EVALUATION OF AN ANTIMICROBIAL STEWARDSHIP PROGRAM IMPLEMENTATION FOR SURGICAL PROPHYLAXIS IN A REFERRAL HOSPITAL IN THE KINGDOM OF SAUDI ARABIA

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2023

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by

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Thesis submitted in fulfillment of the requirements
for the degree of
Doctor of Philosophy

December 2023

ACKNOWLEDGEMENT

First of all, I would like to thank almighty Allah for giving me the strength to complete my PhD study. I want to extend my sincere gratitude to my supervisor Dr. Amer Hayat Khan at the Discipline of Clinical Pharmacy, School of Pharmaceutical Sciences, Universiti Sains Malaysia, Malaysia for giving me the opportunity to work with him. Even when I left for Jordan and Saudi Arabia, he was incredibly supportive. I would not have completed this work without his guidance, support, and inspiration. I would also like to thank my co-supervisors Prof. Dr. Mohamed Azmi Hassali at social and administrative pharmacy, School of Pharmaceutical Sciences, Universiti Sains Malaysia, Malaysia and Dr. Abdul Haseeb at the department of Clinical Pharmacy, Umm Al-Qura University, Saudi Arabia for their time and expertise in improving the quality of my work. I truly appreciate their support thorough my PhD journey. I would also like to thank Dr. Emad Elazab (infectious disease physician), Dr. Salwa Mahmoud (physician), and Dr. Ali Guzu (physician), Dr. Khalid Amin (pharmacists), Dr. Dina Fouda (Clinical pharmacist), Dr. Enas ElSaid (physician) in Al-Kharj and Riyadh hospitals for their coordination and support in providing me all the data associated with using antimicrobial especially in the surgery department. Finally, I would like to thank my parents, wife, family, friends, and my coworkers for their support and for their praying for me in this journey. I would like to thank you for all of your support, love, and patience.

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AMR	Antimicrobial resistance
AMS	Antimicrobial stewardship
ASP	Antimicrobial stewardship program
CAUTI	Catheter-associated urinary tract infections
CDC	Centers for disease control and prevention
CLABSI	Central line-associated bloodstream infection
DDD	Defined daily dose
ECDC	European centre for disease prevention and control
ESBL	Extended spectrum beta-lactamase
HAIs	Health care-associated infections
ICU	Intensive care unit
IDSA	Infectious diseases society of America
MDRO	Multi-drug resistant organism
MRSA	Methicillin-resistant Staphylococcus aureus
NAP	National action plan for combating antibiotic-resistant bacteria
PDR	Pan drug-resistant
SSI	Surgical site infection
VAP	Ventilator-associated pneumonia
VRE	Vancomycin-resistant enterococci
WHO	World health organization
XDR	Extensively drug-resistant

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PENILAIAN PELAKSANAAN PROGRAM PENGAWASAN ANTIMIKROB BAGI PROFILAKSIS PEMBEDAHAN DI SEBUAH HOSPITAL RUJUKAN DI KERAJAAN ARAB SAUDI

ABSTRAK

Stewardship antimikrobial merujuk kepada usaha-usaha yang diselaraskan untuk meningkatkan penggunaan agen-agen antibiotik dengan menggalakkan penggunaan pemilihan antibiotik yang betul, kaedah pentadbiran, dos antimikrobial, dan tempoh terapi. Kajian terkini ini bertujuan untuk menentukan keberkesanan langkah-langkah stewardship antimikrobial dalam meningkatkan penggunaan antibiotik pada pesakit pembedahan. Meta-analisis kami menunjukkan bahawa cefazolin sama berkesan dengan cefamandole, cefuroxime, dan ceftriaxone dan bahawa profilaksis antibiotik dos berganda sama berkesan dengan profilaksis antibiotik dos tunggal dalam mencegah jangkitan tapak pembedahan. Fasa pertama termasuk tinjauan untuk mengkaji pengetahuan, sikap, dan persepsi penyedia penjagaan kesihatan terhadap program stewardship antimikrobial, serta halangan-halangan terhadap pelaksanaannya di Arab Saudi. Lebih separuh responden sedar akan program stewardship antimikrobial, dan 45% daripadanya mempunyai pengalaman stewardship antimikrobial sebelum ini. Pakar-pakar penjagaan kesihatan mempunyai sikap positif terhadap pelaksanaan program stewardship antimikrobial. Mereka bersedia untuk mengambil bahagian dalam sebarang inisiatif kesedaran antimikrobial yang menggalakkan stewardship antibiotik (78.42%). Selain itu, kajian terkini mendapati bahawa halangan utama dalam melaksanakan program stewardship antimikrobial ialah kurangnya dasar-dasar dalaman dan garis panduan (60.98%), serta peluang latihan yang terhad (56.40%). Ketersediaan pengajaran dan latihan

didaktik (65.85%) adalah pembantu utama dalam pelaksanaan program stewardship antimikrobial. Fasa kedua kajian melihat prevalen pelbagai jangkitan bakteria dan kadar ketahanan antibiotik di Hospital Tentera Al Kharj, Hospital Raja Khalid di Al Kharj, dan Pusat Perubatan Raja Saud di Riyadh antara 2019 dan 2021. Klebsiella pneumonia, Proteus mirabilis, Acinetobacter baumannii, Enterococcal species, dan Staphylococcus epidermidis semua mempunyai kadar ketahanan yang tinggi. Klebsiella pneumonia sangat tahan terhadap ampicillin (98.9%), cephalothin (75.0%), nitrofurantoin (71.8%), dan aztreonam (62.0%). Proteus mirabilis menunjukkan ketahanan yang tinggi terhadap ampicillin (67.8%), nitrofurantoin (98.6%), dan trimethoprim-sulfamethoxazole (64.6%). Kerentanan spesies Enterococcal kepada erythromycin (20%) dan tetracycline (48.3%) adalah rendah. Acinetobacter baumannii sangat tahan terhadap aztreonam (100.0%), ceftazidime (72.9%), imipenem (83.8%), dan levofloxacin (76.5%). Staphylococcus epidermidis mempunyai kadar kebolehterimaan yang lemah terhadap erythromycin (23.5%), oxacillin (21.3%), penicillin (6.6%), ampicillin (7.3%), dan azithromycin (29%). Fasa ketiga mengkaji prevalen jangkitan yang berkaitan dengan penjagaan kesihatan di Hospital Tentera Al Kharj pada tahun 2019,2020, dan 2021. Penemuan menunjukkan kadar jangkitan yang berkaitan dengan penjagaan kesihatan yang rendah (0.43% pada tahun 2019 dan 0.1% pada tahun 2020). Selain itu, kadar jangkitan tapak pembedahan adalah 0.41% pada tahun 2019 dan turun menjadi 0.04% pada tahun 2020 selepas meningkatkan pematuhan dengan paket penjagaan dan melaksanakan garis panduan profilaksis pembedahan. Fasa keempat menyelidiki kesan penggunaan intervensi stewardship antimikrobial dalam jabatan pembedahan Hospital Tentera Al Kharj. Kajian ini merangkumi pesakit yang menjalani pembedahan gastrointestinal. Ia membandingkan penggunaan antibiotik sebelum pelaksanaan program antimikrobial (Jun hingga Disember 2019) dengan penggunaannya selepas pelaksanaannya (Januari hingga Julai 2020). Program profilaksis antibiotik pembedahan termasuk sesi pendidikan, pembangunan garis panduan, dan semakan bulanan preskripsi. Kesesuaian pemilihan antibiotik meningkat dari 51.2% hingga 53.1%, kesesuaian dos ubat meningkat dari 32.7% hingga 53.7%, kesesuaian masa adalah 64.8% sebelum pelaksanaan intervensi dan meningkat hingga 74.4% selepas pelaksanaannya, kesesuaian cara pentadbiran ubat meningkat dari 66.7% hingga 76.8%, dan kesesuaian tempoh profilaksis meningkat dari 14.2% hingga 19.5%. Selepas pelaksanaan intervensi tersebut, kadar jangkitan tapak pembedahan menurun dari 0.4% hingga 0.04%. Mematuhi garis panduan dan melaksanakan intervensi stewardship antimikrobial adalah komponen penting yang boleh diterapkan untuk meningkatkan penggunaan profilaksis antibiotik dan penggunaan antibiotik yang betul secara amnya.

EVALUATION OF AN ANTIMICROBIAL STEWARDSHIP PROGRAM IMPLEMENTATION FOR SURGICAL PROPHYLAXIS IN A REFERRAL HOSPITAL IN THE KINGDOM OF SAUDI ARABIA

ABSTRACT

Antimicrobial stewardship refers to the coordinated efforts to enhance the use of antimicrobial agents by encouraging the use of proper antibiotic selection, method of administration, antimicrobial dose, and duration of therapy. The current study sought to determine the efficacy of antimicrobial stewardship measures in improving antibiotic use in surgical patients. Our meta-analyses showed that cefazolin is as effective as cefamandole, cefuroxime, and ceftriaxone and that multiple-dose is as effective as single-dose antibiotic prophylaxis in preventing surgical site infections. The first phase included surveys to examine healthcare providers' knowledge, attitude, and perception towards the antimicrobial stewardship programme, as well as the barriers to its implementation in Saudi Arabia. More than half of the respondents are aware of antimicrobial stewardship programmes, and 45% of them have prior antimicrobial stewardship experience. Healthcare professionals have a positive attitude towards the implementation of the antimicrobial stewardship programme. They are willing to participate in any antimicrobial awareness initiative that promotes antibiotic stewardship (78.42%). Furthermore, the current study found that the major obstacles to implementing antimicrobial stewardship programmes were a lack of internal policies and guidelines (60.98%), as well as limited training opportunities (56.40%). The availability of didactic instruction and training (65.85%) was the main facilitator of antimicrobial stewardship programme implementation. The second phase of the study looked at the prevalence of various bacterial infections

and antibiotic resistance rates in Al Kharj Military Hospital, King Khalid Hospital in Al Kharj, and King Saud Medical City in Riyadh between 2019 and 2021. Klebsiella pneumonia, Proteus mirabilis, Acinetobacter baumannii, enterococcal species, and Staphylococcus epidermidis all had high resistance rates. Klebsiella pneumonia was highly resistant to ampicillin (98.9%), cephalothin (75.0%), nitrofurantoin (71.8%), and aztreonam (62.0%). Proteus mirabilis exhibited high resistance to ampicillin (67.8%), nitrofurantoin (98.6%), and trimethoprim-sulfamethoxazole (64.6%). The susceptibility of Enterococci species to erythromycin (20%) and tetracycline (48.3%) was low. Acinetobacter baumannii was highly resistant to aztreonam (100.0%), ceftazidime (72.9%), imipenem (83.8%), and levofloxacin (76.5%). Staphylococcus epidermidis had a poor susceptibility rate to erythromycin (23.5%), oxacillin (21.3%), penicillin (6.6%), ampicillin (7.3%), and azithromycin (29%). The third phase examined the prevalence of infections associated with healthcare in Al Kharj Military Hospital in 2019, 2020, and 2021. The findings revealed a low rate of healthcare-associated infections (0.43% in 2019 and 0.1% in 2020). Furthermore, the rate of surgical site infections (SSIs) was 0.41% in 2019 and dropped to 0.04% in 2020 after improving compliance with the care bundles and implementing surgical prophylaxis guidelines. The fourth phase investigated the impact of applying antimicrobial stewardship interventions in the surgery department of Al Kharj Military Hospital. The study included patients who had gastrointestinal surgeries. It compared the use of antibiotics before the implementation of the antimicrobial programme (June to December 2019) with the use after the implementation (January to July 2020). The surgical antibiotic prophylaxis programme included educational sessions, the development of a guideline, and a monthly review of prescriptions. The appropriateness of antibiotic selection increased from 51.2% to 53.1%, the appropriateness of drug dosage increased from 32.7% to 53.7%, the appropriateness of timing was 64.8% before the implementation of the interventions and increased to 74.4% after the implementation, the appropriateness of the drug administration route increased from 66.7% to 76.8%, and the appropriateness of prophylaxis duration increased from 14.2% to 19.5%. Following the implementation of the interventions, the rate of SSIs decreased from 0.4% to 0.04%. Adherence to guidelines and the implementation of antimicrobial stewardship interventions are important components that can be applied to improve antibiotic prophylaxis use and the correct use of antibiotics in general.

CHAPTER 1
INTRODUCTION

1.1 Background

1.1.1 The emergence of bacterial resistance

Antibiotics are drugs that have saved the lives of many patients while also contributing significantly to key advances in surgery and medicine (Gould & Bal, 2013). They have successfully treated or prevented infections in patients with chronic illnesses such as diabetes, end-stage renal disease, or cancer, as well as those who have undergone complex surgeries such as cardiac surgery, joint replacement, or organ transplants (Gould & Bal, 2013; Wright, 2014; CDC, 2013; Rossolini et al., 2014).

Infections caused by resistant bacteria are spreading rapidly around the world, jeopardising the effectiveness of antibiotics that have saved millions of lives. Antibiotic resistance is currently one of the most serious health issues (Golkar et al., 2014; Gould & Bal, 2013; Wright, 2014; Sengupta et al., 2013; CDC, 2013). According to the Centres for Disease Control and Prevention (CDC), at least 2.8 million people in the United States are infected with antibiotic-resistant bacteria each year, with more than 35,000 of them dying as a result (CDC, 2019). Numerous public health organisations, including the CDC, have used words like "nightmare scenario" and "crisis" to describe the rapid rise and spread of antibiotic resistance (Viswanathan, 2014).

According to Shallcross et al. (2015), if antibiotic resistance is not controlled, we may enter a "post-antibiotic era" of medicine in which minor surgery to major transplants may no longer be possible, mortality will rise, and healthcare costs will skyrocket as we switch to newer, more expensive antibiotics and endure longer hospital stays. The World Health Organisation (WHO) issued a dire warning about antibiotic resistance in 2014 (Michael et al., 2014). Antibiotic-resistant bacteria can cause serious illness, increased hospitalisations, a higher risk of complications, and higher mortality rates (Paul et al., 2010; Livermore, 2012). Unfortunately, the vast majority of antibiotics developed up to this point are no longer effective against a wide range of microbes (CDC, 2013).

The most serious threat to gram-positive bacteria is the global pandemic spread of resistant Enterococcus species and Staphylococcus aureus (CDC, 2013; Rossolini et al., 2014). Rossolini et al. (2014) reported that antibiotic resistance in common gram-positive infections, such as those caused by Streptococcus pneumonia and Mycobacterium tuberculosis, is increasing globally.

The emergence of multidrug-resistant gram-negative bacteria, on the other hand, has had an impact on medical practices in a variety of specialties. Acinetobacter, Enterobacteriaceae such as Klebsiella pneumoniae, and Pseudomonas aeruginosa are the organisms that cause the most severe gram-negative infections in hospitals. Furthermore, the prevalence of bacteria that produce extended-spectrum beta-lactamases, such as Escherichia coli and Neisseria gonorrhoeae, is increasing in community settings (CDC, 2013; Rossolini et al., 2014). Antibiotic resistance has increased as a result of inappropriate and excessive antibiotic use, as well as a lack of innovation in the pharmaceutical industry caused by onerous regulatory restrictions and diminishing financial incentives (Viswanathan, 2014; Read & Woods, 2014; Nature, 2013; Lushniak, 2014; Gross, 2013; Piddock, 2012; Bartlett et al., 2013; Michael et al., 2014).

Antimicrobial resistance was a high priority for global public health prior to the coronavirus 2019 (COVID-19) pandemic (Knight et al., 2021). Lai et al. reported that aside from the SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) infection, an increase in antibiotic resistance threatens the existing situation of the COVID-19 (coronavirus disease 2019) pandemic. Extended-spectrum-lactamase-producing Klebsiella pneumoniae, carbapenem-resistant New Delhi metallo-lactamase-producing Enterobacterales, Acinetobacter baumannii, and methicillin-resistant Staphylococcus aureus, pan-echinocandin-resistant Candida glabrata, and multi-triazole-resistant Aspergillus fumigatus are among the multidrug-resistant organisms. The aetiology is multifaceted, with high rates of antimicrobial drug use in COVID-19 patients, with a low rate of co- or secondary infection being a major contributor (Lai et al., 2021).

SSIs continue to be a burden to postoperative patients despite the use of prophylactic antibiotics before and after surgery, as well as other preventive measures like enhanced operating room ventilation, sterilisation procedures, barrier use, and surgical technique. This has primarily been linked to the emergence of antimicrobial resistance as a result of irrational antibiotic use (Hope et al., 2019).

Poor prescribing practices, widespread agricultural antibiotic use, a lack of novel medicines, regulatory limits, and antibiotic misuse, according to Ventola (2015), have all contributed to the development of the antibiotic crisis. According to Llor and Bjerrum (2014), in order to slow the development of bacterial resistance, we should encourage the wise use of antibiotics in addition to limiting antibiotic use. According to Dryden et al. (2011), giving the right antibiotic to the right patient at the right dose, for the right length of time, and at the right time reduces the possibility of selective pressure, which can lead to the emergence and spread of antibiotic resistance. According to the CDC, the emergence of antimicrobial resistance (AMR) is primarily due to antimicrobial overuse or misuse (CDC, 2013).

According to D'Arcy et al. (2021) and Rout et al. (2019), more than 50% of antibiotic use in the hospital setting is incorrect, which is related to negative patient outcomes and the emergence of AMR. Knowledge and comprehension of facts relating to antimicrobial activity and its association with resistance may be useful when developing programmes to increase antibiotic use (Li et al., 2017; WHO, 2019). Implementing antimicrobial stewardship programmes in healthcare settings is one of these initiatives. This is an important strategy that promotes antibiotic use and has shown significant benefits (WHO, 2019). Pharmacists, for example, play a significant role in overcoming the AMR challenge because they are responsible for providing proper healthcare by delivering medications and giving patients instructions on how to utilise their medications (Kirby et al., 2020; Sakeena et al., 2018).

1.1.2 The implementation of antimicrobial stewardship programs

To protect patients from the risks of excessive antibiotic use and to combat antibiotic resistance, it is critical to change the way antibiotics are prescribed and administered by instituting antibiotic stewardship (Davey et al., 2017). The CDC has developed four strategies to combat antibiotic-resistant bacteria: preventing infections and halting the spread of resistance; tracking; improving antibiotic prescription and use; and developing new medications and diagnostic tools (CDC, 2013). Antimicrobial stewardship programmes (ASPs), according to Fishman et al., can help clinicians prescribe and use antibiotics more effectively. Antibiotic stewardship activities encourage the selection of the best antimicrobial regimen, which includes the course of treatment, dosage, and method of administration, to improve and measure antimicrobial medication utilisation (Fishman et al., 2012).

In recent years, the term "antimicrobial stewardship," which typically refers to programmes and plans aimed at maximising the use of antibiotics, has gained popularity (Dyar et al., 2017). Antimicrobial stewardship programmes were developed in various settings, so the characteristics of these programmes may vary to best meet the needs of different settings (Septimus and Owens, 2011). An antimicrobial stewardship programme, as defined by the WHO, is a healthcare approach that promotes the safe use of antibiotics by implementing evidence-based interventions (WHO, 2019). Antibiotic stewardship is required in all healthcare work settings, and efforts to optimise antibiotic use will be successful only if everyone participates. People, corporations, healthcare systems, hospitals, and clinics, as well as government officials, will need to work together to achieve success (CIDRAP, 2017).

ASPs are multifaceted and use interventions such as education, de-escalation, clinical decision support, audit and feedback, and formulary restriction to change prescribing behaviour (Barlam et al., 2016). The primary goal of antimicrobial stewardship is to improve patient care, optimise favourable clinical outcomes, reduce toxicity, and slow the development of resistance. Furthermore, antimicrobial stewardship aims to reduce the cost of medical care (File et al., 2014; Schuts et al., 2016). In the fight against AMR, pharmacists play critical roles in patient education and improving the use of antibiotics (WHO, 2019).

1.1.3 The perceptions and attitudes of healthcare providers toward AMR and AMS programs

Any educational initiatives about AMR and ASPs, according to Al-Harthi et al. (2013), will fail if healthcare providers' perceptions and attitudes towards AMR are not understood. The majority of healthcare workers in Saudi Arabia's Eastern

Province, according to Baraka et al., lack prior ASPs experience. Furthermore, they stated that medical professionals have favourable attitudes towards the deployment of ASPs because they are confident in their antimicrobial prescribing skills and knowledge (Baraka et al., 2019). It is also important to know the barriers to the implementation of ASPs. There are several obstacles to implementing ASPs. The main barriers to implementing ASPs, according to the CDC, are a lack of awareness of the proper indications, patient demands and satisfaction, time constraints, workload, decision fatigue, concern over complications, and diagnostic ambiguity (CDC, 2018).

1.1.4 Healthcare-associated infections

Infections acquired by patients while undergoing medical or surgical procedures are referred to as "healthcare-associated infections" (HAIs) (Murhekar et al., 2022). HAIs, according to Revelas, develop 48 hours or more after hospitalization or within thirty days of receiving health care (Revelas, 2012). HAIs are among the most common complications encountered while providing healthcare services and are frequently caused by endemic multidrug-resistant organisms as a result of improper antibiotic use (WHO, 2020). Surgical site infections (SSIs), ventilator-associated pneumonia (VAP), catheter-associated urinary tract infections (CAUTIs), and central line-associated bloodstream infections (CLABSIs) are examples of healthcare-associated infections (HAIs) (CDC, 2014). HAIs are connected with increased morbidity and mortality rates, longer hospital stays, and increased healthcare expenditures (Murhekar et al., 2022).

1.1.5 Surgical site infections and the use of surgical antimicrobial prophylaxis

Surgical site infections (SSIs) are among the most common infections associated with healthcare (HAIs). Infections of the incision, space, or organ that occur after a surgical procedure are known as surgical site infections (CDC, 2017). Longer postoperative hospitalisations, the need for additional surgery, the need for critical care, and increased attributable morbidity and mortality are all associated with SSIs (ECDC, 2022). The administration of antibiotics prior to surgery to help reduce the occurrence of postoperative infections is known as surgical antimicrobial prophylaxis (Crader and Varacallo). According to Bratzler et al. (2013), the rationale for surgical antimicrobial prophylaxis is to provide enough antibiotic exposure at the surgical site to cover the microbes that are frequently associated with SSIs.

Antimicrobial stewardship programmes are critical for optimising antibiotic use prior to surgery. According to Sarang et al. (2020), antimicrobial stewardship programmes are critical for lowering SSI rates and reducing antibiotic resistance.

1.2 Study Justification

The present study was conducted in Al Kharj, which is located in the centre of Saudi Arabia. It is located south of Riyadh, Saudi Arabia's capital city. According to the general statistical authority, 376,846 people live in Al Kharj (220484 men and 156362 women) (GaStat, 2010). The city's two main medical facilities are King Khaled Hospital and Al Kharj Military Hospital. Additionally, there are smaller clinics and hospitals. The majority of people in Al Kharj are served by these hospitals.

Over 500,000 nosocomial infections are caused by surgical site infections each year, making them the most common among surgical patients (Salkind & Rao, 2011). Antibiotics are commonly used for surgical antimicrobial prophylaxis, and they are associated with a high rate of inappropriateness (CDC, 2013; Davey et al., 2013; Charani et al., 2017; Ierano et al., 2019). According to the CDC, inappropriate perioperative antibiotic use is to blame for the high incidence of surgical site infections (CDC, 2013).

Antibiotics were commonly prescribed in both outpatient and inpatient hospital settings in Al Kharj. The first steps toward developing antibiotic use guidelines are being taken by Al Kharj hospitals. The Saudi Arabian Ministry of Health's Central Committee proposed the implementation of an antimicrobial stewardship programme in all of the country's hospitals in a report released in late 2014 (Alomi, 2017). To assess the effectiveness of the stewardship programmeme, the central committee requested information on antibiotic use and the pattern of microbial resistance at the beginning and end of the programme. The programme, according to Alomi, will be expanded to include all public and private hospitals in the coming years (Alomi, 2017). Alghamdi et al. reported that antibiotic stewardship programs in hospitals have long been proven to reduce antimicrobial resistance rates. However, its uptake in hospitals remains modest, particularly in poor nations such as Saudi Arabia. One of the most significant challenges to adoption is a lack of knowledge of how to implement them (Alghamdi et al., 2021).

In Saudi Arabia, there was insufficient information on the prevalence of bacterial resistance, the prevalence of HAIs, healthcare professionals' knowledge and attitudes towards the use of antibiotics and bacterial resistance, the use of antibiotics for surgical prophylaxis, and the implementation of antimicrobial stewardship.

1.3 Study Objectives

The main aim of the study was to describe the use of antibiotics before surgical procedures, assess adherence to antimicrobial surgical prophylaxis guidelines, and evaluate the impact of the implementation of antimicrobial stewardship interventions in the surgery department of Al Kharj Military Hospital.

Al Kharj Military Hospital and King Khalid Hospital are the main hospitals in Al Kharj, and King Saud Medical City is the main hospital in Riyadh. Among these hospitals, only Al Kharj Military Hospital formed an antibiotic use committee and started the implementation of an antimicrobial stewardship program. The surgery department was chosen because antibiotics are prescribed excessively and inappropriately in surgical departments. Approximately 30–50% of antibiotic use in hospital practice is now for surgical prophylaxis (Dettenkofer et al., 2002), and the use of antibiotics for surgical antimicrobial prophylaxis is associated with a high rate of inappropriateness (CDC, 2013; Davey et al., 2013; Charani et al., 2017; Ierano et al., 2019).

The study objectives are:

1. To determine the perception and attitude of healthcare workers towards implementing an antimicrobial stewardship programme and the barriers and facilitators to its implementation.
2. To determine the antimicrobial resistance incidence in Al Kharj Military Hospital, King Khalid Hospital in Al Kharj, and King Saud Medical City in Riyadh.
3. To determine the prevalence of healthcare-associated infections, particularly surgical site infections, in Al Kharj Military Hospital.
4. To evaluate the implementation of antimicrobial stewardship interventions in the surgery department at Al Kharj Military Hospital.

1.4 Thesis Overview

Eight distinct chapters made up the thesis. The introduction and literature review are the first two chapters. These two chapters outline the emergence of antibiotic resistance, list the relevant studies, discuss the attitude of healthcare professionals towards antibiotic resistance and antibiotic use, discuss the occurrence of infections linked to healthcare, such as surgical site infections, and provide strategies for lowering their occurrence. In addition, the first two chapters provide an overview of the implementation of antimicrobial stewardship programmes and the interventions that could be put in place to enhance the use of antibiotics and lessen the unfavourable effects of their improper use.

Chapter three included a meta-analysis of clinical trials that compare the effectiveness of cefazolin to cefamandole, ceftriaxone, and cefuroxime in reducing the rate of surgical site infection and a meta-analysis of clinical trials that compare the use of a single dose and multiple doses in reducing the rate of surgical site infection. The methods used in the various sections of the current study are compiled in Chapter four. The study design, study setting, inclusion and exclusion criteria, data collection, and data analysis are all covered in this chapter. The practice, perception, and attitude of healthcare professionals regarding antimicrobial stewardship programmes are discussed in chapter five, along with the primary obstacles and facilitators to their implementation in Saudi Arabia to set the landscape of the healthcare professionals' attitude and perception, hence the practice in Al Kharj hospitals.

Chapter Six discusses the frequency of infections brought on by different grammeme-positive and grammeme-negative bacteria as well as the prevalence of antibiotic resistance in several hospitals in Saudi Arabia. The rates of various healthcare-associated infections, such as bloodstream infections linked to central lines, urinary tract infections linked to catheters, pneumonia linked to ventilators, and surgical site infections, are also summarised in Chapter Six. The usage of antibiotics in the surgery department is assessed in Chapter seven, along with the results of applying antimicrobial stewardship measures to enhance antibiotic use and avoid surgical site infections, which is the main aim of the study. The final chapter presents the thesis's recommendations, limitations, and conclusions.

CHAPTER 2
LITERATURE REVIEW

2.1 The Emergence of Bacterial Resistance

2.1.1 Introduction

Antimicrobial resistance (AMR) is a problem in which bacteria, parasites, fungi, and viruses evolve and become resistant to treatments, making infections more difficult to treat and increasing the risk of disease transmission, life-threatening illness, and death. Drug resistance renders antibiotics and other antimicrobial medications ineffective, making infection treatment more difficult or impossible (WHO, 2021). According to Breijyeh et al., antibiotic resistance is one of the major global health crises and the greatest threat to humanity today. In addition, they reported that some bacterial strains have developed resistance to nearly all antibiotics (Breijyeh et al., 2020). According to the CDC, antimicrobial resistance is a serious worldwide health issue. In 2019, antimicrobial resistance was linked to approximately 5 million deaths. The CDC also stated that in the United States, more than 2,800,000 antimicrobial-resistant infections occur annually (CDC, 2022).

The WHO has declared AMR to be one of the most serious global health threats. Long-term disease, according to the WHO, not only increases the risk of mortality and disability but also lengthens hospital stays, necessitates the use of more expensive medications, and strains the finances of those affected (WHO, 2021). Breijyeh et al. reported that unnecessary antibiotic dispensing and irresponsible antibiotic use result in the development of antibiotic-resistant bacterial strains (Breijyeh et al., 2020).

According to the WHO, antibiotic misuse is a major cause of the emergence of drug-resistant pathogens (WHO, 2021). Antibiotics are becoming increasingly ineffective as drug resistance spreads globally, resulting in difficult-to-treat infections and rising mortality rates. According to the WHO priority pathogen list, new antibiotics are urgently needed to treat carbapenem-resistant bacterial infections. However, if people do not change the way antibiotics are currently used, these novel medicines will suffer the same fate as current antibiotics and become obsolete (WHO, 2021). Because it necessitates longer hospital stays and more expensive and intensive treatment, AMR has a significant financial impact on national economies and health systems (WHO, 2021).

The WHO stated that in 2020, AMR is expected to have been responsible for a third of as many deaths as COVID-19 (WHO, 2020). Antibiotics are ineffective against viruses, including the virus responsible for COVID-19. Antibiotic resistance is caused by the overuse and misuse of antibiotics during the COVID-19 outbreak (WHO, 2023). During the pandemic, an irrational consumption of antibiotics has occurred because some COVID-19 cases also had bacterial infections (Saini et al., 2021; Ghosh et al., 2021).

Langford et al. (2023) reported that the COVID-19 pandemic may have accelerated the onset and spread of AMR, notably in hospital settings for gramme-negative crobes. Since the start of the COVID-19 epidemic, certain countries have been monitoring and reporting on antibiotic resistance in order to retain the majority of the achievements made in the last decade in terms of antimicrobial resistance. According to the information provided by these countries, an alarming proportion of bacterial diseases are becoming more resistant (Harding et al., 2020; Huttner et al., 2020; Hsu, 2020; WHO, 2020).

2.1.2 The prevalence of multidrug-resistant gram-negative bacteria

Gram-negative bacteria cause meningitis, bloodstream infections, pneumonia, wound infections, and surgical site infections. According to the CDC, most antibiotics are no longer effective against gram-negative bacteria (CDC, 2011). The bacterial outer membrane is the primary cause of gram-negative bacteria's resistance to antibiotics such as quinolones, beta-lactams, colistin, and others (Breijyeh et al., 2020).

There are several mechanisms for resistance development. Miller reported that Acinetobacter baumanii isolates resistant to almost all clinically useful antibiotics have recovered and have recently developed clinically significant resistance to imipenem as a result of porin transport channel loss (Miller, 2016). Miller (2016) also reported that, due to tobramycin's loss of outer membrane permeability, many Pseudomonas aeruginosa isolates have significant clinical resistance to the drug. Previous research has shown that gram-negative bacteria can develop resistance by altering the outer membrane (for example, by changing the hydrophobic properties or by mutations in porins and other factors) (Miller, 2016; Datta & Gupta, 2019; Exner et al., 2017).

Resistant gram-negative bacteria cause the vast majority of ventilator-associated pneumonia cases, bloodstream infections caused by catheters, and other ICU-acquired sepsis cases. The most common gram-negative bacteria that cause complications are non-fermenting gram-negative bacteria such as Pseudomonas aeruginosa and Enterobacteriaceae (Breijyeh et al., 2020). According to Uc-Cachón et al. (2019), Escherichia coli is the most common multidrug-resistant gram-negative bacteria (91.57%) in Yucatán, Mexico. According to Patolia et al. (2018), nearly

26% of the gram-negative bacteria at a university hospital in Missouri were multidrug-resistant.

Antimicrobial resistance is on the rise internationally, affecting the management of surgical infections, particularly in low-resource settings. Third-generation cephalosporin-resistant and carbapenem-resistant Enterobacteriaceae are of particular concern to surgeons (Rickard, 2020). At Fortis Hospital in Mumbai, Nagvekar et al. (2020) discovered multidrug-resistant Escherichia coli, Klebsiella, Acinetobacter, Pseudomonas, and Enterobacter. According to Hadavand et al. (2019), the most common gram-negative bacteria in Tehran were Escherichia coli (31.2%), Klebsiella spp. (20.3%), and Pseudomonas spp. (13.2%). In a two-year study of the prevalence and antibiotic resistance pattern of gram-negative bacteria isolated from surgical site infections in northern Iran, Hemmati et al. discovered that Klebsiella isolates had the highest isolation rate (29.5%), followed by Enterobacter (28.2%), and Acinetobacter (16.7%). They also discovered that 62.8% of the isolates were multidrug-resistant (Hemmati et al., 2020).

Klebsiella pneumoniae (91.0%), Escherichia coli (78.2%), and Pseudomonas aeruginosa (73.6%) were found to have high rates of antibiotic resistance in a general hospital in Kuwait, according to Alali et al. Furthermore, multi-drug resistance was found in 50.3% of E. coli isolates, 51.3% of Klebsiella Pneumoniae isolates, and 48.7% of Pseudomonas aeruginosa isolates (Alali et al., 2020). According to Beyene et al. (2022), a large proportion of gram-negative enteric bacterial pathogens in Ethiopia are resistant to tetracycline, ampicillin, amoxicillin, and trimethoprim-sulfamethoxazole. They also reported a 70.56% (CI = 64.56-76.77%) pooled prevalence of multidrug resistance (Beyene et al., 2022).

According to Zowawi et al. (2015), the number of Enterobacteriaceae that produce carbapenemase or lactamase enzymes is increasing at an alarming rate around the world. They also reported that resistance to other antibiotics, such as aminoglycosides, quinolones, and sulphonamides, is escalating (Zowawi et al., 2015). Saeed et al. (2010) discovered that 32.4% of Acinetobacter bacteria in Oman were multidrug-resistant. According to Al Hamdan et al. (2022), 64.5% of gram-negative bacteria in Eastern Saudi Arabia were multidrug-resistant. Said et al. (2021) conducted a study in Saudi Arabia's Ha'il Hospitals and reported that Acinetobacter baumannii bacteria were pandrug-resistant (resistant to all antibiotics) and Pseudomonas aeruginosa bacteria were extensively drug-resistant (remain susceptible to only one or two categories). According to Faidah et al., Acinetobacter baumannii, Pseudomonas aeruginosa, Klebsiella pneumoniae, and Escherichia coli were 99.13%, 62.4%, 38%, and 5.59% resistant to carbapenem, respectively. Al-Sultan reported that Acinetobacter baumannii isolates in the Saudi cities of Makkah and Al-Madinah were highly resistant to carbapenems (82.5%) (Al-Sultan, 2021).

According to Taher et al. (2019), gram-negative bacteria were resistant to the majority of the tested antimicrobials, including ampicillin, fluoroquinolones, cephalosporins, nitrofurantoin, trimethoprim-sulfamethoxazole, aztreonam, and fosfomycin in Aljouf. According to Kabrah (2022), 20.6% of gram-negative pathogens in Makkah produce extended-spectrum beta-lactamase (ESBL), while 79.4% are carbapenem-resistant gram-negative bacteria. Kabrah also discovered that all ESBL-producing and carbapenem-resistant bacteria were multidrug-resistant pathogens. According to Baig et al. (2015), gram-negative bacteria in their study were extremely resistant to cephalosporins (ranging from 94% to 98%). Carbapenem resistance was found in 98% of Acinetobacter baumannii isolates and 89% of

Pseudomonas aeruginosa isolates. They also claimed that more than 90% of Acinetobacter baumannii isolates were drug-resistant.

2.1.3 The prevalence of multidrug-resistant gram-positive bacteria

Multidrug-resistant gram-positive organisms are significant human pathogens that cause infections in both clinical and community settings. The CDC has identified methicillin-resistant Staphylococcus aureus (MRSA), drug-resistant Streptococcus pneumonia, and vancomycin-resistant Enterococcus faecium (VRE) as serious health threats (CDC, 2013).

Antimicrobial resistance is on the rise internationally, particularly in low-resource settings. Chandel et al. reported that linezolid resistance was found in 25% of coagulase-negative staph isolates, 24% of staphylococcus isolates, and 20% of streptococcus isolates at India's Gandhi Medical College Hospital (Chandel et al., 2022). Gebremariam et al. discovered gram-positive cocci isolates with high antimicrobial resistance rates. They reported that 44% of the gram-positive cocci tested positive for multiple drugs (Gebremariam et al., 2022). Overall multi-drug resistance was observed in approximately 60.5% of the bacterial isolates, according to Fenta et al. They discovered that approximately 78.9% of isolated Staphylococcus aureus bacteria were multi-drug resistant (Fenta et al., 2022). Methicillin resistance was found in 91% of coagulase-negative staphylococci and 47% of Staphylococcus aureus bacteria, according to Pourakbari et al. (2018). Bacterial growth is widespread in surgical sites, according to Chaudhary et al., and the most common bacteria was Staphylococcus aureus (47.4%), followed by Escherichia coli (20.60%). They reported that 39.2% of the isolates were multi-drug resistant (Chaudhary et al., 2017).

In the United States, antibiotic resistance rates in coagulase-negative staphylococci have been reported to be as high as 90% for methicillin, 78.6% for levofloxacin, 68% for ciprofloxacin, and 48.5% for clindamycin, according to May et al.'s (2014) study. MRSA isolation rates from blood or cerebrospinal fluid (CSF) are highest in Romania (>50%), while rates range from 25% to 50% in the other five European countries (Cyprus, Greece, Hungary, Italy, and Spain), according to the ECDC (ECDC, 2013). Eisner et al. reported that Staphylococcus aureus (27.1%), Staphylococcus epidermidis (20.6%), Enterococcus faecalis (13.6%), Escherichia coli (5.1%), and Pseudomonas aeruginosa (3.7%) were the most common pathogens in surgical site infections of trauma patients, and that 29.4% of them were multi-resistant. They found that multi-resistant species such as Staphylococcus epidermidis are an increasing challenge in trauma operations. About 80% of the Staphylococcus epidermidis isolates were resistant to oxacillin and, consequently, to the majority of beta-lactam antibiotics.

Vancomycin-resistant enterococci (VRE) are now uncommon in Saudi Arabia, according to Yezli et al.; however, Enterococcus faecium and Enterococcus faecalis isolates with significant penicillin, sulfamethoxazole, macrolides, tetracycline, and aminoglycoside resistance have been recorded in the Kingdom (Yezli et al., 2012). According to Shibl et al., enterococci and beta-hemolytic streptococci do not exhibit widespread antibiotic resistance in Saudi Arabia. Nonetheless, resistance in pneumococci and staphylococci is widespread (Shibl et al., 2014). Alhumaid et al. (2021) conducted a study on antimicrobial resistance in bacteria at three Saudi hospitals. They discovered that gram-positive isolates were highly susceptible to linezolid (91.8%) but were extremely resistant to doxycycline (55.9%), ampicillin (52.6%), and cefoxitin (54.2%).

According to Asghar, the resistance rates of Staphylococcus aureus and Coagulase-negative staphylococci isolates to oxacillin in Makkah hospitals were

39.4% and 82.4%, respectively. Streptococcus pneumoniae was resistant to ampicillin 21.1% of the time and erythromycin 16.7% of the time (Asghar, 2011). According to Helmi et al. (2013), 20% of the 98 MRSA isolates in Jeddah were multidrug-resistant. They also reported that only two Enterococcus faecium isolates were resistant to glycopeptides, while all strains were sensitive to linezolid and tigecycline. Al Mutair et al. (2021) conducted a study in several Saudi hospitals and discovered that both gram-negative and gram-positive bacteria had an overall resistance of more than 15%. Alharbi (2022) studied the bacteriological profile of wound swabs in a Saudi tertiary care hospital and discovered that Staphylococcus aureus was the most common isolate (17.1%) and that 12.5% of the Staphylococcus aureus isolates were multidrug-resistant.

Regarding fungal resistance, according to the CDC, some fungi, such as Candida auris, can develop resistance to all antifungal medicines used to treat these infections. Resistance is especially concerning for individuals suffering from invasive fungal infections, which are severe illnesses that affect the blood, heart, brain, eyes, or other organs (CDC, 2022). According to Hendrickson et al., the global rise of antifungal resistance among Candida spp. and Aspergillus spp. is a growing hazard to public health, partly due to the increased use of antifungals in both clinical and agricultural settings (Hendrickson et al., 2019). In Saudi Arabia, antifungal resistance is modest but increasing. According to Aldardeer et al., 21% of Candida species were resistant to one or more antifungals (Aldardeer et al., 2020). Fluconazole sensitivity in non-albicans Candida species was 39.5%, according to Al-Ahmadey et al. Caspofungin, on the other hand, was effective against all species (Al-Ahmadey et al., 2023). According to Ahmed et al., Candida isolates represented approximately 7.72 percent of all isolates collected during their study period.

Candida albicans was the most common Candida species (55.32%), followed by Candida tropicalis (28.72%) and Candida auris (8.51%). Candida glabrata, Candida tropicalis, Candida albicans, and Candida parapsilosis were all susceptible to all antifungal drugs tested (showing low resistance rates) (Ahmed et al., 2022).

2.1.4 Bacterial Resistance in Surgical Infections

Surgical site infections are common infections that are commonly caused by Staphylococcus aureus, enterococci, Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae, and Bacteroides species (Neu, 1995). Surgical-site infections are rising in low- and middle-income nations, with anecdotal evidence of antibiotic resistance (Velin et al., 2021). Antimicrobial resistance is rising worldwide, making surgical infection control difficult, especially in low-resource settings. Third-generation cephalosporin-resistant and carbapenem-resistant Enterobacteriaceae are major problems for surgeons (Rickard, 2020). Evans and Sawyer reported that antimicrobial-resistant microorganisms are a serious concern in surgical patients, and infections produced by these organisms are related to increased morbidity and death. The rise of multidrug-resistant bacteria in hospitals has become a global concern for surgeons treating healthcare-associated infections (Evans and Sawyer, 2009).

According to Mengesha et al. (2014), surgical site wound infection is a prevalent infection, and multidrug resistance was found in 82.92% of the isolates, leaving doctors with few options for treating patients with postsurgical wound infections. Yehouenouet al. reported that in gastrointestinal surgery, gram-negative bacteria were prevalent, with E. coli being the most common 8.4%). They also reported that 90.8% of the aerobic bacteria were multidrug-resistant (Yehouenou et al., 2020). Prolonged antibiotic therapy contributes significantly to the development of resistance microorganisms in post-operative patients (Yehouenou et al., 2020; Fatima et al., 2022).

2.2 Healthcare-Associated Infections (HAIs)

2.2.1 Introduction

Healthcare-associated infections (HAIs) develop in healthcare facilities while patients are receiving medical treatment. HAIs typically manifest 48 hours or more after hospitalisation or within thirty days of receiving medical care (Haque et al., 2018).

HAIs are among the most common and serious health issues. They are linked to increased mortality and morbidity in hospitalised patients (Saleem et al., 2019; Allegranzi et al., 2011; Vrijens et al., 2012). According to the WHO, 7% of patients in high-income acute care hospitals and 15% of patients in low-income acute care hospitals will contract at least one HAI (WHO, 2022).

Healthcare-associated infections (HAIs) not only endanger patients' health and lives, but they also place an additional financial burden on patients and the healthcare system, resulting in direct financial loss and prolonged hospital stays (Jia et al., 2019). Previous research found that HAI doubled mortality and increased healthcare costs, with prolonged hospital stays accounting for half of the additional costs (Roberts et al., 2010; Arefian et al., 2016; Nosrati et al., 2010).

2.2.2 The prevalence of healthcare-associated infections

According to the CDC, more than 687,000 American patients admitted to hospitals experienced HAIs in 2015, with 72,000 of them dying as a result of these infections (CDC, 2015). According to Russo et al. (2019), the prevalence of HAIs was 9.9% (95% CI: 8.8–11.0) at 19 major public acute-care hospitals in Australia.

Furthermore, they stated that surgical site infections, pneumonia, and urinary tract infections accounted for 64% of all HAIs discovered.

Kritsotakis et al. (2017) discovered a 9.1% HAI rate in 37 Greek hospitals. Based on data from 18 studies, Alemu et al. (2020) estimated the rate of healthcare-associated infections in Ethiopia to be 16.96% (95% CI: 14.10%–19.82%). In a study of healthcare-associated infections in Turkey, Erdem et al. (2020) discovered that the incidence of HAIs in clinics and critical care units was 10.31/1000 patient-days and 1.70/1000 patient-days, respectively.

Versporten et al. (2018) found that the overall rate of HAIs in 53 different countries was 11.9%. Huerta-Gutiérrez et al. (2019) found a 12% prevalence of HAI in four Latin American countries. Furthermore, they stated that surgical site infections and pneumonia were the most common among the countries studied. SSIs are common because most of these infections are caused by microorganisms on the patient's skin or internal organs that contaminate the surgical incision. Pneumonia is a prevalent HAI because it can be easily transferred in healthcare settings via respiratory droplets and contaminated surfaces. Patients who are already weak due to sickness or surgery are more likely to acquire pneumonia. Fortaleza et al. (2017) discovered that the average rate of HAI in numerous Brazilian hospitals was 10.8%. Chernet et al. (2020) found that the rate of HAI at an Ethiopian hospital was 9.7 cases per 1000 person-days (95% CI: 7.1–12.9).

Alshamrani et al. (2019) conducted a study in 2017 among patients at six Saudi hospitals and discovered a 6.8% prevalence of HAIs. They also discovered that the most common types of infections were pneumonia, urinary tract infections, and bloodstream infections. According to Kuwaiti and Subbarayalu (2017), the HAI rate at a university hospital in Al Khobar, Saudi Arabia, was 3.92%. According to Al-

Zahrani et al. (2013), the prevalence of healthcare-associated infections in a governmental hospital in Taif was found to be 6.03%.

Enani et al. (2019) found 14 patients with HAI out of 398 in three private hospitals in Jeddah (3.5%). Alrebish et al. (2022) discovered a low prevalence of HAIs in Qassim City. They discovered that the rate of surgical site infections was 0.1%, catheter-associated UTIs were 0.76 for every 1000 catheter days, central line-associated bloodstream infections were 2.6 for every 1000 central line days, and ventilator-associated pneumonia was 1.1 cases per 1000 ventilator days.

2.3 The knowledge, attitude, and perceptions of healthcare professionals about antimicrobial use and resistance

To limit the spread of antimicrobial resistance, future healthcare professionals' knowledge of antibiotic use must be improved. Prior to that, it is important to evaluate their knowledge, attitude, and practices (Gupta et al., 2019). Several factors, including doctors with little experience, an ambiguous diagnosis, and patient influence on the decision of the doctor, have been linked to incorrect antibiotic prescribing (Suaifan et al., 2012). According to Barchitta et al. (2021), identifying healthcare professionals with less knowledge of antibiotic use and resistance is a challenge for public health because it may aid in the development of new educational and training initiatives tailored to specific subgroups of professionals. The ECDC stated that it is critical to identify the barriers to prudent antibiotic use to develop and implement interventions that raise awareness and knowledge and ultimately modify behaviour around antibiotic use (ECDC, 2019).

According to Al-Taani et al. (2022), Jordanian medical students scored higher than 76% on knowledge of antibiotic proper use, overuse, and adverse effects, as well as 65.2% on knowledge of antibiotic resistance emergence. Some participants agreed that prudent antibiotic use has been widely promoted (21.0%). Participants

(53.9%) stated that they need more information on antibiotic resistance (Al-Taani et al., 2022). Nisabwe et al. conducted a study about the knowledge of healthcare students from Level 3 to Level 6 at the University of Rwanda about antimicrobial resistance and antimicrobial stewardship and found that 49% of healthcare students had not yet explored antimicrobial resistance as part of their curriculum, and 83% were unfamiliar with antimicrobial stewardship (Nisabwe et al., 2020). Sunusi et al. (2019) reported that only 21.3% of Sudanese medical students had very good knowledge of resistance, and only 24.8% of them had a positive attitude. Fetensa et al. (2020) discovered that Wollega University's graduating health science students in Ethiopia had a poor understanding of antibiotic identification, function, side effects, and resistance, as well as an unfavourable attitude towards their use.

The ECDC discovered that 97% of responding healthcare workers were well aware that antibiotics have no effect when treating self-limiting infections such as the common cold in a study about healthcare workers' knowledge, practices, and attitudes regarding antibiotic use and antibiotic resistance. However, less was known about whether healthy people can harbour antibiotic-resistant bacteria (88%), and whether antibiotic-resistant infections increase with antibiotic use (75%; ECDC, 2019). According to Ashiru-Oredope et al. (2022), less than 80% of UK healthcare professionals believe that giving antibiotics increases the risk of a patient contracting an infection that is resistant to antimicrobial treatment or that the transmission of drug-resistant bacteria occurs between humans. Furthermore, while the majority of healthcare professionals (81%) agreed that their antibiotic prescribing practices contribute to the development of antibiotic-resistant bacteria, only 64% believed that they play an important role in decreasing antibiotic resistance. According to Balliram et al. (2021), 91.2% of South African healthcare professionals agreed that