sorted and queued into Microsoft office excel 2019 for further categorization and coding to ease subsequent analysis that was done using Stata version 16 processing software. Analyzed data, together with interview findings, together forming quantitative and qualitative data, was compared with the secondary data extracted to answer the proposed research questions.

3.10 Quality Control

The assistance of a well-trained data collector at the GARH and IT Officer to provide access to patient records was employed in the collection of data, after which it was reviewed periodically by the principal investigator before final analysis is performed.

3.10.1 Good Clinical Practice

The principal investigator is good clinical practice (GCP) certified professional.

3.10.2 Monitoring

Data collected by the team was queued into Google spread sheets for remote access and review prior to finally being arranged into Microsoft Office Excel 2019. The data collected was meticulously reviewed by the Principal Investigator of this study for continuous monitoring purposes.

3.10.3 Data Management

To assure good quality of data, the obtained data was entered twice in the data management system by the research assistant and principal investigator.

3.11 Ethical Consideration

3.11.1 Informed consent

The quantitative aspect of the study involves the review of collected laboratory investigations ran on patients who had parental consent for the procedure and assent in cases applicable. The qualitative aspect involves the provision of a clearly worded informed consent sheet which was provided to literate participants and administered to non-literate participants to acquire the consent of all participating. Judging by the nature of individuals participating in the qualitative interviews and focused group discussions, consideration was given for the time spent away from work to avoid decrease in productivity.

3.11.2 Criteria for stopping and discontinuing Research

Individuals are at liberty to refuse, discontinue or withdraw their consent at any given time without consequence.

3.11.3 Ethical Approval

Ethical Approval was sought from the Ghana Health Service Ethics Review Committee. No study procedures took place prior to receiving approval.

3.11.4 Safety Considerations

There is no increased risk of the study in data extraction process as it is mainly about collecting and organizing data from electronic laboratory records. To ensure personal patient records are kept safe and secure. The study relied only on de-identified data. Every study subject was given a specific and completely anonymous study identification number. There was no disclosure of participants' information to others.

3.11.5 Covid Safety Measures

Interviews and focused group discussions which involve face-to-face and in person interactions was organized with all Covid-19 safety protocols observed. Including but not limited to appropriate social distancing measure, wearing of facemasks and using alcohol hand rub.

CHAPTER FOUR

PRESENTATION OF RESULTS

This Chapter outlines results of the study following analysis of data collected. The data from this study are both qualitative and quantitative in nature. This chapter gives the general overview of data collected during research process.

4.1 NICU Quantitative Results

4.1.1 Demographic Characteristics of NICU Patient Samples

Majority of the 195 NICU blood culture samples with MDROs sampled were of male patients comprising one hundred and seven of 195 blood culture samples representing 54.87%. The females were 88 in number representing 45.13% as represented in table-3 below

Table 1: Sex distribution of NICU patients

SEX	Frequency	Percent
Female	88	45.13
Male	107	54.87
Total	195	100

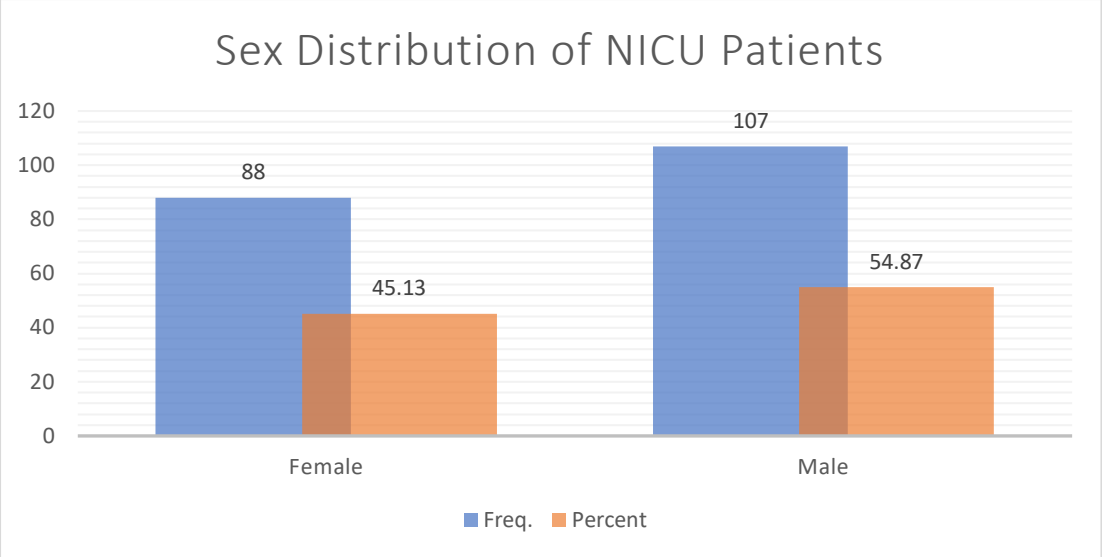


Figure 2 : Sex Distribution of NICU Patients

The age at diagnosis in days is negatively skewed as per the gaussian distribution and thus the appropriate summary statistic is the Median. The median age at diagnosis and admission is the first day of life. The amount of days life for admission ranged between (0-10) days as shown in figure 2 below. The mean number of days 1.0 95% CI (0.8-1.3)

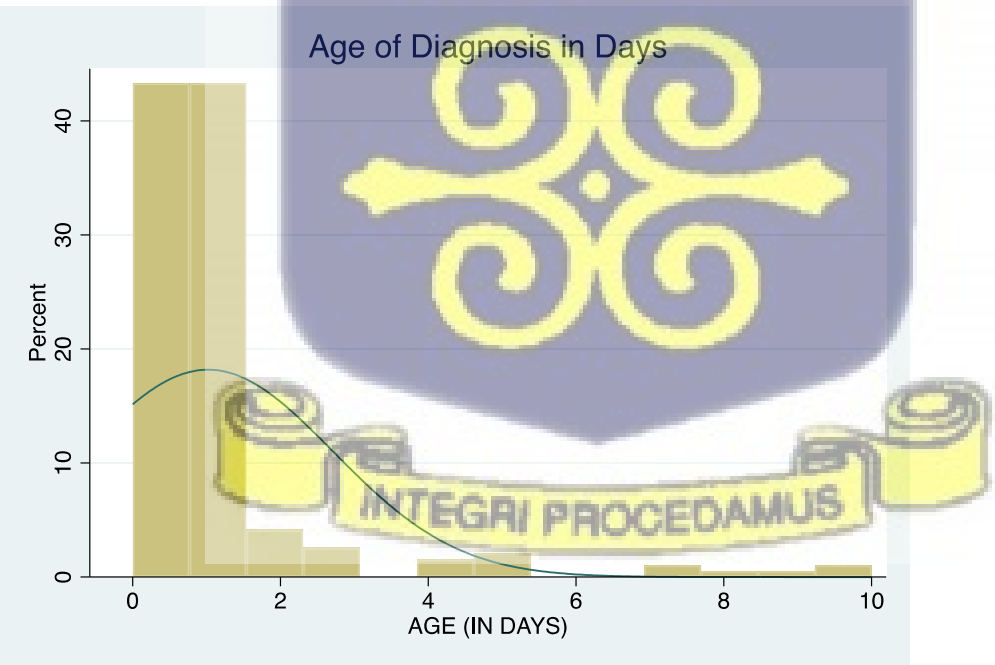
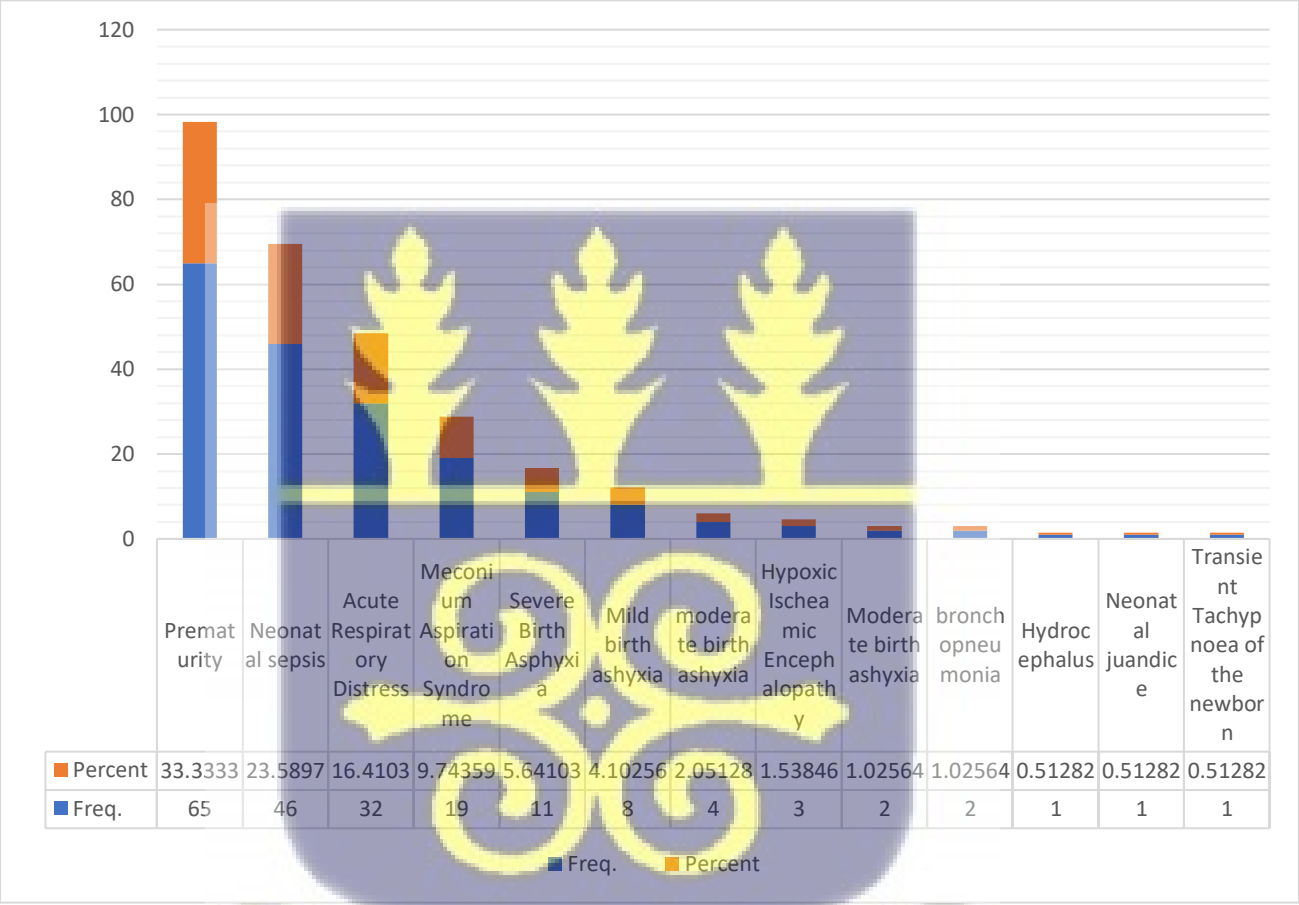


Figure 3 : Age of diagnosis and admission in days of NICU patients

4.2 Diagnosis Associated With MDRO

The diagnosis most commonly associated with neonates with MDROs was prematurity diagnosed (33.3%) of the time followed by neonatal sepsis and acute respiratory distress accounting for (23.6%) and 16.4% respectively. Meconium Aspiration syndrome was the fifth most common diagnosis associated with NICU admissions who had Multidrug resistant organism infection contributing a total of 9.7% of all admissions with MDROIs



	Prematurity	Neonatal sepsis	Acute Respiratory Distress	Meconium Aspiration Syndrome	Severe Birth Asphyxia	Mild birth ashyxia	moderate birth ashyxia	Hypoxic Ischeamic Encephalopathy	Moderate birth ashyxia	bronchopneumonia	Hydrocephalus	Neonatal juandice	Transient Tachypnoea of the newborn
Percent	33.3333	23.5897	16.4103	9.74359	5.64103	4.10256	2.05128	1.53846	1.02564	1.02564	0.51282	0.51282	0.51282
Freq.	65	46	32	19	11	8	4	3	2	2	1	1	1

Figure 4: Diagnosis associated with MDRO

4.3 Prevalence of MDRO Infection in the NICU

Out of all records reviewed, a total of 1,043 blood samples were taken and processed successfully for blood cultures in the NICU. One hundred and ninety-five of them cultured multidrug resistant organisms constituting about 18.7%. As indicated in Figure 4 below.

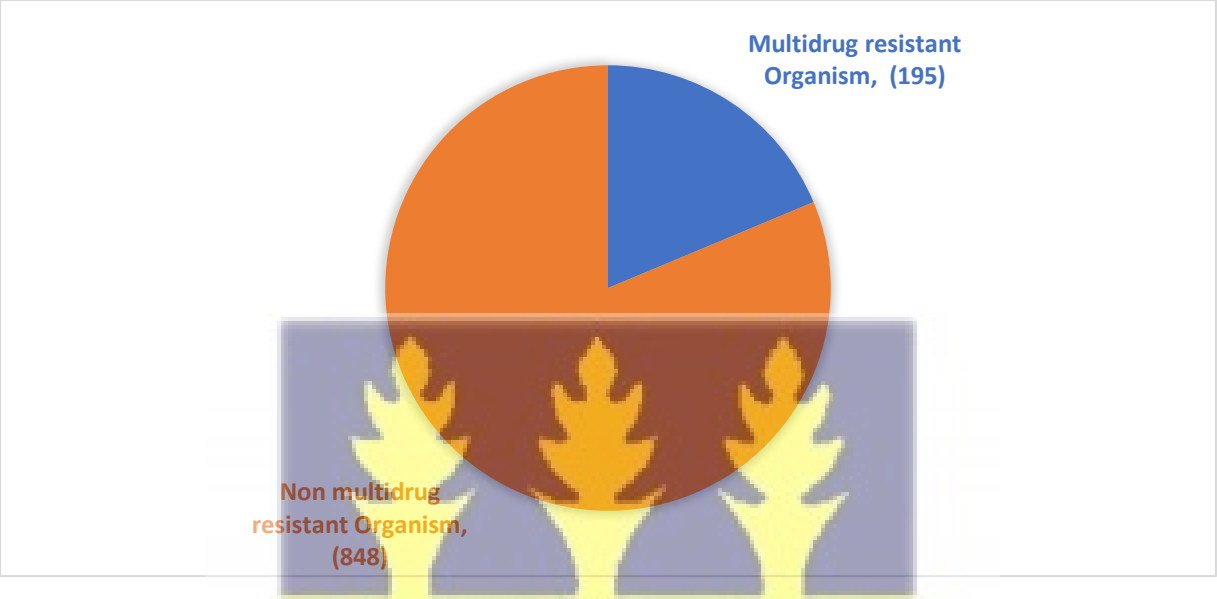


Figure 5: prevalence of MDRO in the NICU at GARH

4.4 Antibiotics Prescribed

Ampicillin and Gentamicin were the most often given antibiotics combination in the NICU, accounting for 58.9 percent of all prescriptions for patients with blood cultures indicating MDRO infections. The second and third most common were Ampicillin and Cefotaxime, and Amikacin and Flucloxacillin accounting for 25.6% and 9.7% respectively. Thus, the single most prescribe antibiotic for patient in the NICU within the study period June 2020 to May 2021 was Ampicillin. Ampicillin formed part of about 84.5% of all initial first line antibiotics prescribed for patients with MDRO infections.

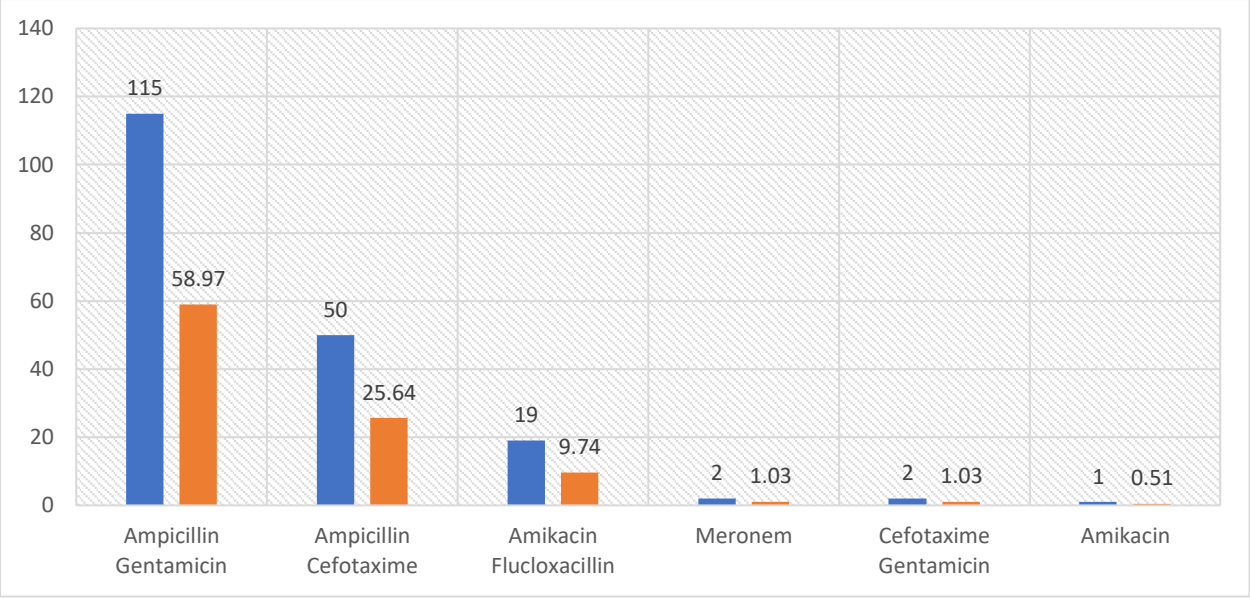


Figure 6: First line antibiotics prescribed

Table 2: First-line Antibiotics Prescribed

FIRST LINE ANTIBIOTIC PRESCRIBED	Frequency	Percent
Ampicillin Gentamicin	115	58.97
Ampicillin Cefotaxime	50	25.64
Amikacin Flucloxacillin	19	9.74
Meronem	2	1.03
Cefotaxime Gentamicin	2	1.03
Amikacin	1	0.51
Amikacin Tobramycin eye drops	1	0.51
Cefotaxime Flucloxacillin	1	0.51
Ciprofloxacin Tobramycin eye drops	1	0.51
Tobramycin eye drops	1	0.51
X-Penicillin Ampicillin	1	0.51
X-Penicillin Gentamicin	1	0.51
Total	195	100

4.5 Morbidity and Mortality Associated with MDROS in the NICU

The case fatality rate associated with patients in the NICU infected with Multidrug resistant organisms at GARH was found to be about (51/195) 26.2 % over the study time period

(1st June 2020- 31st May 2021) as indicated in figure 6 below. The burden of morbidity associated with patients admitted to the NICU with MDRO over the study period was noted to be 18.7% as shown in figure 4 above.

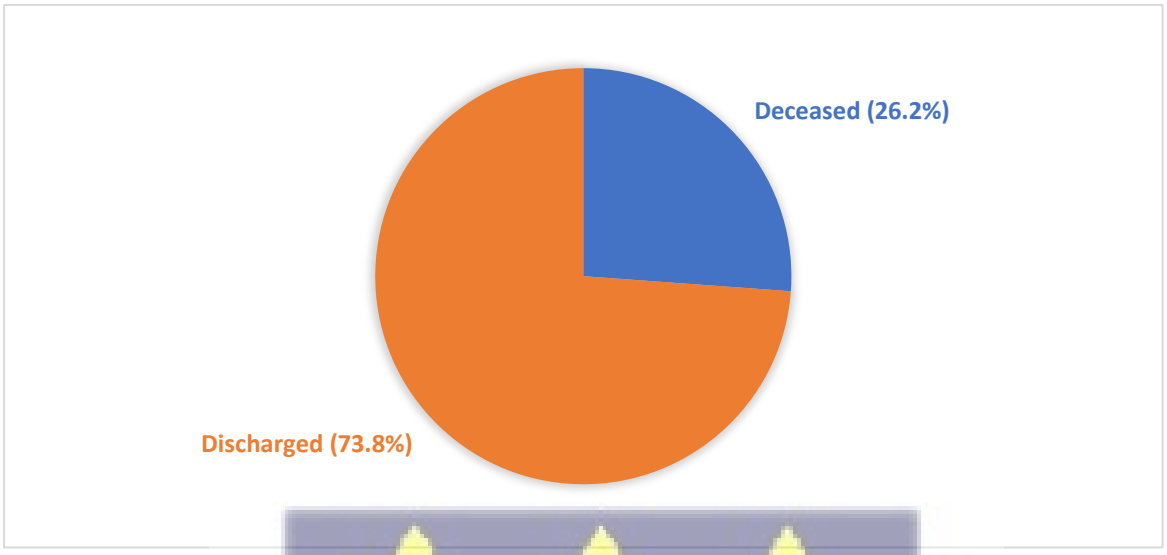


Figure 7: Outcome of management

The median duration of stay in the NICU for patient with MDRO Infection was 11 days however the days on admission ranged between (73-1) days as indicated in Figure 7 below. The Mean number of days spent on admission for patients diagnosed with MDRO infections is 14.6 95% CI (12.7 -16.4)

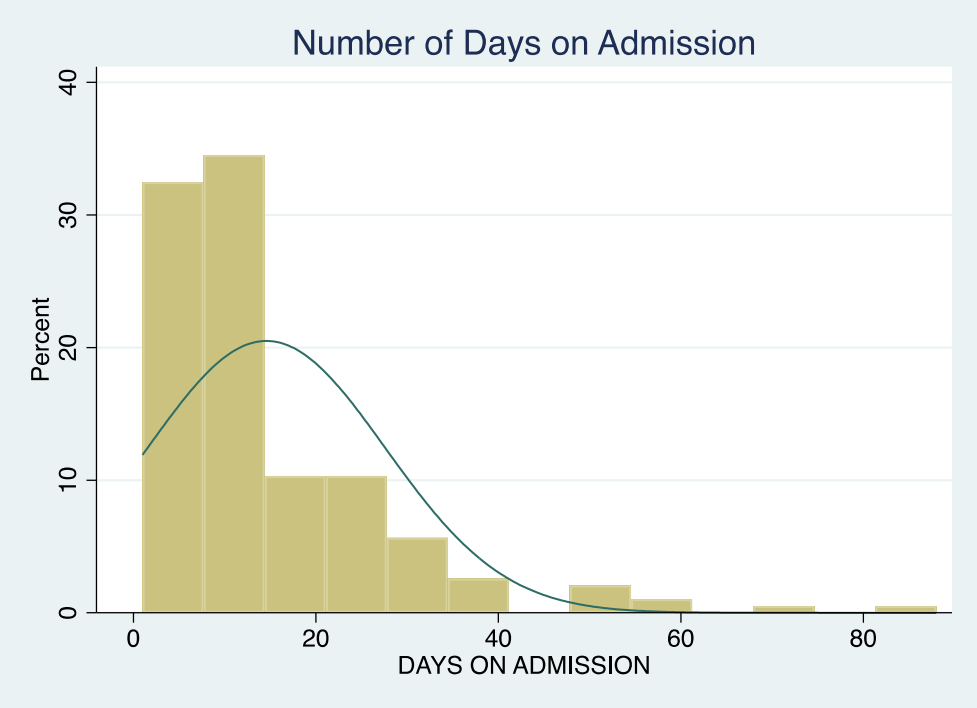


Figure 8 - Number of days on admission

4.6 Organisms Isolated

The most commonly isolated specific organism causing MDRO infection in the MICU of GARH was *Staphylococcus aureus* contributing 40 samples (20.51%) out of 195 MDRO cultured as shown in Table 6 below. The predominantly isolated pathogenic organism species was *Klebsiella spp* 31.2% (61/195) and *Staphylococcus aureus* 20.5% (40/195). Additionally, 38 coagulase negative Staphylococci such as *Staphylococcus hemolyticus* and *Staphylococcus epidermidis* also contributed 10.8% and 5.1% respectively. Gram negative rods such as Klebsiella spp, E Coli, Klebsiella Pneumoniae, Pseudomonas spp and Pseudomonas aeruginosa contributed a total of (83/195) 42.6% of all MDROs cultured in the NICU over the period of 1st June 2020 to 31st May 2021.

Among the *Klebsiella spp* resistance to ampicillin, cefotaxime and gentamicin was 72.1%, 39.3% and 52.4%, respectively, while carbapenem resistance was 10.4%. Mortality among neonates with MDR BSI was 26.2% (51/195).

Table 3 : Organisms Isolated

ORGANISM(S) ISOLATED	Freq.	Percent
Staph aureus	40	20.51
Klebsiella spp	32	16.41
Klebsiella pneumoniae	25	12.82
Staph haemolyticus	21	10.77
E. Coli	11	5.64
Staph epidermidis	10	5.13
Pseudomonas aeruginosa	7	3.59
Enterobacter spp	5	2.56
Pseudomonas spp	4	2.05
Enterobacta claocae	3	1.54
Klebsiella oxytoca	3	1.54
Citrobacter spp	3	1.54
Staph capitis	3	1.54
Aerococcus spp	2	1.03
Empedobacter brevis	2	1.03
Acinetobacter baumannii	2	1.03
Enteroccocus faecalis	2	1.03
Micrococcus sp	2	1.03
Neisseria spp	2	1.03
Staphylococcus capitis	2	1.03
Acinetobacter Iwoffi	1	0.51
Enteroccocus spp	1	0.51
Enterococcus faecium	1	0.51
Klebsiella aerogenes	1	0.51
Kluyvera ascorbata	1	0.51
Pantonea spp	1	0.51
Staph horminis	1	0.51
Staph intermedius	1	0.51
Staph saprophyticus	1	0.51
Staphylococcus intermedius	1	0.51
Streptococcus group B	1	0.51
Streptococcus pneumoniae	1	0.51
Total	195	100

4.7 Antimicrobial Susceptibility and Resistance Profile of NICU Blood Cultures

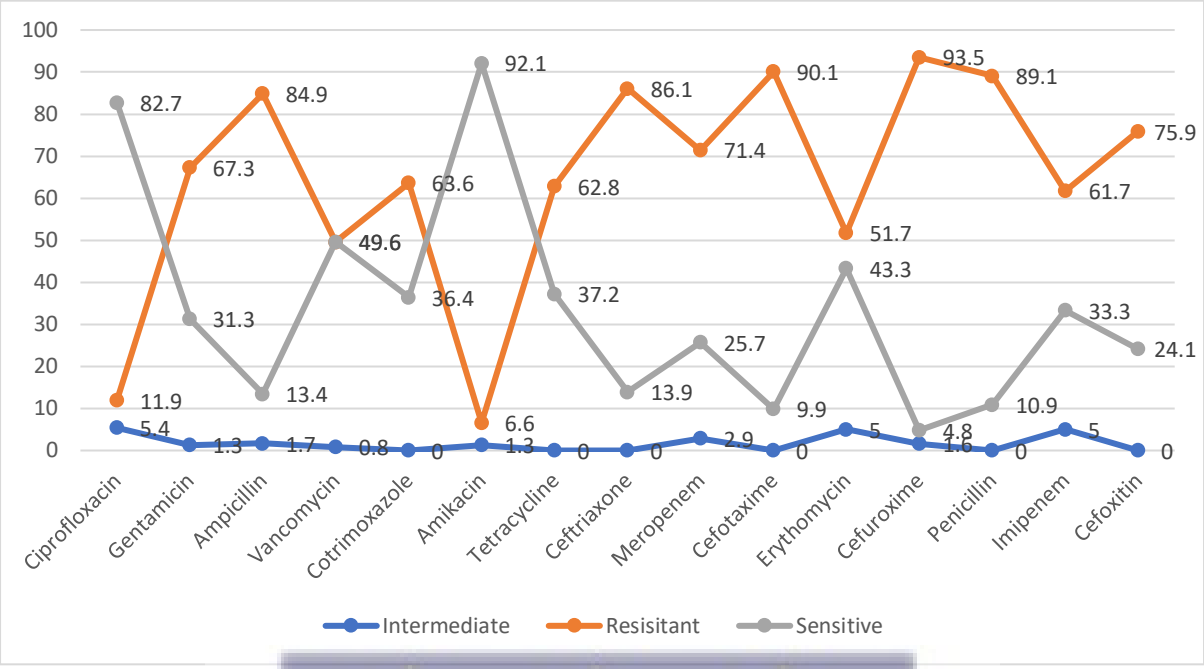


Figure 9 : Resistance and Susceptibility Profile of Most Used Antibiotics [N > 55]

The above graph in Figure 8 shows the antibiotic susceptibility and resistance profiles of the most frequently used antibiotics or microbial susceptibility testing. Amikacin showed the overall lowest percentage resistance at 6.6% and the highest percentage susceptibility at 92.1%. In the NICU however, Amikacin was used only used as a first line medication 9.8% of the time.

The antibiotics with the lowest percentage sensitivities were Cefuroxime, Cefotaxime, Penicillin, Ampicillin and Ceftriaxone at 4.8%, 9.9%, 10.9%, 13.4% and 13.9%, respectively. Ciprofloxacin and Vancomycin showed the second and third best susceptibility at 82.7% and 49.6% respectively.

Gentamicin which formed part of the most prescribed first line antimicrobial combination was noted to have a percentage resistance point of 67.3% and a percentage susceptibility point of 31.3%.

The figure below shows a representation of all antibiotics used during the study period on organisms isolated in decreasing order of resistance and increasing order of susceptibility. The figure also shows the variations noted in intermediate susceptibility and resistance amongst isolates.

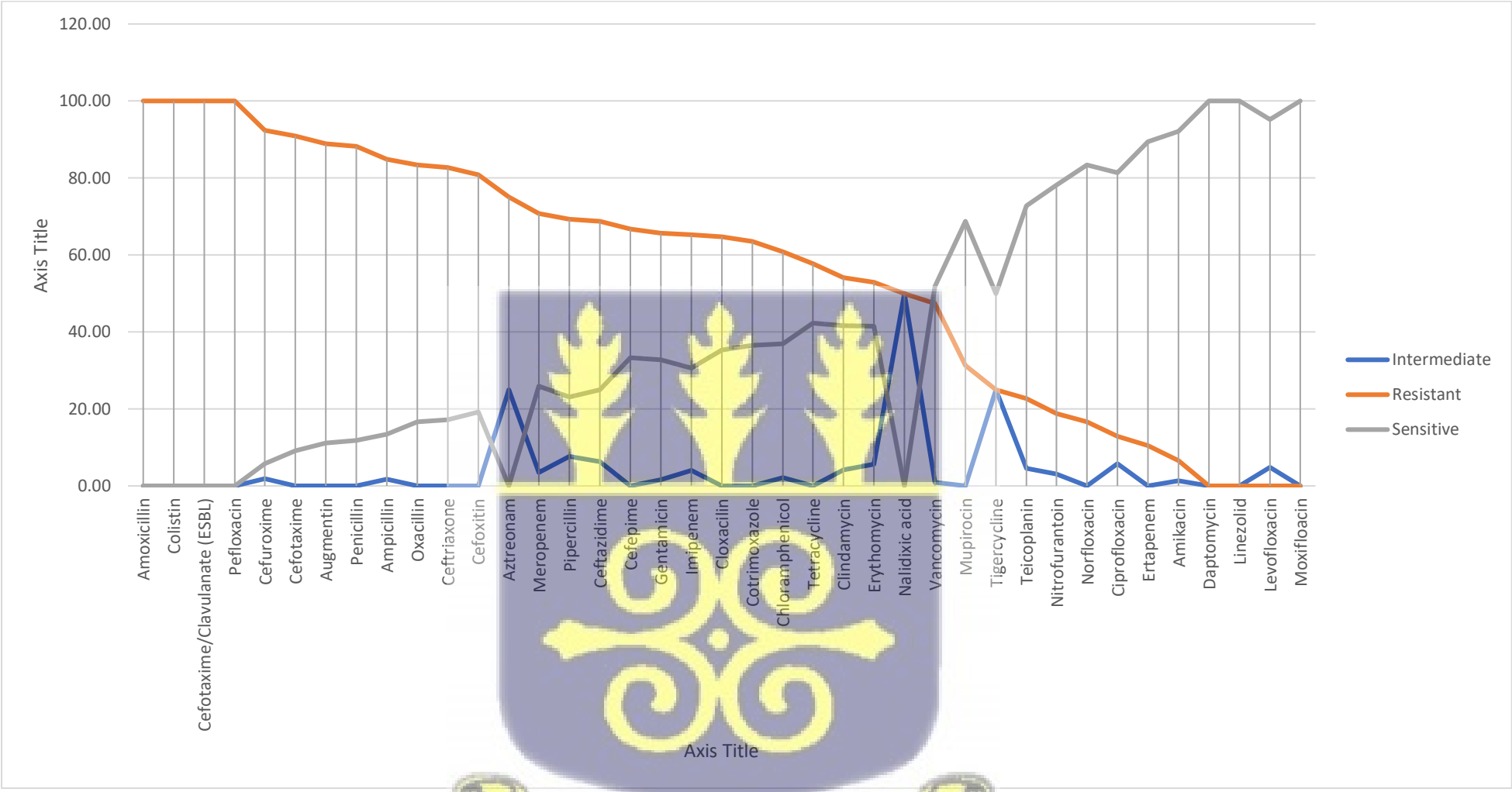


Figure 10 Percentage resistance and susceptibility of antimicrobials used in susceptibility testing

Table 4: Cross tabulation of Most Frequently Prescribed Firstline Antimicrobials against Gentamicin Susceptibility

CROSSTABULATION OF MOST FREQUENTLY PRESCIBED FIRSTLINE ANTIMICROBIALS AGAINST GENTAMICIN SUCEPTIBILITY					
		Gentamicin			
		-	I	R	S
FIRST LINE ANTIBIOTIC PRESCRIBED	Amikacin	0	0	1	0
	Amikacin Flucloxacillin	5	0	8	2
	Amikacin Tobramycin eye drops	0	0	1	0
	Ampicillin Cefotaxime	11	1	22	8
	Ampicillin Gentamicin	16	1	46	31
	Cefotaxime Flucloxacillin	0	0	1	0
	Cefotaxime Gentamicin	0	0	1	0
	Ciprofloxacin Tobramycin eye drops	1	0	0	0
	Gentamycin Cefotaxime	0	0	0	1
	Meropenem	0	0	2	0
	Tobramycin eye drops	0	0	1	0
	X-Penicillin Ampicillin	1	0	0	0
	X-Penicillin Gentamicin	0	0	1	0
Total		34	2	84	42

Gentamicin susceptibility cross tabulated against first line antibiotic prescribed revealed that 46 (49%) out of the 94 times that the antibiotic combination of ampicillin gentamicin was prescribed as first line the micro-organism isolated was resistant to gentamicin. The antimicrobial has intermediate susceptibility to gentamicin on one occasion when prescribed as first line in combination with ampicillin. Gentamicin sensitivity percentage when prescribed was 34%. The study data revealed that 16 (17%) out of 94 times gentamicin was used as first line antibiotic in the NICU, antimicrobial sensitivity testing for Gentamicin was not conducted on the isolated organism.

Gentamicin was most frequently prescribed in combination with Ampicillin as first line antibiotic in the NICU. However, it was also prescribed in combination with Cefotaxime and X-penicillin.

Table 5: Crosstabulation of Most Frequently Prescribed First Antimicrobials Against Ampicillin Susceptibility

CROSSTABULATION OF MOST FREQUENTLY PRESCIBED FIRST ANIT MICROBIALS AGAINST AMPICILLIN SUCEPTIBILITY					
		Ampicillin			
		-	I	R	S
FIRST LINE ANTIBIOTIC PRESCRIBED	Amikacin	0	0	1	0
	Amikacin Flucloxacillin	5	1	8	1
	Amikacin Tobramycin eye drops	0	0	1	0
	Ampicillin Cefotaxime	10	0	26	6
	Ampicillin Gentamicin	27	1	57	9
	Cefotaxime Flucloxacillin	0	0	1	0
	Cefotaxime Gentamicin	0	0	1	0
	Ciprofloxacin Tobramycin eye drops	0	0	1	0
	Gentamycin Cefotaxime	0	0	1	0
	Meropenem	1	0	1	0
	Tobramycin eye drops	0	0	1	0
	X-Penicillin Ampicillin	0	0	1	0
	X-Penicillin Gentamicin	0	0	1	0
Total		43	2	101	16

Ampicillin susceptibility cross tabulated against first line antibiotic prescribed revealed that 57 (61%) out of the 94 times that the antibiotic combination of ampicillin gentamicin was prescribed as first line the microorganism isolated was resistant to Ampicillin. Ampicillin was prescribed in combination with Cefotaxime 42 times, and 62% of the time the organism isolated was resistant to ampicillin. Organism isolated had intermediate susceptibility to Ampicillin on

one occasion when prescribed as first line in combination with gentamicin was used when the organism showed intermediate susceptibility.

Ampicillin sensitivity percentage when prescribed with both gentamicin and cefotaxime was 11%. The study data also revealed that 37 (27%) out of 137 times Ampicillin was used as first line antibiotic in the NICU, antimicrobial sensitivity testing for Ampicillin was not conducted on the isolated organism.

Table 6 : Crosstabulation of Most Frequently Prescribed First Line Antimicrobials against Cefotaxime Susceptibility

CROSSTABULATION OF MOST FREQUENTLY PRESCIBED FIRST LINE ANTIMICROBIALS AGAINST CEFOTAXIME SUCEPTIBILITY				
		Cefotaxime		
		-	R	S
FIRST LINE ANTIBIOTIC PRESCRIBED	Amikacin	0	0	1
	Amikacin Flucloxacillin	10	5	0
	Amikacin Tobramycin eye drops	1	0	0
	Ampicillin Cefotaxime	27	14	1
	Ampicillin Gentamicin	61	30	3
	Cefotaxime Flucloxacillin	1	0	0
	Cefotaxime Gentamicin	1	0	0
	Ciprofloxacin Tobramycin eye drops	1	0	0
	Gentamycin Cefotaxime	1	0	0
	Meropenem	2	0	0
	Tobramycin eye drops	1	0	0
	X-Penicillin Ampicillin	1	0	0
	X-Penicillin Gentamicin	0	1	0
Total		107	50	5

Cefotaxime susceptibility cross tabulated against first line antibiotic prescribed revealed that 14 (33%) out of the 42 times that the antibiotic combination of Ampicillin Cefotaxime was

prescribed as first line the microorganism isolated was resistant to Cefotaxime. Cefotaxime was prescribed in combination with Gentamicin 2 times. The study data also revealed that 29 (66 %) out of 44 times Cefotaxime was used as first line antibiotic in the NICU, antimicrobial sensitivity testing for Cefotaxime was not conducted on the isolated organism.

4.8 Qualitative Results

Table 7 - Socio demographics of health care professionals

Demographic				
Age (yrs.)	**Sex**	**occupation**	**Work experience**	**Years in health care**
24	**female**	**Lab tech**	**<1yr**	**1-2 yrs**
47	**male**	**Microbiologist**	**1-2 yrs**	**>10 yrs**
26	**Male**	**Microbiologist**	**1-2 yrs**	**1-2 yrs**
30	**female**	**NICU nurse**	**3-5 yrs**	**3-5 yrs**
25	**female**	**NICU Nurse**	**1-2 yrs**	**3-5yrs**
27	**Female**	**NICU nurse**	**<1yr**	**1-2 yrs**
23	**Female**	**NICU Nurse**	**<1 yr**	**<1yr**
28	**male**	**Lab Tech**	**3-5 yrs**	**3-5 yrs**
22	**Female**	**Microbiologist**	**<1yr**	**1-2yrs**
30	**Female**	**NICU Nurse**	**3-5yrs**	**>10yrs**

Initially a total of 20 health care professionals who worked in the NICU as well as the Microbiology labs were invited to take part in the in-depth interviews and focused group discussions. Six lab technicians and microbiologists declined on account of busy work schedules and sample backlog in the labs and were unable to honour rescheduled interview dates. Three NICU nurses invited were unable to join the Focused Group Discussion due to high work load and patient emergencies.

In-depth interviews were carried out amongst 5 healthcare workers and one focused group discussion was carried out amongst 5 health care professionals. The Healthcare professionals constituted (n= 5, 50%) NICU nurses (n= 3, 30%) microbiologists and (n= 2, 20%) laboratory technicians working in the Microbiology lab. Majority of Health care workers (n= 7, 70%) interviewed were between the ages of 20-29 years. More than half (n= 7, 70%) of the Healthcare workers interviewed have worked in this facility for between 1-5years with the remaining minority (n= 3, 30%) having under 1 years' experience. Sixty percent (60%) of participants were female with the remaining 40% being male.

Important themes that emerged from the interviews and focused group discussion with Health care professionals who had experience culturing Multidrug resistant organisms and taking care of patients with MDRO infections include the following;

1. The understanding of the concept and definitions of Multidrug resistance
2. Existing factors contributing to development of MDR in the hospitals and in the communities
3. Possible interventions already in place in the facility and in the communities
4. Factors in place to prevent the rise of Multidrug resistant antimicrobial infection

THEME 1: THE UNDERSTANDING OF THE CONCEPT AND DEFINITIONS OF MULTIDRUG RESISTANCE

Definition

The phenomenon of multidrug resistance was conceptualized amongst respondents as microbes building an opposition or resistance to at least 2 classes of antimicrobials. The knowledge of this concept was very general and not exceptionally in-depth.

"They are organisms that build resistance to drugs".

(Lab Technician, 1-2yrs experience)

"*Is it when particular bacteria are able to resist let's say different classes of medication."*

(NICU nurse, 3-5 yrs. experience)

"….. Multidrug resistance occurs with resistance being seen in more than 2 antibiotic classes"

(Senior microbiologist, >10yrs experience)

First encounter and Frequency of encounter with MDROs

Accounts of interviewees revealed that there is an increase in frequency of encounter of such organisms cultured in the laboratory in recent time and also an increase in morbidity and mortality associated with such patients admitted to the NICU.

"…Yeah, yeah. It was quite unusual because for some patients it wasn't the case but for one particular patient, he was actually resistant. I think it was E. coli yeah, I think it was E. coli. We used all the antibiotics and we did a sensitivity test and all of them were resistant but that was not the case for some of the patients but for that particular patient all the antibiotics were resistant"

(Lab Technician, 3-5yrs experience)

"So, I think the baby came…. they were twins and one passed so we were trying as much as possible to keep the other one. Unfortunately, we lost the baby. So, we started with ampicillin and gentamicin then when…as at that time the second twin was around yeah, was better so we started with ampicillin and gentamicin for that one and then when one started deteriorating, we changed ampicillin and gentamicin to flucloxacillin and amikacin. ……. But both passed away after initiating flucloxacillin and amikacin"

(NICU nurse, 3-5 yrs. experience)

"Well, TB gene expert, TB gene expert is what makes me aware of that. Also, ESBL and MRSA. Frequency is Maybe once in three days …."

(Senior microbiologist, >10yrs experience)

"First encounter was this isolate, proteus, the amikacin and some of the antibiotics, it was like sensitive and at the same time resistant. That's the intermediate…. But normally we have a ruler. So, after you're about to read the plate, you measure. Each of them if it's resistant it has a dimension. The sensitive ones have theirs as well as the intermediate"
(Lab Technician, 1-2yrs service)

THEME 2: EXISTING FACTORS CONTRIBUTING TO DEVELOPMENT OF MDR IN THE HOSPITALS AND IN THE COMMUNITIES

Community factors

The existence and persistence of taking 'over the counter' medication was noted from discussions to be a major contributory factor to the development of MDROs in the community.

"Personally, I think that people have been taking too much of unprescribed drugs like anytime they feel unwell they just go to the pharmacy." ***(Microbiologist, 2yrs work experience)***

THEME 3: FACTORS IN PLACE TO PREVENT THE RISE OF MULTIDRUG RESISTANT ANTIMICROBIAL INFECTION

According to Healthcare workers interviewed the factors in place to prevent the development of MDR were noted to be few and insufficient at best.

"Well, I've not seen any input. I mean you are the first person I've seen conducting this study no one has really come out to talk about these things." ***(22yrs, Lab Tech, 1-2yrs experience in health)***

"…. there are more processes in place for adverse drug reactions and none for MDRO reporting in this facility." ***(47yrs, microbiologist, >10yrs work experience)***

THEME 4: POSSIBLE INTERVENTIONS TO PUT PLACE IN THE FACILITY AND IN THE COMMUNITIES

Education, awareness and Prescriber retraining

The thoughts garnered from the Healthcare workers reflected that educating the public and creating an awareness was the primary way of introducing the concept to the community and promoting understanding amongst health care workers, providing a framework and guidelines for antimicrobial stewardship was also recommended as a possible intervention to prevent the emergence of MDROs in both the hospitals and community at large.

"Yeah, I mean to raise awareness, people are always talking about the disease, disease but then they are not talking about the fact that the patient is not getting well and actually that is not on the doctors' part but related to the drug. Like we should actually talk about that." ***(22yrs, Lab Tech, 1-2yrs experience in health)***

"I think always they should try and get tested, like bring the specimen for us to know which isolate which bacteria is causing that particular infection. If we're able to get that type of bacteria, we'll be able to know which antibiotics to be able to treat them..."
(26yrs, Microbiologist, 1-2yrs experience in current job)

Adequacy of antibiotics

The issue of inadequate antibiotics to treat existing infections was also explored as a possible factor leading to MDROs and the need for review of current standard operating procedures was emphasized

"We not coming up reviewing our data. Maybe if we would come up with reviewing all our labs, we know that yeah now ampicillin and gentamicin is not really working for our babies then we know that we are stopping ampicillin and gentamicin as our first line then we start with our second line."
(NICU nurse, 4 years' work experience)

4.9 Conclusion

In this research, I discovered that 18.5 percent of new born blood samples had MDRO blood culture positive. Negative for coagulase although the specific pathogenic function of Staphylococcus species could not be identified, they were the second most usually isolated gram-positive bacteria. Members of the Enterobacteriaceae family (*Pseudomonas species*, *Enterobacter species*, *Klebsiella species*) were the most often isolated Gram-negative bacteria. The isolated bacterium showed very strong resistance to ampicillin/gentamicin and ampicillin/cefotaxime combinations, while showing comparatively high sensitivity to Amikacin.

The qualitative results surmised healthcare workers interviewed were aware of the presence and existence or MDROs, and a collective reportage of increased encounter with MDROs in recent times. The study also revealed that factors currently in place to manage and curb AMR are insufficient. The study showed that suggested ways to improve and mitigate the current situation of AMR in GARH included public education programs, awareness creation activities and provider in-service training.

CHAPTER FIVE

DISCUSSION

The goal of this study was to investigate multidrug-resistant-organism bloodstream infections in the Greater Accra Regional Hospital's Neonatal Intensive Care Unit (NICU).

5.1 Demographic Distribution

In a tertiary hospital in the Greater Accra region of Ghana, a total of 195 cases of multidrug resistant bacterial isolates were identified from 1,043 NICU samples taken throughout the year. The patient samples consisted of (n = 88, 45.1%) females and (n = 107, 54.9%) males. A recent multicenter prospective cohort study conducted by Labi et al. (2021) in Korle-Bu Teaching hospital and 37 military hospitals showed a similar sex distribution of (n = 1878, 45.3%) females and, (n = 2266, 54.7%) males as well as (n = 592, 46.5%) females and (n = 680, 53.5%) males respectively. About a third of patients who came in with prematurity were also at risk of sepsis (AROS). The average age of admission to the facility was one day after birth. Approximately 90% of all patients were seen within the 48 hours following birth, and about 96.9% of patients were seen within the first week after delivery. A study conducted by Yadav et al. (2021) in the NICU of a tertiary hospital in Nepal also noted that 82.4% of patients seen with neonatal blood stream infection were seen in the first week of life.

5.2 Antimicrobial Susceptibility

In this study it was found that Gram negative organisms formed the majority of all cultured multidrug resistant organisms from the NICU samples taken, which are a significant cause of neonatal blood stream infections. Gram negative rods such as *Klebsiella spp, E Coli, Klebsiella Pneumoniae, Pseudomonas spp and Pseudomonas aeruginosa* contributed a total percentage of (83/195) 42.6% of all MDROs cultured. A similar study conducted in the NICU of Korle-

Bu Teaching Hospital (KBTH) by Enweronu-Laryea and Newman, (2007) showed similar findings with gram negative bacteria such as *Klebsiella spp, E Coli, Pseudomonas spp and Enterobacter spp* causing 54% of infections. Research conducted by Yadav et al., (2021) in Nepal also showed gram negative rod *Pseudomonas spp* had contributed to 78.4% of positive cultures followed by Coagulase negative staphylococci contributing about 23.0%. Out of 195 MDRO cultured, Staphylococcus aureus was responsible for (20.51%) of the samples which shows differing findings to work done in KBTH by Enweronu-Laryea and Newman, (2007) which recorded isolation of *Staphylococcus aureus* at 10.7% and 10.8% in 2002 and 1992 respectively. Findings similar to other research work conducted as a systematic review of data in sub-Saharan Africa which shows that *Staphylococcus aureus* accounted for 25% of culture positive bacteremia or sepsis (Okomo et al., 2019). A study also conducted by (Sharma et al., 2013) showed that Staphylococcus aureus accounted for about 51.9% of culture isolated bacteria.

Another study also showed Coagulase negative Staphylococcus (CoNS) contributed a much higher percentage of 31.9%; however, this study showed CoNS such as *Staphylococcus hemolyticus* and *Staphylococcus epidermidis* contributed a total of 15.9 % that is 10.8% and 5.1% respectively. According to a study conducted in KBTH by Enweronu-Laryea and Newman, (2007) Coagulase Negative Staphylococci (CoNS) were not isolated in 1992 however in 2002 it accounted for 31.9% being the most frequently isolated gram-positive coccus. Further research conducted in the same facility a decade on by Labi et al., (2016) revealed CoNS accounted for the most common pathogen isolated in early onset infections (EOS) (59.1%) and late onset infections (LOS) (52.8 percent). The study does not show the same alarming trend of the rise of CoNS however it shows that CoNS is the second most common gram-positive coccus in the NICU. The pathogenicity of CoNS is usually called in

question as it is considered a skin contaminant that is found in blood due to inappropriate skin preparation prior to blood cultures rather than a pathogenic cause of Blood stream infections. Work done by Labi et al., (2021) showed case fatality rates of CoNS infection similar to culture negative Neonates.

5.3 Most Frequently Prescribed First-Line Antibiotics

The majority of bacteria identified were found to be resistant to the first-line medicines. Most organisms cultured were resistant to gentamicin and ampicillin; however, Ampicillin and Gentamicin were the most commonly administered antibiotics combination as first line in the NICU, accounting for 58 percent of all prescriptions for patients with blood cultures with MDRO infections. Research conducted by Enweronu-Laryea and Newman, 2007 showed that in the KBTH NICU less than 40% of all bacterial isolates were susceptible to gentamicin ampicillin and cloxacillin. Gentamicin which formed part of the prescribed first line antimicrobial combination was noted to have a percentage resistance point of 65.63% and a percentage susceptibility point of 32.81%. The resistance trends in the above sited work are similar to the work conducted in GARH. *Streptococcus agalactiae* (Group B Strep) had a low percentage amongst isolated MDRO of 0.62% which is consistent with the low levels noted in a metanalysis done in sub-Saharan African population where 0.06% of the samples were found to have *Streptococcus agalactiae*. Research conducted by Slotved et al., (2017) shows a 25.5% carriage rate of Group B Strep in pregnant women in Ghana.

Amikacin showed the overall lowest percentage resistance at 6.58% and the highest percentage susceptibility at 92.11%. In the NICU Amikacin was used as a first line medication 10.5% of the time. The antibiotics with the lowest percentage sensitivities were noted to be Cefuroxime (5.77 %,), Cefotaxime (9.09 %,), Penicillin (11.76 %,), Ampicillin (13.45%) and Ceftriaxone

(17.24%). Ciprofloxacin and Vancomycin showed the second and third highest percentage of susceptibility at 81.29% and 51.75% respectively.

Prematurity was the most prevalent diagnosis linked with newborns with MDROIs in this study, accounting for 29 percent of the cases, followed by neonatal sepsis and acute respiratory distress, which accounted for 24 percent and 17 percent of the cases, respectively. Birth asphyxia was the fourth most common diagnosis associated with NICU admissions who had multidrug resistant organism infection contributing a total of 15.4% of all admissions with MDROIs. A study by Abdul-Mumin et al., (2021) conducted in Tamale Teaching hospital also showed similarly that Preterm delivery problems (49.6%) and birth asphyxia (21.7%) to be some of the leading causes of neonatal deaths over the 5-year study period. Prematurity tends to increase length of stay in hospitals and predispose patients to more severe morbidity.

In this study, the multidrug resistant organism culture positivity was 18.7%, comparable to similar studies conducted in Ghana by Labi et al. (2016) which found a 21.9% culture positivity. A study conducted in two centers by Labi et al., (2021) showed an overall culture positivity rate of 24.2 %. The above sited studies were conducted in the same facility and have shown a significant rising trend in culture positivity. The study conducted however the first of its type in GARH is and thus more work should be done retrospectively on existing data to reveal trends. There is an urgent need for antimicrobial stewardship programs (ASP) in all hospitals. To conserve the efficacy of the current antibiotics and stall the development of AMR, ASPs are a very essential step (Dramowski et al., 2020). According to Dramowski et al., (2020) Neonatal units must first be enabled to measure and monitor trends in their antimicrobial usage in order to create robust and effective ASPs and to provide locally suitable treatment guidelines, institutions need data on pathogen profiles and AMR trends. This Study found the most

frequently prescribed antibiotic and the AMR trends and infectious organism isolates in the NICU. this provides a foundation for more extensive AMR research and the development of ASPs in the facility.

5.4 Morbidity and Mortality Associated with Multidrug-Resistant Organisms

The antimicrobial resistance (AMR) crisis refers to the rising global occurrence of infectious illnesses affecting humans that are resistant to all known antibiotics. As noted in an earlier study as the incidence and scope of both disabling and deadly illnesses rise, this catastrophe will have a disastrous impact on human civilization (Michael et al., 2014). In this study morbidity associated with AMR in the NICU is 18.7% and the case fatality rate associated with patients in the NICU infected with Multidrug resistant organisms at GARH was found to be about (51/195) 26.2 %. The factors contributing to the development of AMR according to this study was over use of antimicrobials and lack of adequate stewardship frameworks for antibiotic monitoring, over prescription of antimicrobials when not required is another pertinent and obvious cause of AMR and its attendant issues. Michael et al., (2014) support the conclusions that antimicrobials' widespread, strong, and polarized use has resulted in widespread, strong, and polarized selection pressure on the microbial world. As a result, today's AMR rates are on the rise. The patients who still rely on the paying out of pocket for services in hospitals are very high; thus, patient care is unduly delayed leading to longer stays in hospitals and reduction in quality of patient care. This study showed that a staggering total of about 97.5% of patients who had blood cultures preformed paid out of pocket and did not have insurance coverage. The average age at diagnosis in this study was found to be on the first day of life comparable to studies conducted in low and middle income countries show that earl onset neonatal sepsis dominates the conversation on neonatal blood stream infections. In a study conducted by Sharma et al., (2013) it was noted that 63.35% of the total number of

isolates causes early onset neonatal sepsis. However late onset neonatal sepsis as seen in a study conducted by Mudzikati and Dramowski, (2015) showed that the pattern of late onset sepsis was associated with horizontal infection transmission involving hospital acquired infections and were by and large preventable.

5.5 Impact of BSIs on Cost, Length of Stay and Case Fatality

In this study the duration of hospital stays ranges between 1-73 days with a median of 11 days. These findings were similar to findings from research conducted by Labi et al., (2021) which showed a median duration of stay for neonates with Blood stream infections to be 14 days. Another study conducted by Mudzikati and Dramowski, (2015) showed a median hospital stay duration of 15 days. Although longer hospital stays tend to be associated with late onset neonatal sepsis, participants of this study developed early onset neonatal sepsis. Research work conducted on cost analysis and length of stay by Fenny et al., (2021) showed an association between neonatal Blood Stream Infection (BSI) and higher costs of hospital bills as well as longer duration of stay (LOS). Patients infected with antimicrobial-resistant organisms incur higher expenses ($6,000–$30,000) than patients infected with antimicrobial-susceptible organisms (Cosgrove, 2006).

The case fatality associated with MDR BSI in the NICU of this study was 24.1% comparable to the case fatality rate of 19.7% found in a similar study conducted by Labi et al., (2021) in Korle-Bu Teaching Hospital and 37 Military Hospital. The case fatality rate of Multidrug resistance is higher in this study which is cause for increased interest and a more in-depth look.

5.6 Knowledge of MDROs amongst Health Workers

The study showed that healthcare workers had acceptable knowledge of MDROs. A few did not have adequate information on MDROs. Research by Kose and Colak, (2021) showed that

following graduation, further training may be critical in minimizing antibiotic overuse which is a contributory factor to MDROs. Overuse, self-medication, overcrowding, and lapses in cleanliness or poor infection control management are all general risk factors for the development of resistant bacteria in hospitals and the community (Fair & Tor, 2014).

5.7 Factors Contributing to MDROs

In 2004, just 1.6 percent of medications in clinical development by the world's 15 major pharma corporations were antibiotics, according to work done by Dougherty and Pucci, (2011). From this research conducted, one of the main factors notably absent from responses was the lack of adequate back up antibiotics and lack of overall interest of pharmaceutical companies in developing new antimicrobials. According to work done by Renwick et al. (2016) the antimicrobial discovery void shows that despite the growing problem of antimicrobial resistance, pharmaceutical and biotechnology corporations are hesitant to research new antibiotics due to a number of commercial failures. Work done by Klein et al., (2018) shows that antibiotic consumption increased globally from 2000 to 2015 by 68 percent and the sharpest increase was observed in LMICs with 114 percent over the 15-year period. This exponential increase is consistent with the rising levels of antimicrobial resistance that has been seen in LMICs. The lack of reliable AMR surveillance data is an important missing component of the fight against AMR in the study site. Work done by Malania et al., (2021) showed that the implementation of quality management systems, standardization of guidelines, and training, together with focused capacity building, resulted in enhanced laboratory standards and bloodstream infection control.

The current study also noted that educating the public and raising awareness were the primary methods of introducing the concept to the public and promoting understanding among health care workers. Providing a framework and guidelines for antimicrobial stewardship was also

suggested as a possible intervention to prevent the emergence of MDROs in both hospitals and the general public.

5.8 Measures in Place to Prevent Antimicrobial Resistance

The qualitative results aspect of the study revealed that the measures in place to address antimicrobial resistance in the Greater Accra Regional Hospital were inadequate. The interventions that exist in literature as strategies to handle AMR according to work done by Murray et al., (2022) tend to fall into five main groupings. Majority of these groupings were noted in the responses gathered in the qualitative results. The First of which is the principle of infection control and prevention. This encompasses both hospital-based measures of infection control and prevention and community-based measures to promote clean water, sanitation and hygiene. The study results showed that hospital workers suggested that infection control and sanitation was one of the ways to improve upon AMR control and transmission both in the hospitals and the community at large. However, there was more emphasis placed on educating the public on the existence of AMR and raising awareness on prevention techniques.

The second principle as discussed by Murray et al., (2022) is prevention through vaccinations. Vaccine development is a sure way to dramatically reduce the need for antibiotics and is a crucial player in the fight against AMR. Of the six leading pathogens as described by WHO only *S pnemoniae* has a vaccine. During the research study this method of preventing AMR was not mentioned or discussed as viable option for prevention. The third strategy is to reduce human exposure to antibiotics through control of antibiotic misuse in farming. The direct causal link of animal related antibiotic exposure is yet inconclusive. A study conducted by Wu et al., (2013) on ESBL (extended spectrum beta-lactamase) positive *E. coli* isolates from both animals and humans noted that efforts in public health should be maintained at controlling human to human transmission as Animal served as a reservoir.

The fourth strategy to minimise the development of AMR was the misuse of antibiotics that are not necessary to improve human health. For instance, in the case of viral infections there is a lot of antibiotics misuse when clinicians are unable to differentiate between bacterial and viral infections. In this regard work done by van Houten et al., (2017) to externally validate a protein-based assay differentiating bacterial from viral infections in children with lower respiratory tract infection revealed potential to reduce antibiotic misuse. The fifth option to prevent AMR is to improve upon development and access to second line antibiotics in areas without access the study revealed that there is a general paucity of measures in place to prevent the rise of AMR in the GARH. According to Healthcare workers interviewed the factors in place to prevent the development of MDR were noted to be few and insufficient at best. A study conducted by (Hervas et al., 2001) noted that adherence to infection prevention measures reduced the propagation of multidrug resistant organism infection.

CHAPTER SIX

6.1 Conclusion

This Study was conducted to assess multidrug resistant-organism Bloodstream infections in Neonatal Intensive care unit (NICU) in Greater Accra Regional Hospital in Ghana. The prevalence of Multidrug resistant organism blood stream infections was 18.7% in the NICU of GARH. Within the NICU the most frequently prescribed first line antimicrobials to treat infections were ampicillin and gentamicin, accounting for 58 percent of all prescriptions for patients with blood cultures with MDRO infections. The Antibiotic susceptibility profile revealed that the most commonly isolated organism causing MDRO infections in the NICU was Staphylococcus aureus however cefotaxime, the second most prescribed antibiotic showed a resistance point of 90.1%. The case fatality rate associated with MDRO infections in the NICU was 24.1%. The current measures in place are insufficient and inadequate

The findings show the need to review antibiotic protocols, the need for extensive health education for both prescribers and general public on the present problem of antimicrobial resistance that exists in our communities and hospitals. According to research work conducted by Michael et al., (2014) the CDC described the world to be in a 'post-antibiotic' era as far back as 2013, the WHO also stated that the AMR crisis is becoming dire in 2014. AMR and MDRO are no longer an imminent or emerging problem they are a now public health emergency requiring urgent attention from the health sector, country and the world at large. The issue of MDRO in the NICU of GARH is only a microcosm of the much larger problem occurring in our communities and hospitals nationwide and on a much more global scale.

This Study was conducted to keep the conversation about antimicrobial resistance and multidrug resistance going. Standard empirical therapy is unlikely to improve the outcome of BSIs in poor and medium income countries due to the variety of etiologic agents and the high

probability of antibiotic resistance. Access to dependable clinical microbiologic services would be required for such advancements.(Labi et al., 2021)

6.2 Recommendations

1. According to the findings of this study there is a need for the NICU in collaboration with the microbiology department to have an in-depth evaluation of the current first line antibiotics in the NICU of GARH due to high levels of antimicrobial resistance against current first line options.
2. The Management of the GARH, to bridge the knowledge gap amongst both health care providers and community is recommended to organize in-service training and health promotion activities in the for the health care providers and the general public respectively.
3. The management of the GARH should in collaboration with the heads of the NICU develop and implement infection prevention measures incorporated into routine practice in the NICU to guard against development and spread of AMR.

6.3 Importance of the Study

This research project is the first of its kind assessing Multidrug resistance in such a vulnerable population neonatal ICU patient in this department. Additionally, the study opens the door for further work to be carried out on existing data on other microbiological sample specimen within this population that will furnish the local and global scientific community. This study shows AMR patterns in the NICU during the height of the Covid-19 pandemic. The Mixed method approach of using both qualitative and quantitative methods provide data that complements each other and hence improving upon the authenticity of the work done. Interviewing health care professionals who come into contact with and are familiar with isolating and culturing

such organisms and also caring for patients with such organism infections provides an in-depth view of the experiential knowledge of MDROs and not only quantitative analysis of figures.

PROPOSED AREAS FOR FURTHER RESEARCH

This initial research endeavor provides the platform for future research endeavors that build up on the findings of this study.

- A more extensive review of all types MDROs over a longer period to make comparison over time periods.
- A study on MDROs cultured in the emergency room over time in the GARH.

6.4 Limitations of the Study

The time period of review does not allow comparison of patterns over time to show AMR patterns before and after Covid-19 pandemic. The study was conducted on specifically of blood cultures. The study was conducted in only one hospital and cannot be generalized to other facilities

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APPENDIX A: PARTICIPANTS INFORMATION SHEET

Title of Study:

MULTIDRUG-RESISTANT ORGANISM AT THE NEONATAL INTENSIVE CARE UNIT (NICU) IN THE GREATER ACCRA REGIONAL HOSPITAL IN GHANA

Introduction:

My Name is Abena Odurowaa Yeboah, a Masters student of University of Ghana, School of Public Health. I am the Principal Investigator (PI). I am responsible for the activities of this project and can be contacted via email at odurowaayeboah@gmail.com.

Background and Purpose of research:

This research topic aims to assess multidrug resistant organism infection at the neonatal intensive care unit in the Greater Accra Regional Hospital. This work being carried out seeks to assess the burden and understand from varying perspectives the causes and influences of this phenomenon and proposed ways resolution.

Nature of research:

The study is interested in identifying what is known to be an increasing trend of microbial resistance that is changing the trend of antibiotic usage and efficacy in the field of medicine. This study is a mixed method study which involves both qualitative and quantitative aspects. The qualitative aspect involves interviews and focused group discussions with medical professionals involved in the diagnosis and treatment of multidrug resistant organism infection in the neonatal ICU and Microbiology lab.

Participant's involvement:

- **Duration /what is involved:** Participants in this study who partake in the In-depth interviews will spend about 40 minutes of their time. Participants involved in the Focused group discussion with spend about an hour.
- **Potential Risks:** Partaking in this study will not involve any risk to the participants involved.
- **Benefits:** There will be no direct benefits to the study participants for volunteering their time to this study. The findings of this study will however enrich the scientific community at large, influence the choice of antibiotics and improve upon antibiotic stewardship within the NICU of Greater Accra Regional Hospital.
- **Costs:** There is no direct monetary cost to the participants involved in this study. Nevertheless, it will come at a cost of work hours.
- **Compensation:** Participants will be given refreshment after their participation in the study.
- **Confidentiality:** Participant information will be kept confidential. Participant identification numbers to ensure anonymity. Audio Recordings from interview sessions and Focused group discussions will be kept by principal investigator only.
- **Voluntary participation/ Withdrawal:** Participants are free to withdraw from the study at any time with no consequence.
- **Outcome and Feedback:** The outcome of the project will be shared with the scientific community, the units from which the data was collected.
- **Funding Information:** This study is fully funded by the principal investigator (PI).
- **Provision of Information:** Participants will be given copies of the information sheet as well as consent forms after signing

Kindly note that for further information you can contact

Dr Abena Odurowaa Yeboah, 0547587478, odurowaayeboah@gmail.com

Nana Abena Apatu, 0503539896, ethics.research@ghsmail.org

APPENDIX B (CONSENT FORM)

CONSENT FORM

STUDY TITLE: MULTIDRUG-RESISTANT ORGANISM AT THE NEONATAL INTENSIVE CARE UNIT (NICU) IN THE GREATER ACCRA REGIONAL HOSPITAL IN GHANA

PARTICIPANTS' STATEMENT

I acknowledge that I have read or have had the purpose and contents of the Participants' Information Sheet read and all questions satisfactorily explained to me in a language I understand (English, Twi) I fully understand the contents, give permission to have my audio recorded and acknowledge any potential implications as well as my right to change my mind (i.e., withdraw from the research) even after I have signed this form.

I voluntarily agree to be part of this research.

Name of Participant……...

Participants' Signature …….. OR Thumb Print……

Date……

INTERPRETERS' STATEMENT

I interpreted the purpose and contents of the Participants' Information Sheet to the afore named participant to the best of my ability in the (English, Twi) language to his proper understanding.

All questions, appropriate clarifications sort by the participant and answers were also duly interpreted to his/her satisfaction.

Name of Interpreter……

Signature of Interpreter…….. OR Thumb Print …….....

Date:……

STATEMENT OF WITNESS

I was present when the purpose and contents of the Participant Information Sheet was read and explained satisfactorily to the participant in the language he/she understood (English, Twi).

I confirm that he/she was given the opportunity to ask questions/seek clarifications and same were duly answered to his/her satisfaction before voluntarily agreeing to be part of the Research.

Name:……

Signature…….... OR Thumb Print …….....

Date:……

INVESTIGATOR'S STATEMENT AND SIGNATURE

I certify that the participant has been given ample time to read and learn about the study. All Questions and clarifications raised by the participant have been addressed.

Researcher's name: ……

Signature ……

Date……

APPENDIX C (DATA EXTRACTION FORM)

NICU Research Data extraction form

No	Age (days)	Sex	Location/ Address	Diagnosis	Date of diagnosis	Date of 1st culture	Organism(s) isolated	Antibiotic resistance profile	Antibiotic susceptibility profile	Antibiotic prescribed	Days on admission	Outcome of management

APPENDIX D: INTERVIEW GUIDE

Participant ID:…….

1. Age:……

2. Are you: (please tick as necessary) □ Male □ Female

3. What is your professional background?

□ Neonatal ICU Nurse

□ Lab Technician/ Microbiologist

□ Pediatrician/Neonatologist/ Medical officer

□ Other: (please describe) _____

4. How many years of experience have you had in this current job?

□ <1 Year □ 1-2 Years

□ 3-5 Years □ 5-10 Years

□ >10 Years

5. Experience in Health Care (optional):

□ <1 Year □ 1-2 Years

3-5 Years □ 5-10 Years

□ >10 Years

Guiding questions

- What is multidrug resistant organism infection?
- What was your first encounter with this and how often do you come into contact with them?
- How do you think these infections come about?

- How concerning do you think these infections are to patients and healthcare workers? And why?
- What factors do you think are contributing to this phenomenon?
- Do you think the antibiotics we have are adequate to handle the current climate of infection?
- In your experience during your practice, how much have the frequently used antibiotics changed over time?
- In your view what is the antibiotic situation in your facility?
- What factors are in place to curb this in our communities and in our hospitals?
- What else can be done to curb this emerging problem?

FOCUSED GROUP DISCUSSION GUIDE

Participant ID: ……

Please answer the following questions in the spaces provided, circle or tick the most appropriate options.

1. Age: ……

2. Are you: (please tick as necessary) □ Male □ Female

3. What is your professional background?

□ Neonatal ICU Nurse

□ Lab Technician/ Microbiologist

□ Pediatrician/Neonatologist/ Medical officer

□ Other: (please describe) _____

5. How many years of experience have you had in this current job?

□ <1 Year □ 1-2 Years

□ 3-5 Years □ 5-10 Years

□ >10 Years

6. Experience in Health Care (optional):

□ <1 Year □ 1-2 Years

3-5 Years □ 5-10 Years

□ >10 Years

Round of Introductions

- First, I'd like everyone to introduce themselves.

Introductory question

I am just going to give you a couple of minutes to think about your experience of diagnosis and/or managing a neonatal patient with Multidrug resistant infection. Is anyone happy to share his or her experience?

Guiding questions

- What is multidrug resistant organism infection?
- What was your first encounter with this and how often do you come into contact with them?
- How do you think these infections come about?
- How concerning do you think these infections are to patients and healthcare workers? And why?
- What factors do you think are contributing to this phenomenon?
- Do you think the antibiotics we have are adequate to handle the current climate of infection?
- In your experience during your practice, how much have the frequently used antibiotics changed over time?
- In your view what is the antibiotic situation in your facility?
- What factors are in place to curb this in our communities and in our hospitals?
- What else can be done to curb this emerging problem?

Concluding question

- Of all the things we've discussed today, what would you say are the most important issues you would like to express about multidrug resistant organism infection?

Concluding remarks.

Thank you for taking the time to participate. This has been a really productive discussion; your input will be quite useful to the study. I hope you enjoyed the discussion Please speak with me later if there is anything you are unsatisfied with or wish to complain about. I'd like to remind you that any comments you make will remain anonymous in this report. Please turn in your completed personal information questionnaire before leaving.

APPENDIX E: ETHICAL CLEARANCE

GHANA HEALTH SERVICE ETHICS REVIEW COMMITTEE

In case of reply the number and date of this Letter should be quoted.

My Ref. GHS/RDD/ERC/Admin/App/22/118
Your Ref. No.

Research & Development Division
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P. O. Box MB 190
Accra
Digital Address: GA-050-3303
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Tel: +233-302-681109
Email: ethics.research@ghsmail.org
21st March, 2022

Abena Odurowaa Yeboah
P. O. Box YK 465, Kanda, Accra

The Ghana Health Service Ethics Review Committee has reviewed and given approval for the implementation of your Study Protocol.

GHS-ERC Number	**GHS-ERC 035/01/22**
Project Title	Multidrug-Resistant Organism at the Neonatal Intensive Care Unit (NICU) and Pediatric Intensive Care Unit (PICU) in the Greater Accra Regional Hospital in Ghana
Approval Date	21st March, 2022
Expiry Date	20th March, 2023
GHS-ERC Decision	**Approved**

This approval requires the following from the Principal Investigator

- Submission of yearly progress report of the study to the Ethics Review Committee (ERC)
- Renewal of ethical approval if the study lasts for more than 12 months,
- Reporting of all serious adverse events related to this study to the ERC within three days verbally and seven days in writing.
- Submission of a final report after completion of the study
- Informing ERC if study cannot be implemented or is discontinued and reasons why
- Informing the ERC and your sponsor (where applicable) before any publication of the research findings.
- Please note that any modification of the study without ERC approval of the amendment is invalid.

The ERC may observe or cause to be observed procedures and records of the study during and after implementation.

Kindly quote the protocol identification number in all future correspondence in relation to this approved protocol

SIGNED… .....
Dr. James Akazili
(Head, Ethics & Research Management Department)

Cc: The Director, Research & Development Division, Ghana Health Service, Accra