



**The Assessment of Antifungal Stewardship Implementation in a
Tertiary Care Hospital in South Africa: Evaluating Knowledge,
Attitudes and Practices of Healthcare Professionals and
Developing Evidence-Based Guidelines**

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A Dissertation submitted to the Faculty of Health Sciences, University of the
Witwatersrand, Johannesburg, in fulfilment of the requirements for the degree of
Master of Pharmacy.

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Declaration

I, Kiara Sudu, declare that this Dissertation is my own, unaided work. It is being submitted for the Degree of Master of Pharmacy at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.



Kiara Sudu

27 day of March 2025 in Johannesburg

Ethics declaration

I, Kiara Sudu, declare that I am registered with the University of the Witwatersrand for the degree in Master of Pharmacy and have read the University's current research ethics guidelines. I accept responsibility for the conduct of the procedures in accordance with the University of the Witwatersrand Human Research Ethics Committee (WITS-HREC). I have obtained ethical approval from WITS-HREC (M230520 M230810-B-001, Appendix A) and received permission from the tertiary care hospital of study ethics and research committee to conduct this research (Appendix B).



Kiara Sudu

27 day of March 2025 in Johannesburg

Dedication

To my parents, Dees and Preshni Sudu, for their unwavering support, love and belief in me.

Abstract

Antifungal resistance is a growing concern in healthcare settings worldwide, driven by the overuse and misuse of antifungal agents. This issue is particularly severe in South Africa, where a high burden of fungal diseases is further complicated by a large immunocompromised population due to HIV and tuberculosis. Antifungal stewardship aims to optimise the use of antifungal medications to improve patient outcomes, reduce resistance, and minimize adverse effects. However, successful implementation of these programs requires a thorough understanding of healthcare professionals' knowledge, attitudes, and practices (KAP) regarding antifungal use. This study seeks to evaluate the current KAP of healthcare professionals, including doctors, pharmacists, and nurses, towards antifungal prescribing and management at a tertiary public healthcare setting, in Gauteng, South Africa. This research endeavours to enhance antifungal stewardship efforts, promote responsible antifungal use, and improve patient care outcomes within the hospital setting.

A quantitative research approach was adopted to garner data on the KAP of the study population towards antifungal stewardship, whilst a retrospective prescription analysis undertaken to assess antifungal prescribing practices. Results from the KAP survey demonstrated that 60.6% of healthcare professionals lacked confidence in their knowledge and practices related to antifungal agents, with only 14.5% being familiar with local guidelines. A significant 96.0% agreed on the need for more education on invasive fungal infections, and 91.8% recognized the need for a rational use framework that is specific to the use of antifungal agents in addition to the Standard Treatment Guidelines. Study participants felt that the primary factor contributing to inappropriate antifungal use was the prescribers' lack of knowledge of antifungal agents which may include a broad spectrum of considerations such as indication, dose, dosing interval, duration of therapy or drug related interactions. An analysis of 370 antifungal prescriptions from the various departments within a tertiary care hospital setting revealed that only 37.0% of the patients receiving an antifungal agent were diagnosed with a fungal infection. A total of 75 prescription errors were observed ranging from duration to dosing interval errors. Microbiological culturing was only performed in 10.5% of cases, with susceptibility testing in only 0.3%. Fluconazole was the most frequently prescribed antifungal.

As one of the earliest studies conducted in South Africa to focus exclusively on antifungal agents and antifungal stewardship, the findings highlight a critical need for improved antifungal stewardship and more comprehensive education for healthcare professionals to ensure positive antifungal treatment outcomes. This study emphasises the importance of a collaborative approach to antifungal stewardship, involving ongoing education and shared responsibility among all healthcare professionals.

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List of publications and presentations arising from this study

Presentations (Appendix C)

1. Sudu, K., Booth, Z., and Leigh, S. The assessment of antifungal stewardship implementation in a tertiary care hospital in South Africa. Faculty of Health Sciences Research Day, 5 September 2024, University of the Witwatersrand, Johannesburg. [poster presentation]

Publications

1. Sudu, K., Booth, Z., and Leigh, S. The Assessment of Antifungal Stewardship Implementation in a Tertiary Care Hospital in South Africa: Evaluating Knowledge, Attitudes and Practices of Healthcare Professionals and Developing Evidence-Based Guidelines. Publication in draft, to be submitted to the South African Medical Journal in April 2025.

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Chapter 1: Introduction

This chapter provides a brief introduction to fungal infections, the emergence of antifungal resistance and its' impact on the management of invasive fungal infections. Antifungal stewardship is also briefly discussed in this chapter with its' importance being highlighted particularly due to the emergence of antifungal resistance as justification of this study.

1.1 Research Context

Generally, humans coexist peacefully with the micro-organisms that surround them, however, when the immune system is compromised or when pathogen concentration reaches remarkably high levels, infection may ensue (Janbon et al., 2019). Most infections go undetected, but in some instances, the infectious agent triggers a response in the body that causes clinically apparent signs and symptoms. Fungal infections or mycoses are those disease conditions whereby fungal pathogens elicit an immune response causing an array of signs and symptoms (Janbon et al., 2019; Reddy et al., 2022) A single fungal pathogen can infect multiple tissues or organs of the same host depending on the host's immunological state (Pathakumari et al., 2020).

Common causative pathogens of these infections include *Candida*, *Cryptococcus* and *Aspergillus* species, causing oral or vaginal thrush, fungal nail infections, and athlete's foot (Kohler, et al., 2015). These conditions may be bothersome and sometimes even debilitating but they can very often be treated effectively upon diagnosis (National Institute for Communicable Diseases (NICD), 2018). However, invasive fungal infections can be life-threatening to conventionally healthy patients, but more so for immunocompromised individuals, such as those who are HIV-positive, transplant patients receiving immunomodulating drugs, as well as oncology patients undergoing aggressive immunosuppressive therapy (Enoch et al., 2017; Kainz et al., 2020; Centers for Disease Control and Prevention (CDC), 2022). The Global Action for Fungal Infections Foundation (GAFFI) estimates that more than 300 million people of all ages suffer from serious fungal infections worldwide each year, with more than 1.5 million of these people dying as a result (Rodrigues and Nosanchuk, 2020).

Currently, only five main classes of antifungal agents are available for the treatment of fungal infections, namely azoles, echinocandins, polyenes, allylamines and pyrimidine analogues (Hoenigl et al., 2024). Invasive fungal infections are challenging to treat and prove fatal in immunocompromised patients, resulting in prescriber pressure to initiate antifungal treatment in immunocompromised patients (Muñoz et al., 2015), where the practice of empiric antifungal therapy is prevalent. In addition, the use of antifungal agents for prophylaxis or prevention, particularly in immunocompromised patients, results in increased cost and unnecessary exposure to medicines (Muñoz et al., 2016). The practice of empiric antifungal therapy and prophylactic initiation of antifungal therapy significantly contributes to the emergence of antifungal resistance, similarly to that seen with antimicrobial resistance development to antibiotics due to irrational prescribing (Greener, 2022; Hendrickson et al., 2019).

1.1.1 Antifungal resistance

Antifungal resistance is becoming an increasing threat to public health, particularly due to the increase in the use of antifungal agents with the burden of fungal infections peaking in low- and middle-income countries, with most invasive fungal pathogens being opportunistic, infecting immunocompromised patients (Hendrickson et al., 2019; Greener, 2022). This has a significant impact on treatment outcomes, as most of the antifungal agents used are ineffective due to the development of resistance (Campoy and Adrio, 2017).

Over the past 10 years, multidrug-resistance *Candida auris* has spread throughout the world, causing large outbreaks in hospitals (NICD, 2018). This growth in resistance is often the result of improper use of antifungal agents, thus contributing significantly to the treatment burden (Gross et al., 2015). In South Africa, multidrug-resistant *Candida auris* is highly prevalent in hospitals, with most isolates being resistant to azole antifungals (Maphanga et al., 2021). Owing to the limited availability of antifungal agents as well as the substantial cost implications, the emergence of single-drug and now multi-drug resistance is much more difficult to manage (Prasad et al., 2016).

1.1.2 Antifungal Stewardship

Over recent years, the formation and implementation of global antibiotic stewardship (ABS) programs have been established due to developing resistance to available antibiotics (Ziv-On et al., 2021). The main objective of ABS is to ensure the appropriate use of antibiotics to

preserve the future effectiveness of these agents as well as optimise patient outcomes (Dyar et al., 2017). Based on previous research, antibiotic stewardship programs have proven to be beneficial in increasing compliance to targeted therapy and reducing antibiotic consumption and cost, ultimately improving patient outcomes, and reducing the development of resistance (Siachalinga et al., 2022). Antifungal stewardship (AFS) shares a similar aim to ABS but has features and challenges specific to the management of invasive fungal infections (Richardson, 2016). However, very little is known about AFS, hence it is not as routinely practiced in hospitals as compared to ABS (Muñoz et al., 2016). The exploration of AFS is still in the early stages of development in most settings with further research needed regarding its implementation (Gohlar and Hughes, 2019). Clinical practice guidelines are developed to create and distribute the best existing evidence to guide clinical practice; with the purpose of increasing quality care and reducing inappropriate interventions (Ryan, 2017). Antifungal stewardship is multifaceted and goes far beyond “policing prescribing”, with several interdependent and mutually reinforcing factors which need to be considered such as risk assessment, antifungal toxicity, spectrum of activity, tolerability and fungal diagnostics (Ananda-Rajah et al., 2020; Nivoix et al., 2020). The main goals of AFS are optimised care, de-escalation or, if appropriate, discontinuation of antifungal therapy, reduced costs and reduced fungal resistance without adverse effects on morbidity and mortality. Therefore, the incorporation of AFS within antimicrobial stewardship programs can prove to be tremendously advantageous (Gómez-Gómez and Cornejo-Juárez, 2019).

1.2 Problem statement

In South Africa’s public health sector, adherence to the Standard Treatment Guidelines (STG) and Essential Drug List (EDL) in public healthcare facilities is paramount to ensure appropriate treatment choices in resource constrained environments. For physicians to adhere to these guidelines, they must first be cognisant of such guidelines, rationally agree with them, implement them in their daily care and consistently adhere to them. If a lack of awareness of these guidelines and procedures exists, it is highly unlikely that good practice will follow (Alamin and Kheder, 2020). South Africa has the highest number of people living with HIV in the world (Zuma et al., 2022). In addition, South Africa has one of the highest rates of tuberculosis (TB) per capita in the world (Moyo et al., 2022). With such a high disease burden, research on AFS can play an important role in improving antifungal resistance patterns and reducing the incidence of antifungal resistance. With an increase in antifungal resistance as

well as a high disease burden, it is important to determine how antifungals are being utilised and managed in South Africa.

1.3 Rationale for study

This study was conducted in a public health care facility, a crucial asset to the majority of South Africans who rely on the public healthcare sector to meet their health needs (Maphumulo and Bhengu, 2019). In addition, the high burden of disease that South Africa is facing due to HIV and AIDS as well as other opportunistic diseases, makes this study imperative as it will provide vital insight on antifungals and antifungal stewardship. Due to limited data and resources surrounding AFS, understanding the knowledge, attitudes, and practices of AFS amongst doctors, pharmacists, and nurses, can build a foundation for baseline learnings on AFS. Evaluation of antifungal prescribing practices by analysing antifungal prescriptions can be useful in identifying gaps or errors which may contribute to improper antifungal utilisation and antifungal resistance. Hence findings from this study can be beneficial in improving patient outcomes. The results garnered from this study can then be expanded on to improve antifungal prescribing patterns as well as understand doctors, pharmacists and nurses' knowledge regarding AFS, which can support its' exploration. This will assist in developing an antifungal stewardship policy and prescribing guideline which will ultimately have a positive impact on treatment outcomes and improved patient care.

1.4. Aim of study

To evaluate the knowledge, attitudes and practices of doctors, pharmacists, and nurses in a tertiary care hospital in South Africa in implementing antifungal stewardship.

1.5 Objectives

The aim of the study will be met through the following objectives:

1.5.1 To determine the knowledge and attitudes of doctors, pharmacists, and nurses towards antifungal stewardship by means of survey analysis.

1.5.2. To determine the practices of doctors towards antifungal stewardship by means of a retrospective analysis of antifungal prescribing practices in the intensive care, surgical, medical and ARV outpatient departments at a tertiary care hospital in South Africa.

1.5.3. To suggest an antifungal stewardship policy and prescribing guideline based on the findings of objective 1 and 2 to form the basis of antifungal stewardship management.

Chapter 2: Literature Review

This chapter begins with a concise introduction to fungal infections, encompassing an exploration of human fungal pathogens, the categorisation of fungal infections, and strategies for their treatment. Extensive attention is devoted to the critical issue of antifungal resistance, emphasising its profound implications for public health, and underscoring the need for antifungal stewardship. Moreover, this chapter delves into the diverse facets of antifungal stewardship to offer a thorough comprehension of its significance within healthcare.

2.1. Human mycoses

Most fungi are heterotrophic saprophytes that occur naturally in the environment and are responsible for contributing to a healthy ecosystem (Sun et al., 2020; Woods et al., 2023). Although the majority of fungi are non-hazardous, a small subset of them can inflict catastrophic diseases on humans, plants and other animals (Case et al., 2022). This has a detrimental effect on biodiversity, agriculture and public health (Fisher et al., 2020).

There are two main mechanisms by which fungi gain access to host tissues: either by direct contact or by inhalation of fungal spores (Walsh et al., 2019). The most common portals of entry are the respiratory tract, gastrointestinal tract, and blood vessels with the size of the inoculum, the extent of tissue damage, the ability of fungi to multiply in tissues, as well as the immunological state of the host all being factors that affect the severity of the fungal disease (Reddy et al., 2022). For fungi to infect humans, they need to display certain characteristics including thermal resistance whereby fungi can grow at or above 37°C, the ability of the fungi to reach internal host tissues by penetrating or evading host barriers, the ability to digest and absorb human tissue, as well as the ability to circumvent the human immune system (Köhler et al., 2017).

Mycoses may be classified according to various categories such as the site of infection or the route of transmission. When classified according to the site of infection, fungal infections are considered as superficial, cutaneous, subcutaneous or deep (Guidry et al., 2017). Superficial mycoses are limited to the stratum corneum and do not trigger inflammation, whereas cutaneous mycoses involve the integument and its appendages including hair and nails where the stratum corneum or deeper layers of the epidermis may be affected and cause inflammation

if the skin is brought on by the pathogen or its byproducts (Kaushik et al., 2015; Howell, 2023). Subcutaneous mycoses are defined by an infection of the subcutaneous tissues, typically near the site of traumatic inoculation with an inflammatory reaction that extends into the epidermis (Bhat et al., 2016). Deep mycoses may involve the lungs, abdominal viscera, bones and or central nervous system (Wen et al., 2022)

When classified according to the route of transmission, fungal infections may be considered as exogenous or endogenous in origin. Exogenous fungal infections occur when infecting fungal organisms gain entry via direct inoculation and may be transmitted by airborne, cutaneous or percutaneous routes, whereas endogenous fungal infections may be acquired from colonization or reactivation of latent infection (De Pauw, 2011; Sheu, 2017).

2.2 Human fungal pathogens

There are various types of human fungal pathogens that are responsible for causing serious infection and even mortality in many patients if left undetected or untreated (Martins-Santana et al., 2023) Common human fungal pathogens are highlighted in Table 1.

Table 1: Human fungal pathogens

Pathogen	Description	Reference
<i>Candida</i> spp.	In healthy individuals, <i>Candida</i> is found in the human gastrointestinal tract, oral cavity and skin microbiome. Fungi belonging to this group of species become pathogenic causing candidiasis when the immune system is compromised, or the balance of the human microbiome is altered by agents such as antibiotics.	Pappas et al., 2018; Tedila et al., 2019
<i>Aspergillus</i> spp.	Commonly found in the soil causing aspergillosis in immunocompromised individuals. In addition, <i>Aspergillus</i> may be an allergen, triggering a severe immune response in people who have pre-existing lung conditions.	Latgé and Chamilos, 2020; Kashyap et al., 2023

<i>Cryptococcus</i> spp.	An invasive fungus that infects the lungs and/or central nervous system causing infections such as cryptococcal meningitis. <i>Cryptococcus</i> is the leading cause of meningitis in certain parts of the world with mortality rates of 100% if left untreated.	Iyer et al., 2021; Diniz-Lima et al., 2021 INMS
<i>Pneumocystis</i> spp.	<i>Pneumocystis</i> is the micro-organism responsible for <i>Pneumocystis</i> pneumonia, which is characterized by non-specific symptoms that usually indicate pneumonia. Extrapulmonary illness is not common. Suspicion of the illness is increased when other more common bacterial and viral diseases have been ruled out, as well as when the patients' immunological state and other relevant risk factors are considered.	Skalski et al., 2015; White et al., 2019
<i>Mucormycetes</i> spp.	Causes a life-threatening infection called mucormycosis in individuals whose immune system has been weakened. <i>Mucormycetes</i> can spread locally or via the bloodstream, resulting in aggressive and difficult to treat infections in organs such as the brain, eyes, lungs and skin. The region affected by the fungi appears black hence mucormycosis is commonly referred as the black fungus.	Dogra et al., 2022; Sharma and Goel, 2022

In 2022, the World Health Organization (WHO) introduced the first fungal priority pathogens list, known as the WHO FPPL (Figure 1), following the successful publication of the bacterial pathogens' priority list (WHO BPPL) in 2017. This landmark publication was motivated by the need to address the growing threat posed by fungal infections, globally (Fisher and Denning, 2023). Inclusion of fungal pathogens on this list is guided by various criteria, including the incidence and prevalence of infections caused by the pathogen, its geographic distribution,

mortality rates post-treatment, accessibility of diagnostic and treatment options, transmissibility, outbreak potential, and concerns regarding antifungal resistance (Fisher and Denning, 2023). The WHO FPPL comprises nineteen fungal pathogens categorised into three priority classification groups: critical, high priority, and medium priority. Notably, *Aspergillus fumigatus*, *Candida albicans*, *Candida auris*, and *Cryptococcus neoformans* are among the fungal pathogens classified as critical, reflecting their significant clinical impact and the urgency of addressing their associated challenges (Rodrigues and Nosanchuk, 2023).

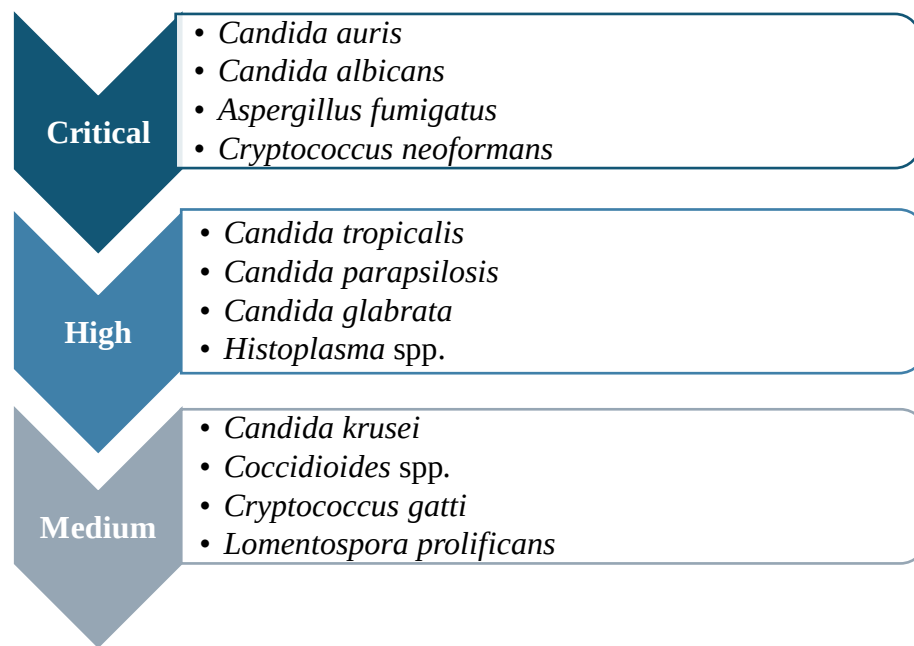


Figure 1: The WHO Fungal Priority Pathogens List (FPPL) adapted from: WHO fungal priority pathogens list to guide research, development and public health action (WHO, 2022).

Invasive fungal infections have emerged as a global concern, with candidiasis and candidemia accountable for the lion's share of cases (Enoch et al., 2017). While fungi can potentially affect healthy individuals, the most severe consequences are often observed in patients with compromised innate or acquired immunity (Fisher et al., 2020). This vulnerable group encompasses individuals such as those with HIV infection (Fisher et al., 2020). Moreover, the widespread use of intensive immunosuppressive therapies, particularly in oncology and transplant patients, along with the increased utilization of invasive medical devices like central venous catheters, further elevates the risk of invasive fungal infections (Enoch et al., 2017). The introduction of new immunomodulating drugs has extended this risk to a broader spectrum of patients (Enoch et al., 2017). Additionally, the burden of fungal diseases in South Africa is overwhelming, affecting over 3.2 million individuals annually, constituting approximately

7.1% of the population (Schwartz et al., 2019). A study conducted by Schwartz et al. (2019), found that cryptococcal meningitis accounts for approximately 8,357 cases each year, while pneumocystis pneumonia affects around 4,452 individuals. Invasive aspergillosis, a severe fungal infection, is estimated to afflict 3,885 individuals annually. Additionally, candidemia and candida peritonitis collectively contribute to 5,421 and 1,901 cases, respectively (Schwartz et al., 2019). The pervasive epidemic of pulmonary tuberculosis likely drives the prevalence of chronic pulmonary aspergillosis to 99,351 cases annually, potentially one of the highest rates globally. Furthermore, fungal asthma poses a significant concern, potentially impacting over 100,000 adults. Mucosal candidiasis, a common complication of HIV infection, presents a substantial burden, with approximately 828,666 cases annually, including 135,289 affecting the oral and oesophageal regions (Schwartz et al., 2019). These findings, based on data from 2019, provide a snapshot of the burden of fungal diseases in South Africa during that period. Though the data may have shifted in subsequent years due to evolving health trends and advancements in medical interventions, it highlights a significant burden of fungal infections within that timeframe.

Despite their profound impact, the significance of fungal infections on human health remains unrecognized (Cook and Drummond, 2023). Invasive fungal infections impose a substantial public health burden, with mortality rates varying from 30% to 90%, contingent upon both the specific fungal pathogen and the characteristics of the affected patient population (Fisher et al., 2020). Moreover, diagnosing many invasive fungal infections presents a formidable challenge due to their nonspecific clinical manifestations and the limited sensitivity of conventional microbiological testing methods (Antinori et al., 2018).

2.3. Treatment of fungal infections

There are five main classes of antifungal drugs approved for use in humans including azoles, polyenes, echinocandins, pyrimidine analogues and allylamines (Table 2). Each of these antifungal drugs has a different mechanism of action by which they combat fungal infections (Vanreppelen et al., 2023).

Table 2: Classes of antifungal agents

Antifungal Class	Mechanism of action	Example	Reference
Azoles	Destabilize the fungal membrane by inhibiting the synthesis of ergosterol. This inhibition of ergosterol results in its' depletion altering the stability, permeability and function of the fungal membrane and the enzymes associated with the membrane.	Drugs that fall within this group form largest class of antifungal drugs available including fluconazole, itraconazole, miconazole, clotrimazole, ketoconazole, econazole, tioconazole, sulconazole and luliconazole	Hossain et al., 2022
Polyenes	This class on antifungal drugs were initially isolated from <i>Streptomyces</i> . Polyenes bind to ergosterol in the fungal cell membrane resulting in the formation of aqueous pores which alters ionic equilibrium and disrupts the membrane-dependent active transport mechanisms. Polyenes can be fungistatic or fungicidal.	Amphotericin B, nystatin, natamycin and pimaricin	Ciesielski et al., 2016

Echinocandins	Non-competitively inhibit glucan synthase activity by disrupting the synthesis of β -(1,3)-d-glucan which results in fungal cell death mediated by instability of the fungal cell wall.	Anidulafungin, caspofungin and micafungin	Hüttel, 2021
Pyrimidine analogues	This group of antifungals may be considered as prodrugs since they have to be activated within the cell. These agents diffuse into fungal cells usually with the aid of a membrane transporter and are converted to cellular nucleotides by purine or pyrimidine metabolic pathway enzymes. Fungal cellular activity is suppressed by prevention protein synthesis or DNA replication.	Flucytosine	Derissen and Beijnen, 2020
Allylamine and Thiocarbamates and Morpholines	Thiocarbamates inhibit the enzyme squalene-epoxidase which participates in ergosterol synthesis ultimately affecting fungal cell membrane stability.	Terbinafine is an example of an allylamine and tolnaftate is an example of a thiocarbamate	Mazu et al., 2016; Hammoudi Halat et al., 2022

As a consequence of the limitation in array of available antifungal agents, the morbidity and mortality associated with fungal infections are substantially increasing (Wiederhold, 2017). South Africa's EDL recognises the severity of many of these fungal infections and has included antifungal agents necessary for their treatment (NICD, 2018). In South Africa, the primary classes of antifungal agents include azoles, polyenes, echinocandins, and allylamines, with fluconazole being the most commonly prescribed agent (Truter and Graz, 2012). However, a few life-saving antifungal agents are still not accessible for treatment of fungal infections since they are not registered by the South African Health Products Regulatory Authority (SAHPRA); or the cost of treatment is exorbitant (NICD, 2018).

In recent times, the emergence of antifungal resistance poses a consequential threat to public health with resistance to any class of antifungal agents significantly limiting patients' treatment options (Rabaan et al., 2023).

2.4. Antifungal resistance

Resistance arises when micro-organisms develop the ability to overcome drugs intended to eradicate them, rendering them less susceptible to a particular drug (Salam et al., 2023). Consequently, resistant pathogens evade destruction and continue to proliferate, posing significant challenges and, in severe cases, rendering infections untreatable with potentially life-threatening consequences (Salam et al., 2023). Antifungal resistance, specifically, manifests when antifungal treatments lose their efficacy against fungal infections (Hossain et al., 2022). This phenomenon occurs as fungi employ various mechanisms to evade or counteract available antifungal agents (Hossain et al., 2022).

It is crucial to distinguish between antifungal resistance and antifungal tolerance. While resistance entails genetic alterations in pathogenic fungi, increasing the likelihood of treatment failure, tolerance involves non-heritable cellular adaptations that enable fungal pathogens to persist when exposed to antifungal agents (Arastehfar et al., 2020). In simpler terms, antifungal tolerance refers to the ability of drug-susceptible fungal pathogens to thrive in the presence of an antifungal agent at concentrations exceeding the minimum inhibitory concentration (MIC) (Berman and Krysan, 2020). Notably, antifungal tolerance is reversible, with tolerant cells reverting to susceptible MIC levels upon re-culturing (Arastehfar et al., 2020).

Antifungal resistance encompasses two main categories: intrinsic and acquired resistance. Intrinsic resistance occurs when fungi naturally possess resistance to specific antifungal agents, irrespective of prior exposure (Reygaert, 2018). Acquired resistance, on the other hand, results from prolonged or prophylactic antifungal use (Pathakumari et al., 2020). This form of resistance is associated with overexpression or modification of antifungal targets, increased multidrug transporter activity, and adaptive mechanisms triggered by stress responses (Pathakumari et al., 2020).

Antifungal resistance can be acquired via several mechanisms. These mechanisms include:

- Inappropriate use of antifungal agents such as missed doses, subtherapeutic dosing or early cessation of antifungal therapy causing fungi to master mechanisms of evading the therapeutic effects of the antifungal agent (Chowdhary et al., 2022).
- Transmitted resistance whereby a contagious drug-resistant fungal infection may be passed onto another individual resulting in that individual acquiring a drug-resistant fungal infection even though they may not have been exposed to or utilised that specific antifungal agent (Baxter et al., 2015).
- Spontaneous antifungal resistance which occurs when fungal mutations result in the cessation of the fungal pathogens to respond to antifungal therapy which were previously effective with no obvious reason (Couce et al., 2016).
- Over exposure to antifungal agents due to prolonged or extended treatment which leads to the development of drug resistance (Wiederhold, 2017).

Antifungal resistance is a complex phenomenon involving interactions between environmental conditions, virulence factors, and alterations in gene expression. Understanding these interlinked factors is crucial for developing effective strategies to combat resistance and improve clinical management of fungal infections (Alastruey-Izquierdo and Martín-Galiano, 2023; Osset-Trénor et al., 2023). Inappropriate clinician prescribing and inadequate use by consumers form platforms for the emergence of antifungal resistance (Vitiello et al., 2023). Furthermore, the lack of adherence by patients to antifungal therapy results in suboptimal systemic drug concentrations, increasing the likelihood of the development of antifungal resistance (Science and Timberlake, 2020). Due to the severely limited market entry of novel antifungal agents and the exponential increase in vulnerable populations, the advancement of antifungal resistance is on the rise (Vitiello et al., 2023). Fungal pathogens have acquired several resistance mechanisms, summarized in Table 3.

Table 3: Antifungal resistance mechanisms

Resistance Mechanisms		Impact	Reference
1. Biofilm Formation	Biofilms are clusters of fungal cells that produce an extracellular matrix by embedding to the surface of the fungal cell. The formation of a biofilm enables the fungal pathogen to survive in extreme environments as they serve as a shield protecting the pathogen against the hosts immune systems as well as antifungal agents.	An <i>in-vitro</i> study conducted to investigate the biofilm formation capability of chromoblastomycosis fungi <i>Fonsecae pedrosoi</i> and <i>Phialophora verrucosa</i> , as well as its implications in antifungal resistance, revealed that both fungi exhibited the capacity to generate intricate networks of filamentous forms, comprising entangled and interconnected cells, on a polystyrene surface—resembling the characteristic microbial biofilm formation observed in other filamentous fungi. Subsequently, these biofilm-forming fungi were subjected to susceptibility testing against various classes of antifungals, including azoles, polyenes, and allylamines. The results underscored that the minimum inhibitory concentration (MIC) values for all tested antifungals were significantly higher in biofilm-forming cells compared to their planktonic counterparts, regardless of whether it was <i>F. pedrosoi</i> or <i>P. verrucosa</i> .	Hokken et al., 2019; Pajohesh et al., 2022; Sousa et al., 2022
2. Target Site Alterations	One of the most common mechanisms of antifungal resistance resulting in genetic mutations or enzymatic alterations in the antifungal target causes structural alterations	The findings from an in-vitro study demonstrated that <i>Saccharomyces cerevisiae</i> cells carrying the T123I substitution exhibited a fourfold elevation in minimum inhibitory concentration (MIC) values for fluconazole	Wu et al., 2017; Hokken et al., 2019; Ruiz-Baca et al., 2021

	which result in a reduction of the binding affinity of the antifungal to the target bringing about resistance.	and voriconazole, in contrast to cells with the wild-type enzyme. This suggests that amino acid alterations in Erg11p are common in azole-resistant strains, with the T123I substitution specifically conferring resistance to both fluconazole and voriconazole.	
3. Metabolic Bypass	Antifungal resistance via metabolic bypass occurs when the pathogenic fungi “bypass” the metabolic pathway that are inhibited by specific antifungal agents.	In <i>Candida albicans</i> , the enzyme Erg3p plays a crucial role in converting 14- α -methylated sterols, produced in response to azole exposure, into a toxic 3,6-diol derivative. This derivative contributes to the effectiveness of azoles against the fungus. However, loss-of-function mutations in the ERG3 gene, which encodes Erg3p, can lead to resistance by preventing the production of this toxic metabolite. As a result, <i>Candida albicans</i> is able to bypass the metabolic pathway targeted by azole antifungals, rendering them less effective against the fungus.	Munita and Arias, 2016; Sanglard, 2016
4. Efflux-pump Overexpression	Some fungal pathogens possess the ability to excrete antifungal agents. An increase in fungal gene expression results in the formation of efflux pump protein complexes which causes the expulsion of the antifungal agents outside of the fungal cell.	A study conducted in North India spanning from 2015 to 2018 focused on the examination of clinical isolates of <i>Candida tropicalis</i> obtained from a tertiary care centre. The findings of this study revealed a significant correlation between the overexpression of efflux-pump transporter genes, notably MDR1, ERG11, and CDR1,	Hokken et al., 2019; Amsalu et al., 2020; Pandey et al., 2020

		and the development of fluconazole resistance in <i>Candida tropicalis</i> .	
5. Mitochondrial Alterations	Mitochondria are referred to as the powerhouse of the cell responsible for the generation of energy required by the cell for survival. Any alteration or loss of function of the mitochondria plays a vital role in the development of antifungal resistance.	A study conducted in China shed light on a crucial link between <i>Aspergillus fumigatus</i> mutants exhibiting multidrug resistance and mitochondrial dysfunction, a condition arising from deficiencies in heme A biosynthesis. This dysfunction imposes a significant fitness cost on the organism, triggering calcium signalling pathways within its cellular machinery. Subsequently, a complex cascade of events unfolds, culminating in the widespread upregulation of various genes containing calcineurin-dependent-response elements. Ultimately, this upregulation confers antifungal resistance, revealing the intricate interplay among mitochondrial function, calcium signalling, and the evolution of drug resistance in <i>A. fumigatus</i> .	Li et al., 2020; Siscar-Lewin et al., 2021; Singh and Sarma, 2022
6. Stress pathway Activation	Upon exposure to an antifungal agent, the fungal pathogen experiences stress. However, activation of multiple stress response pathways results in the ability of the fungal pathogen to adapt or tolerate these stressful conditions. Some of these stress response pathways include the cell wall integrity pathway, Protein Kinase C (PKC), mitogen	<i>Aspergillus fumigatus</i> , a fungus notorious for its pathogenicity, develops resistance to azole drugs through a multifaceted process including activation of stress response pathways. Central to this adaptation is the upregulation of the calcium signalling pathway, which enables the fungus to perceive and counteract the stress induced by azole drugs. By enhancing the activity	Healey and Perlin, 2018; Li et al., 2019; Víglaš and Olejníková, 2021

	activated protein kinase (MAPK) and the cyclic AMP/Protein Kinase A (PKA) signalling pathway.	of this pathway, <i>A. fumigatus</i> strengthens its resilience against azole-induced inhibition, allowing it to sustain growth and proliferation despite drug exposure.	
7. Membrane Homeostatic Adjustment	Specific antifungal agents work by affecting membrane homeostasis which leads to destabilization of the cell membrane resulting in cell lysis. However, certain fungal pathogens have the ability to adjust their membrane either by increasing rigidity or fluidity resulting in a homeostatic imbalance contributing to antifungal drug resistance	Research findings indicate that azole resistance in <i>Candida albicans</i> primarily hinges on two categories of membrane transporters: ATP-binding cassette transporters (ABC-Ts) and major facilitator superfamily transporters (MFS-Ts). ABC-Ts utilise ATP-derived energy to facilitate the movement of molecules across membranes, while MFS-Ts operate by leveraging a proton gradient. Both transporter types possess the ability to bind azoles and extrude them from the cell, thereby diminishing the drug's intracellular concentration and enabling the fungus to withstand antifungal treatment.	Hokken et al., 2019; Czajka et al., 2023

Antifungal resistance poses a significant concern in healthcare, and its proliferation is fuelled by several accelerating factors. These factors compound the challenges associated with combatting antifungal resistance.

2.5. Factors accelerating the rate of antifungal resistance

Several factors contribute to the acceleration of antifungal resistance, including overuse of antifungal agents, global travel facilitating the spread of resistant strains, fungal adaptability, and environmental changes. Understanding these factors is crucial for developing effective strategies to combat antifungal resistance and preserve the efficacy of existing treatments.

2.5.1. Antifungal misuse and overuse

The misuse and overuse of antifungal agents, influenced by factors like insufficient regulation and physician prescribing practices shaped by patient demands, contribute to toxicity and antifungal resistance evolution (Lee and Lee, 2018; Dadgostar, 2019). Studies reveal prevalent inappropriate antifungal use across various healthcare settings, including tertiary care hospitals (Sachdev et al., 2022). For instance, a study in India found that half of 100 patients with fungal infections received inappropriate antifungal treatment due to errors like delays in treatment and confusion over fungal identification (Sachdev et al., 2022). Similarly, in Iran, a study involving 151 patients showed widespread inappropriate antifungal use concerning diagnostic approaches, indications, selection, doses, treatment duration, and administration techniques (Atashgar et al., 2023). Addressing these challenges in healthcare demands strategies such as regulatory reinforcement, promoting proper prescribing practices, and raising public awareness.

2.5.2. Agricultural use of antifungals

Environmental fungicides, including azoles and natamycin, are commonly employed in agriculture and horticulture to combat fungal crop decay. Natamycin, a polyene antifungal agent, is favoured as a food preservative due to its efficacy against filamentous fungi while sparing bacteria (Dalhoff, 2018). However, the dual use of agricultural fungicides and antifungals as food preservatives poses a significant risk of fostering antifungal resistance (Dalhoff, 2018). Specifically, the application of azole fungicides in agriculture has been

implicated in the emergence of azole-resistant strains of *Aspergillus fumigatus*, a pathogenic fungus (Berger et al., 2017). This resistance primarily stems from mutations in the *cyp51A* gene, which have been observed in patients who have not undergone azole treatment, suggesting an environmental origin of resistance (Berger et al., 2017). The research indicates that exposure to azole fungicides in the environment, whether through food consumption or inhalation, may contribute to the development of resistance observed in clinical settings (Berger et al., 2017).

2.5.3. Increase in income levels

The correlation between rising income levels and increased antimicrobial consumption, as highlighted by Dadgostar et al. (2019), presents a significant public health challenge, particularly concerning antimicrobial resistance (AMR). Pathadka et al. (2022) documented a notable rise in antifungal consumption globally from 2008 to 2018, with high-income countries leading the trend. In these wealthier nations, where access to antifungal agents is more readily available, consumption increased from 0.50 to 0.92 defined daily doses per 1000 people per day. This heightened access to antifungal medications in higher-income regions may be contributing to the growing concern over antifungal resistance. Overuse and misuse of these drugs in countries with better access can accelerate the development of resistant fungal strains, complicating treatment options for fungal infections.

2.5.4. Rising incidence of travel

The ease and surge in local and international travel have emerged as significant catalysts in the global proliferation of antimicrobial resistance (Dadgostar, 2019). Research indicates that the extensive network of convenient travel routes available to humans, animals, and goods has played a pivotal role in disseminating resistance worldwide (Dadgostar, 2019). Notably, human travellers, when exposed to resistant pathogens during their journeys, become potent carriers, inadvertently spreading resistant strains of fungal pathogens upon returning to their home countries (Frost et al., 2019). This phenomenon is vividly illustrated by studies on the spread of *Trichophyton indotineae*, a fungus resistant to common treatments. Research, such as that conducted by Chowdhary et al. (2022) suggests a strong correlation between the movement of people and the dispersion of this resistant fungus. Notably, cases in Europe and North America have been traced back to travel or immigration from regions like the Indian subcontinent,

indicating the role of human mobility in introducing resistant strains to new areas (Chowdhary et al., 2022).

2.5.5. Biological Considerations

Antifungal resistance can arise through various mechanisms, including unsolicited mutations or evolutionary processes (Read and Woods, 2014). Spontaneous mutations within the fungal pathogen's genome, as well as genes acquired through horizontal gene transfer from resistant fungal pathogens, can confer resistance to antifungal agents (Schroeder et al., 2018). These mutations can occur spontaneously, independent of external stressors, and are often neutral or harmful to human health, contributing to the escalating issue of antifungal resistance (Schroeder et al., 2018). A study by Calo et al (2014) sheds light on the specific mechanisms through which resistance can develop. They found that the fungus *Mucor circinelloides* can acquire resistance to the drug tacrolimus through two distinct pathways: stable genetic mutations and unstable changes that do not alter the DNA sequence. This illustrates the complex nature of antifungal resistance and underscores the importance of understanding both stable and unstable genetic alterations in combating this phenomenon.

2.5.6. Knowledge deficit

Generalized knowledge and data concerning antifungal utilisation and resistance are not as widely understood among clinicians and hospital staff (Ray et al., 2023). Understanding and addressing antifungal resistance and the genomes of fungal species are critical in combating resistance across various human fungal pathogens (Fisher et al., 2022). A cross-sectional study conducted among pharmacy students at a university in Zambia between June and July 2023 revealed that although most students demonstrated good knowledge (85.9%) and positive attitudes (86.7%) towards antifungal resistance and stewardship, their practices fell short of optimal standards (65.8%) (Mudenda et al., 2023). Given that patients often rely on healthcare providers for reliable medical advice and optimal treatment, these professionals represent a key avenue for educating patients about prudent antifungal use and resistance management.

2.6. Impact of antifungal resistance

Since the early 1990s, the introduction and widespread use of triazoles have marked a significant turning point in fungal infection management. However, this advancement has come with its challenges. Resistance in both *Candida* and *Aspergillus* species has now become a global concern (Jaiswal and Kumar, 2023; Martins-Santana et al., 2023). Notably, the rise of azole-resistant non-*Candida* species and multidrug-resistant *Candida strains*, such as *Candida glabrata* or *Candida auris*, is alarming (Jangir et al., 2023). Of particular concern is the emergence of triazole-resistant *Aspergillus* species. Azoles stand as the primary oral therapeutic option for the prevention and long-term management of invasive fungal diseases, making the development of resistance in *Aspergillus* species particularly worrisome (Kontoyiannis, 2017).

Candida species are the main causative pathogens in 50-70% of systemic fungal infections with candidemia accounting for approximately 15% of bloodstream infections (de Oliveira Santos et al., 2018). There is a poor understanding of the pathogenesis of *Candida* species with a sturdy increase in resistance to conventional antifungal therapy (de Oliveira Santos et al., 2018). Prolonged use of fungistatic azole drugs such as fluconazole, which is the most used azole antifungal used for prophylaxis and treatment of *Candida* infections, results in the development of resistance due to over-expression of membrane transporters, altered ergosterol biosynthesis and altered sterol import to name a few (Bhattacharya et al., 2020). *Candida auris* resistance poses a serious health threat, particularly in South Africa, as found in study conducted between 2016 and 2017, which focused on laboratory-based surveillance for candidemia (Maphanga et al., 2021). Susceptibility testing was conducted on 400 *C. auris* isolates, of which, 90% were resistant to fluconazole with 5% being resistant to both fluconazole and amphotericin B (Maphanga et al., 2021). This is of grave concern as treatment options become grossly limited with a substantial increase in treatment costs. In the United States of America, one study found that the average direct cost per patient with candidemia and invasive candidiasis ranged from \$48,487 to \$157,574 (equivalent to R901 055,74 to R2 928 268,55) (Wan Ismail et al., 2020).

Aspergillus fumigatus, the primary causative pathogen in various forms of aspergillosis, is predominantly susceptible to triazoles, which serve as the sole oral antifungal option (Denning, 2022). However, the emergence of triazole resistance, attributed to factors such as excessive use of azole fungicides and prolonged therapy, pose a serious challenge (Denning, 2022). The cost implications of treating aspergillosis are also noteworthy, particularly in regions like South Africa where the cost of treatment using a standard daily dose of 400mg oral itraconazole for

any form of aspergillosis was found to be \$14,81 (equivalent to R 275,22) per day (Kneale et al., 2016).

Although there is an apparent variety of antifungal agents available, resistance within any class poses a significant challenge, especially when considering other variables including drug interactions and toxicity profiles (Logan et al., 2022). Furthermore, antifungal agents remain among the more expensive anti-infective agents on hospital formularies, with vulnerable populations increasingly presenting with invasive fungal infections, driven by factors such as immunosuppression from cancer treatments, organ transplantation, HIV/AIDS, and other immunosuppressant usage (Nami et al., 2019; Johnson et al., 2020).

Given this scenario, it's imperative to integrate antifungal stewardship programs within antibiotic stewardship initiatives to address antifungal resistance, minimize treatment costs, and enhance patient therapeutic outcomes.

2.7. Antifungal stewardship

Antifungal stewardship encompasses proactive interventions aimed at monitoring and regulating the prudent use of antifungal agents to achieve optimal clinical outcomes while minimizing adverse events (Hamdy et al., 2017). Rooted in the principles of established antimicrobial stewardship programs, antifungal stewardship optimises prescribing practices by considering various factors associated with antifungal agents and therapeutic effectiveness (Hamdy et al., 2017). Its core objective lies in improving the use of antifungal drugs by leveraging the expertise and knowledge of healthcare professionals to address challenges hindering appropriate utilisation (Agrawal et al., 2016).

2.7.1. Benefits of antifungal stewardship

Antibiotic stewardship programs have demonstrated numerous benefits in optimising healthcare, and similarly, the implementation of antifungal stewardship programs can bring about several positive changes in the use of antifungal agents. In a study by Ray et al. (2023) various advantages associated with appropriate antifungal use were highlighted:

- Antifungal stewardship programs promote the judicious use of intravenous antifungal therapy, as many fungal infections can effectively be treated with oral antifungal agents.

This approach leads to cost reduction and fewer drug-related adverse events. By selecting appropriate antifungal agents, the minimum inhibitory concentration for the specific causative fungal pathogen remains stable, resulting in enhanced efficacy, shortened treatment duration, reduced costs, and minimized toxicities.

- Such programs limit the probability of emergence of resistant fungal pathogens.
- Implementation of antifungal stewardship programs have shown to improve mortality rates among patients suffering from candidemia.
- Timely discontinuation of antifungal therapy and appropriate switch from intravenous to oral therapy contribute to decreased costs associated with antifungal treatment.

Despite the manifold benefits offered by antifungal stewardship, its routine implementation in clinical settings remains limited (Aldossary and Shah, 2021). However, viable stewardship interventions can assist clinicians in selecting suitable antifungal treatments, thereby improving patient outcomes, and reducing healthcare costs (Albahar et al., 2023). Management in healthcare facilities should allocate adequate resources to support stewardship programs (Vergidis et al., 2023). Moreover, healthcare professionals and personnel involved in antifungal stewardship programs must possess fundamental knowledge and expertise in managing fungal infections, especially in high-risk and vulnerable populations (Vergidis et al., 2023).

2.7.2. Antifungal stewardship program development

Before embarking on the establishment of an antifungal stewardship program, it's essential to carefully consider several critical steps. Drawing insights from updated literature on the deployment of antimicrobial stewardship programs, these steps can be tailored to suit the implementation of antifungal stewardship initiatives. Seven pivotal focal points emerge as integral to the development of an effective antifungal stewardship program, each elaborated upon in Table 4.

Table 4: Antifungal stewardship program development

Recommendation		Reference
1. Collaboration with Senior Hospital Management	Institutional senior leadership is vital for supporting infection prevention, including antifungal stewardship programs. Management endorsement and encouragement for extending stewardship goals are	Spellberg et al., 2016; Pulcini et al., 2019;

Leadership Towards Antifungal Stewardship	crucial. Antifungal stewardship, due to its costs and impact on vulnerable populations, should be integrated into broader stewardship discussions for comprehensive effectiveness.	Johnson et al., 2020
2. Accountability and Responsibilities	Forming a multidisciplinary team with expertise in managing fungal infections is crucial for effective antifungal stewardship. Team members must possess detailed knowledge in various aspects, such as diagnostics, dosing, and adverse event management with clearly defined roles to enhance program success.	Agrawal et al., 2016; Pulcini et al., 2019; Johnson et al., 2020
3. Available Expertise on Infection Management	Facilities that commonly encounter or treat patients for invasive fungal infections ought to have access to routine and non-culture based diagnostic testing methods such as polymerase chain reaction and β -D-glucan which are crucial diagnostic tools for the early detection of invasive fungal infections in patients who are either neutropenic or non-neutropenic. Additionally, it is important to have healthcare professionals who have access to, are trained and have experience in the management of invasive fungal infections including diagnosis, treatment and prevention, as part of the stewardship team.	Pulcini et al., 2019; Johnson et al., 2020
4. Education and Practical Training	Educating and training all stakeholders involved in antifungal stewardship programs is crucial for improving prescribing patterns. Various methods such as seminars, online modules, short courses, and scenario-based learning have proven effective. Studies have highlighted gaps in prescriber knowledge, including distinguishing fungal colonization from infection and understanding prophylaxis indications for empiric antifungal treatment. Therefore, by providing education and training to stewardship committee members, these knowledge gaps will be addressed, and program effectiveness will be enhanced.	Valerio et al., 2015; Pulcini et al., 2019; Johnson et al., 2020; Satterfield et al., 2020

5. Other Actions Aiming at Responsible Antifungal Use	Invasive fungal infections are widely recognized for their complexity, with mortality rates among the highest of all infectious diseases. Timely development and sequential implementation of guidelines are essential to enhance diagnosis and treatment, maximizing patient outcomes and reinforcing healthcare professional education. Studies indicate that non-adherence to antimicrobial guidelines can lead to unfavourable clinical outcomes.	Pulcini et al., 2019; Johnson et al., 2020; Kara et al., 2021
6. Monitoring and Surveillance	Close monitoring of patients suspected or diagnosed with invasive fungal infections is essential. Adherence to antifungal treatment guidelines is more likely when evidence-based options are tailored to local settings with input from local clinicians. Continuous surveillance is crucial for assessing the burden of invasive fungal infections, identifying trends, and containing emerging threats such as multi-drug resistant fungal pathogens.	Pulcini et al., 2019; Johnson et al., 2020
7. Reporting and Feedback	Facilities aiming to establish an antifungal stewardship program should generate reports and offer feedback on interventions. Providing feedback to prescribers facilitates the adoption and implementation of learnings. This approach optimises antifungal prescribing patterns and treatment options, leading to improved patient outcomes and meaningful changes.	Pulcini et al., 2019; Johnson et al., 2020

By incorporating the aforementioned factors into the development and implementation of an antifungal stewardship program, there is a strong likelihood of success, if recommendations are tailored to local contexts. The routine practice and expansion of antifungal stewardship are necessary for optimising the care of patients susceptible to invasive fungal infections.

2.8. Core members of an antifungal stewardship committee

The primary step in advancing and implementing an antifungal stewardship program is to establish a multidisciplinary team with expertise in managing invasive fungal infections

(Agrawal et al., 2016). It is crucial to ensure representation from key clinical specialties within the group. The effectiveness of the team relies on the expertise and active involvement of its members, as well as their respective roles within the institution (Agrawal et al., 2016). Success also hinges on exemplary communication and networking skills, a willingness to collaborate with other experts, and a readiness to share responsibilities (Garraghan, 2022). While the exact composition may vary based on local settings, the team should ideally include a clinical pharmacist, a microbiologist, and a clinician (Figure 2), all actively engaged in invasive fungal infection management (Agrawal et al., 2016).

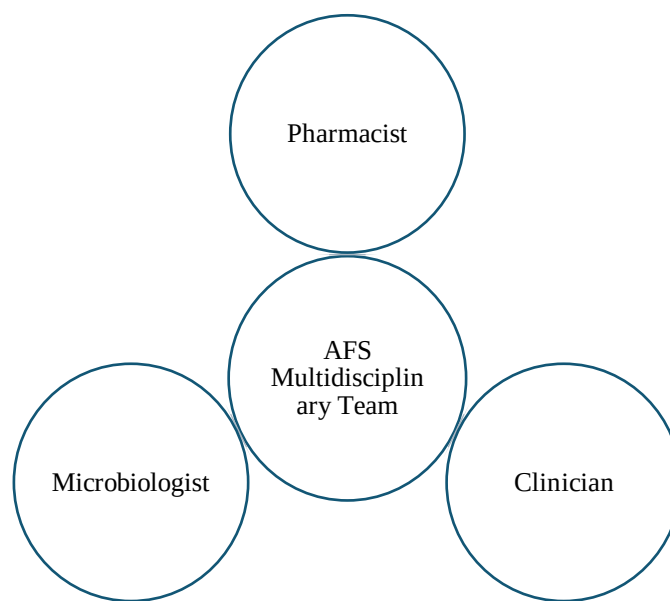


Figure 2: Core members of an antifungal stewardship committee

2.8.1. Pharmacist

Pharmacists are integral members of the antifungal stewardship team, contributing significantly to the appropriate use of antifungal agents in managing invasive fungal infections reference. The role of a pharmacist encompasses several key responsibilities, including collaborating with the multidisciplinary team to develop local guidelines and formulary suggestions, recommending intravenous to oral switching when applicable, identifying opportunities for therapy de-escalation, monitoring for drug interactions, ensuring optimal antifungal dosing, and assessing clinical outcomes following antifungal use (Jantarathaneewat et al., 2022). To fulfill these responsibilities effectively, pharmacists must possess a deep understanding of the underlying mechanisms and scientific evidence for various antifungal agents, as well as extensive knowledge of their pharmacokinetic properties (Agrawal et al., 2016).

2.8.2. Microbiologist

Microbiologists are highly specialized scientists with extensive knowledge of various microorganisms, including human fungal pathogens therefore their collaboration with the antifungal stewardship team is essential for ensuring the appropriate use of antifungal agents (Agrawal et al., 2016). The role of microbiologists is pivotal in directing therapy accurately. This involves identifying patients who are unlikely to have invasive fungal infections, thereby avoiding unnecessary antifungal therapy. Additionally, microbiologists ensure early detection of invasive fungal infections before the onset of symptoms and accurately diagnose patients with such infections, enabling targeted therapy directed at the specific fungal pathogen (Kelley, 2014).

2.8.3. Clinician

Clinicians play a role across various settings whereby they are responsible for the management of an array of infections including invasive fungal infections. They are responsible for the diagnosis and treatment of fungal infections including following good prescribing practices of antifungal agents. Clinicians generally work more independently and have the ability to make decisions on their own accord (Holm, 2011). As a result, clinician involvement within antifungal stewardship initiatives plays a crucial role in ensuring stewardship principles are met. Clinician knowledge of antifungal agents may not be as they are perceived. There may be an existing knowledge gap regarding antifungal utilisation amongst clinicians which contribute to the misuse of antifungal agents (Muñoz et al., 2016). A successful antifungal stewardship program is partly based on clinician buy-in since clinician opposition to antifungal stewardship programs pose a significant challenge which may hinder the success of the program (Charani et al., 2013).

Antifungal stewardship is a complex endeavour that requires the integration of various factors. Establishing a multidisciplinary team is crucial for the successful development and implementation of any antifungal stewardship program. The collaboration of highly skilled healthcare professionals working together synergistically is essential for mitigating the impact of antifungal resistance and optimising patient outcomes. Such collaborative efforts set a benchmark for future advancements in both medical and scientific fields.

2.9. Antifungal stewardship interventions

While antifungal stewardship programs differ in complexity and clinical considerations from antimicrobial stewardship, they share the common objective of improving appropriate drug utilisation through the development, implementation, and optimisation of institutional regimens. When implementing an antifungal stewardship program, several factors must be considered to ensure optimal use of antifungal agents and to mitigate associated mismanagement. Evaluation of appropriate antifungal agent use involves assessing factors such as dosage, microbiological adjustments, route of administration, duration of therapy, and drug-drug interactions, each of which is elaborated below.

2.9.1. Indication

Choosing the most appropriate antifungal agent for a suspected or confirmed fungal infection is paramount. Availability of institutional antibiograms offers several benefits including assisting clinicians in choosing the most suitable antifungal agent for empiric therapy when culture results are still outstanding (Morency-Potvin et al., 2017). Antifungal resistance is challenging, particularly where indication is concerned as existing fungal resistance to a specific antifungal agent extends to its entire class, severely limiting patients' treatment options (Vitiello et al., 2023)

2.9.2. Antifungal dosage

Ensuring dosing regimens effectively combat both susceptible fungal pathogens and those that have mutated is imperative to prevent or minimize antifungal resistance. To achieve effectiveness, antifungal agents must reach the infection site, with each agent exhibiting varying pharmacokinetic properties, including absorption, distribution, metabolism, and elimination (Odovic et al., 2020). Understanding these properties is essential, as it assists clinicians in adjusting antifungal dosage to achieve effective serum concentrations at target sites. The dosing of antifungal agents entails a delicate balance with implications at both ends of the spectrum. Suboptimal dosing may lead to treatment failure, with potentially severe consequences, as insufficient drug concentrations at the infection site can hasten antifungal resistance emergence. Conversely, supratherapeutic dosing poses a heightened risk of toxicity and adverse events (Chau et al., 2021). Therefore, to optimise dosage, enhance efficacy, mitigate resistance emergence, and minimize adverse events, therapeutic drug monitoring becomes indispensable (Fisher et al., 2022).

2.9.3. Microbiological adjustment

The misuse of antifungals often stems directly from misinterpretation or inappropriate utilisation of available microbiological test results (Atashgar et al., 2023). Several factors contribute to this issue, including errors in laboratory testing, lack of microbiologically confirmed diagnoses, submission of inadequate culture samples, and the reliance on empiric antifungal therapy without consideration for confirmed susceptibility results (Morency-Potvin et al., 2017). Antifungal susceptibility reports are crucial for ensuring the proper use of antifungal agents, as they indicate the most effective antifungal agent for a particular fungal infection. However, selective reporting poses challenges with antifungal agents, as typically only one isolate of a fungal pathogen is tested under the assumption that the susceptibility pattern will be consistent across all isolates of that pathogen (Alastruey-Izquierdo and Martín-Galiano, 2023). Additionally, the costs associated with antifungal testing further complicate comprehensive testing (Durand et al., 2021). Factors such as the site of infection, tissue penetration, and toxicity may be overlooked in these reports, highlighting the need for comments to be included to address these oversights (Khanina et al., 2021). In patients receiving empiric antifungal therapy, only a fraction of them will have a definitive fungal infection (Schöning et al., 2021). However, clinicians often fail to adjust therapy based on susceptibility results (Muñoz et al., 2015). Therefore, it is imperative that clinicians consistently refer to antifungal susceptibility test reports to ensure the appropriate selection of antifungal agents. These sensitivity reports also play a crucial role in discontinuing improper antifungal agents in cases where resistance is a contributing factor.

2.9.4. Route of administration

To effectively manage invasive fungal infections, clinicians initially employ intravenous formulations of antifungal agents to ensure optimal concentrations at the infection site. However, prolonged use of intravenous antifungal agents is associated with drawbacks such as increased hospital stays, elevated costs, and heightened risk of line infections (Yang et al., 2021). Transitioning from intravenous to oral formulations, where suitable for the patient, presents numerous advantages for both patients and institutions. These include mitigating the risk of intravenous-related adverse effects, reducing hospital stays, alleviating the workload on medical staff involved in preparation, dispensing, and administration of intravenous formulations, and yielding cost savings for the institution (Béïque and Zvonar, 2015).

2.9.5. Duration of therapy

Prolonged antifungal therapy may be associated with several drawbacks including an increased risk of adverse effects and toxicity, undue hospital costs and the grave threat of emerging antifungal resistance (Bassetti et al., 2020). In addition, compliance to therapy is reduced and there is an increased risk for drug toxicities and resistance (Bassetti et al., 2020). Fungi also exhibit the ability to mutate through environmental adaptation which promotes the emergence of resistant fungal pathogens (Vitiello et al., 2023)

2.9.6. Drug-drug interactions

Optimal antifungal therapy requires careful consideration of drug interactions, as they can influence serum drug levels and increase the risk of toxicity (Memisoglu, 2020). Severe interactions, such as those observed between azole antifungal agents and antiretroviral regimens, can compromise first-line antifungal treatment (Gohlar and Hughes, 2019). To effectively manage drug interactions, antifungal stewardship programs should involve healthcare professionals like clinical pharmacists, who possess in-depth knowledge of antifungal pharmacology (Ibrahim et al., 2023). Their expertise allows them to anticipate potential drug interactions that could adversely affect patients' clinical outcomes (Hamdy et al., 2017).

By intervening on the various factors mentioned, antifungal therapy can be optimised to greatly improve clinical outcomes and address the issue of antifungal resistance. Even though antifungal stewardship interventions are highly variable and may differ amongst various institutions, existing evidence demonstrates that antifungal stewardship can tremendously decrease antifungal consumption and optimise antifungal utilisation.

2.10. Knowledge, attitudes and practices of healthcare providers towards antifungal stewardship implementation and performance

Healthcare providers encounter numerous challenges in antifungal stewardship, grappling with issues such as limited knowledge, inadequate training, resistance to change, and resource constraints (Bahl, 2022; Kourti et al., 2023). Furthermore, complexities arise from factors such as dosing variability, drug resistance, and the necessity for therapeutic drug monitoring in managing invasive fungal infections (Ibrahim et al., 2023). The emergence of drug-drug interactions, notably with azoles, further complicates antifungal therapy (Memisoglu, 2020).

Especially in critical care settings, healthcare providers exhibit varying levels of knowledge and practices concerning antifungal stewardship. Research underscores a significant knowledge deficit among clinicians prescribing antifungal therapy, with only a minority possessing adequate expertise (Ibrahim et al., 2023). Antifungal stewardship programs play a pivotal role in addressing these challenges, guiding appropriate antifungal use to mitigate unnecessary exposure and optimise patient outcomes (Osset-Trénor et al., 2023). Tailored training initiatives are essential to support healthcare providers in navigating these complexities (Talento et al., 2021). Integrating practical checklists into antifungal stewardship programs is pivotal in preventing antifungal misuse and fostering judicious utilisation, as advised by expert panels (Gómez-López et al., 2023). Despite these hurdles, collaborative decision-making and the integration of antifungal stewardship into broader antimicrobial stewardship programs offer avenues for improvement (Bio et al., 2023; Fallas-Mora et al., 2023).

Moreover, healthcare providers' attitudes toward AFS exhibit variability. A study in Uganda demonstrated a significant proportion of providers expressing positive attitudes towards AFS (Kimbowa et al., 2022). Conversely, a survey among colleagues of the Study Group of Medical Mycology in Spain revealed discrepancies between common practices and recommended attitudes toward antifungal monitoring, indicating a need for educational interventions and further research in this domain (Gómez-López et al., 2023).

In summary, while some healthcare providers demonstrate favourable attitudes towards AFS, there remains considerable scope for aligning monitoring practices with established guidelines.

2.11. Relevance and importance of the study

Research aimed at understanding the knowledge, attitudes, and practices of healthcare professionals towards antifungal resistance and antifungal stewardship in South Africa is crucial for several reasons. Antifungal resistance can lead to treatment failures, increased morbidity, and mortality among patients with fungal infections, particularly in immunocompromised individuals (Osset-Trénor et al., 2023; Vitiello et al., 2023). South Africa faces a high burden of fungal infections, such as candidiasis and cryptococcosis, especially in people living with HIV/AIDS, complicating treatment and worsening patient outcomes (Schwartz et al., 2019). With one of the highest HIV/AIDS prevalence rates globally, South Africa is particularly vulnerable to the impact of antifungal resistance on the clinical outcomes of immunocompromised individuals (Oladele et al., 2020; Zuma et al., 2022). Moreover, the

limited number of available antifungal drugs compared to antibiotics for bacterial infections heightens the risk of treatment failure as resistance emerges (Osset-Trénor et al., 2023). Additionally, antifungal resistance raises healthcare costs due to longer hospital stays, the need for more expensive drugs, and additional diagnostic testing (Hossain et al., 2022).

Globally, antifungal resistance is a growing public health threat, and research conducted in South Africa can contribute to understanding resistance mechanisms and epidemiology, informing global strategies for surveillance, prevention, and management. By examining antifungal resistance and prescribing practices, as well as the knowledge and attitudes of healthcare professionals, South Africa can develop better stewardship programs to improve patient outcomes and reduce the burden of drug-resistant fungal infections, ultimately contributing to global efforts to combat antimicrobial resistance.

2.12. Policy and guideline development

Policy and guideline development on antifungal use and stewardship in South Africa is crucial to combat antifungal resistance, particularly given the country's high burden of fungal infections and the limitations of current guidelines. Key improvements include establishing antifungal stewardship programs, developing comprehensive standardized treatment guidelines, enhancing surveillance of antifungal resistance, and improving healthcare professional training. Additionally, better access to diagnostics, stricter regulation of antifungal drug use, and public health campaigns promoting rational antifungal use are essential to prevent resistance. While the Standard Treatment Guidelines (STGs) are valuable tools for managing fungal infections, they often fail to address the full range of fungal infections, especially those caused by emerging or rare pathogens and resistant strains. Currently, the STGs furnishes medical recommendations on a limited range of fungal infections including dermatophyte and cryptococcal infections as well as infections caused by *candida* species. However, treatment options for fungal infections such as pulmonary aspergillosis do not appear in these guidelines.

As fungal infections evolve, these guidelines can become outdated, leaving healthcare providers without adequate guidance for complex cases. Therefore, more comprehensive and adaptive treatment frameworks are needed to improve patient outcomes and align with global strategies against antimicrobial resistance.

2.13. Conclusion

Antifungal therapy stands as a pivotal pillar in the comprehensive care of patients grappling with fungal infections. Yet, the emergence of single and multidrug resistance against antifungal agents presents a formidable challenge to clinicians and the medical community at large. As resistance burgeons, the efficacy of treatment wanes, amplifying the risk of treatment failure, prolonged infection, and heightened mortality rates among susceptible patient populations.

While researchers ardently pursue the development of novel antifungal agents, pinning hopes solely on this approach to counter the tide of antifungal resistance appears somewhat futile. The journey towards new antifungal agents is fraught with numerous challenges, distinct from those encountered in the development of other antimicrobial agents (Baid, 2022).

The COVID-19 pandemic serves as a stark reminder of how swiftly newly discovered and emerging infections can traverse the globe. Even as health authorities grappled with the novel coronavirus, pre-existing drug-resistant strains of fungal pathogens posed an equally if not greater menace to public health (Denning, 2022).

Although antifungal stewardship programs are beginning to emerge as integral components of antimicrobial stewardship initiatives, scant literature exists on such programs. Given the multifaceted issues associated with antifungal misuse, including heightened mortality rates among patients with invasive fungal infections, escalating antifungal resistance, and exorbitant treatment costs, the adoption of antifungal stewardship programs becomes imperative to monitor and advocate for judicious antifungal prescribing practices. While evidence from effective antifungal stewardship programs underscores significant benefits, ongoing research efforts must be sustained.

These programs hold the potential to elevate the quality and safety of patient care. Moreover, by curbing antifungal consumption, antifungal stewardship initiatives can directly alleviate treatment costs without compromising clinical outcomes (De Pascale et al., 2023).

Chapter 3: Research methodology

An introduction to the research design employed for the study is given at the beginning of this chapter. The study site, study design—which includes details on instruments, population and sampling, study protocol, data analysis, reliability and validity of the study, ethical considerations and dissemination and translation—are highlighted and explained in the section that follows.

3.1. Ethical considerations

Applications for ethical approval was made via the University of Witwatersrand Human Medical Research Committee (HMRC) (Appendix A). Permission to peruse medical records such as patient prescriptions and charts as well as disseminate the surveys to study participants was obtained from the CEO and Research Committee at the Tertiary Care Hospital in this study (Appendix B). Once protocol approval was obtained (Appendix D), the researcher applied for ethical approval via the University of Witwatersrand Medical Human Research Committee. Further permission to conduct the study was then obtained from the Gauteng Department of Health. Prescriptions, patient files and information garnered from doctors, pharmacists and nurses were kept strictly confidential. The protocol was be published on the National Department of Health Research database in accordance with the conditions for using publicly available information.

3.2. Objective 1: To determine the knowledge and attitudes of doctors, pharmacists and nurses towards antifungal stewardship by means of survey analysis.

3.2.1. Study site

This study was conducted at a tertiary care hospital in South Africa. Tertiary hospitals play a larger role in the provision of medical education and scientific research by operating as medical centers, serving multiple regions, and offering services that surpass primary and secondary hospitals (Yan et al., 2020). A similar study was conducted at this Tertiary Care Hospital with the focus being on antibiotic agents (Osei Sekyere et al., 2024). Since this study focused on

antifungal agents, a more comprehensive representation of that facility in terms of antimicrobials was obtained.

3.2.2. Study design and instrumentation

A quantitative research approach was used to garner data on the knowledge, attitudes and practices amongst doctors, pharmacists, and nurses towards antifungal stewardship in a public sector tertiary care hospital. Quantitative research comprises collecting and analysing structured data which can be represented numerically (Taguchi, 2018). Quantitative data is collected by utilising tools such as surveys. This method assists in obtaining accurate and reliable measurements. The rationale for using a quantitative research approach over a qualitative research approach is that quantitative research yields more objective results which can then be used to analyse trends and tests hypotheses hence suitable for this study.

A study information document (Appendix E) and survey instrument (Appendix F) to ascertain the knowledge and attitudes amongst doctors, pharmacists and nurses was developed by the researcher by means of reviewing previously used research tools and studies (Labi et al., 2018; Alamin and Kheder, 2020; Ashraf et al., 2022). Prior to the development of the survey, the objectives and target population of the study was defined. This was followed by the drafting of the survey questions. Developed surveys from previous studies were analysed and questions were adapted to suit the context of this study. The survey (Appendix F) consisted of four sections: participant demographics, perceptions on antifungal stewardship, knowledge on antifungal stewardship and attitudes of antifungal prescribing. The survey was adapted to a South African tertiary hospital context. Survey questions focused on various aspects related to antifungal agents and antifungal stewardship including participants understanding of antifungal stewardship principles, appropriate and inappropriate use of antifungal agents, antifungal prescribing patterns as well as antifungal resistance.

3.2.2.1. Tool validation

A pilot study comprising 10% of the cohort population was conducted to determine the tool's reliability and effectiveness, as well as whether the tool could be adapted to the South African healthcare setting. The pilot study was conducted by the researcher as a preliminary method on a smaller scale for the researcher to determine how the study needed to be modified. The survey

was disseminated to 19 doctors, 1 pharmacist, and 29 nurses at the Tertiary Care Hospital prior to the commencement of the study.

3.2.3. Population and sampling

Population refers to the sum of all the units who meet the inclusion criteria valid for an investigation (Majid, 2018). For this study, the population comprised of all practicing doctors, pharmacists and nurses working at the Tertiary Care Hospital who meet the inclusion criteria.

3.2.3.1. Inclusion criteria

Doctors who have completed their MBChB degree and are registered with The Health Professions Council of South Africa (HPCSA), were included in this study. This included intern and community service doctors. Pharmacists who have completed their BPharm degree and are registered with The South African Pharmacy Council (SAPC) were invited to participate in this study. This included pharmacist interns and community service pharmacists. Only Registered Nurses (RN) who were registered with the South African Nursing Council (SANC) were included in this study given that registered nurses are responsible and accountable for the administration of medicines.

3.2.3.2. Exclusion criteria

University students were excluded from this study. In addition, enrolled nurses and enrolled nursing auxiliaries were excluded from this study due to their scope of practice in relation to medicines administration.

3.2.4. Sampling size and sample method

3.2.4.1. Sample size

The sample size for the study was calculated using the formula below:

Equation 1. Sample Size Equation

$$n = \frac{Nz^2P(1 - P)}{d^2(N - 1) + z^2P(1 - P)}$$

N = population

P = expected prevalence (in proportion to 1)

n = sample size

d = precision $d=(0.5(1-P))$

z = stats for CI ($CI=z.d$)

The Tertiary Care Hospital employs 349 doctors, 23 pharmacists and 1182 registered nurses working in their facility. Based on a 5% margin of error, 95% confidence interval and 50% response distribution calculation, the sample size for this study was calculated to be 184 doctors, 22 pharmacists and 291 registered nurses. The sample sizes have been calculated based on the internationally accepted sample size calculation as indicated above, using Raosoft® software. Study participants were randomly selected until saturation was obtained.

3.2.4.2. Sampling method

The selection of participants from the inclusion criteria for the study was conducted using the probabilistic random sampling method. This method was used to reduce the likelihood of bias by ensuring generalizability. Doctors, pharmacists and registered nurses were randomly selected to participate in the study provided they met the inclusion criteria. Their participation in the study was voluntary and randomized sampling was conducted until saturation was obtained. The selection of participants is based on the principle of randomization whereby each participant has an equal probability of being chosen so that an unbiased representation of the total population can be obtained.

3.2.5. Study procedure

Upon obtaining ethical approval from the University of Witwatersrand Medical Human Research Ethics Committee (HREC) [M230520 M230810-B-0001], the researcher provided a study information document (Appendix E) and a developed survey (Appendix F) adapted from previously published articles (Labi et al., 2018; Alamin and Kheder, 2020; Ashraf et al., 2022) to question the study participants (doctors, pharmacists, and nurses). Healthcare Professionals who met the inclusion criteria were invited to attend an information session where the study was explained to them by the researcher. Any questions raised by the study participants were answered by the researcher during the information session.

3.2.5.1. Information session

An information session was conducted by the researcher with participants who met the inclusion criteria at the tertiary care hospital to obtain permission to disseminate the survey. The researcher explained the purpose of the study and allowed feedback to clarify any concerns. A preference list was drawn up to determine whether participants favored a hard copy of the survey, or an electronic copy and surveys were distributed according to the preference list. A study information document (Appendix E) including information on the purpose of the study, a description of the study, the benefits of the study, the risks of the study, an estimation on the time required to complete the survey as well as an approximation of time the researcher will take to complete the study was provided. All participants were informed that strict confidentiality and anonymity will be maintained throughout the study. By opening the email link and completing the survey constituted consent. Data collected from completed electronic surveys remained anonymous to the researcher as the REDCap software prohibits disclosure of participant identities to the researcher. Subsequent emails were sent at two-week intervals to encourage study participants to complete the survey. The researcher did not document any identifiable information that could have been used to identify participants. Findings were stored on REDCap and are password protected to maintain data confidentiality and security. Only the researcher and supervisor will have access to the password.

3.2.6. Data Analysis

The survey was created using REDCap (Research Electronic Data Capture), a secure web application developed by Vanderbilt University in 2004. Survey tools were available in both electronic and paper formats. The data obtained from the survey were transcribed and downloaded into a Microsoft Office Excel spreadsheet for quantitative statistical analysis. Statistica was software utilised for analysing data.

3.2.7. Statistical analysis

This descriptive cross-sectional study used frequencies and percentages to measure prevalence. Logistic regression was used to determine relationships and correlations of the data. This provided odds ratios which was then used to judge 'probability'. Since the odds ratio can be calculated as a measure of association (Setia, 2016), it was found to be suitable for the type of data obtained for the above objective.

3.3. Objective 2: To assess antifungal prescribing patterns of doctors in a tertiary care hospital via retrospective analysis

3.3.1. Study design

A retrospective quantitative study of antifungal prescribing patterns by doctors at a tertiary care hospital was conducted by reviewing antifungal prescriptions dispensed over a twelve-month period.

3.3.2. Study site

The study was conducted at a tertiary care hospital, as per Section 2.1.1. Following obtaining permission from The Gauteng Department of Health District Management as well as the University of Witwatersrand Medical Human Research Committee, the researcher manually reviewed each patient file to assess if an antifungal agent was prescribed for the patient within the study period as determined by ethical clearance. Prescriptions from the intensive care, surgical, medical and ARV outpatient departments were analysed as these departments represent a large proportion of the targeted study population, namely immunocompromised patients.

3.3.3. Population and sampling

3.3.3.1. Inclusion criteria

All prescriptions containing antifungal agents were included in the study regardless of patient demographics.

3.3.3.2. Exclusion criteria

Any prescription that did not meet legal requirements according to South African Health legislature as well as illegible prescriptions will be excluded.

3.3.4. Sampling size and sampling method

3.3.4.1. Sample size

The sample size was calculated using Equation 3.1. as described under section 3.1. The tertiary care hospital dispensed 198 704 prescriptions over a period of twelve months from January 2022 to December 2022. Based on a 5% margin of error, 95% confidence interval and 5%

prevalence rate of an antifungal agent prescribed, the sample size was calculated as 370 prescriptions that needed to be reviewed by the researcher. Each prescription was randomly selected until saturation of 370 prescriptions was obtained. The sample size has been calculated based on the internationally accepted sample size calculation described above, using Raosoft® software. The sample size was achieved as the tertiary care hospital makes use of an electronic retrieval system. The 5% prevalence was taken from literature where antifungal prescription incidence ranges from 2.4% to 5.8% (Kaur et al., 2022).

3.3.4.2. Sampling method

The probabilistic random sample approach was used to select prescriptions within the inclusion criteria. This method involves randomly selecting study samples or populations ensuring that each sample or participant has an equal opportunity of being selected. By guaranteeing generalizability, this technique lowers the risk of bias. All prescriptions within the inclusion criteria were perused by the researcher and randomly selected until saturation was obtained.

3.3.5. Study procedure

An antifungal prescription review tool (Appendix G) was developed by the researcher to analyse antifungal prescriptions. This tool was developed after perusing resources such as the Good Pharmacy Practice (GPP) as well as previously conducted studies which made use of prescription review tools (Kakkar et al., 2021). The tool comprised of three sections including patient demographics, antifungal prescription overview as well as antifungal prescribing pattern. If the antifungal agent was dispensed within the twelve-month study period, the prescription from the patient file was included in the study. Numbers were assigned randomly to each prescription containing an antifungal agent. This was to ensure patient anonymity was maintained. Prescriptions were assigned an alphabet based on the ward in which the patient was admitted in followed by numerical assignment. For example, the first prescription from the ICU was numbered I001 while the second prescription reviewed from that same ward was numbered I002. The first prescription reviewed from the surgical ward was numbered S001 and the second prescription reviewed was numbered S002. A similar trend was followed for all prescriptions reviewed from the various wards throughout the facility. Any additional information pertaining to the patient such as symptoms, diagnosis or if the patient has received the same antifungal repeatedly during the study period, were recorded on a data collection sheet. Antifungal prescriptions dispensed within the twelve-month study period were checked for errors or omissions. Prescription reviews were conducted by assessing the appropriateness

of antifungal agent, dose, and dosing frequency. In addition, drug interactions and completion of the prescription were also checked. Prescribed treatment was then compared to recommendations in accordance with the South African Standard Treatment Guidelines and Essential Drugs List as well as the South African Antibiotic Stewardship Program (SAASP). Study material such as the South African Medicines Formulary (SAMF), South African Standard Treatment Guidelines and Essential Medicines List and Lexicomp, a software application that detects drug interactions, were used as references by the researcher. EMGuidance, a digital platform was used as a reference source by the researcher as this application provides an assortment of information related to treatment guidelines and medicines. Prescription validity was accounted for to ensure validity of the study. The researcher evaluated possible errors in the prescriptions which may attribute to antifungal resistance such as improper use of antifungal agents including inadequate or irregular use of the antifungal (Nigam, 2015). Data collected was then recorded on the data collection sheet. Additional information including patient symptoms, diagnosis (ICD 10 code) and number of antifungal agents prescribed were recorded on the data collection sheet (Appendix G). Patient demographics were recorded for further correlation of data as well as trend analysis. Any omissions on the prescription were recorded on the data sheet as this will aid in further analysis. Since the study was a retrospective one, the researcher did not require patient consent to access their files. Any identifying information was omitted to maintain confidentiality; instead, prescriptions were uniquely numbered.

3.3.6. Data analysis

The researcher independently entered and evaluated the results that have been obtained on the data collection sheet onto Microsoft Excel (Microsoft Office 365). The data collected was then analyzed for quantitative statistical analysis using pivot tables, frequencies and percentages.

3.3.7. Statistical analysis

Frequencies and percentages were used in this retrospective study to calculate prevalence. Data linkages and correlations were found using logistic regression. This provided odds ratios that were used to assess "probability." The odds ratio was appropriate for the sort of data acquired from this study as it may be calculated as a measure of association (Setia, 2016).

3.4. Objective 3: To suggest an antifungal stewardship policy and prescribing guideline based on the findings of objective 1 and 2.

3.4.1. Study design

After reviewing the findings from objective 1 and 2, the researcher presented the data to the relevant stakeholders for them to make use of and translate to the development and implementation of a structured antifungal stewardship policy and prescribing guideline. Reference material such as the Standard Treatment Guideline and Essential Drug List, the South African Medicines Formulary, Lexicomp, EMGuidance as well as evidence-based medicine was utilised to review and analyse results.

3.4.2. Study site

Findings from the study were presented to the antimicrobial stewardship committee at tertiary care hospital since this committee is responsible for driving responsible and appropriate antimicrobial use at the facility.

3.4.3. Study Procedure

Upon completion of data review and analysis, existing policies and guidelines such as STG/EDL, SAASP and evidence-based medicine were reviewed by the researcher including policies that the facility makes use of as well as national circulars. The researcher perused literature and evidence-based medicine to search for solutions to existing problems that have been encountered at the public health care facility as well as the available public healthcare guidelines. Findings and suggested recommendations were then shared with the hospitals' antimicrobial stewardship committee and other relevant personnel to assist them in implementing an antifungal stewardship program which can aid in ensuring appropriate antifungal prescribing, manage antifungal resistance and improve patient outcomes.

3.5. Reliability, validity and bias

In order for realistic reporting on the data obtained, the data collected for objective 1 and 2 was recorded accurately; and thoroughly compared to present data that was accessible from existing

literature. Prejudice was avoided as both study the supervisors verified the data's interpretation and dependability.

Chapter 4: Results and Discussion

In this chapter, we present the findings of our study and discuss their implications. The primary objectives of this research were to determine the knowledge and attitudes of doctors, pharmacists, and nurses towards antifungal stewardship, in addition to assessing antifungal prescribing patterns of doctors in a South African tertiary care hospital. Based on these findings, a suggested antifungal stewardship policy and prescribing guidelines was developed. This chapter presents the results in detail along with a comprehensive discussion that interprets these finding within the context of existing literature and theoretical framework.

4.1. Objective 1: The knowledge, attitudes and perceptions of doctors, pharmacists and nurses towards antifungal stewardship by means of survey analysis.

In the realm of healthcare, understanding the knowledge, attitudes and perceptions of medical professionals regarding specific practices is crucial for improving patient outcomes. The main objective of the survey was to determine the knowledge, attitudes and perceptions of doctors, pharmacists, and nurses towards antifungal stewardship. A total of 497 healthcare professionals from the various departments at the tertiary care hospital participated in this survey including 184 doctors, 22 pharmacists and 291 registered nurses.

4.1.1. Participant demographics

From the survey, it was determined that majority of the participants across the three professions were female (59.8%; n=297; Figure 3).

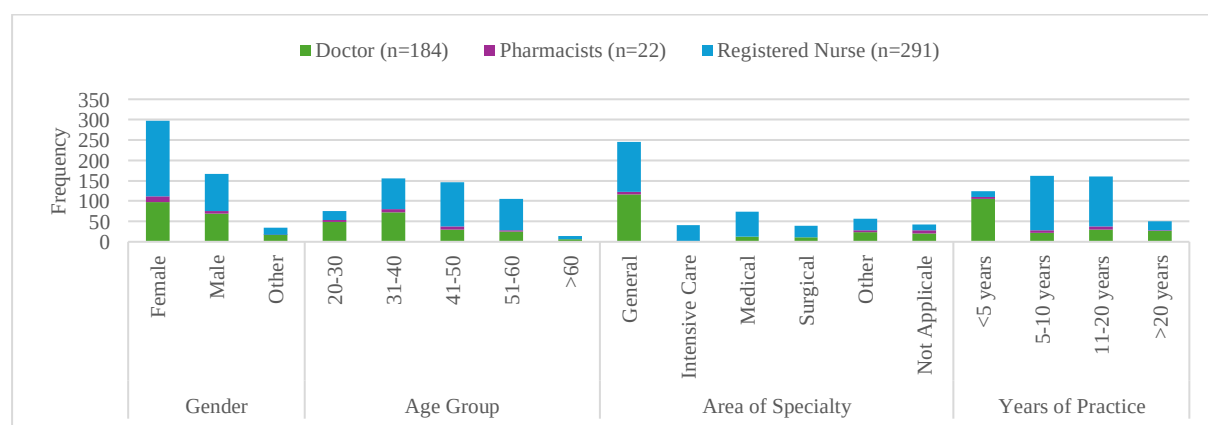


Figure 3: Participant demographics

A study conducted by Balliram et al. (2021) assessing the knowledge and practices of doctors, pharmacists and nurses on antimicrobials, antimicrobial resistance and antimicrobial stewardship in South Africa, found that 60.3% of their study participants were female, aligning the gender distribution from our study to theirs. When considering data per age category, the majority of the healthcare professionals who participated in this study (60.8%; n=302) fell within the 31-to-50-year age group. A study by Matseke (2023) aimed to determine the available healthcare workforce when COVID-19 emerged in South Africa in March 2020. One of the findings from this study was that 56.9% of the South African healthcare workforce fell within the 35-to-54-year age group which is similar to the observation made in this study. Almost half (49.3%; n=245) of the total study participant population specialized in general healthcare. Since general healthcare professionals, particularly in relation to prescribing physicians, often serve as the first point of contact for patients and play a crucial role in prescribing medications, their knowledge and attitudes towards antifungal stewardship are crucial as this can potentially impact the overall knowledge and attitudes towards antifungal stewardship within the facility (Edwards and Landon, 2017). Regarding years of practice, 68.2% (n=15) of the pharmacists and 87.6% (n=255) of the registered nurses fell within the 5-to-10 and 11-to-20-year categories. Quite the opposite was observed for doctors, with most of the doctors (57.6%; n=106) having less than five years of practice. This finding potentially suggests that the tertiary care hospital in this study may have a higher proportion of medical interns and community service doctors compared to fully qualified medical officers. In South Africa, medical graduates are required to complete a two-year internship followed by a year of community service before they can register as independent practitioners (Boden et al., 2023). This mandatory structure naturally leads to a significant presence of interns and community service doctors in public healthcare facilities, as reflected in the overall response rate of doctors in this study according to their years of practice. Another factor that may have influenced the response rate, particularly concerning years of practice, is that junior doctors were more willing to participate in the survey compared to medical officers or other prescribers. Research indicates that junior doctors are often more eager to engage in surveys and other research activities to enhance their clinical expertise and stay current with advances in modern medicine (Al Absi et al., 2024). The survey results are categorised into three sections: knowledge, attitudes, and perceptions of doctors, pharmacists, and nurses toward antifungal stewardship. This information serves to establish baseline learnings in order to improve antifungal prescribing practices ultimately improving patient outcomes and mitigating antifungal resistance (Gómez-López et al., 2023).

Table 5: The knowledge of doctors, pharmacists and nurses towards antifungal stewardship

		Doctors (n=184)			Pharmacists (n=22)			Registered Nurses (n=291)			
	Question	Strongly Agree and Agree	Neutral	Disagree and Strongly Disagree	Strongly Agree and Agree	Neutral	Disagree and Strongly Disagree	Strongly Agree and Agree	Neutral	Disagree and Strongly Disagree	p values
Knowledge	I am familiar with the term "Antifungal Stewardship"	54 (29.4%)	51 (27.7%)	79 (42.9%)	7 (31.8%)	10 (45.5%)	5 (22.7%)	61 (21.0%)	189 (65.0%)	41 (14.1%)	2.8×10^{-3}
	Inappropriate use of antifungals can cause harm to patients	120 (65.2%)	43 (23.4%)	21 (11.4%)	12 (54.6%)	6 (27.3%)	4 (18.2%)	188 (64.6%)	49 (16.8%)	54 (18.6%)	1.8×10^{-1}
	Inappropriate use of antifungals can cause the emergence of antifungal resistance	113 (61.4%)	61 (33.2%)	10 (5.4%)	13 (59.1%)	7 (31.8%)	2 (9.1%)	213 (73.2%)	65 (22.3%)	13 (4.5%)	1.5×10^{-1}
	I am familiar with local antifungal treatment guidelines in the management of fungal infections	25 (13.6%)	51 (27.7%)	108 (58.7%)	6 (27.3%)	6 (27.3%)	10 (45.5%)	41 (14.1%)	54 (18.6%)	196 (67.4%)	9.9×10^{-1}
	Infection, prevention and control plays a significant role in antifungal stewardship	161 (87.5%)	21 (11.4%)	2 (1.1%)	19 (86.4%)	2 (9.1%)	1 (4.6%)	272 (93.5%)	17 (5.8%)	2 (0.7%)	2.5×10^{-1}
	Antifungal resistance does not play an important role in patient safety	24 (13.0%)	46 (25.0%)	114 (62.0%)	6 (27.3%)	3 (13.6%)	13 (59.1%)	25 (8.6%)	37 (12.7%)	229 (78.7%)	7.2×10^{-2}

A Likert scale was used to measure knowledge, attitudes and perceptions. Respondents indicated their level of agreement or disagreement with a series of statements which was then analyzed.

4.1.2. The knowledge of doctors, pharmacists and nurses towards antifungal stewardship

By identifying knowledge gaps regarding antifungal resistance and stewardship, interventions can be more effectively designed to address these specific gaps and educational programs can be tailored to meet the actual needs of the population. Table 5 Provides an overview of the results obtained from the survey assessing the knowledge of doctors, pharmacists and nurses towards antifungal stewardship.

A greater proportion of pharmacists (45.5%; n=10) and registered nurses (65.0%; n=189) maintained a neutral stance regarding their familiarity with the term antifungal stewardship. Doctors on the other hand, were predominantly unfamiliar with the term (42.9%; n=79). This finding reveals a critical area for improvement in education, policy and practice in relation to antifungal stewardship. However, most participating healthcare professionals agreed that the inappropriate use of antifungal agents can not only cause patient harm (64.4%; n=320), but also result in the emergence of antifungal resistance (68.2%; n=339). This somewhat aligned with a study conducted by Mudenda et al. (2023), who found that most of their respondents (93.9%) agreed that the misuse of antifungal medications contributes to the development of antifungal resistance. With respect to the role antifungal resistance plays in patient safety, the majority of respondents (71.6%; n=356) disagreed with the statement, “antifungal resistance does not play an important role in patient safety.” This further correlates with Mudenda et al. (2023), who found that 89.3% of their respondents agreed with the statement that prolonged illness and higher mortality rates may occur resulting from antifungal resistance. Of the total cohort (n=497), 63.2% (n=314) were unfamiliar with local antifungal treatment guidelines. Unfamiliarity with local antifungal guidelines can lead to inappropriate antifungal therapy choices, such as selecting the incorrect antifungal agent for the organism or site of infection, inadequate dosages and failure to adjust therapy based on test results (Sachdev et al., 2022), as seen in this study. This can result in delayed or ineffective treatment, potentially impacting patient outcomes.

In addition to the Likert scale, the survey comprised of a series of questions relating knowledge, attitudes and perceptions to antifungal agents, resistance, and stewardship. The results from

those questions are depicted in the subsequent tables represented as percentages, with the corresponding discussions below each table.

4.1.2.1. Knowledge: Factors contributing to the inappropriate use of antifungal agents

Study participants were asked to determine which of the factors listed in Table 6 contribute to the inappropriate use of antifungal agents.

Table 6: Factors contributing to the inappropriate use of antifungal agents

Which of the following factors contribute to the inappropriate use of antifungal agents	%
South Africa has a high burden of disease	30.0
Lack of prescribers' knowledge on antifungal agents	49.0
Lack of knowledge of fungal aetiology or epidemiology	13.6
Increase in the emergence of antifungal resistance	5.1
Other	2.4

The results of the survey shed light on the key factors that healthcare professionals believed contributed to the inappropriate use of antifungals in South Africa. In this study, respondents believed that the most significant contributor, accounting for nearly half of the total responses (49.0%), is the lack of prescribers' knowledge on antifungal agents. This finding aligned with a study conducted by Ibrahim et al., (2023) who evaluated systemic antifungal prescribing knowledge and practice in the critical care setting among ICU physicians and clinical pharmacists. The study found that the majority of participating healthcare providers demonstrated either moderate (46.0%) or poor (50.8%) knowledge regarding systemic antifungal prescribing in the critical care setting. Only a small percentage (3.2%) had overall good knowledge. Another significant factor that participants believed contributed to the inappropriate use of antifungals, is the high burden of disease in South Africa (30.0%). This potentially indicates that the overwhelming demand for healthcare services and the pressure on healthcare providers might lead to the misuse of antifungal treatments as practitioners may opt for broad-spectrum or empirical antifungal use without proper diagnostics (Mhlanga, 2021; Micallef et al., 2023). Lack of knowledge of fungal aetiology or epidemiology was responsible for 13.6% of inappropriate antifungal use as per healthcare professional beliefs. This suggests that there is a belief that a considerable portion of misuse stems from the uncertainty or

unawareness regarding specific fungal pathogens and their local epidemiological patterns. Therefore, by improving clinicians' knowledge on fungal aetiology or epidemiology, more informed treatment decisions can be made, leading to better patient outcomes (Hadrach and Ayadi, 2018). The increase in the emergence of antifungal resistance contributed to 5.1% of healthcare professionals beliefs in factors contributing towards inappropriate antifungal use. This factor, though lower in percentage, points to a worrying trend where resistance patterns might be leading to improper prescribing practices.

4.1.2.2. Knowledge: Factors contributing to antifungal resistance

Antifungal resistance is an increasing concern in healthcare, as it diminishes the effectiveness of treatments against fungal infections. To gain insight into this issue, participants were surveyed to identify factors they believe contribute to antifungal resistance. The results of this survey are presented in Table 7.

Table 7: Factors contributing to antifungal resistance

What one factor contributes to antifungal resistance	%
Overuse of antifungal agents	38.8
Inappropriate duration of therapy	20.9
Self-medication	17.3
Inappropriate choice of antifungal for empiric therapy	12.7
Other	3.6
Suboptimal dosing	3.4
Patient demand and expectations	3.2

Healthcare professionals in this study believed that the most significant factor contributing to antifungal resistance is the overuse of antifungal agents, which accounted for 38.8% of the responses. A study by Singh and Xess (2020) found that the overuse of antifungal agents in clinical settings led to multidrug-resistant strains of fungal organisms such as *Candida auris*, which poses a high mortality risk and has the potential to cause an outbreak. Inappropriate duration of therapy was also a significant factor (20.9%) that healthcare professionals believed contributed to antifungal resistance. Duration errors, such as premature cessation of antifungal treatment can result in reduced exposure of the causative pathogen to the antifungal agent

resulting in treatment failure and the development of antifungal resistance (Salmanton-García et al., 2024). The practice of self-medication, which accounted for 17.3% of the total responses. Individuals that self-medicated on antifungal agents without proper medical guidance can result in incorrect dosing, inappropriate choice of medication and misuse, all of which can foster the development of antifungal resistance. The remaining responses for factors contributing to antifungal resistance were inappropriate choice of antifungal for empiric therapy, suboptimal dosing, patient demand and expectations and other relating factors, amounting to 22.9%. The inappropriate choice of antifungal agents for empiric therapy occurs when healthcare providers prescribe broad-spectrum antifungals without precise knowledge of the specific fungal pathogen involved, potentially promoting resistance in non-target-species (Mhlanga, 2021; Micallef et al., 2023). Patient demand and expectations also play a role in the development of antifungal resistance as patients often request quick relief from symptoms, pressuring clinicians to prescribe antifungals even when they might not be necessary or when a different treatment might be more appropriate, ultimately contributing to antifungal resistance.

4.1.2.3. Knowledge: Familiarity with the term ‘Candida Score’

The *Candida* score is a clinical tool used to identify patients who are of high risk for invasive candidiasis (Juneja et al., 2022). Respondents were surveyed on their familiarity with the *Candida* score. The survey results reveal that a slight majority of respondents, 53.1%, are not familiar with the term "*Candida* Score." This distribution suggests that the *Candida* Score is not widely recognized among the surveyed population. A study by (Laine et al., 2019) highlighted that the *Candida* score, although a useful tool, is not widely recognized or applied effectively in medical intensive care units. They found that only 37% of patients with candidemia had a positive *Candida* score indicating a gap in its application and understanding among healthcare professionals in these settings. While the *Candida* score is a useful tool, its effectiveness can vary based on patient demographics. For instance, in some studies, the score's thresholds and predictive values differ from those initially validated, indicating the need for context specific adjustments (Falces-Romero et al., 2023). The lack of familiarity as highlighted by this survey indicates a need for increased awareness and education among healthcare professionals. For those involved in critical care or infectious disease management, understanding and utilising the *Candida* Score is essential, suggesting that additional training or resources may be required to ensure broader familiarity with this tool.

The results from this survey could also prompt further research into the barriers preventing the dissemination and adoption of the evidence-based practices like the *Candida* Score in clinical practice. Barriers including time constraints, lack of resources and resistance to change amongst healthcare professionals can impede the integration of tools like the *Candida* score into everyday practice (Aishammari et al., 2020). Addressing these barriers through targeted educational strategies could improve knowledge and application of the score. Ultimately, increasing the familiarity and proper use of the *Candida* Score among healthcare providers could lead to better clinical practices and improved patient care outcomes by ensuring timely and appropriate antifungal treatment.

4.1.2.4. Knowledge: Familiarity with different strains of fungal organisms

Having a sound knowledge of the different strains of resistant fungal organisms is imperative for selecting the most effective treatment, preventing outbreaks and guiding public health interventions. Study participants were surveyed on their familiarity with the different strains of fungal organisms. According to our results, only 9.0% of the healthcare professionals reported that they are familiar with the different strains of resistant fungal organisms. Of the total study cohort, 43.0% indicated that they are not familiar with the strains, suggesting a substantial gap in awareness or education on this topic within the study participant population. Meanwhile, nearly half of the respondents, 48.0%, reported that they are partially familiar with the resistant fungal strains. This partial familiarity could imply that while there is some level of awareness, it may not be comprehensive or detailed. Our findings aligned with a study published by Gupta et al., (2023), who found that many healthcare professionals in the United States of America have limited familiarity with drug-resistant fungal organisms.

4.1.3. The attitude of doctors, pharmacists and nurses towards antifungal stewardship

Assessing the attitudes of doctors, pharmacists and nurses towards antifungal stewardship aids in understanding their underlying beliefs and values which may then influence their behavior and decision making. This will provide valuable insights into potential resistance or support for changes, which can then facilitate better management of change.

Table 8: The attitudes of doctors, pharmacists and nurses towards antifungal stewardship

		Doctors (n=184)			Pharmacists (n=22)			Registered Nurses (n=291)			
	Question	Strongly Agree and Agree	Neutral	Disagree and Strongly Disagree	Strongly Agree and Agree	Neutral	Disagree and Strongly Disagree	Strongly Agree and Agree	Neutral	Disagree and Strongly Disagree	p values
Attitude	I believe that it is necessary to get more knowledge on invasive fungal infections and antifungal agents	174 (94.6%)	10 (5.4%)	0 (0.0%)	20 (90.9%)	1 (4.6%)	1 (4.6%)	283 (97.3%)	7 (2.4%)	1 (0.3%)	9.5×10^{-1}
	There is a need to establish a course on the rational use of antifungal agents	163 (88.6%)	18 (9.8%)	3 (1.6%)	20 (90.9%)	1 (4.6%)	1 (4.6%)	273 (93.0%)	12 (4.12%)	6 (2.1%)	3.3×10^{-1}
	I feel confident about my knowledge and practice regarding prescribing/dispensing/administration of antifungal agents	15 (8.2%)	60 (32.6%)	109 (59.2%)	8 (36.4%)	4 (18.2%)	10 (45.5%)	42 (14.4%)	67 (23.0%)	182 (62.5%)	8.9×10^{-2}
	It is better to over-prescribe than under-prescribe antifungal agents	13 (7.1%)	29 (15.8%)	142 (77.2%)	2 (9.1%)	1 (4.6%)	19 (86.4%)	15 (5.2%)	57 (19.6%)	219 (75.3%)	7.7×10^{-1}
	I believe that some antifungal agents available at my facility are of suboptimal quality and therefore do not work	39 (21.2%)	96 (52.2%)	49 (26.7%)	6 (27.3%)	9 (40.9%)	7 (31.8%)	20 (6.9%)	205 (70.5%)	66 (22.7%)	2.0×10^{-1}

Our study found that 59.2% of doctors lacked confidence in their prescribing of antifungal agents (Table 8). This finding is similar to a study conducted by Balliram et al., who found that diminished levels of confidence were observed in 60.2% of the doctors who participated in their study. A lack of prescriber confidence in antifungal prescribing can have significant and multifaceted implications. It may lead to treatment failures as hesitant prescribers might opt for suboptimal or inappropriate treatments, resulting in prolonged infections and increased rates of resistance (Riera et al., 2023). This uncertainty can further drive prescribers to rely on broad-spectrum antifungals or empiric therapy, which may not effectively target the specific pathogen and can contribute to the development of resistance. Additionally, delays in initiating treatment or extensive diagnostic procedures due to prescriber hesitation can exacerbate infections, leading to higher patient morbidity and mortality (Tedla et al., 2020). Such treatment inefficacies can increase healthcare costs through extended hospital stays, additional testing, and more complex interventions. Furthermore, patients may lose trust in their healthcare providers if they perceive a lack of confidence, potentially impacting adherence to treatment and follow-up care (Chikodiri Nwosu et al., 2023).

The majority of the participants agreed that it is not only necessary to get more knowledge on invasive fungal infections and antifungal agents (96.0%; n=477), but there is also a need to establish a course on the rational use of antifungal agents (91.8%; n=456). This finding aligned with a study by Wasserman et al., (2017), whereby, 95% of their study cohort reported that they would appreciate more education on the appropriate use of antibiotics while 90% of the study cohort reported requiring more education on antibiotic resistance in general. Farley et al., also reported that numerous prescribers requested more education on appropriate antimicrobial use.

A positive finding from this study was that 76.5% (n=380) of the respondents disagreed with the statement that it is better to over-prescribe than to under-prescribe antifungal agents. Neither over-prescribing nor under-prescribing antifungal agents is ideal (Muñoz et al., 2015).. Both approaches have several significant drawbacks. Over-prescribing antifungal agents can not only result in antifungal resistance but also result in increased toxicity and higher healthcare costs (Muñoz et al., 2015). The excessive use of antifungals has been linked to a global rise in antifungal resistance, which complicates treatment of invasive fungal infections and shifts their aetiology (Muñoz et al., 2015). Long term use of azole antifungals, commonly prescribed for prophylaxis and treatment, can lead to severe adverse effects such as hepatotoxicity, hormone-related issues, peripheral neuropathies, pancreatitis and even squamous cell carcinoma (Benitez

and Carver, 2019). One of the primary risks associated with under-prescribing of antifungal agents is subtherapeutic exposure, which can lead to treatment failure and increased mortality (van der Elst et al., 2015).

4.1.4. The perceptions of doctors, pharmacists and nurses towards antifungal stewardship

The results from the survey assessing the perceptions of doctors, pharmacists and nurses towards antifungal stewardship are represented in Table 9. More than half of the respondents (57.1%; n=284) maintained a neutral stance regarding antifungal stewardship being an effective programme for the management of antifungal utilisation. This finding contrasted the findings from Mudenda et al., (2023) whereby 94.2% of their study participants agreed that antifungal stewardship programs aim to improve the use of these agents. In order to shift perceptions towards a more positive view of antifungal stewardship programs, institutions should increase awareness and education through training and informative materials, provide evidence and data highlighting program success, and enhance communication with regular updates and feedback mechanisms (Sachdev et al., 2022). Demonstrating strong institutional support, involving key stakeholders in the process, and addressing implementation challenges are crucial (Spellberg et al., 2016; Pulcini et al., 2019; Johnson et al., 2020). Additionally, highlighting cost-effectiveness, monitoring and reporting outcomes, addressing cultural and attitudinal barriers, and fostering a collaborative environment with peer support and professional networks help build trust and credibility (Spellberg et al., 2016; Pulcini et al., 2019; Johnson et al., 2020).

The majority of nurses (77.0%; n=224) remained neutral about the presence of appropriate government guidelines for the proper use of antifungal agents at the tertiary care hospital in this study. In contrast, 56.5% (n=104) of doctors and 40.9% (n=9) disagreed with this statement. Many African countries, including South Africa, suffer from inadequate diagnostic capacity and low awareness among healthcare workers and policymakers (Oladele et al., 2020).

Table 9: The perceptions of doctors, pharmacists and nurses towards antifungal stewardship

		Doctors (n=184)			Pharmacists (n=22)			Registered Nurses (n=291)			
	Question	Strongly Agree and Agree	Neutral	Disagree and Strongly Disagree	Strongly Agree and Agree	Neutral	Disagree and Strongly Disagree	Strongly Agree and Agree	Neutral	Disagree and Strongly Disagree	p values
Perception	Antifungal Stewardship is an effective programme for the appropriate management of antifungal utilisation	95 (51.6%)	53 (28.8%)	36 (19.6%)	9 (40.9%)	11 (50.0%)	2 (9.1%)	68 (23.4%)	220 (75.6%)	3 (1.0%)	2.1×10^{-1}
	Antifungal Stewardship programmes offer no benefits to healthcare	17 (9.2%)	44 (23.9%)	123 (66.9%)	2 (9.1%)	7 (31.8%)	13 (59.1%)	4 (1.4%)	145 (49.8%)	142 (48.8%)	1.0×10^{-1}
	Antifungals are used appropriately in my hospital	108 (58.7%)	35 (19.0%)	41 (22.3%)	9 (40.9%)	10 (45.5%)	3 (13.6%)	65 (22.3%)	201 (69.1%)	25 (8.6%)	3.7×10^{-3}
	There are appropriate government guidelines in place for the proper use of antifungal agents in my hospital	20 (10.9%)	60 (32.6%)	104 (56.5%)	8 (36.4%)	5 (22.7%)	9 (40.9%)	46 (15.8%)	224 (77.0%)	21 (7.2%)	8.2×10^{-17}
	Antifungal resistance is not a concern in my facility	37 (20.1%)	73 (39.7%)	74 (40.2%)	2 (9.1%)	9 (40.9%)	11 (50.0%)	11 (3.8%)	46 (15.8%)	234 (80.4%)	3.9×10^{-2}
	Antifungal resistance is not as important as antibiotic resistance	10 (5.4%)	56 (30.4%)	118 (64.1%)	1 (4.6%)	6 (27.3%)	15 (68.2%)	10 (3.4%)	51 (17.5%)	230 (79.0%)	9.8×10^{-3}
	The development of new antifungal agents can combat the emergence of antifungal resistance	156 (84.8%)	15 (8.2%)	13 (7.1%)	20 (90.9%)	2 (9.1%)	0 (0.0%)	249 (85.6%)	18 (6.2%)	24 (8.3%)	6.2×10^{-1}

The South African National Department of Health has released guidelines for antimicrobial stewardship programs, but their implementation faces significant challenges, particularly in public hospitals, where the health system is under severe strain (Scheepers et al., 2023). Moreover, the availability of essential antifungal medications like flucytosine is limited, despite its proven effectiveness in reducing mortality in *Cryptococcal* meningitis, highlighting the need for urgent registration and inclusion in treatment guidelines (Mashau et al., 2022). Therefore, while there are some government guidelines in place, the overall framework for the judicious use of antifungal agents in South Africa is incomplete and requires substantial improvement to effectively address the high burden of fungal diseases.

In order to combat the emergence of antifungal resistance, most of the respondents (85.5%; n=425) agreed that the development of novel antifungal agents will facilitate this process. This finding although potentially true in terms of mitigating resistance, is worrisome, because the developmental process is a complex and lengthy process, often taking many years from discovery to clinical use. This extended timeline is due to several factors, including the limited number of selective targets available for antifungal drug development, as fungi are eukaryotic organisms like humans, which makes it challenging to find targets that do not also affect human cells (Butassi et al., 2023). Despite the urgent need for new antifungal agents, no new classes have been introduced in the past two decades (Hoenigl et al., 2021). Therefore, while the need for new antifungal agents is pressing, the pace of their development has not kept up with the rapid emergence of antifungal resistance, highlighting a significant gap in the current antifungal treatment landscape.

4.1.5. Perceptions: The benefit of antifungal stewardship at a tertiary care hospital

Antifungal stewardship programs offer several benefits. Study participants were surveyed to determine why they believed antifungal stewardship programs would be beneficial at their facility. The results from the survey are represented in Table 10.

Table 10: The benefit of antifungal stewardship at a tertiary care hospital

Why do you think antifungal stewardship programs would be beneficial in my facility	%
South Africa has a high burden of disease	37.6%
Lack of knowledge of fungal aetiology or epidemiology	27.4%

Lack of prescribers' knowledge on antifungal agents	22.5%
Increase in the emergence of antifungal resistance	11.1%
Other	1.4%

In this study, health care professionals believed that antifungal stewardship programs will be beneficial at their facility because South Africa has a high burden of fungal disease (37.6%). South Africa faces a substantial burden of fungal diseases (Schwartz et al., 2019), and stewardship programs are crucial for managing this high disease burden effectively. By promoting optimal antifungal use, these programs can help ensure that treatments are both appropriate and effective, ultimately improving patient outcomes. Another significant factor driving the need for stewardship programs is the knowledge deficit regarding fungal aetiology and epidemiology (27.4%) and antifungal agents (22.5%). Generalized knowledge and data regarding antifungal utilisation and resistance are often limited among clinicians and hospital staff. According to Ray et al., (2023), this lack of understanding can contribute to suboptimal use of antifungal agents and increased risk of resistance. Antifungal stewardship programs aim to address these gaps by providing targeted education, improving prescribing practices, and monitoring resistance patterns. By enhancing clinicians' knowledge and promoting evidence-based practices, these programs can help mitigate resistance and improve patient outcomes.

4.1.6. Summary of findings related to the knowledge, attitudes and perceptions of doctors, pharmacists and nurses towards antifungal stewardship at a tertiary care hospital

Nearly half (49.3%) of the study participants specialized in general healthcare. A significant proportion of doctors (42.9%) were unfamiliar with the term "antifungal stewardship." Despite this, the majority of healthcare professionals agreed that the inappropriate use of antifungals can cause patient harm and contribute to antifungal resistance. A large proportion of the study cohort (63.2%) were also unfamiliar with local antifungal treatment guidelines. Most participants believed in the necessity of gaining more knowledge on antifungal agents (96.0%) and the importance of establishing courses on their rational use (91.8%). Many healthcare providers did not feel confident about their knowledge and practice regarding antifungal agents. Although healthcare professionals viewed antifungal stewardship as effective and necessary, a substantial proportion (49.0%) attributed inappropriate use to a lack of prescribers' knowledge. The overuse of antifungal agents was identified as the predominant factor contributing to

antifungal resistance. Only 9.0% of the study cohort were familiar with different strains of fungal organisms. Overall, the results highlighted a significant knowledge gap among the respondents in relation to antifungal stewardship.

4.2. Objective 2: The assessment of antifungal prescribing patterns of doctors in a tertiary care hospital via retrospective analysis

Antifungal prescribing practices involve the careful selection and use of antifungal medications to treat fungal infections, balancing efficacy with safety to manage and eradicate the infection while minimizing adverse effects and resistance development. Effective antifungal prescribing requires a multidisciplinary approach involving infectious disease specialists, pharmacists, microbiologists, and other healthcare professionals to ensure the best possible outcomes for patients with fungal infections.

For this study, a sample size of 370 prescriptions was determined, with each prescription randomly selected until saturation was reached. The analysed prescriptions were sourced from the intensive care, surgical, medical, and ARV outpatient departments, which represent a significant portion of the targeted study population, specifically immunocompromised patients (Figure 4).

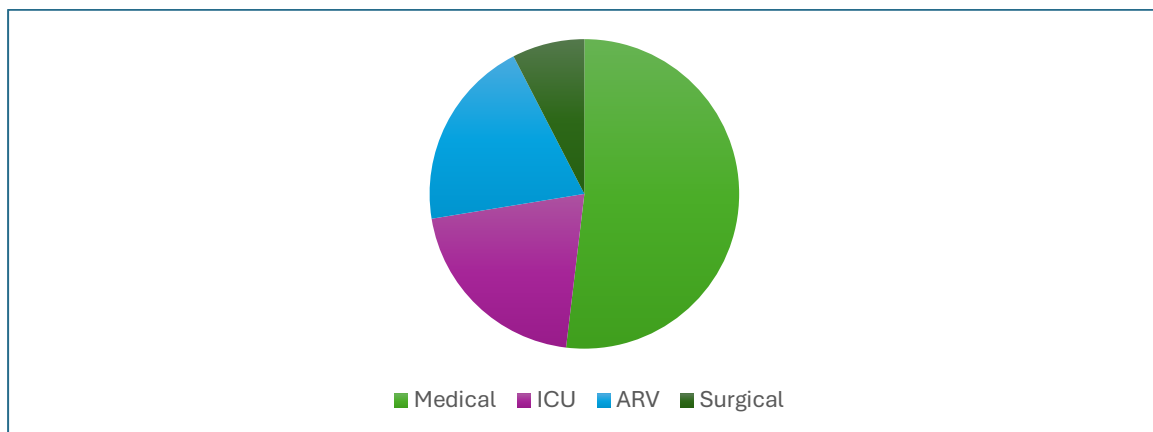


Figure 4: The distribution of antifungal prescriptions across the four departments.

The analysis of antifungal prescriptions revealed that the majority were issued by the medical department, accounting for 192 (51.9%) prescriptions of the total. This is followed by the ICU, with 76 (20.5%) prescriptions and the ARV department, with 74 (20.0%) prescriptions. The surgical department had the fewest antifungal prescriptions, totalling 28, which is 7.6% of the overall antifungal prescriptions. These findings are consistent with a study conducted by

Valerio et al., (2014), who reported that patients receiving antifungal agents were primarily admitted to the medical department (42.0%), followed by the intensive care units (21.0%) and surgical wards (12.0%).

The primary aim of this objective was to evaluate the quality of antifungal prescriptions dispensed at a tertiary care hospital, focusing on identifying errors or omissions that could impact patient outcomes and contribute to antifungal resistance. This evaluation aimed to report on the appropriateness of the prescribed antifungal agents, dosing regimens, dosing frequencies, and potential drug interactions. By comparing these prescriptions against the standards set by the South African Standard Treatment Guidelines, Essential Drugs List, and the South African Antibiotic Stewardship Program (SAASP), we were able to assess adherence to national guidelines and identify common deviations. Additional data including patient demographics, clinical symptoms, diagnoses, and details of the antifungal agents prescribed were collected, to facilitate a comprehensive analysis of prescribing patterns and trends across the various departments within the facility. These findings are reported and discussed in the sections that follow.

4.2.1. Patient demographics

Understanding patient demographics is crucial to healthcare as it aids in identifying trends in disease prevalence, treatment outcomes, and healthcare needs across different population groups (Purnell et al., 2016). Our study included gender, age group and retroviral disease (RVD) status as demographic parameters (Table 11).

4.2.1.1. Gender

Following the analysis of the prescriptions, patient demographics indicate that overall, females (53.8%; n=199) are slightly more prevalently prescribed antifungals as compared with males (46.2%; n=171) in the total patient population. Gender plays a significant role in the prevalence and severity of fungal infections (Kraševac, 2022). Studies have shown that gender differences impact the incidence of various fungal infections, with some diseases being more prevalent in males, such as invasive *Aspergillosis*, *Mucormycosis*, *Cryptococcosis*, *Coccidioidomycosis*, *Histoplasmosis*, and *Blastomycosis* (Kraševac, 2022).

Table 11: Demographics of patients receiving antifungal treatment

Parameter	Present	Medical (n = 192)	ICU (n = 76)	ARV (n = 74)	Surgical (n = 28)	Total (n = 370)
Gender	Male	83 (43.2%)	41 (54.0%)	35 (47.3%)	12 (42.9%)	171 (46.2%)
	Female	109 (56.8%)	35 (46.1%)	39 (52.7%)	16 (57.1%)	199 (53.8%)
Age Group (years)	0 - 17	22 (11.5%)	2 (2.6%)	2 (2.7%)	0 (0.0%)	26 (7.0%)
	18 - 30	40 (20.8%)	14 (18.4%)	15 (20.3%)	8 (28.6%)	77 (20.8%)
	31 - 40	60 (31.3%)	21 (27.6%)	22 (29.7%)	9 (32.1%)	112 (30.3%)
	41 - 50	34 (17.7%)	10 (13.2%)	11 (14.9%)	3 (10.7%)	58 (15.7%)
	51 - 60	15 (7.8%)	13 (17.1%)	13 (17.6%)	3 (10.7%)	44 (11.9%)
	61+	21 (10.9%)	16 (21.1%)	11 (14.9%)	5 (17.9%)	53 (14.3%)
Retroviral Disease (RVD) Status	Yes	44 (22.9%)	23 (30.3%)	74 (100.0%)	7 (25.0%)	148 (40.0%)
	No	135 (70.3%)	43 (56.6%)	0 (0.0%)	17 (60.7%)	195 (52.7%)
	Unknown	13 (6.8%)	10 (13.2%)	0 (0.0%)	4 (14.3%)	27 (7.3%)

4.2.1.2. Age

The age distribution amongst patients varied across all four departments. The results from this study indicated that the 31-to-40-year age group was the most prevalent followed by the 18-to-30-year age group. A study conducted in India demonstrated just this whereby more than 50% of patients with fungal infections fell within this age range (Meda et al., 2022). The oldest patient was 82 years of age, and the youngest patient was 3 months of age. The mean age of patients was 40 (n=370).

4.2.1.3. Retroviral Disease (RVD) Status

A significant proportion of the patients receiving antifungal treatment were RVD positive (40.0%; n=148). HIV in South Africa has evolved into a significant public health crisis over the past few decades. The epidemic began with isolated cases in the late 1980s and has since escalated to an estimated 6.4 million people living with HIV, making South Africa the country with the largest number of HIV-infected individuals globally, contributing to about 17% of the global burden of HIV infection (Gouws and Karim, 2010; Simelela et al., 2015). HIV infection significantly increases the risk of fungal infections, with opportunistic mycoses being a common concern among HIV-positive individuals (Magaji and Moi, 2022). Studies have shown that patients with CD4 counts below 200/cm³ are particularly vulnerable to life-threatening fungal infections (Chen et al., 2022). A study conducted in Jharkhand, East India, revealed that 47.45% of HIV/AIDS patients with CD4+ count ≤ 200 cells/mm³ had opportunistic fungal infections with *Candida* species, *Cryptococcus neoformans*, *Aspergillus* species, and dermatophytes being the most commonly isolated fungi (A. K. Sharma et al., 2023). Furthermore, the prevalence of invasive fungal infections, such as *Pneumocystis pneumonia* and *Cryptococcosis*, is notably higher in people living with HIV, leading to increased morbidity and mortality (Patel, 2020). Invasive fungal infections contribute significantly to the overall disease burden in HIV-positive populations (Bongomin et al., 2022). They often require extensive antifungal treatment, which can be costly and have numerous side effects. Therefore, there is a critical need for targeted interventions and resource allocation to manage fungal infections in HIV-positive populations, particularly in South Africa, where there is high HIV disease burden.

4.2.2. Antifungal treatment options available at the tertiary care hospital

In South Africa, the STG and EDL are key frameworks for healthcare. While the STG provides evidence-based protocols for diagnosing and treating common conditions across all levels of care, ensuring consistency and in medical practice, the EDL, categorised by care level, lists essential medications to meet the population's priority health needs, focusing on safe, effective and affordable treatments. At the tertiary care hospital in this study, antifungal agents from three classes are available in their respective formulations (Table 12). These include amphotericin B, fluconazole, clotrimazole, ketoconazole and micafungin.

The frequency of antifungal agents prescribed among the 370 prescriptions amounted to 405 with fluconazole being the most commonly prescribed antifungal agent across all four departments (n=353; 87.2%). This was followed by amphotericin B and clotrimazole topical cream (n=21; 5.2% and n=15; 3.7% respectively). Micafungin use was limited to the ICU and accounted for only 3.5% (n=14) of all antifungals prescribed. Both clotrimazole vaginal cream and ketoconazole only accounted for 0.3% (n=1) each.

Table 12: The distribution of antifungal agents prescribed across the various departments at the tertiary care hospital

	Medical	ICU	ARV	Surgical	Total
Amphotericin B (Intravenous)	8 (3.8%)	2 (2.5%)	11 (12.9%)	-	21 (5.2%)
Clotrimazole (Topical)	13 (6.2%)	-	1 (1.2%)	1 (3.3%)	15 (3.7%)
Clotrimazole (Vaginal)	-	-	-	1 (3.3%)	1 (0.3%)
Ketoconazole (Oral)	-	-	-	1 (3.3%)	1 (0.3%)
Fluconazole (Intravenous, oral)	189 (90.0%)	64 (80.0%)	73 (85.9%)	27 (90.0%)	353 (87.2%)
Micafungin (Intravenous)	-	14 (17.5%)	-	-	14 (3.5%)
Total	210 (100.0%)	80 (100.0%)	85 (100.0%)	30 (100.0%)	405 (100.0%)

Our findings aligned with a study conducted by Shuping et al. (2021) which found that the most commonly prescribed antifungals in public health care settings in South Africa were amphotericin B deoxycholate alone, fluconazole alone, and a combination of amphotericin B deoxycholate with fluconazole. Among the cases with known treatment, 35.0% received amphotericin B deoxycholate alone, 32.0% were prescribed fluconazole alone, and 30.0% received a combination of amphotericin B deoxycholate with fluconazole (Shuping et al., 2021). Fluconazole's status as the most commonly prescribed antifungal agent at the tertiary care hospital in this study may be attributed to several key factors that make it a practical and effective choice in this region. First, clinical guidelines and treatment protocols in South Africa frequently recommend fluconazole for common fungal infections, accounting for its widespread use. Its broad spectrum of activity allows it to target a wide range of fungal infections, particularly those caused by *Candida* species, which are prevalent in South Africa (Partha et al., 2022). The availability of fluconazole in both oral and intravenous formulations add to its versatility, enabling healthcare providers to use it in different clinical settings, from outpatient treatment to more severe cases requiring hospitalisation. The drug's good safety profile, with relatively few side effects, makes it a favourable option for long-term use, which is often necessary for treating fungal infections (Cokro et al., 2022; Ramírez-Carmona et al., 2023). Additionally, fluconazole is cost-effective, which is a significant consideration in a resource-limited setting like South Africa (Rajasingham et al., 2022). Its affordability ensures that it is accessible to a larger portion of the population, thereby improving public health outcomes (Kneale et al., 2016). Moreover, the straightforward dosing regimen of fluconazole promotes better patient compliance, as simpler medication schedules are easier for patients to follow consistently.

In this study, it was revealed that Amphotericin B use was limited to *Cryptococcal* infections particularly cryptococcal meningitis. *Cryptococcal* meningitis, primarily caused by *Cryptococcus neoformans*, is the most common cause of adult meningitis in the country (Naicker et al., 2021). Despite advances in antiretroviral therapy and disease managements, the burden of this disease persists (Otto et al., 2020). A systematic review revealed that from 1969 to 2021, approximately 40 948 cases of cryptococcosis were reported in Africa, with the highest prevalence in Southern Africa (Ibe et al., 2023). The limited use of micafungin suggests a conservative approach towards its' prescribing potentially to ensure adherence to established guidelines and to avoid unnecessary costs associated with this class of antifungal agents (Dlamini et al., 2019) A study in Turkey found that micafungin incurred a higher total cost

compared to liposomal amphotericin B, with an additional cost of €341 (approximately R6683,06) per treated patient (Neoh et al., 2018). These findings align with broader trends observed in public health care settings in South Africa, emphasising the need for accessible and effective antifungal treatments to address the significant burden of fungal infections in the region.

The majority of the antifungal agents were administered by the oral route (n=258; 69.7%) followed by the parenteral route (n=107; 28.9%), topical route (n=2; 0.5%), vaginal route (n=2; 0.5%) and lastly via nasogastric tube (n=1; 0.3%). These findings are consistent with a study conducted by Al Balushi et al., (2016), who found that most of the antifungals analysed in their study were administered by the oral route (73.4%), followed by the parenteral route (23.7%), topical route (2.0%), and then vaginal route (1.0%). The data indicates a clear preference for oral administration of drugs, reflecting its convenience and ease of use, which enhances patient compliance. Parenteral administration is also significant, often necessary for rapid drug action or when oral administration is not feasible. The low usage of topical and vaginal routes suggests their specific application to localized treatments, while the minimal use of the nasogastric tube highlights its role in specialized care for patients with severe swallowing issues.

4.2.3. Antifungal prescription analysis

When reviewing the antifungal prescriptions across the various departments within the tertiary care hospital, the appropriateness of antifungal use based on patients' diagnoses was thoroughly assessed (Table 13). This evaluation aimed to ensure that antifungal agents were prescribed in accordance with clinical guidelines and that treatment was justified by the presenting symptoms and diagnoses. Additionally, a detailed review of the incidence of microbiological and susceptibility testing was conducted for those prescriptions containing an antifungal agent (Table 13). This analysis was crucial to determine whether the use of antifungals was supported by laboratory evidence of fungal infection or resistance patterns. The review highlighted the importance of integrating microbiological data into clinical decision-making to optimize antifungal therapy, reduce the risk of resistance development, and enhance patient outcomes.

Table 13: Overview of the antifungal prescriptions reviewed at a tertiary care hospital in South Africa

Variable	Present	Medical (n = 192)	ICU (n = 76)	ARV (n = 74)	Surgical (n = 28)	Total (n = 370)	p-value
Does the current treatment align with recommended guidelines (Standard Treatment Guidelines, Essential Drug List, South African Antimicrobial Stewardship Program, Evidence-Based Medicine)	Yes	72 (37.5%)	4 (5.3%)	58 (78.4%)	3 (10.7%)	137 (37.0%)	5.0×10^{-8}
	No	120 (62.5%)	72 (94.7%)	16 (21.6%)	25 (89.3%)	233 (63.0%)	
Are there any microbiology results available or were any samples taken to be cultured?	Yes	11 (5.4%)	2 (2.6%)	26 (35.1%)	0 (0.0%)	39 (10.5%)	9.9×10^{-11}
	No	181 (94.3%)	74 (97.4%)	48 (64.9%)	28 (100.0%)	331 (89.5%)	
Were antifungal susceptibility testing conducted - results	Yes	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	1 (0.3%)	1.0×10^{-1}
	No	192 (100.0%)	76 (100.0%)	73 (98.7%)	28 (100.0%)	369 (99.7%)	

4.2.3.1. Prescription analysis: Diagnosis

For this study, appropriate antifungal use was based on diagnosis whereby antifungal use was deemed to be appropriate if the patient was diagnosed with a fungal infection. Only 37.0% (n=137) of the patients who were prescribed antifungal agents were diagnosed with fungal infections. Fungal diagnoses in this study ranged from superficial to systemic infections. *Cryptococcal* infections accounted for 30.0% (n=41) of the diagnosed fungal infections, followed by tinea infections (28.0%; n = 38), oropharyngeal candidiasis (15.0%; n=20), oesophageal candidiasis (14.0%; n=19) and other fungal infections (14.0%; n=19) such as genital and systemic candidiasis. There is a significant association between patients who were receiving an antifungal agent and being diagnosed with a fungal infection, as indicated by the p-value of <0.001 (p value 5.0×10^{-8}). This finding aligns with a study conducted by Al Balushi et al., (2016) who found that only 35.2% of their patients who were prescribed antifungal agents were diagnosed with a fungal infection.

There may be several reasons for patients receiving antifungal therapy despite the lack of a definitive diagnosis including prophylaxis or empiric therapy for underlying conditions such as immunocompromised status which may make these patients more susceptible to invasive fungal infections. However, receiving an antifungal agent without a confirmed fungal diagnosis carries several substantial risks. One primary concern is the potential for adverse side effects and drug interactions, which can be particularly severe in patients with comorbidities or those undergoing intensive treatments such as chemotherapy or transplantation (Dubrovskaya et al., 2019; Taynton et al., 2022). The misuse or overuse of antifungal agents can also lead to the development of antifungal resistance, making future infections harder to treat and increasing healthcare costs.

4.2.3.2 Prescription analysis: Microbiological testing

Microbiological testing was conducted in only a small proportion of the reviewed prescriptions (10.5%; n=39) and was found to be statistically significant (p value 9.9×10^{-11}). Cryptococcal antigen (CrAg) screening is a critical intervention in South Africa, particularly for individuals with advanced HIV disease, as it helps in the early detection and prevention of cryptococcal meningitis, a leading cause of death in this population (Mohamed et al., 2022). South Africa was the first country to implement reflexive laboratory CrAg screening nationally in 2016, following WHO recommendations for pre-emptive therapy to prevent cryptococcal meningitis

and associated mortality (DeSanto et al., 2022). At the tertiary care hospital in this study, cryptococcal antigen screening is practised in at-risk patients presenting with signs and symptoms of *cryptococcal* infection. From the total number of patients diagnosed with *Cryptococcal* infections or presented with signs of meningitis (n=41), cryptococcal antigen screening results were available for 37 (90.2%) of these cases. These findings demonstrate the positive impact of cryptococcal antigen screening on the early detection and prevention of infections caused by cryptococcus species, particularly, cryptococcus meningitis which may be associated with significant mortality rates if left undetected and untreated. The remaining cases where microbiological results were available were for individual cases of systemic *Candida auris* infection as well as a non-specific superficial fungal infection (2.6%; n=1 respectively).

4.2.3.3. Prescription analysis: Susceptibility testing

Antifungal susceptibility testing in public health care facilities is of paramount importance due to the rising prevalence of fungal infections and the emergence of antifungal resistance. In this study, susceptibility testing was only conducted in one case (0.3%). Even though susceptibility testing was not statistically significant (p value 1.0×10^{-1}), it is still an important factor to take note of. Antifungal susceptibility testing (AFST) is seldom performed in public healthcare facilities in South Africa. The diagnostic capacity for fungal diseases is generally limited across many African countries, including South Africa, with significant gaps in the availability of essential diagnostic tests such as fungal cultures and histopathological examinations (Badiane et al., 2023; Mushi et al., 2023). This limitation is exacerbated by the high cost of diagnostics, which restricts their usage in resource-limited settings (Badiane et al., 2023). Additionally, the complexity of antifungal treatment, which requires specialized knowledge and careful management of drug interactions, further complicates the implementation of AFST in public health systems that are already fragmented and under-resourced (Cole et al., 2017). Low antifungal susceptibility testing has significant consequences for patient management and public health. One major issue is the potential for misguiding treatment decisions which can lead to ineffective treatments, prolonged infections, and increased morbidity and mortality, particularly in immunocompromised patients such as those with HIV/AIDS (Erfaninejad et al., 2023; Wu et al., 2023).

Table 14: Antifungal prescribing practices at a tertiary care hospital in South Africa for prescriptions with a fungal infection diagnosis

Antifungal Prescribing Practices (n = 137)							
Variable	Present	Medical (n = 72)	ICU (n = 4)	ARV (n = 58)	Surgical (n = 3)	Total (n = 137)	p value
Appropriate Antifungal Choice	Yes	72 (100.0%)	4 (100.0%)	58 (100.0%)	2 (66.7%)	137 (100.0%)	-
	No	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (33.3%)	0 (0.0%)	
Appropriate Antifungal Dose	Yes	65 (90.3%)	3 (75.0%)	56 (95.6%)	3 (100.0%)	127 (92.7%)	2.5 x 10 ⁻¹
	No	7 (9.7%)	1 (25.0%)	2 (3.5%)	0 (0.0%)	10 (7.3%)	
Appropriate Antifungal Dosing Interval	Yes	49 (68.1%)	4 (100.0%)	57 (98.3%)	2 (66.7%)	112 (81.8%)	4.2 x 10 ⁻⁶
	No	23 (31.9%)	0 (0.0%)	1 (1.7%)	1 (33.3%)	25 (18.2%)	
Appropriate Antifungal Duration	Yes	52 (72.2%)	3 (75.0%)	47 (81.0%)	2 (66.7%)	104 (75.9%)	2.2 x 10 ⁻¹
	No	20 (27.8%)	1 (25.0%)	11 (19.0%)	1 (33.3%)	33 (24.1%)	
Drug - Drug Interactions	Yes	1 (1.4%)	2 (50.0%)	3 (5.2%)	1 (33.3%)	7 (5.1%)	7.0 x 10 ⁻¹
	No	71 (98.6%)	2 (50.0%)	55 (94.8%)	2 (67.7%)	130 (94.9%)	

4.2.4. Antifungal prescribing practices at a tertiary care hospital in South Africa

The prescriptions for those patients diagnosed with a fungal infection (n=137) were further analysed to assess appropriateness in terms of choice, dose, dosing interval, duration and drug-drug interactions (Table 14).

4.2.4.1. Prescription analysis: Antifungal choice

All of the prescriptions were appropriate in terms of antifungal choice. Due to the limited availability of antifungal agents in terms of variation, fluconazole remained the antifungal of choice for the treatment of various fungal infections (n=133; 97.1%). This included fluconazole as monotherapy or in combination with other antifungal agents such as amphotericin B for the treatment of cryptococcal infections or in combination with topical antifungal agents such as clotrimazole topical cream for the management superficial fungal infections. This is potentially owing to its' broad spectrum of activity making it able to target a wide variety of fungal infections as well as the indication for use as per SAASP and STG.

4.2.4.2. Prescription analysis: Antifungal dose

Antifungal dose was not statistically significant (p value 2.5×10^{-1}) across all four departments. Dosing errors were ascertained in 7.3% (n=10) of the 137 prescriptions after comparing prescribed doses to those in recommended guidelines such as the STG/EDL, SAASP and evidence-based medicine. Overdosing accounted for 60.0% (n=6) of the dosing errors with underdosing accounting for the remaining 40.0% (n=4). A concerning find was that of the prescriptions where underdosing was observed, three of those patients were being treated for cryptococcal meningitis. Cryptococcal meningitis is associated with a high mortality rate (Kajeekul et al., 2023). Underdosing, can lead to treatment failure and poor patient outcomes as seen in this study where one of the patients who received subtherapeutic dosing of fluconazole demised. Although there may have been several compounding factors that may have led to this patients' demise, the incorrect antifungal dosing may have facilitated this patients' poor outcome. Even though antifungal dosing was not statistically significant in this study, it remains an important factor that always needs to be taken into consideration. The correct antifungal dose is crucial for ensuring the drug's effectiveness in eradicating infections, preventing the development of resistant strains, minimizing toxicity, and accounting for pharmacokinetic and pharmacodynamic properties (Carmo et al., 2023). Dosing must also be

tailored to individual patient factors such as age, weight, organ function, and concurrent medications (More et al., 2023). Proper dosing ensures effective treatment, reduces risks, and leads to better patient outcomes.

4.2.4.3. Prescription analysis: Antifungal dosing interval

Inappropriate antifungal dosing intervals were observed in 18.3% (n=25) of the 137 prescriptions. The correlation between appropriateness and dosing interval was found to be statistically significant (p-value 4.2×10^{-6}). A greater proportion of patients who received antifungals at incorrect dosing intervals were being treated for dermatophytosis (84.0%; n=21), with the remaining patients being treated for vulvovaginal candidiasis (16.0%; n=4). Topical antifungal treatment is generally effective for the management of dermatophytosis. Research has shown that weekly dosing of fluconazole may be beneficial in more severe cases. (Rengasamy et al., 2017; Jartarkar et al., 2021). However, in this study, patients diagnosed with dermatophytosis were receiving daily dosing of fluconazole. Just as with the treatment of dermatophytosis, topical preparations of short duration are preferred over systemic treatment for the management of vulvovaginal candidiasis to avoid the adverse effects associated with oral antifungal therapy (Satora et al., 2023). Where systemic treatment is necessary, the SAMF suggests a single dose of oral fluconazole, however all the patients in this study received daily dosing. Incorrect antifungal dosing intervals can lead to subtherapeutic or supratherapeutic drug levels. This may result in ineffective treatment, prolonged infections, and increased risk of resistance development, or toxic levels, resulting in severe side effects and organ damage (Lewis and Andes, 2021). These dosing errors can extend hospital stays, elevate healthcare costs, and increase mortality risk, particularly in severe infections, while also negatively impacting patient quality of life and adherence to treatment (Vena et al., 2020). Ensuring appropriate dosing intervals is crucial for effective infection control and positive patient outcomes.

4.2.4.4. Prescription analysis: Antifungal Duration

Antifungal duration errors were observed in 24.1% (n=33) of the 137 prescriptions. This finding is similar to the findings of a study conducted by Valerio et al., (2014), who found that duration errors occurred in 27.0% of the antifungal prescriptions that were reviewed. The observed trend regarding treatment duration was that treatment was often too short (75.8%;

n=24) rather than too long (24.2%; n=8). This finding is concerning for patients diagnosed with serious fungal infections requiring a longer duration of therapy. Treatment guidelines are designed to incorporate the latest evidence-based recommendations for the management of common infections and disorders, highlighting the imperative need to follow these guidelines to ensure optimal patient care. For instance, the Standard Treatment Guidelines provides a detailed treatment plan for the management of cryptococcal meningitis which includes a two-week induction phase, an eight-week consolidation phase and a maintenance phase whereby treatment duration depends on patients CD4 count. In this study, antifungal duration errors occurred in thirteen patients being treated for *cryptococcal* infections. This is alarming as incorrect treatment duration, particularly regarding *cryptococcal* infections, may result in treatment failure and poor patient outcomes. Even though inappropriate duration was not statistically significant (p value 2.2×10^{-1}), maintaining appropriate antifungal duration of therapy is essential for effectively treating fungal infections as some infections may be resilient and may require a specific duration of therapy to eliminate the pathogen from the body (Bassetti et al., 2020). Stopping treatment prematurely can lead to persistent infection or recurrence.

4.2.4.5. Prescription analysis: Drug-drug interactions

Drug-drug interactions (DDIs) were observed in 5.1% (n=7) of the 137 prescriptions. The most common drug-drug interaction observed was that between fluconazole and rifampicin (n=4), a combination of four first line agents used in the treatment of tuberculosis, which amounted to 57.1% of the total drug-drug interactions. From the seven cases where drug-drug interactions were observed, three of these patients (42.9%), were being treated for cryptococcal meningitis. The remaining four cases were being treated for oesophageal candidiasis. All seven cases where drug interactions were observed were receiving oral antifungal therapy. Possible suggestions for mitigating the interaction between rifampicin and fluconazole include adjusting the dose of fluconazole, considering alternative antifungals, monitoring therapeutic levels of fluconazole, adjust administration timing, and closely observing treatment effectiveness (Rajasingham et al., 2018). Although drug-drug interactions only occurred in a small percentage of the prescriptions and were not statistically significant (p value 7.0×10^{-1}) in respect to this study, it is still a pivotal factor associated with antifungal prescribing patterns. DDIs involving antifungal agents can significantly impact their therapeutic efficacy and safety profile. These interactions can be pharmacodynamic, where the combined effect of drugs can be synergistic or antagonistic, or pharmacokinetic, where one drug alters the absorption, metabolism, or

excretion of another (Gupta et al., 2018). For instance, the interaction between fluconazole and rifampicin, as observed in this study. Fluconazole is a known inhibitor of the cytochrome P450 enzyme system, particularly CYP2C9, CYP2C19, and CYP3A4, which can lead to increased plasma concentrations of drugs metabolized by these enzymes (Yamashita et al., 2010). Rifampicin, a component of rifampin, is a potent inducer of CYP3A4, which can significantly reduce the plasma concentration of drugs metabolized by this enzyme, including fluconazole (Yamashita et al., 2010). This interaction can result in subtherapeutic levels of fluconazole, potentially compromising its antifungal efficacy. Additionally, the interaction between rifampicin and fluconazole can be complex and unpredictable, as rifampicin's induction of hepatic enzymes can persist even after discontinuation, necessitating careful monitoring of fluconazole levels and possible dosage adjustments (Yamashita et al., 2010). The interaction between fluconazole and rifampin is noteworthy since South Africa is known to have one of the highest incidences of tuberculosis in the world (Moyo et al., 2022). To manage these interactions, clinicians must be proactive, employing preventative measures and careful monitoring, especially in high-risk patients. Resources such as online databases and smartphone apps have been developed to assist healthcare providers in identifying and managing these interactions effectively (Lempers and Brüggemann, 2016). Thus, understanding and managing drug-drug interactions is crucial to optimising antifungal therapy and ensuring patient safety.

4.2.5. Summary of findings related to antifungal prescribing practices of doctors at a tertiary care hospital via retrospective analysis

- The medical department issued the majority of antifungal prescriptions (51.9%)
- Females comprised a slightly higher proportion (53.8%) of patients receiving antifungal prescriptions
- Fluconazole was the predominant antifungal agent prescribed, accounting for 87.2% of all prescriptions
- Cryptococcal infections were the most frequently diagnosed fungal infections (30%)
- A significant number proportion of patients (63.0%) received antifungal agents without diagnosis of a fungal infection
- Microbiological testing was conducted for only 10.5% of the prescriptions, predominantly for cryptococcal infections

- Incorrect antifungal dosing intervals were observed in 18.3% (p value<0.001) of the prescriptions with a fungal infection, while duration errors accounted for 24.1% of these prescriptions.

4.3. Correlations between the results obtained from the survey and retrospective prescription analysis

Correlations between the survey results and the retrospective prescription analysis can provide insights into the alignment between healthcare providers' knowledge, attitudes and perceptions and the actual prescribing patterns observed. This comparison can help identify discrepancies or confirm consistencies between what is reported in surveys and what is documented in prescription records, ultimately informing interventions to improve prescribing practices.

4.3.1. Correlation between doctors' familiarity with local antifungal guidelines with appropriate antifungal prescribing and antifungal prescription errors

The researcher drew a comparison between the doctors' familiarity with local antifungal guidelines and antifungal prescriptions with a fungal diagnosis as well as antifungal prescription errors (Figure 5).

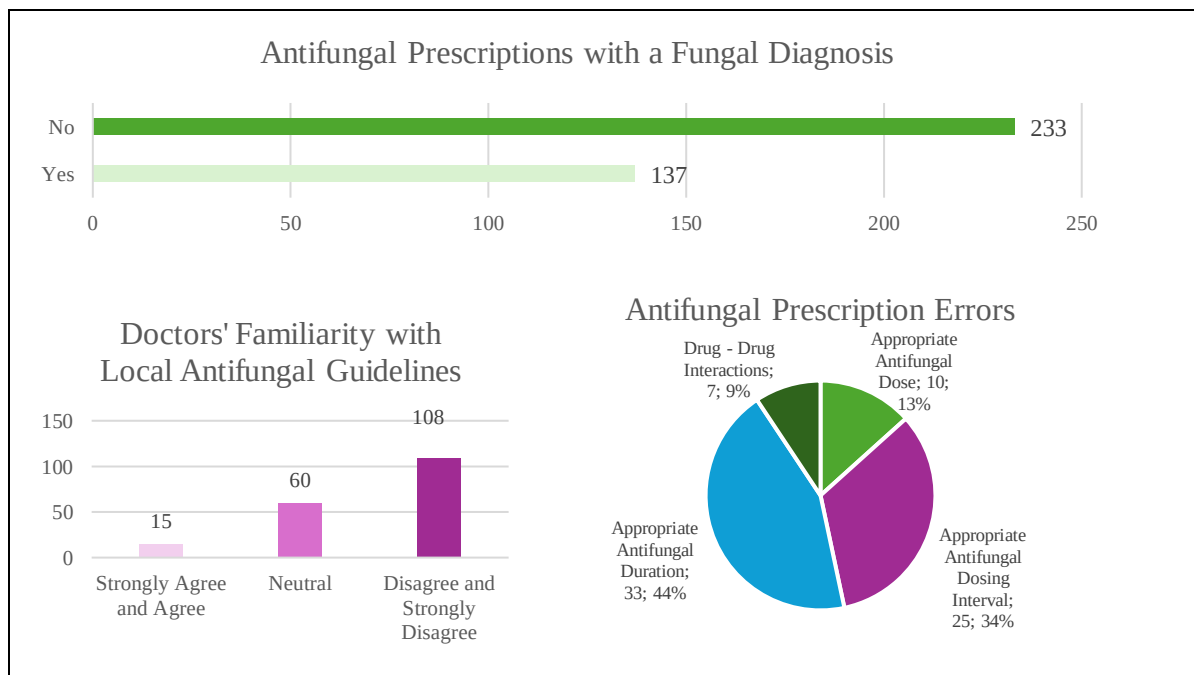


Figure 5: Correlation between doctors' familiarity with local antifungal guidelines with appropriate antifungal prescribing practices and antifungal prescription errors

Alamin and Kheder (2020) stated that in order for physicians to adhere to recommended guidelines, they must first be aware of guidelines. If a lack of awareness of guidelines and procedures exists, it is highly unlikely that good practice will follow. This is clearly demonstrated from the results of this study. The majority of the doctors (58.7%; n=109) who participated in this study were unfamiliar with local antifungal guidelines. This unfamiliarity potentially resulted in poor antifungal prescribing practices as depicted in this study whereby only 37.0% (n=137) of the analysed prescriptions (n=370) were for diagnosed fungal infections. In addition, a total of 75 prescription errors were observed ranging from duration to dosing interval errors. Drug-drug interactions were also included in these observations.

A review by Hassan et al., (2021) identified prescribers' lack of knowledge and awareness to surgical antimicrobial prophylaxis (SAP) guidelines as a common barrier to the adherence of these guidelines. Lack of awareness about latest medical knowledge can result in patients being managed with outdated information, which could potentially cause harm Grimshaw et al., (2012). Another study conducted by Jamaluddin et al., (2024) assessed antimicrobial prescribing patterns, guidelines compliance, and antimicrobial prescribing in surgical-practice units at a Malaysian teaching hospital. The findings from the study revealed that the compliance rate with guidelines was at 32.8% and an appropriateness level at 55.2%. The findings from these studies validate the observation made in our study where a lack of prescribers' familiarity with local antifungal guidelines resulted in poor antifungal prescribing practices.

In a recent study by Govender et al., (2021) that made use of questionnaires to explore the use of the STG and EDL and the rational use of medicines among physicians and prescribing nurses, several notable findings emerged. A small proportion of prescribers had received training on the STGs and EDLs, yet most doctors considered themselves knowledgeable about these guidelines and were not interested in further training. Although physicians had greater access to the STGs and EDLs, they reported using them only occasionally (79.4%). In contrast, prescribing nurses, who had less access, demonstrated slightly better adherence to the guidelines. These results further suggest a potential knowledge gap among physicians regarding current guidelines, indicating an opportunity for antifungal stewardship interventions, such as enhanced education and ongoing training for prescribers.

Although there are little to no distinct antifungal prescribing guidelines, the STG and EDL provides insights on various fungal infections and corresponding treatment approaches. Awareness to guidelines can be achieved through dissemination via medical journals,

conferences, training programs, and digital platforms (Hamdy et al., 2017). Improving prescriber understanding and agreement to guidelines can be fostered through evidence-based practice, demonstrating the benefits and efficacy of the guidelines with clinical research and case studies (Vincenzi et al., 2012). Integrating guidelines into daily practice involves practical measures, such as incorporating them into electronic health records, developing checklists, and providing tools to facilitate easy adoption. Ensuring regular adherence to guidelines requires continuous education, audits, feedback mechanisms, and fostering a culture of quality improvement within healthcare institutions. Therefore, ongoing education and robust communication strategies are essential to bridge this gap.

4.4. Objective 3: To suggest an antifungal stewardship policy and prescribing guideline based on the findings of objective 1 and 2.

A strategy to improve antifungal prescribing at the tertiary care hospital in this study is to develop and implement an antifungal stewardship policy and prescribing guideline.

4.4.1. Antifungal Stewardship Policy and Prescribing Guidelines

The main objective of this antifungal stewardship policy and prescribing guideline is to form an additional rational prescribing framework for the tertiary institution. The overall findings from this study revealed that there is a significant knowledge gap surrounding antifungal stewardship and the judicious use of antifungal agents. Additionally, poor antifungal prescribing practices were observed in majority of the antifungal prescriptions analysed. Below is a general template of the aforementioned guideline which can be adapted to suit the specific requirements of the healthcare facility.

4.4.2. Optimising Antifungal Use: A Stewardship Policy and Prescribing Guideline

4.4.2.1. Purpose

The purpose of this policy is to promote the appropriate use of antifungal agents, improve patient outcomes, reduce fungal resistance, and optimise resource utilisation.

4.4.2.2 Scope

This policy applies to all healthcare professionals involved in the prescribing, dispensing, and administration of antifungal medications within the tertiary care hospital.

4.4.2.3. Definitions

- Antifungal Stewardship: A coordinated program that promotes the appropriate use of antifungal agents to improve patient outcomes and reduce resistance (Ray et al., 2023).
- Empiric Therapy: The initiation of treatment based on clinical experience and observation, prior to a definitive diagnosis (Golan, 2015).
- Definitive Therapy: Treatment based on identified pathogens and their susceptibility profile (Abike, 2018).

4.4.2.4. Responsibilities

- Antifungal Stewardship Team: A multidisciplinary team responsible for overseeing antifungal use (Agrawal et al., 2016). This team may include infectious disease specialists, clinicians, clinical pharmacists, microbiologists, infection control personnel and nursing.
- Clinicians: Ensure appropriate use of antifungal agents according to guidelines.
- Clinical Pharmacists: Review antifungal prescriptions for appropriateness and provide recommendations.
- Registered Nurses: Administer antifungal agents as prescribed and monitor for adverse effects.

4.4.2.5. Monitoring and Follow-Up

(Pulcini et al., 2019; Johnson et al., 2020)

- Monitor patients for clinical response and adverse effects.
- Adjust therapy based on clinical and microbiological data.
- Regularly review antifungal use and resistance patterns within the facility.

4.4.2.6. Education and Training

(Valerio et al., 2015; Pulcini et al., 2019; Johnson et al., 2020; Satterfield et al., 2020)

- Provide ongoing education and training to healthcare professionals on antifungal stewardship.
- Update staff on changes in guidelines and resistance patterns.

4.4.2.7. Quality Improvement

(Pulcini et al., 2019; Johnson et al., 2020)

- Conduct regular audits of antifungal use and compliance with guidelines.
- Implement changes based on audit results to improve antifungal stewardship practices.
- An antifungal stewardship policy like the template provided, is essential for promoting the judicious use of antifungal agents, improving patient care, reducing resistance, and optimising healthcare resources. By implementing such a policy, the tertiary care hospital can achieve better health outcomes, cost savings, and regulatory compliance, all while maintaining a high standard of care.

An antifungal stewardship policy like the template provided, including a general antifungal prescribing guideline (Table 15) as well as an antifungal prescribing guideline for common fungal infections (Table 16) is essential for promoting the judicious use of antifungal agents, improving patient care, reducing resistance, and optimizing healthcare resources. By implementing such a policy, healthcare facilities can achieve better health outcomes, cost savings, and regulatory compliance, all while maintaining a high standard of care.

Table 15: Antifungal Stewardship Prescribing Guideline

Criteria	Description	Reference
Assessment and Diagnosis	Perform appropriate diagnostic tests to confirm fungal infections. Use clinical criteria and risk factors to assess the likelihood of fungal infections.	Kaewpoowat et al., 2016; Kaufman et al., 2019
Empiric Therapy	Initiate empiric antifungal therapy based on clinical judgment, patient risk factors, and local epidemiology. Re-evaluate empiric therapy based on culture results and clinical response.	Kanj et al., 2022; Shah et al., 2011
Definitive Therapy	Modify therapy based on microbiological results and susceptibility patterns. De-escalate therapy to the narrowest effective agent and duration.	Shah et al., 2011; van Engen et al., 2017
Prophylaxis	Use antifungal prophylaxis in high-risk patients (e.g., immunocompromised) as per guidelines. Evaluate the need for continued antifungal prophylaxis regularly.	Kourti et al., 2023; Zhou et al., 2023

Table 16: Treatment options for common fungal infections using available antifungal agents at the tertiary care hospital

Fungal Infection	Causative Organism(s)	First-Line Treatment	Alternative Treatment	Comment	Reference
Candidiasis (Oral)	<i>Candida albicans</i>	Nystatin Fluconazole	Ketoconazole	Common in immunocompromised patients. Topical treatment is effective for mild cases, while systemic treatment is reserved for more severe or refractory cases	Pappas et al., 2009
Candidiasis (Vaginal)	<i>Candida albicans</i>	Clotrimazole Vaginal Cream	Fluconazole	Recurrent infections may require maintenance therapy with weekly fluconazole. Non-albicans species may require alternative treatments.	Workowski et al., 2021
Oesophageal Candidiasis	<i>Candida albicans</i>	Fluconazole	Micafungin or Amphotericin B	Fluconazole remains the first-line agent for the treatment of oesophageal candidiasis however, patients experiencing fluconazole refractory oesophageal candidiasis may be treated with micafungin or amphotericin B.	Mohamed et al., 2019
Invasive Candidiasis	<i>Candida albicans</i> , <i>Candida parapsilosis</i> , <i>Candida tropicalis</i>	Fluconazole	Micafungin	Although echinocandins are considered the drugs of choice for the initial treatment of most cases of invasive candidiasis, fluconazole is widely in low-income countries with a low prevalence of azole resistance as the first therapeutic choice in all types of invasive <i>Candida</i> infections. Patients with invasive candidiasis and no previous exposure to azoles may receive azoles as initial therapy	Barantsevich and Barantsevich, 2022
	<i>Candida krusei</i> , <i>Candida glabrata</i>	Fluconazole	Amphotericin B		

	<i>Candida auris</i>	Fluconazole	Micafungin		
Cryptococcal Meningitis	<i>Cryptococcus neoformans</i>	Amphotericin B + Fluconazole	Fluconazole	Amphotericin B is combined with fluconazole for the initial phase of treatment (2 weeks), followed by a consolidation phase with high dosing of fluconazole only (8 weeks) and thereafter maintenance therapy with prolonged fluconazole therapy to prevent relapse.	Mkoko et al., 2020
Nonmeningeal cryptococcosis	<i>Cryptococcus</i> spp.	Fluconazole	Amphotericin B	Fluconazole is used for mild to moderate disease, while amphotericin B is reserved for more severe or disseminated cases.	Spadari et al., 2020
Dermatophytosis (Tinea)	<i>Trichophyton</i> spp. <i>Epidermophyton</i> spp. <i>Microsporum</i> spp.	Clotrimazole cream	Fluconazole	Topical treatment is usually sufficient however systemic therapy may be needed for extensive involvement	Jeya et al., 2023
Onychomycosis	Dermatophytes Nondermatophytic molds and yeasts	Clotrimazole cream	Fluconazole	Topical treatment alone is complicated by factors such as limited access to the nail bed and nail penetration. Treatment is long and requires and systemic therapy is generally needed for successful treatment	Maskan Bermudez et al., 2023)
Invasive Pulmonary Aspergillosis	<i>Aspergillus</i> spp.	Amphotericin B	Micafungin	Mortality rates from invasive pulmonary aspergillosis are still high and treatment is still challenging. As soon as there is a clinical suspicion of invasive pulmonary aspergillosis, therapy should be considered while the investigation is still in progress.	Kousha et al., 2011

Note: This table provides a general overview of antifungal treatment options for various fungal infections. Resistance patterns can vary geographically hence this table should be used in conjunction with local susceptibility and resistance patterns where available as well as individual patient factors

Chapter 5: General discussion and conclusions

This chapter aims to reflect on the research objectives, evaluate the extent to which they have been achieved, and consider the broader significance of the findings. Additionally, it addresses the limitations encountered during the research process and suggests avenues for future investigation. By drawing together the various threads of analysis and discussion, this concluding chapter offers a cohesive summary and reinforces the overall impact of the study.

5.1. The achievement of study objectives

The primary objectives of this study were to determine antifungal prescribing practices at a tertiary care hospital in South Africa as well as to assess the knowledge, attitudes and perceptions of doctors, pharmacists and nurses towards antifungal stewardship. Chapter two provided a comprehensive review of the literature in relation to fungal aetiology and epidemiology, global trends pertaining to fungal infections and the implications thereof, antifungal resistance and antifungal stewardship. Further to this, the objectives of the study were addressed as follows;

Objective 1: To determine the knowledge and attitudes of doctors, pharmacists, and nurses towards antifungal stewardship by means of survey analysis.

A total of 497 healthcare professionals participated in this study, comprising 184 doctors, 22 pharmacists, and 291 registered nurses. Nearly half of the doctors (49.3%) were unfamiliar with the term "antifungal stewardship," while registered nurses and pharmacists maintained a more neutral stance. Although the majority of healthcare professionals agreed that the inappropriate use of antifungal agents can harm patients and lead to the emergence of antifungal resistance, most were unfamiliar with local antifungal guidelines.

Participants identified the overuse of antifungal agents as the main factor driving antifungal resistance, with a significant lack of prescriber knowledge contributing to their inappropriate use within the facility. Many participants cited South Africa's high burden of disease as a reason why antifungal stewardship would benefit their facility. Additionally, there was a consensus on

the need for more education about invasive fungal infections and antifungal agents, as well as the establishment of a course on the rational use of antifungal agents.

Objective 2: To determine the practices of doctors towards antifungal stewardship by means of a retrospective analysis of antifungal prescribing practices in the intensive care, surgical, medical and ARV outpatient departments at a tertiary care hospital in South Africa.

A total of 370 prescriptions containing an antifungal agent were analysed to assess prescribing practices at the tertiary care hospital in this study. It was found that only 37.0% of patients receiving antifungal agents were diagnosed with a fungal infection. Microbiological and susceptibility testing were performed in only a small fraction of cases, indicating that antifungal agents were predominantly used empirically or prophylactically.

Further analysis of the prescriptions for patients with a confirmed fungal diagnosis evaluated appropriateness in terms of dosing, dosing intervals, duration, and drug-drug interactions. Seventy-five prescription errors were observed, with errors in duration and dosing intervals accounting for the majority of these mistakes.

The findings from the prescription analysis revealed that antifungal use was mainly empiric or prophylactic as only a small margin of the patients receiving an antifungal agent was diagnosed with a fungal infection.

Objective 3: To suggest an antifungal stewardship policy and prescribing guideline based on the findings of objective 1 and 2 to form the basis of antifungal stewardship management.

To effectively manage fungal infections while maintaining the judicious use of antifungal agents, an antifungal stewardship policy and prescribing guideline should be implemented. Our study found that antifungal prescribing practices at the tertiary care hospital can be improved as poor antifungal prescribing potentially occurred due to a lack in knowledge surrounding fungal aetiology and epidemiology as well as a lack in knowledge of local antifungal guidelines. Currently, there are no distinct antifungal prescribing guidelines at the tertiary care hospital in this study with healthcare professionals making use of the Standard Treatment Guidelines and Essential Medicines Lists as a treatment guide for fungal infections. As a result, an antifungal stewardship policy and prescribing guideline was developed by the researcher to

aid prescribers in improving their antifungal prescribing practices. This guideline, Chapter 4, section 4.4.1. aims to ensure the appropriate use of antifungal agents, enhance patient outcomes, reduce fungal resistance, and optimise resource utilisation. By involving a multidisciplinary team of healthcare professionals, this structured policy emphasises accurate diagnosis, judicious use of empiric and definitive therapies, and regular monitoring and follow-up. Prophylaxis is recommended for high-risk patients, and ongoing education and quality improvement initiatives are integral to the program. These measures collectively contribute to better patient care, reduced resistance, and more efficient use of healthcare resources.

5.2. Limitations of the study

This study focused exclusively on a single public tertiary care hospital within the City of Johannesburg, excluding private hospitals and those from other municipalities within Gauteng or South Africa. By concentrating solely on one public hospital and not including private facilities, which may differ significantly in patient demographics, resource availability, and healthcare protocols, the study's findings may have limited generalizability. Additionally, the antifungal prescription review only analysed prescriptions over twelve-month period, potentially missing long-term trends or patterns in antifungal use and patient outcomes. This limitation could result in an incomplete understanding of prescribing behaviours over time and may not fully reflect the broader context of antifungal stewardship practices. The scarcity of studies on antifungal prescribing practices made it challenging to contextualize the findings within broader trends and best practices, potentially affecting the depth and applicability of the conclusions drawn.

5.3. Recommendations and suggestions

5.3.1. Improve education and training surrounding appropriate antifungal use and stewardship

Improving education and training surrounding appropriate antifungal use and stewardship is crucial for enhancing healthcare practices and patient outcomes. The findings of this study highlight that healthcare providers not only need more education on the judicious use of antifungal agents and antifungal stewardship, but there is also a strong demand for it. Comprehensive training programs should be developed to cover antifungal pharmacology, mechanisms of action, resistance patterns, and clinical applications. Incorporating case-based

learnings and real-life scenarios into these programs can provide a more practical and applicable approach for healthcare professionals.

Regular workshops, seminars, online courses, and webinars can maintain the knowledge and skills acquired from these training programs, ensuring that healthcare providers stay updated with the latest research, guidelines, and advancements in antifungal therapy. Such continuous education promotes the judicious use of antifungals, helping to mitigate the development of resistance and preserving the efficacy of these essential medications. To further encourage participation, offering formal certification in antifungal stewardship upon completion of these programs can recognize expertise and promote ongoing professional development. This comprehensive and continuous approach to education and training ensures that healthcare professionals are well-equipped to make informed decisions, leading to more effective treatments and improved patient outcomes.

5.3.2. Provide antifungal-specific guidelines and policies to improve antifungal prescribing practices

Antifungal-specific guidelines and policies can significantly improve antifungal prescribing practices by providing a standardized framework for healthcare providers to follow. While the South African Standard Treatment Guideline is available for the management of fungal infections, an antifungal-specific guideline would streamline decision-making and may be timesaving for clinicians. This standardisation ensures consistency in care, as all clinicians adhere to the same evidence-based protocols, which reduces variability in treatment approaches and enhances the overall quality of care. These specialised guidelines also simplify decision-making by offering clinicians straightforward recommendations, helping them make informed choices quickly, particularly in complex cases or when dealing with less common infections. Additionally, these guidelines encapsulate best practices, highlighting first-line treatments and alternative options tailored to patient-specific factors and local resistance patterns.

An antifungal-specific guideline may also serve as an excellent educational tool, enhancing the knowledge base of healthcare professionals. They provide a reliable reference for training programs, ensuring that all team members are well-versed in the latest research and clinical evidence. This comprehensive understanding fosters a more knowledgeable and confident healthcare workforce, better equipped to handle antifungal therapies effectively. Furthermore,

when guidelines are clearly communicated and readily accessible, they promote adherence, as clinicians can easily refer to them during their practice. This accessibility and clarity will lead to more consistent application of recommended practices, ultimately improving patient outcomes and combating antifungal resistance more effectively.

5.4. Areas for future study

This study focused on evaluating the knowledge, attitudes, and practices of doctors, pharmacists, and nurses in a tertiary care hospital in South Africa regarding antifungal stewardship. Several areas for future study have emerged as a result of this study. One critical area is the impact of education and training programs on healthcare professionals' knowledge and practices towards the judicious use of antifungal agents and stewardship. Future research should assess the long-term effectiveness of educational interventions on healthcare providers' knowledge and practices, determining whether regular training sustains improved prescribing behaviours.

Another area of interest is the barriers to implementation. Future studies should explore both general and institutional barriers that hinder the effective implementation of antifungal stewardship programs, such as workload, resource limitations, and administrative support. Examining behavioural and attitudinal barriers that impact the adoption of stewardship practices, including resistance to change, risk perception, and personal biases, will provide valuable insights on approaches that can be undertaken to enhance the implementation of antifungal stewardship programs.

Research should also focus on patient outcomes and resistance patterns. By evaluating the direct impact of antifungal stewardship programs on patient outcomes, such as treatment success rates, adverse events, and mortality rates, we will be able to gauge if these programs directly improve patient. Monitoring changes in antifungal resistance patterns in response to stewardship interventions will provide data to continuously refine and adapt guidelines. Since antifungal stewardship programs requires the involvement of a multidisciplinary team, investigating interdisciplinary collaboration in improving antifungal stewardship and identifying best practices for fostering effective teamwork among doctors, pharmacists, and nurses will be beneficial. Due to several advancements in technology, another area for future study involves examining the role of technological innovations to support antifungal stewardship programs. These studies may be beneficial as such studies could explore how

electronic health records, decision support systems, and other digital tools can enhance adherence to guidelines and improve prescribing practices.

5.5. Conclusion of the study

This study aimed to assess the knowledge, attitudes, and practices of doctors, pharmacists, and nurses regarding antifungal stewardship in a tertiary care hospital in South Africa. To our knowledge, it is one of the first studies conducted in South Africa to focus exclusively on antifungal agents and antifungal stewardship rather than on antimicrobials and antimicrobial stewardship in general.

The findings highlight a critical need for improved antifungal stewardship and more comprehensive education for healthcare professionals. Notably, gaps in knowledge about antifungal prescribing practices pose significant challenges to patient outcomes and public health. Traditionally, physicians have had a predominant role in prescribing decisions due to their "power of the pen," and their influence will likely continue to shape practices. However, the study emphasises the importance of a collaborative approach to antifungal stewardship, involving ongoing education and shared responsibility among all healthcare professionals.

By expanding the focus to include nurse practitioners and pharmacists, we can achieve more effective and informed antifungal prescribing practices. This shift will not only enhance the quality of care but also foster a balanced and thorough approach to managing the burden of fungal diseases in South Africa. Ultimately, the study underscores the need for a multi-disciplinary effort to advance antifungal stewardship, improve prescribing practices, and mitigate antifungal resistance, thereby improving patient outcomes.

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Appendix A: WITS-HREC (Medical) certificate



R14/49 Mrs Kiara Sudu

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL) **CLEARANCE CERTIFICATE NO. M230520 M230810-B-0001**

NAME: Mrs Kiara Sudu
(Principal Investigator)

DEPARTMENT: Pharmacy and Pharmacology - School of Therapeutic Science
[REDACTED] Provincial Tertiary Hospital - Intensive Care, Medical, Surgical and ARV Outpatient departments

PROJECT TITLE: The Assessment of Antifungal Stewardship Implementation in a Tertiary Care Hospital in South Africa: Evaluating Knowledge, Attitudes and Practices of Healthcare Professionals and Developing Evidence-Based Guidelines

DATE CONSIDERED: 26-May-2023

DECISION: Approved unconditionally

CONDITIONS: N/A

NOTE: Application Number: MED23-04-238

SUPERVISOR: Dr Stephanie Leigh-de Rapper and Mrs Zelna Booth

APPROVED BY: _____
Prof P. Ruff, Chairperson, HREC (Medical)

DATE OF APPROVAL: 10-Aug-2023 **EXPIRY DATE:** 10-Aug-2028

This clearance certificate is valid for 5 years from data of approval. Extension may be applied for.

DECLARATION OF INVESTIGATOR(S)

I/we fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report** in the month date of convened meeting each year until study is closed. Failure to submit annual report will result in ethics clearance certificate suspension. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. Unreported changes to the application may invalidate the clearance given by the HREC (Medical). Email a signed copy of ethics clearance certificate to HREC-Medical.ResearchOffice@wits.ac.za

Signature of Principal Investigator

17-Aug-2023

Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix B: Site approval from the tertiary care hospital in this study



GAUTENG PROVINCE

107 41711
REPUBLIC OF SOUTH AFRICA

TERTIARY HOSPITAL
Enquiries: Dr [REDACTED] CEO

PR NO: [REDACTED]

Tel: [REDACTED]

E-mail: [REDACTED]@gauteng.gov.za

To : Ms Kiara Sudu

Subject : Permission to conduct research at [REDACTED] Tertiary Hospital

From : [REDACTED] Chief Executive Officer

Date : 29 August 2023

This is to notify you that you have been granted permission to conduct research in our institution for the following study:

Study Title: The Assessment of Antifungal Stewardship Implementation in a Tertiary Care Hospital in South Africa: Evaluating Knowledge, Attitudes and Practices of Healthcare Professionals and Developing Evidence-Based Guidelines

NHRD Reference Number: GP_202305_055

Permission with the following restrictions:

- The study should not interfere with service provision.
- Data collection should not be done by hospital staff but the researcher themselves

Permission to conduct research as per study protocol

Please note the institution requires for all data collection and interaction with staff to be as outlined in the study protocol and within the constraints of ethics approval obtained for this study. Should any of these parameters or professional conduct be violated at any stage then the [REDACTED] Research Committee reserves the right to review and change the decision to allow the researcher to conduct research at the institution.

Please report to the undersigned chair of the Research Committee with all your documents on the first day at the institution for further instructions and introductions.

You are requested to share the research findings with [REDACTED] Tertiary Hospital Team at the conclusion of the study.

Recommended by: [REDACTED]

[REDACTED] Research Committee

Signature: [REDACTED]

Date: 29 August 2023

Approved by:

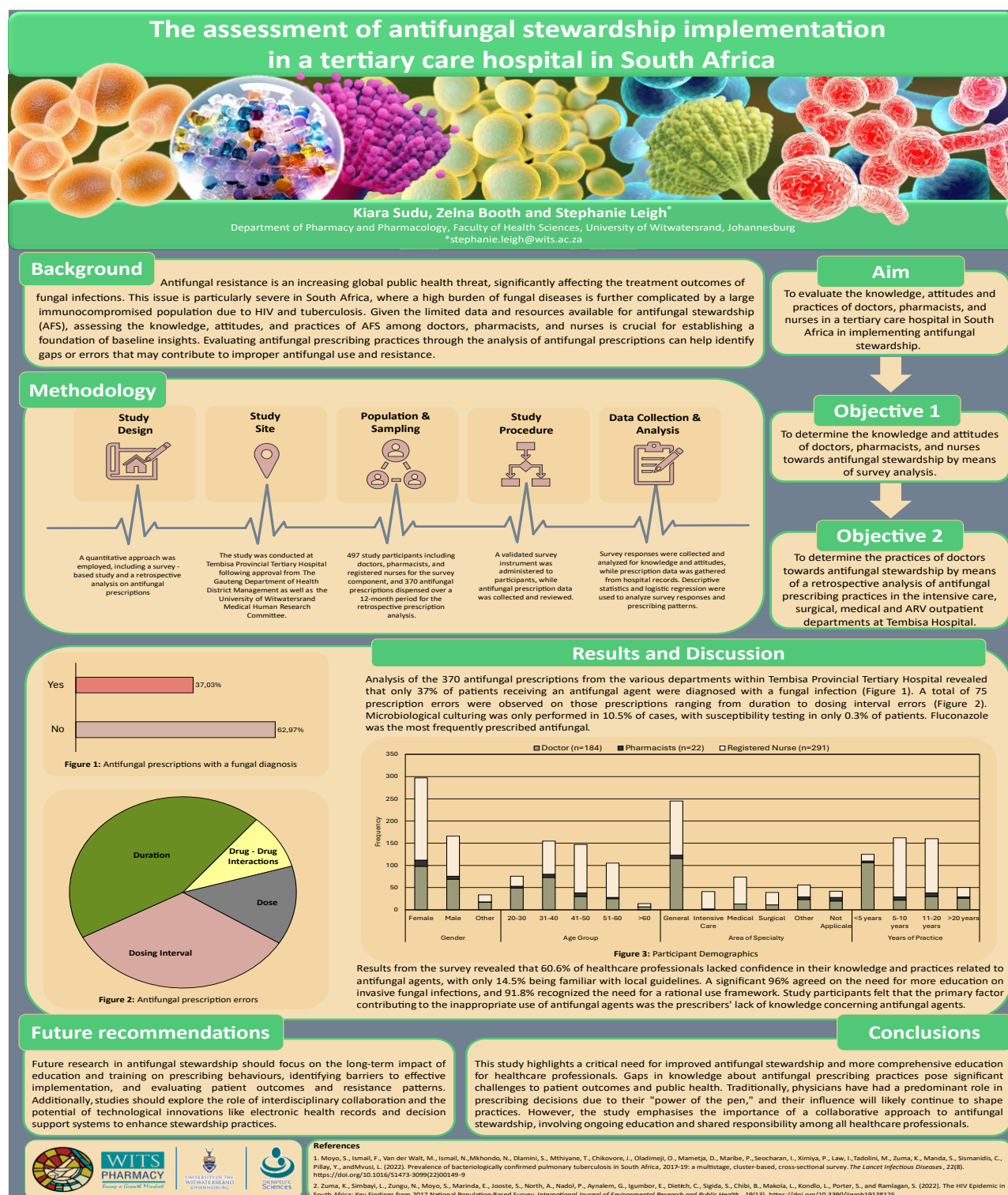
Dr [REDACTED]

Acting CEO, [REDACTED] Tertiary Hospital

Signature: [REDACTED]

Date: 30/08/2023

Appendix C: Faculty of Health Sciences Research Day poster submission



Appendix D: Approved study protocol



CANDIDATE'S SURNAME: SUDU [Please print]	FIRST NAME/S: KIARA	STUDENT NUMBER: 2751986
CURRENT QUALIFICATIONS: BPharm (University of KwaZulu Natal)		
TEL: N/A	CELL: 0836319348	E-MAIL: kiara.sudu@gmail.com FAX: N/A
DEGREE FOR WHICH PROTOCOL IS BEING SUBMITTED: MPharm		
PART-TIME OR FULL-TIME: Full-Time		
FIRST REGISTERED FOR THIS DEGREE: 2023	TERM: First Term	YEAR: 2023
DEPARTMENT: Department of Pharmacy and Pharmacology		
TITLE OF PROPOSED RESEARCH: The Assessment of Antifungal Stewardship Implementation in a Tertiary Care Hospital in South Africa: Evaluating Knowledge, Attitudes and Practices of Healthcare Professionals and Developing Evidence-Based Guidelines		
CANDIDATE'S SIGNATURE:		DATE: 16.04.2023
SUPERVISOR 1 (NAME & SURNAME): Dr Stephanie Leigh-de Rapper		50% Supervision
SUPERVISOR'S QUALIFICATIONS: BPharm, MPharm, PhD		
SUPERVISOR'S DEPARTMENT: Department of Pharmacy and Pharmacology		
SUPERVISOR'S ADDRESS / TEL / E-MAIL: University of Witwatersrand, Medical School, Faculty of Health Sciences, 7 York Rd, Parktown, Johannesburg, 2193. 0117172268, stephanie.derapper@wits.ac.za		
SUPERVISOR 2 (NAME & SURNAME): Ms. Zelna Booth		50% Supervision
SUPERVISOR'S QUALIFICATIONS: BPharm, MPharm		
SUPERVISOR'S ADDRESS / TEL / E-MAIL: University of Witwatersrand, Medical School, Faculty of Health Sciences, 7 York Rd, Parktown, Johannesburg, 2193. 0117172912, zelna.booth@wits.ac.za		
SYNOPSIS OF RESEARCH: Introduction and Justification of the study: Globally, antifungal resistance is becoming an increasing threat to public health, having a substantial impact on treatment outcomes. With a limited number of antifungal agents currently available to manage these infections, the judicious use of these agents needs to be encouraged. South Africa has a high burden of fungal disease due to a large portion of the population being immune-compromised due to HIV-infection and tuberculosis. Currently, the exploration of antifungal stewardship in South Africa is still in the early stages of development with further research required regarding its implementation. Aim: To evaluate antifungal stewardship knowledge, attitudes and practices amongst doctors, pharmacists, and nurses in a tertiary care hospital in South Africa. Methods: The study will be conducted by means of health care professionals completing a survey as well as the researcher reviewing antifungal prescriptions dispensed in the previous twelve months at a tertiary care hospital within the City of Johannesburg. Findings from the study will be reported to the study site education committee for evaluation. Expected outcome/s: The outcomes from this study will demonstrate antifungal prescribing patterns within tertiary public health care settings as well as ascertain doctors, pharmacists and nurses knowledge, attitudes and perceptions regarding antifungal stewardship.		
WITS ETHICS PENDING: Yes	WITS ETHICS APPROVED: Pending	IF Y SUPPLY ETHICS CLEARANCE CERTIFICATE AS ATTACHMENT AND INCLUDE ETHICS NUMBER HERE:
*Please note the final human ethics clearance certificate or animal ethics certificate must be available prior to starting research		
As supervisor/s, I/we confirm that I have read the protocol which has been submitted for assessment.		
SIGNATURE OF SUPERVISOR/S:		
PROTOCOL ACCEPTED BY HEAD OF DEPARTMENT/RESEARCH COORDINATOR	SIGNATURE:	DATE: 16.04.2023

1. Introduction

Fungal infections include any disease conditions that are caused by fungi (Janbon et al., 2019). Common causative pathogens of these infections include *Candida*, *Cryptococcus* and *Aspergillus*, causing oral or vaginal thrush, fungal nail infections, and athlete's foot (Kohler et al., 2015). These conditions may be bothersome and sometimes even debilitating but they can very often be treated effectively upon diagnosis (NICD, 2019). However, invasive fungal infections can be life-threatening to conventionally healthy patients, but more so for immunocompromised individuals, such as those who are HIV-positive, transplant patients receiving immunomodulating drugs, as well as oncology patients undergoing aggressive immunosuppressive therapy (Enoch et al., 2016; Kainz et al., 2020; CDC, 2022). The Global Action for Fungal Infections Foundation (GAFFI) estimates that more than 300 million people of all ages suffer from serious fungal infections worldwide each year, with more than 1.5 million of these people dying as a result (Rodrigues & Nosanchuk, 2020).

Currently, only five main classes of antifungal agents are available for the treatment of fungal infections, namely azoles, echinocandins, polyenes, allylamines and pyrimidine analogues (Fuentefria et al., 2018). These antifungal agents are expensive, making the treatment of invasive fungal infections costly (Ou et al., 2017). Invasive fungal infections are challenging to treat and prove fatal in immunocompromised patients, resulting in prescriber pressure to initiate antifungal treatment in immunocompromised patients (Muñoz et al., 2015), where the practice of empiric antifungal therapy is prevalent. In addition, the use of antifungal agents for prophylaxis or prevention, particularly in immunocompromised patients, results in increased cost and unnecessary exposure to medicines (Muñoz & Bouza, 2016). The practice of empiric antifungal therapy and prophylactic initiation of antifungal therapy significantly contributes to the emergence of antifungal resistance, similarly to that seen with antimicrobial resistance development to antibiotics due to irrational prescribing. Antifungal resistance is becoming an increasing threat to public health, particularly due to the increase in the use of antifungal agents with the burden of fungal infections peaking in low- and middle-income countries, with most invasive fungal pathogens being opportunistic, infecting immunocompromised patients (Hendrickson et al., 2019; Greener, 2022). This has a significant impact on treatment outcomes, as most of the antifungal agents used are ineffective due to the development of resistance (Campoy and Adrio, 2017).

Mechanisms of drug resistance includes modified drug-target interactions, reduced cellular drug concentrations facilitated by drug efflux transporters, barriers in biofilm permeability and gene mutations (Perlin et al., 2017). Over the past 10 years, multidrug-resistance *Candida auris* has spread throughout the world, causing large outbreaks in hospitals (NICD, 2019). This growth in resistance is often the result of improper use of antifungal agents, thus contributing significantly to the treatment burden (Gross et al., 2015). In South Africa, multidrug-resistant *Candida auris* is highly prevalent in hospitals, with most isolates being resistant to azole antifungals (Maphanga et al., 2021). Owing to the limited availability of antifungal agents as well as the substantial cost implications, the emergence of single-drug and now multi-drug resistance is much more difficult to manage (Prasad et al., 2016).

Over recent years, the formation and implementation of global antibiotic stewardship (ABS) programs have been established due to developing resistance to available antibiotics. The main objective of ABS is to ensure the appropriate use of antibiotics to preserve the future effectiveness of these agents as well optimize patient outcomes (Dyar et al., 2017). Based on previous research, antibiotic stewardship programs have proven to be beneficial in increasing compliance to targeted therapy and reducing antibiotic consumption and cost, ultimately improving patient outcomes, and reducing the development of resistance (Siachalinga et al., 2022). Antifungal stewardship (AFS) shares a similar aim to ABS but has features and challenges specific to the management of invasive fungal infections (Richardson, 2016). However, very little is known about AFS, hence it is not routinely practiced in hospitals as compared to ABS (Muñoz & Bouza, 2016; Hart et al., 2019). The main goals of AFS are optimized care, de-escalation or, if appropriate, discontinuation of antifungal therapy, reduced costs and reduced fungal resistance without adverse effects on morbidity and mortality. Therefore, the incorporation of AFS within antimicrobial stewardship programs can prove to be tremendously advantageous (Gómez-Gómez & Cornejo-Juárez, 2019).

The exploration of AFS is still in the early stages of development in most settings with further research needed regarding its implementation (Gohlar & Hughes, 2021). Clinical practice guidelines are developed to create and distribute the best existing evidence to guide clinical practice; with the purpose of increasing quality care and reducing inappropriate interventions (Ryan, 2017). Antifungal stewardship is multifaceted and goes far beyond “policing prescribing”, with several interdependent and mutually reinforcing factors which

need to be considered such as risk assessment, antifungal toxicity, spectrum of activity, tolerability and fungal diagnostics (Ananda-Rajah et al., 2020; Nivoix et al., 2020).

1.1. Problem Statement

In South Africa's public health sector, adherence to the Standard Treatment Guidelines and Essential Drug List is paramount to ensure appropriate treatment choices. For physicians to adhere to these guidelines, they must first be cognisant of these such guidelines, rationally agree with them, implement them in their daily care and consistently adhere to them. If a lack of awareness of these guidelines and procedures exists, it is highly unlikely that good practice will follow (Alamin & Kheder, 2020). South Africa has the highest number of people living with HIV in the world (Zuma et al., 2022). In addition, South Africa has one of the highest rates of tuberculosis (TB) per capita in the world (Moyo et al., 2022). With such a high disease burden, research on AFS can play an important role in improving antifungal resistance patterns and reducing the incidence of antifungal resistance. With an increase in antifungal resistance as well as a high disease burden, it is important to determine how antifungals are being utilized and managed in South Africa.

1.2.Rationale for study

This study will be conducted in a public health care facility which is crucial as majority of the South African population rely on the public health sector to meet their healthcare needs (Maphumulo, W.T. and Bhengu, B.R, 2019). In addition, the high burden of disease that South Africa is facing due to HIV and AIDS as well as other opportunistic diseases such as tuberculosis, makes this study imperative as it will provide vital insight on antifungals and antifungal stewardship. Due to limited data and resources surrounding AFS, understanding the knowledge, attitudes, and practices of AFS amongst doctors, pharmacists, and nurses, can build a foundation for baseline learnings on AFS. Evaluation of antifungal prescribing practices by analysing antifungal prescriptions can be useful in identifying gaps or errors which may contribute to improper antifungal utilization and antifungal resistance. Hence findings from this study can be beneficial in improving patient outcomes. The results garnered from this study can then be expanded on to improve antifungal prescribing patterns as well as understand doctors, pharmacists and nurses' knowledge regarding AFS, which can support its' exploration. This will assist in developing an antifungal stewardship policy and prescribing guideline which will ultimately have a positive impact on treatment outcomes and improved patient care.

2. Aim and objectives

To evaluate the knowledge, attitudes and practices of doctors, pharmacists, and nurses in a tertiary care hospital in South Africa in implementing antifungal stewardship.

This aim of the study will be met through the following objectives:

2.1 To determine the knowledge and attitudes of doctors, pharmacists, and nurses towards antifungal stewardship by means of survey analysis.

2.2 To determine the practices of doctors, pharmacists, and nurses towards antifungal stewardship by means of a retrospective analysis of antifungal prescribing practices in the intensive care, surgical, medical and ARV outpatient departments at a tertiary care hospital in South Africa.

2.3 To suggest an antifungal stewardship policy and prescribing guideline based on the findings of objective 1 and 2 to form the basis of antifungal stewardship management.

3. Methods

A quantitative research approach will be used to garner data on the knowledge, attitudes and practices amongst doctors, pharmacists, and nurses towards antifungal stewardship in a public sector tertiary care hospital. Quantitative research comprises of collecting and analyzing structured data which can be represented numerically (Taguchi, 2018). Quantitative data is collected by utilizing tools such as surveys. This method assists in obtaining accurate and reliable measurements. The rationale for using a quantitative research approach over a qualitative research approach is that quantitative research yields more objective results which can then be used to analyse trends and tests hypotheses hence suitable for this study.

4.1. Objective 1: To determine the knowledge and attitudes of doctors, pharmacists and nurses towards antifungal stewardship by means of survey analysis.

4.1.1. Study site

A descriptive cross-sectional quantitative analysis of the knowledge and attitudes of doctors, pharmacists, and nurses practicing at a tertiary care hospital towards AFS. Tertiary hospitals play a larger role in the provision of medical education and scientific research. They operate as medical centers, serving multiple regions, and offering services that surpass primary and secondary hospitals (Yan et al., 2020). Similar studies are currently being conducted at the tertiary care hospital with the focus being on antibiotic agents. Since this study focuses on

antifungal agents, a more comprehensive representation of that facility in terms of antimicrobials will be obtained.

4.1.2. Study design and instrumentation

A study information document (Appendix E) and survey instrument (Appendix F) to ascertain the knowledge and attitudes amongst doctors, pharmacists and nurses has been developed by the researcher by means of reviewing previously used research tools and studies (Labi et al., 2018; Alamin & Kheder, 2020; Ashraf et al., 2021). The survey (Appendix F) will record basic information regarding the study participants demographics, knowledge, attitudes and perceptions of antifungal use, antifungal stewardship, antifungal resistance, and education. The survey has been adapted to a South African tertiary hospital context. Survey questions focus on various aspects related to antifungal agents and antifungal stewardship. This includes participants understanding of antifungal stewardship principles, appropriate and inappropriate use of antifungal agents, antifungal prescribing patterns as well as antifungal resistance.

4.1.3. Population and sampling

Population refers to the sum of all the units who meet the inclusion criteria valid for an investigation (Majid, 2018). For this study, the population comprises of all practicing doctors, pharmacists and nurses working at the tertiary care hospital who meet the inclusion criteria.

4.1.3.1. Inclusion criteria

Doctors who have completed their MBChB degree and are registered with The Health Professions Council of South Africa (HPCSA), will be included in this study. This includes intern and community service doctors. Pharmacists who have completed their BPharm degree and are registered with The South African Pharmacy Council (SAPC) will be invited to participate in this study. This includes pharmacist interns and community service pharmacists. Only Registered Nurses (RN) who are registered with the South African Nursing Council (SANC) will be included in this study since registered nurses are responsible and accountable for the administration of medicines.

4.1.3.2. Exclusion criteria

University students will be excluded from this study. Enrolled nurses and enrolled nursing auxiliaries will also not be included in the study since only registered nurses are accountable for medicine administration.

4.1.4. Sampling size and sampling method

4.1.4.1. Sample size

The sample size for the study was calculated using the formula below:

$$n = \frac{Nz^2P(1 - P)}{d^2(N - 1) + z^2P(1 - P)}$$

N = population

P = expected prevalence (in proportion to 1)

n = sample size

d = precision $d=(0.5(1-P))$

z = stats for CI (CI=z.d)

The tertiary care hospital has 349 doctors, 23 pharmacists and 1182 registered nurses working in their facility. Based on a 5% margin of error, 95% confidence interval and 50% response distribution calculation, the sample size for this study is calculated to be 184 doctors, 22 pharmacists and 291 registered nurses. The sample sizes have been calculated based on the internationally accepted sample size calculation as indicated above, using Raosoft® software. Study participants will be randomly selected until saturation is obtained.

4.1.4.2. Sampling method

The selection of participants from the inclusion criteria for the study will be conducted using the probabilistic random sampling method. This method is used to reduce the likelihood of bias by ensuring generalizability. Doctors, pharmacists and registered nurses will be randomly selected to participate in the study provided they meet the inclusion criteria. Their participation in the study is voluntary and randomized sampling will be conducted until saturation is obtained. The selection of participants is based on the principle of randomization whereby each participant has an equal probability of being chosen so that an unbiased representation of the total population can be obtained.

4.1.5. Pilot Study

The researcher will conduct a pilot study using 10% of the cohort population to determine the tool's reliability and effectiveness, and whether the tool can be adapted to the South African healthcare setting. The pilot study will be conducted by the researcher as a preliminary method on a smaller scale for the researcher to determine how the study needs to be modified. The survey will be disseminated to 19 doctors, 1 pharmacist, and 29 nurses at the tertiary care

hospital prior to the commencement of the study. If necessary, changes to the survey will then be made upon completion of the pilot study.

4.1.6. Study procedure

Upon obtaining ethical approval from the University of Witwatersrand Medical Human Research Ethics Committee (HREC), the researcher will provide a study information document (Appendix E) and a developed survey (Appendix F) adapted from previously published articles (Labi et al., 2018; Alamin & Kheder, 2020; Ashraf et al., 2021) to question the study participants (doctors, pharmacists, and nurses). Healthcare Professionals who meet the inclusion criteria will be invited to attend an information session where the study will be explained to them by the researcher. Any questions raised by the study participants will be answered by the researcher during the information session.

4.1.6.1. Information session

An information session will be conducted by the researcher with participants who meet the inclusion criteria at the tertiary care hospital to obtain permission to disseminate the survey. The researcher will explain the purpose of the study and allow feedback to clarify any concerns. A preference list will be drawn up to determine whether participants favor a hard copy of the survey, or an electronic copy and surveys will be distributed according to the preference list. A study information document (Appendix E) including information on the purpose of the study, a description of the study, the benefits of the study, the risks of the study, an estimation on the time required to complete the survey as well as an approximation of time the researcher will take to complete the study will be provided. All participants will be informed that strict confidentiality and anonymity will be maintained throughout the study. Opening the email link and completing the survey constitutes consent. Data collected from completed electronic surveys remain anonymous to the researcher as the REDCap software prohibits disclosure of participant identities to the researcher. Two subsequent emails will be sent at two-week intervals to encourage study participants to complete the survey. The researcher will not document any information that can be used to identify participants. Findings are stored on REDCap and are password protected to maintain data confidentiality and security. Only the researcher and supervisor will have access to the password.

4.1.7. Data Analysis

The survey will be created using REDCap (Research Electronic Data Capture), a secure web application developed by Vanderbilt University in 2004. Survey tools will be available in both electronic and paper formats. Researchers will transcribe the data obtained from the survey and download it into a Microsoft Office Excel spreadsheet for quantitative statistical analysis. Statistica will be the software utilized for analysing data.

4.1.8. Statistical analysis

This descriptive cross-sectional study will use frequencies and percentages to measure prevalence. Logistic regression can be used to determine relationships and correlations of the data. This will provide odds ratios which will then be used to judge 'probability'. Since the odds ratio can be calculated as a measure of association (Setia, 2016), it is suitable for the type of data obtained for the above objective.

4.2. Objective 2: To assess antifungal prescribing patterns of doctors in a tertiary care hospital via retrospective analysis.

4.2.1. Study design

A retrospective quantitative study of antifungal prescribing patterns by doctors in a tertiary care hospital will be conducted by reviewing antifungal prescriptions dispensed over a twelve-month period.

4.2.2. Study site

The study will be conducted at a tertiary care hospital, as per Section 4.1.2. Upon obtaining permission from The Gauteng Department of Health District Management as well as the University of Witwatersrand Medical Human Research Committee, the researcher will manually review each patient file to assess if an antifungal agent was prescribed for the patient within the study period as determined by ethical clearance. Prescriptions from the intensive care, surgical, medical and ARV outpatient departments will be analyzed as these departments represent a large proportion of the targeted study population, namely immunocompromised patients.

4.2.3. Population and sampling

4.2.3.1. Inclusion criteria

All prescriptions containing antifungal agents will be included in the study regardless of patient demographics.

4.2.3.2. *Exclusion criteria*

Any prescription that does not meet legal requirements according to South African Health legislature as well as illegible prescriptions will be excluded.

4.2.4. Sampling size and sampling method

4.2.4.1. *Sample size*

The sample size for the study will be calculated using the formula below:

$$n = \frac{Nz^2P(1 - P)}{d^2(N - 1) + z^2P(1 - P)}$$

N = population

P = expected prevalence (in proportion to 1)

n = sample size

d = precision $d=(0.5(1-P))$

z = stats for CI (CI=z.d)

The tertiary care hospital dispensed 198704 prescriptions over the previous twelve months. Based on a 5% margin of error, 95% confidence interval and 5% prevalence rate of an antifungal agent prescribed, the sample size is calculated as 370 prescriptions that need to be reviewed by the researcher. Each prescription will be randomly selected until saturation of 370 prescriptions is obtained. The sample size has been calculated based on the internationally accepted sample size calculation described above, using Raosoft® software. The sample size will be achieved as the tertiary care hospital makes use of an electronic retrieval system. The 5% prevalence is taken from literature where antifungal prescription incidence ranges from 2.4% to 5.8% (Kaur, H, et al. 2022).

4.2.4.2. *Sampling method*

The probabilistic random sample approach will be used to select prescriptions within the inclusion criteria. This method involves randomly selecting study samples or populations ensuring that each sample or participant has an equal opportunity of being selected. By guaranteeing generalizability, this technique lowers the risk of bias. All prescriptions within

the inclusion criteria will be perused by the researcher and randomly selected until saturation is obtained.

4.2.5. Validity and reliability

Inter-rater reliability testing will be used whereby data collected from random antifungal prescriptions will be independently entered by both the researcher and supervisor, and thereafter compared. This is to confirm accuracy and consistency of the assessment if the researcher and supervisor both infer the same understanding (Scheel et al., 2018). The supervisor will check 10% of the sample for agreement. Should any discrepancies occur, the same data will be re-entered and compared to explore the reasoning behind the discrepancies. Standardization of the variables and procedures will be maintained to minimize discrepancies. Practice of data collection will be conducted by analyzing and comparing data from the pilot study so that potential discrepancies that may arise can be addressed and minimized. The data collected will be accurately inputted and verified to ensure that there are no discrepancies or errors captured. If discrepancies exist and the rate of agreement between the researcher and supervisor is not $\geq 90\%$, the researcher will be required to undergo additional training.

4.2.6. Study procedure

An antifungal prescription review tool (Appendix G) has been developed by the researcher to analyze antifungal prescriptions. If the antifungal agent was dispensed within the twelve-month study period, the prescription from the patient file will be included in the study. Numbers will be assigned randomly to each prescription containing an antifungal agent. This is to ensure patient anonymity is maintained. Prescriptions will be assigned an alphabet based on the ward in which the patient was admitted in followed by numerical assignment. For example, the first prescription from the ICU will be numbered I001 while the second prescription reviewed from that same ward will be numbered I002. The first prescription reviewed from the surgical ward will be numbered S001 and the second prescription reviewed will be numbered S002. A similar trend will be followed for all prescriptions reviewed from the various wards throughout the facility. Any additional information pertaining to the patient such as symptoms, diagnosis or if the patient has received the same antifungal repeatedly during the study period, will be recorded on a data collection sheet. Antifungal prescriptions dispensed within the twelve-month study period will be checked for errors or omissions. Prescription reviews will be conducted by assessing appropriateness of antifungal agent, dose, and dosing frequency. In addition, drug interactions and completion of the prescription will be checked. Prescribed treatment will be

compared to recommendations in accordance with the South African Standard Treatment Guidelines and Essential Drugs List as well as the South African Antibiotic Stewardship Program (SAASP). Study material such as the South African Medicines Formulary (SAMF), South African Standard Treatment Guidelines and Essential Medicines List and Lexicomp, a software application that detects drug interactions, will be used as references by the researcher. EMGuidance, a digital platform will also be used as a reference source by the researcher as this application provides an assortment of information related to treatment guidelines and medicines. Prescription validity will be accounted for to ensure validity of the study. The researcher will evaluate possible errors in the prescriptions which may attribute to antifungal resistance such as improper use of antifungal agents including inadequate or irregular use of the antifungal (Nigam, 2015). Data collected will then be recorded on the data collection sheet. Additional information including patient symptoms, diagnosis (ICD 10 code) and number of antifungal agents prescribed will be recorded on the data collection sheet (Appendix G). Patient demographics will be recorded for further correlation of data as well as trend analysis. Any omissions on the prescription will be recorded on the data sheet as this will aid in further analysis. Since the study is a retrospective one, the researcher does not require patient consent to access their files. Any identifying information will be omitted to maintain confidentiality; instead, prescriptions will be uniquely numbered.

4.2.7. Data analysis

The researcher will independently enter and evaluate the results that have been obtained on the data collection sheet onto Microsoft Excel (Microsoft Office 365). The data collected will then be analyzed for quantitative statistical analysis using pivot tables, frequencies and percentages.

4.2.8. Statistical analysis

Frequencies and percentages will be used in this retrospective study to calculate prevalence. Data linkages and correlations can be found using logistic regression. This will offer odds ratios that can be used to assess "probability." The odds ratio is appropriate for the sort of data acquired from this study as it may be calculated as a measure of association (Setia, 2016).

4.3 Objective 3: To suggest an antifungal stewardship policy and prescribing guideline based on the findings of objective 1 and 2.

4.3.1. Study design

After reviewing the findings from objective 1 and 2, the researcher will present the data to the relevant stakeholders for them to make use of and translate to the development and implementation of a structured antifungal stewardship policy and prescribing guideline. Reference material such as the Standard Treatment Guideline and Essential Drug List, the South African Medicines Formulary, Lexicomp, EMGuidance as well as evidence-based medicine will be utilized to review and analyze results.

4.3.2. Study site

Findings from the study will be presented to the appropriate committees at the tertiary care hospital. Since the study will be conducted at this specific tertiary care hospital, findings and suggestions will be pertinent to this facility.

4.3.3. Study Procedure

Upon completion of data review and analysis, existing policies and guidelines such as STG/EDL, SAASP and evidence-based medicine will be reviewed by the researcher. The researcher will peruse literature and evidence-based medicine to search for solutions to existing problems that have been encountered at the public health care facility as well as the available public healthcare guidelines. Findings and suggested recommendations will then be shared with the hospitals' antimicrobial stewardship committee and other relevant personnel to assist them in implementing an antifungal stewardship program which can aid in ensuring appropriate antifungal prescribing, manage antifungal resistance and improve patient outcomes.

5. Limitations of the study

The study is only focused on one tertiary care hospital located within the City of Johannesburg Metropolitan and excludes hospitals from other municipalities within Gauteng or South Africa. The study only includes a public hospital and not a private hospital, which can exhibit notable variances. Furthermore, only prescribing data will be evaluated. The survey on antifungal stewardship knowledge, attitudes, and perceptions will only be completed by doctors, pharmacists, and nurses. The study excludes other allied healthcare professionals, which may restrict the range of the data. Since the study will only review prescriptions over a twelve-month period, recurrent prescriptions outside of this period will not be reviewed resulting in those prescriptions being omitted.

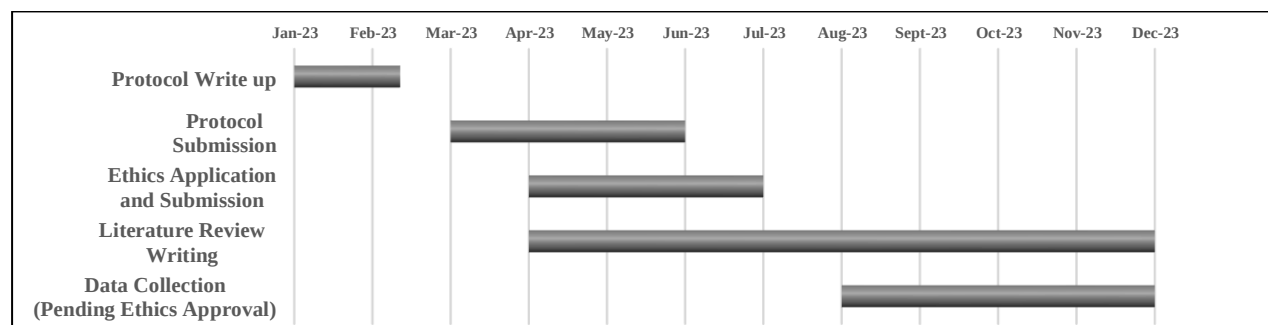
6. Ethics

Applications for ethical approval will be made via the University of Witwatersrand Medical Human Research Committee. Permission to peruse medical records such as patient prescriptions and charts as well as disseminate the surveys to study participants will be obtained from the CEO and Research Committee at the tertiary care hospital. Once approval is obtained, the researcher will apply for ethical approval via the University of Witwatersrand Medical Human Research Committee. Further permission to conduct the study will then be obtained from the Gauteng Department of Health. Prescriptions, patient files and information garnered from doctors, pharmacists and nurses will be kept confidential. The protocol will be published on the National Department of Health Research database in accordance with the conditions for using publicly available information.

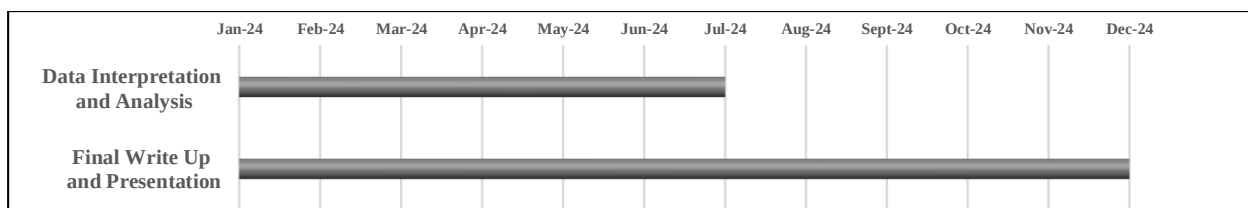
7. Dissemination and Translation

The study will be disseminated to the scientific community via publication. This includes undergraduate and postgraduate researchers, health care professionals as well as all other parties concerned who are interested on pursuing research related to this study. An online version of the study will be made accessible via the University of Witwatersrand scholarly library. The study will also be accessible to the National Department of Health via sharing findings with the National Health Research Database. The study will also be made available to tertiary care hospital involved in this study for the relevant stakeholders to utilize in developing and implementing an antifungal stewardship program at that facility.

8. Timeline



Timeline continued



8. Funding

Funding applications will be made to the National Research Fund. Any additional funding will be obtained through the research supervisors research funds including RINC.

9. Budget

Description	2023	2024
WiFi (External)	R6 000.00 (R250.00pm x 12 months)	R6 000.00 (R250.00pm x 12 months)
REDCap	R0.00	R0.00
Lexicomp (Mobile Version)	R0.00	R0.00
EMGuidance (Mobile Version)	R0.00	R0.00
Statistics training	R0.00	R3 000.00
Transport Distance from PV Tobias Building to the tertiary care hospital = 41km	R6789.60 (R1.38 per km x 41km = R56.58 per trip) Return trip Cost = R113.16 Total cost over 5 months = R6789.60 (3 return trips per week x 5 months)	R0.00
Printing	R5964.00 R2.00 per page x 6 pages per study information document and questionnaire x 497 study participants	R200.00 R2.00 per page x 100 pages
Stationary (Paper, staples etc.)	R760.00	R280.00 R80.00 x 1 ream

	R80.00 per ream Typek copier paper x 6 reams= R560.00 Other (Stapler, staples etc.) – R200.00	Other (Staples, stationary) – R200.00
Total	R19 513.60	R9 480.00

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Appendix E: Study Information Document



STUDY INFORMATION DOCUMENT

Study title: The Assessment of Antifungal Stewardship Implementation in a Tertiary Care Hospital in South Africa: Evaluating Knowledge, Attitudes and Practices of Healthcare Professionals and Developing Evidence-Based Guidelines

Dear Sir/Madam

Introduction:

I, Kiara Sudu, am conducting a research project on the attitudes, perceptions and practices amongst doctors, pharmacists and nurses on antifungal stewardship at a tertiary care hospital. In this study, we want to determine the attitudes, perceptions, and practices of antifungal stewardship amongst doctors, pharmacists and nurses as well as understand physician antifungal prescribing patterns.

Globally, antifungal resistance is becoming an increasing threat to public health and having a substantial impact on treatment outcomes. With a limited number of antifungal agents currently available, we need to ensure that these agents are being judiciously used. The development of an antifungal stewardship program can be beneficial in optimising the use of antifungal agents thereby reducing the incidence of antifungal resistance. South Africa has a high burden of disease due to a large portion of the population being HIV-positive as well as a high incidence of communicable diseases such as tuberculosis. Currently, the exploration of antifungal stewardship in South Africa is still in the early stages of development with further research required regarding its implementation.

Invitation to Participate: I would like to invite you to participate in this study which is entirely on a voluntary basis.

What is involved in the study?

Participants who meet the inclusion criteria and are employed at the tertiary care hospital will be randomly selected to complete the survey. Results from these surveys will aid in ascertaining the knowledge, attitudes, and perceptions of antifungal stewardship knowledge amongst doctors, pharmacists, and nurses at the tertiary care hospital. The REDCaps software will be used to prepare the survey which will comprise of multiple choice-questions. The survey has 4 sections, each of which will take about 10 minutes to complete. Data obtained from all completed surveys will be collated and analysed using the tools provided on REDCap and Statistica.

Risks

There are no risks involved in participating in this study. Strict confidentiality and anonymity will be maintained for all information received.

Benefits

By participating in this study, you will have the opportunity of learning about antifungal stewardship and impact of inappropriate antifungal utilisation on treatment outcomes and patient health. You will also be informed about the opinions of other health care practitioners regarding this.

Voluntary participation

Participation in this study is entirely voluntary, and all your views will remain anonymous. By completing the survey, it will be regarded as you have consented to participate in this study. You are not obliged to participate and have the right not to participate in this study.

Confidentiality and anonymity

Strict confidentiality and anonymity will be maintained in this study with no personal identifying information required to complete the survey,

Who has reviewed the study and given Ethical approval for this study?

The University of Witwatersrand Human Research Ethics Committee has received and ethically approved the study.

Approximate time for study completion

December 2024

A free results summary will be made available on request.

For further information regarding the study or to report any problems, please contact:

Researcher	Supervisor	Co-supervisor
Kiara Sudu	Stephanie de Rapper	Zelna Booth
0836319348	0823104898	0117172912
2751986@students.wits.ac.za	Stephanie.derapper@wits.ac.za	Zelna.booth@wits.ac.za

- This study has been approved by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand, Johannesburg (“Committee”). A principal function of this Committee is to safeguard the rights and dignity of all human subjects who agree to participate in a research project and the integrity of the research.
- If you have any concern over the way the study is being conducted, please contact the Chairperson of this Committee who is Dr Clement Penny, who may be contacted on telephone number 011 717 2301, or by e-mail on Clement.Penny@wits.ac.za The telephone numbers for the Committee secretariat are 011 717 2700/2652/1234 and the e-mail addresses are Mapula.Ramaila@wits.ac.za; Zanele.Ndlovu@wits.ac.za and Rhulani.Mkansi@wits.ac.za

Appendix F: Survey on the knowledge, attitudes and perceptions amongst doctors, pharmacists, and nurses towards antifungal stewardship in a tertiary care hospital.



Dear Sir/Madam

This survey is an adaptation from previously published articles, “Physicians’ knowledge, attitudes, and perceptions concerning antibiotic resistance: A survey in a Ghanaian Tertiary Care Hospital,” by Labi et al, 2018, “Knowledge, attitudes and practices of prescribers towards antimicrobial stewardship at hospitals in Khartoum State - Sudan,” by Alamin and Kheder, 2020, and “Knowledge, attitude and practice of clinicians about antimicrobial stewardship and resistance among hospitals of Pakistan: A Multicenter cross-sectional study,” by Ashraf et al., 2021.

For more information regarding this study, please contact:

Researcher	Supervisor	Co-supervisor
Kiara Sudu	Stephanie de Rapper	Zelna Booth
0836319348	0823104898	0117172912
2751986@students.wits.ac.za	Stephanie.derapper@wits.ac.za	Zelna.booth@wits.ac.za

Please can you answer the following questions, cross or tick the most appropriate option

Do you consent to participating in this study?

- ☐ Yes
☐ No

Please provide your gender

- ☐ Male
☐ Female
☐ Other

Which age group do you fall in (In the current year)?

- ☐ 20-30
☐ 31-40
☐ 41-50
☐ 51-60
☐ >60

What is your profession?

- ☐ Doctor
☐ Pharmacist
☐ Registered Nurse
☐ Other

Area of Specialty?

- ☐ General
☐ Medical
☐ Surgical
☐ Intensive Care
☐ Other
☐ Not applicable

Total years of practice as at the current year?

- ☐ < 5 years
☐ 5 - 10 years
☐ 11 - 20 years
☐ > 20 years

Perceptions on Antifungal Stewardship

What are your perceptions regarding the following statements? Please rate each statement on a scale from strongly agree to strongly disagree.

	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
I am familiar with the term "Antifungal Stewardship."	☐	☐	☐	☐	☐
Antifungal Stewardship is an effective program for the appropriate management of antifungal utilization.	☐	☐	☐	☐	☐
Antifungal stewardship programs offer no benefits to healthcare.	☐	☐	☐	☐	☐
Antifungals are used appropriately in my hospital.	☐	☐	☐	☐	☐
Inappropriate use of antifungals can cause harm to patients.	☐	☐	☐	☐	☐
Inappropriate use of antifungals can cause the emergence of antifungal resistance.	☐	☐	☐	☐	☐

	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
There are appropriate government guidelines in place for the proper use of antifungal agents in my hospital.	☐	☐	☐	☐	☐
Antifungal resistance is not a concern in my facility.	☐	☐	☐	☐	☐
Antifungal resistance is not as important as antibiotic resistance.	☐	☐	☐	☐	☐
I am familiar with local antifungal treatment guidelines in the management of fungal infections.	☐	☐	☐	☐	☐
I believe that it is necessary to get more knowledge on invasive fungal infections and antifungal agents.	☐	☐	☐	☐	☐
There is a need to establish a course on the rational use of antifungal agents.	☐	☐	☐	☐	☐
Infection prevention and control plays a significant role Antifungal Stewardship.	☐	☐	☐	☐	☐
The development of new antifungal agents can combat the emergence of antifungal resistance.	☐	☐	☐	☐	☐
Antifungal resistance does not play an important role in patient safety.	☐	☐	☐	☐	☐
I feel confident about my knowledge and practice regarding prescribing/dispensing/administration of antifungal agents.	☐	☐	☐	☐	☐
It is better to over-prescribe than to under-prescribe antifungal agents.	☐	☐	☐	☐	☐
I believe that some antifungal agents available at my facility are of suboptimal quality and therefore do not work.	☐	☐	☐	☐	☐

Knowledge on Antifungal Stewardship?

Which of the following factors do you think contribute to the inappropriate use of antifungal agents? Select that apply.

- ☐ Limited access to antifungal agents
- ☐ Lack of knowledge on antifungals agents all
- ☐ Limited availability of antifungal guidelines
- ☐ Peer pressure
- ☐ Other, if so, please specify

Which one of the following factors do you think may assist in ensuring the appropriate use of antifungal agents?	☐ Treating infection and not colonization and/or contamination. ☐ Targeted antifungal therapy. ☐ Improved healthcare professional education Improved ☐ local antifungal guidelines. ☐ Knowledge on identified pathogens and antifungal susceptibility test results. ☐ Other, if so, please specify
What one of the following factors do you think contributes to antifungal resistance?	☐ Overuse of antifungal agents ☐ Inappropriate choice on antifungal for empiric therapy ☐ Inappropriate duration of therapy Suboptimal dosing ☐ Patient demand and expectations ☐ Self-medication ☐ Other, if so, please specify
Why do you think Antifungal Stewardship programs would be beneficial in my facility? Select all that apply.	☐ South Africa has high burden of disease. ☐ Lack of prescriber knowledge on antifungal agents ☐ Lack of knowledge of fungal etiology or epidemiology ☐ Increase in the emergence of antifungal resistance ☐ Other, if so, please specify
Are you familiar with the term Candida Score?	☐ Yes ☐ No
Are you aware of the different strains of resistant fungal organisms?	☐ Yes ☐ No ☐ Partially
Attitudes of antifungal prescribing	
Which one of the following factors plays the most important role in antifungal prescribing patterns?	☐ Cost ☐ Local guidelines ☐ Physician ☐ knowledge ☐ Laboratory ☐ findings ☐ Patient factors (history, symptoms, co-morbidities) ☐ Other, if so, please specify
Which one of the following factors influences commencing antifungal treatment?	☐ Patients clinical condition ☐ Positive microbiological results ☐ Pressure from senior medical ☐ officers ☐ Concern of missing a possible infection in a patient ☐ Other, if so, please specify
What is the reason for prescribing antifungals unnecessarily? Select all that apply.	☐ There is no harm in taking an antifungal unnecessarily. ☐ Treatment of fungal colonization to prevent development of an invasive fungal infection. ☐ High-risk or immunocompromised patients need to be on an antifungal. ☐ Feeling of reassurance when using an antifungal even if it may not be necessary. ☐ Prophylactic or preventative use ☐ Other, if so, please specify
Do you think antifungal resistance is considered when prescribing antifungal agents?	☐ Yes ☐ No ☐ Unsure

Appendix G: Retrospective Antifungal Prescription Review Tool



Prescription Code: _____

Date of Visit: _____

Study Site: _____

Table 1: Patient demographics

Age	
Gender	
Co-morbidities	
Medical History	

Table 2: Antifungal prescription overview

		Comments
Patient diagnoses/ ICD10		
Presenting symptoms		
Name of antifungal agent prescribed		
Does the current treatment align with recommended guidelines (Standard Treatment Guidelines,		

Essential Drug List, South African Antimicrobial Stewardship Program)		
Does the current treatment align with current evidence-based medicine?		
Are there any microbiology results available or were any samples taken to be cultured?		
Was antifungal susceptibility testing conducted - results		
Other		

Table 3: Antifungal Prescribing Pattern

	STG/EDL		SAASP		EBM		
	YES	NO	YES	NO	YES	NO	COMMENT
Appropriate antifungal choice							
Appropriate antifungal dose							
Appropriate antifungal dosing interval							
Appropriate duration of therapy							
Drug-drug interactions							

Drug-disease interactions							

Appendix H: Ethics certificate for Kiara Sudu

	Zertifikat Certificat	Certificado Certificate
Promouvoir les plus hauts standards éthiques dans la protection des participants à la recherche biomédicale Promoting the highest ethical standards in the protection of biomedical research participants		
Certificat de formation - Training Certificate Ce document atteste que - this document certifies that		
	Kiara Sudu	
Clinical Trials Centre The University of Hong Kong	a complété avec succès - has successfully completed	
Research Ethics Evaluation		
du programme de formation TRREE en évaluation éthique de la recherche of the TRREE training programme in research ethics evaluation		
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