CURRENT PRACTICES OF URINARY TRACT INFECTION MANAGEMENT: AN OBSERVATIONAL STUDY AT PRIMARY HEALTHCARE LEVEL

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A mini-thesis submitted in partial fulfilment of the requirements for the degree Master of Clinical Pharmacy in the School of Pharmacy, University of the Western Cape.

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20 December 2021

KEYWORDS

Antibiotic

Antibiotic resistance

Antimicrobial stewardship

Medicine label

Urinary tract infection

Pharmacist

Primary healthcare

ABSTRACT

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Introduction: Antibiotic resistance (ABR) is a global healthcare burden complicating the treatment of various infections. The infectious diseases burden is heavy in primary care. Urinary tract infections (UTIs) are common outpatient infections. Miscommunication in healthcare may lead to non-adherence, adverse events and fuel ABR. Labelling antibiotics should be explicit and understood by patients. Treatment of UTIs in primary care in the Western Cape is not well defined. This study's aim is to describe the treatment of UTIs in primary care in the Cape Metropole of the Western Cape province.

Methods: A retrospective multicentre folder review of UTIs was conducted during October 2020 to February 2021. A random selection process was followed to identify two primary care facilities from three different substructures across the Cape Metropole. The facilities could be community day care centres or community healthcare centres. Folders of adult patients diagnosed with a UTI were identified by pharmacists through a selective sampling process. Data was collected from identified folders and labels of dispensed antibiotics using a standardised data collection tool.

Results: A total of 401 UTI episodes occurred in 383 patients. Antibiotics were prescribed in the majority of UTI episodes (98.8%) and UTIs occurred most in females (84.3%). Complicated UTIs accounted for most of the UTI episodes (74.1%). Nitrofurantoin was more commonly prescribed in UTI episodes (57.1%), followed by ciprofloxacin (39.7%). Overall compliance to the standard treatment guideline (STG) recommendations was greater for uncomplicated UTIs (61.5%) and with nitrofurantoin. Antibiotic name, dose and frequency were indicated on all the labels of the dispensed antibiotic. However, duration was mostly omitted (50.4%). The antibiotic name, dose

and frequency indicated on the label of the dispensed antibiotic were mostly compliant with prescriptions (98.7% to 99.7%), expect for duration (43.7%).
Conclusion: Compliance to current STG recommendations for UTI treatment was poor and a multidisciplinary approach is needed to improve patient health outcomes in primary healthcare. Interventions are required to improve compliance to current local guidelines to select appropriate diagnostic investigations, to prescribe appropriate empiric antibiotic therapy, and to recommend appropriate therapy duration. Labels of dispensed antibiotics should include clear instructions for antibiotic use to achieve optimal patient health outcomes.

20 December 2021

DECLARATION

I declare that *Current Practices of Urinary Tract Infection Management: An Observational Study at Primary HealthCare Level* is my own work, that it has not been submitted for any degree or examination at any other university, and that all the sources I have used or quoted have been indicated and acknowledged by complete references.

Full name: Nicole Leanne Keuler

Date: 20 December 2021

Signed: 

ACKNOWLEGEMENTS

Throughout my masters' degree studies and completion of my mini thesis I received wonderful support and guidance.

I wish to express my gratitude and give a special "thank you" to my supervisor, Professor Renier Coetzee, who guided me through this research with patience and support.

I would like to acknowledge and thank my co-supervisor, Ms Yasmina Johnson, for her continuous support, guidance and willingness to help throughout the research.

I would like to acknowledge the School of Pharmacy at the University of the Western Cape (UWC)'s continuous support.

I would like to express gratitude to the following persons and/or institutions:

- The pharmacists from the primary healthcare facilities where the research was conducted.
- Tygerberg Hospital for the opportunity to collect the data.
- The division for post graduate studies at UWC.

Also, I would like to thank my family, friends and colleagues for their continuous support throughout my research.

LIST OF ABBREVIATIONS AND ACRONYMS

ABR	Antibiotic resistance
ACOG	American College of Obstetricians & Gynecologists
AMR	Antimicrobial resistance
AMS	Antimicrobial stewardship
BSAC	British Society for Antimicrobial Chemotherapy
CDC	Centers for Disease Control and Prevention
DoH	National Department of Health [SA]
ED	Emergency department
EML	Essential Medicines List
ESBL	Extended spectrum beta-lactamases
GLASS	Global Antimicrobial Resistance Surveillance System
IPC	Infection prevention and control
JAC	Jack Andy and Carol
MDR	Multi-drug resistant
MUE	Medicine-use evaluation
NHLS	National Health Laboratory Service
SAASP	South African Antibiotic Stewardship Programme
STG	Standard treatment guideline
UTI(s)	Urinary tract infection(s)
WHO	World Health Organisation

LIST OF DEFINITIONS

Adverse effect: Any harmful reaction caused by the use of medicine or medicine errors which leads to a change in dosage regimen, discontinuation of the product or the prevention of future use of the medicine (World Health Organization [WHO], 2012).

Antibiotic resistance (ABR): The ability of bacteria to develop mechanisms to reduce the efficacy of antibiotics (Centers for Disease Control and Prevention, 2018).

Antimicrobial resistance (AMR): The ability of bacteria, fungi and viruses to develop mechanisms to reduce the efficacy of antibiotics, antifungal and antiviral agents (WHO, 2018a).

Antimicrobial stewardship (AMS): A multidisciplinary approach which aims to ensure rational antimicrobial use through optimising antimicrobial regimens which include antibiotics, antifungal and antiviral therapy. It is a strategy to improve antimicrobial use and patient health outcome, as well as combating AMR across various healthcare settings (Dyar, Tebano & Pulcini, 2017). Key principles in humans include selecting the right antimicrobial at the right dose administered at the right time for the right duration through the right route (Dramowski & Woods, 2014; Richards, 2016). Benefits expected from AMS practices include optimal patient health outcomes, reduction in adverse events and ABR (Barlam et al., 2016).

Antimicrobial surveillance: An ongoing systematic approach continuously collecting, analysing and interpreting AMR, antimicrobial use and medicine data to identify interventions to combat AMR at national and local level (National Department of Health, 2014).

Community-acquired urinary tract infection (UTI): A UTI obtained in the community or diagnosed within less than 48 h after hospital admission with no evidence on admission (Kabugo et al., 2016).

Complicated UTI: UTIs in males, pregnant women and patients with structural or functional urinary tract abnormalities (Lee & Le, 2018).

Empiric therapy: Antibiotics used for treating an infection before laboratory results are available. The choice of an empiric antibiotic is based on results from microscopy, based on clinical diagnosis and expertise (Richards, 2016).

Extended spectrum beta-lactamases: Enzymes produced from bacteria which inactivate penicillin, cephalosporins and monobactams through hydrolysis of the beta-lactam ring (Goyal et al., 2019).

Medicine-use evaluation (MUE): A continuous quality improvement process which aims to ensure rational medicine use through evaluation of medicines used, based on specific criteria. The principles of pharmaceutical care are the foundation of MUE with the ultimate aim to enhance optimal patient health outcome and quality of life (Phillips, Gayman & Todd, 1996; Doherty et al., 2004; WHO, 2003).

Multi-drug resistant: An organism resistant to three or more antimicrobials or a key antimicrobial (Magiorakos et al., 2012).

One Health: A multi-sector approach to design and implement programmes, policies, legislation and research to optimise public health outcomes. It is an essential approach recommended by the WHO to combat AMR (WHO, 2017b).

Point-of-care test: A biomedical test of a patient's sample that does not require laboratory analysis. Samples includes blood, saliva, urine and faeces (Cals & Van Weert, 2013).

Prescriber: A healthcare professional who prescribes medicines for a patient. This includes medical (doctor) and non-medical prescribers (nurses, pharmacists, allied health professionals) (Weeks et al., 2016).

Primary healthcare: Essential healthcare services provided to meet the healthcare needs of most patients. These services include preventing, treating, rehabilitating and palliative care. Services provided are aimed at the health and well-being of individuals, families and communities following an essential healthcare approach. Three components have been identified as important to achieve success (WHO, 2019a):

1. Integrating health services to meet the patient's healthcare needs,
2. Implementing evidence-informed public policies across various sectors to address all aspects of health determinants, and
3. Empowering the public to take ownership of their health outcomes.

Rational medicine use: A patient receiving individualised medicine indicated for their clinical need, in appropriate doses meeting individual requirements for the appropriate duration at an affordable price to the patient and community (WHO, 2002).

Recurrent UTIs: A UTI occurring at least three times in a period of 12 months or at least twice in a period of six months. Recurrent UTIs are caused by a re-infection or relapse (Bonkat et al., 2018; Fernandez & Coyle, 2019).

Uncomplicated UTI: UTIs, including acute and recurrent UTIs, in healthy premenopausal women (Bonkat et al., 2018; Lee & Le, 2018).

UTI: An infection of the urinary tract caused by microorganisms which may include bladder and kidney infections (Lee & Le, 2018; Fernandez & Coyle, 2019).

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1 INTRODUCTION

This chapter describes the study in terms of the background, problem statement, research objectives and significance.

1.1 Study background

The management of urinary tract infections (UTIs) at primary healthcare level in the Western Cape, South Africa (SA) is poorly described. Although antimicrobial stewardship (AMS) in the hospital setting has been studied, it has not been fully described in primary healthcare (Brinkmann & Kibuule, 2019). This study's aim was to describe the management of UTIs in primary healthcare in terms of antibiotic prescribing practices and the dispensing process of prescribed antibiotics.

The study had the following objectives:

1. Conduct a literature review on managing UTIs in primary healthcare,
2. Describe treatment of UTIs at primary healthcare level, and
3. Analyse the results and report on the study findings.

Each chapter will describe a different aspect of the study. Chapter 1 introduces the study. Chapter 2 focuses on the literature review, and Chapter 3 on the methodology. Chapter 4 includes the results and discussion, while Chapter 5 includes the conclusions, limitations and recommendations for further research.

1.2 Study rationale

Antimicrobial resistance (AMR) is a global public healthcare threat (Aslam et al., 2018). The Global Action Plan on Antimicrobial Resistance aims to ensure continuous successful treatment and prevention of infectious diseases using a rational medicine use approach. However, to achieve success each healthcare professional should commit to this global action plan by becoming an antibiotic guardian (World Health Organization [WHO], 2016a). Practical interventions can only be implemented after antibiotic prescribing practices, dispensing processes and knowledge, attitudes as well as perceptions of healthcare professionals are understood. AMR surveillance and mapping of various infectious diseases may also

guide the prescriber in choosing an appropriate empiric antibiotic that supports rational medicine use. (WHO, 2015; 2017a). Pharmacists, the gatekeepers of medicine and core members of the AMS team, should act as guardians of antibiotics at all levels of healthcare (DoH, 2014).

In 2018, a South African retrospective study was conducted in eight subdistricts at primary healthcare facilities to determine the adherence to the standard treatment guidelines (STGs). Medical records were reviewed over a two-day period for all patients prescribed antibiotics. A total of 654 patients, mostly females (61.8%), were included and 449 patients (68.7%) received an antibiotic prescription. The overall adherence to STGs for prescribed antibiotics was 45.1%. Most of the non-adherence was due to a diagnosis not being specified (30.5%) and antibiotics not being required (21.6%). Urology infections accounted for 7.5% of the conditions being treated and non-adherence was due to incorrect duration (51.2%), followed by unspecified diagnoses (17.1%) and incorrect antibiotics prescribed (17.1%). The study recommended further investigation into the qualitative assessment of healthcare workers' knowledge, attitude and antibiotic prescribing practices (Gasson, Blockman & Willems, 2018). The study emphasises the need to promote rational prescribing of antibiotics in primary healthcare through AMS implementation and focusing on understanding the prescribers' antibiotic prescribing practices.

In a South African study conducted in both the private and public sector, patients' knowledge, attitude and perceptions were investigated. Patients in the public sector scored lower knowledge scores compared to those in the private sector, while 72% believed that antibiotic resistance (ABR) is a human phenomenon (Farley et al., 2019). This study emphasises the lack of patient education in the healthcare system. Education is a core element that should be incorporated into AMS programmes (Richards, 2016). Educational materials should be individualised for prescribers, pharmacists and patients to meet specific requirements. Patient education should be part of the prescriber-patient interaction and the dispensing process of antibiotics.

UTIs are prevalent infections in the community setting (Barber et al., 2013; Erdem et al., 2018). The process of diagnosing UTIs, antibiotic prescribing practices and dispensing of antibiotics to patients diagnosed with UTIs are not well described in the public sector in primary healthcare in the Western Cape and requires investigation.

1.3 Research aim and objectives

The research aim, objectives and specific research questions are discussed below.

1.3.1 Research aim

The study's aim was to describe the management of UTIs in primary healthcare in the Western Cape.

1.3.2 Research objectives

The study's objectives were to:

1. Conduct a literature review on the management of UTIs in primary healthcare;
2. Describe the diagnosis and management of UTIs in primary healthcare;
3. Report on the findings of how UTIs are diagnosed and managed at primary healthcare level in the Western Cape with recommendations for further research.

1.3.3 Specific research questions

The study had the following specific research questions:

1. How are UTIs diagnosed in primary healthcare in the Western Cape?
2. How are UTIs treated in primary healthcare in the Western Cape?
3. What antibiotics are used for treating UTIs in primary healthcare?
4. How are antibiotics dispensed to patients diagnosed with UTIs?

1.4 Study significance

This novel study aims to describe the management of UTIs, in terms of treating UTIs, at primary healthcare level in the public sector in the Western Cape Metropole district, SA. This study will describe the antibiotic prescribing practices of UTI treatment, identify common antibiotics prescribed for treating UTIs in primary healthcare and determine compliance with the STG recommendations. Further label information of the prescribed antibiotics will be analysed to determine alignment with prescriptions and information included during the dispensing processes. The latter will provide information about the dispensing process and may explore the role of the pharmacist in the dispensing of antibiotics.

The study will identify if the current treatment of UTIs are aligned with the STG recommendations as set out for primary healthcare (DoH, 2018a). Alignment criteria includes antibiotic choice, dose, frequency and duration of antibiotics prescribed. This study addresses the following three objectives of the Global Action Plan on Antimicrobial Resistance (WHO, 2016):

1. Improve awareness and understanding of AMR,
2. Strengthen surveillance and research, and
3. Optimise antimicrobial use in humans.

1.5 Thesis structure

The thesis chapters are arranged as follows.

- Chapter 1: Introduction
- Chapter 2: Literature review
- Chapter 3: Methodology
- Chapter 4: Results
- Chapter 5: Discussion
- Chapter 6: Conclusion, limitations and recommendations

2 LITERATURE REVIEW

In this chapter, the global and local perspective of AMR, AMS at hospital and primary healthcare level, and UTI as a common infection are explored. Further, AMR and stewardship principles particular to UTIs are discussed.

2.1 Introduction

AMR is a growing public healthcare threat (O'Neil, 2014; WHO 2015; 2017a) complicating the treatment of infections globally. Approximately 50% of medicines are prescribed irrationally (Holloway & Van Dijk, 2011). Most antibiotics, approximately 80%, ware physician prescribed in primary healthcare (National Department of Health [DoH], 1997; British Society for Antimicrobial Chemotherapy [BSAC], 2018; Hu, Logue & Robinson, 2020).

AMS is identified as a multidisciplinary approach to combat AMR, to optimise antimicrobial use and patient health outcome (DoH, 2014; Tiong, Loo & Mai, 2016; WHO, 2017a). Although the benefits of AMS have been proven in the hospital setting, the effects and implementation in primary healthcare is limited (Brinkmann & Kibuule, 2019). The South African Antimicrobial Resistance National Strategic Framework (DoH, 2014) entails a strategic framework to combat AMR in SA.

Treating UTIs, a common healthcare condition in primary healthcare (Shively et al., 2018), is becoming as complex as other infectious diseases due to the growing global threat of AMR (Mazzariol, Bazaj & Cornaglia, 2017; Naber & Wagenlehner, 2019). Resistance to *Escherichia coli (E.coli)*, the most common causative organism of UTIs, is increasing both globally and locally (Bamford et al., 2012; WHO, 2017a). Managing UTIs at primary healthcare level is poorly described; thus, there is a dire need to understand the process of diagnosis, prescribing and antibiotic use in UTIs at primary healthcare level to optimise AMS and antimicrobial use in UTI treatment. This study's findings will identify various interventions which might assist in combating AMR, optimise patient health outcome and aid in establishing AMS practices at primary healthcare level.

2.2 AMR

The increase in ABR is driven by inappropriate prescribing and increased antibiotic consumption (Garau et al., 2014). Inappropriate antibiotic use might include overprescribing (Fiore et al., 2017) and overdispensing of antimicrobials, overusing broad-spectrum antibiotics, not adhering to treatment regimens, inappropriately prescribing and increasing hospital-acquired infections (Holloway & Van Dijk, 2011; DoH, 2014; Brink, 2015; WHO, 2018c). Inappropriate prescribing is a modifiable risk factor for ABR (Sanchez et al., 2016). Also, poor infection prevention and control (IPC), poor sanitation and lack of hygiene further fuels AMR (DoH, 2014). More than 50% of medicines globally are prescribed, dispensed and used irrationally (Holloway & Van Dijk, 2011), while approximately 30% of antibiotic prescribing in primary healthcare is unnecessary (Centers for Disease Control and Prevention [CDC], 2019a).

The impact of AMR is extensive, affecting all healthcare sectors, with detrimental impact on patient care both in the hospital- and community-setting across the globe (Llor & Bjerrum, 2014; Van Hecke et al., 2017). AMR's effect is pernicious, prolonging hospital stay, increasing mortality and medical costs, leading to multidrug resistance infections, treatment failure, poor clinical outcomes and threatening life expectancy (Llor & Bjerrum, 2014; WHO, 2015; 2018a; Richards, 2016; Sanchez et al., 2016). It is estimated that approximately 10 million people would die from AMR in 2050 (O'Neil, 2014). Action to combat AMR is an urgent appeal for multisector collaboration across the globe. To successfully address AMR all three pillars of AMR governance need to be addressed: surveillance, IPC and AMS (Chetty et al., 2019).

2.2.1 Global AMR perspective

AMR was classified as one of the 10 urgent global health threats in 2019 (WHO,2019b). In the US, ABR accounts for more than 2.8 million infections and over 35 000 deaths annually (CDC, 2019b). According to the CDC, 20% to 50% of antibiotics prescribed in the US are inappropriate or unnecessary (Sanchez et al., 2016). A multidisciplinary approach is critical to address the AMR dilemma that

the global healthcare system is facing. Neglecting to respond to AMR might result in a post-antibiotic era, increasing mortality attributed to untreatable infections (WHO, 2018a). This impact is not limited to human health, but might affect agriculture including animal and environmental health (Aslam et al., 2018). A One Health approach is needed to combat AMR (WHO, 2017b).

The WHO responded to the global AMR crisis with the Global Action Plan on Antimicrobial Resistance. This plan's goal was to ensure continuity of successful treatment and preventing infectious diseases for as long as possible with medicines that were safe, effective and quality-assured to be used responsibly and to be accessible. The global action plan had the following five objectives (WHO, 2015):

1. To improve awareness and understanding of AMR;
2. To strengthen knowledge through surveillance and research;
3. To reduce incidence of infections;
4. To optimise antimicrobial use; and
5. To ensure sustainable investments to combat AMR.

Thus, it is critical that national action plans should align with the global action plan to build a successful global AMR approach. Implementation of the above objectives is vital to combat AMR. Educating the public is critical in combating AMR (Coates & Hu, 2019).

To support the Global Action Plan on Antimicrobial Resistance, the WHO formed the Global Antimicrobial Resistance Surveillance System (GLASS) to standardise AMR surveillance globally. This surveillance system encouraged collaboration across various sectors and supported a One Health approach (WHO, 2017b). This included collecting, analysing and sharing AMR data across countries. AMR surveillance is critical, to determine the spread of AMR and to influence and improve policy, guidelines and IPC both globally and locally. Another important aspect of GLASS was the inclusion of epidemiological, clinical and population data in the surveillance reporting system (WHO, 2017a). Priority specimens for surveillance included blood, urine, stool and urethral and cervical swabs from

hospital, community or unknown origin. In humans, this approach included preventing infections, reducing overprescribing and overusing antimicrobials, mitigating the spread of resistant bacteria, improving IPC practices and accessing drinking water and sanitation (Collignon & McEwen, 2019).

Further, the WHO urged global collaboration to focus on policy interventions and collaborative practices to combat AMR (WHO, 2017a). Global governance is critical to successfully combat AMR. Rational antimicrobial use should be a priority in each country. It is believed that legal binding should be the gold standard to achieve transformation globally. This approach would ensure accountability and governance (Padiyara, Inoue & Sprenger, 2018; Rochford et al., 2018).

There were many responses to the urgent global AMR plea. The WHO classified antibiotics according to an Access, Watch and Reserve (AWaRe) classification system to ensure safe and effective use (WHO, 2020b). Antibiotics in the Access class are regarded as first- or second-line therapy to ensure an optimal outcome with the lowest risk for ABR. Watch antibiotics are regarded as first- or second-line therapy with a potential to fuel ABR with the need to practice AMS and monitoring. Antibiotics in the Reserve class are classified as a last resort in life threatening infections requiring monitoring and AMS programmes. The WHO aims that 60% of all antibiotics consumed by 2023 should be from the Access class (WHO, 2019c). The Action on Antibiotic Resistance project is a global network focused on action against AMR. It aims to create awareness of AMR for various stakeholders (Gelband & Delahoy, 2014). Point prevalence surveys are another important tool to collect data on antimicrobial use – an important indicator that could not be analysed without antimicrobial consumption data (WHO, 2017a). Point prevalence surveys collect data at a specific point in time (WHO, 2018c).

In a global analysis of strategies to combat AMR (Adeniji, 2018), the UK and Nigeria were used as case examples of high- and low-income countries, respectively. For low-income countries challenges to combat AMR include poverty, surveillance and counterfeit medicine. Adeniji was concerned that low-income

countries require unique strategies and policies to combat AMR since international documents do not address specific challenges faced by low-income countries. Thus, strategies should be individualised according to country specifics addressing local needs.

2.2.2 SA AMR perspective

Antibiotic consumption data in low- and middle-income countries is limited and might be due to a lack of infrastructure for AMR surveillance (WHO, 2018c). Access to clean water, proper sanitation and improving healthcare needs to be addressed to combat AMR especially in low- and middle-income countries (Hu, Logue & Robinson, 2020; Laxminarayan et al., 2020). SA responded to the urgent global appeal to combat AMR with an Antimicrobial Resistance National Strategy Framework. This framework aims to assist in the management of AMR, limits the increase in resistant infections and improve patient outcomes in SA through accountability, roles and responsibilities.

The framework has four objectives (DoH, 2014):

1. To strengthen, co-ordinate and institutionalise interdisciplinary efforts,
2. To optimise surveillance and early detection of AMR,
3. To enhance IPC, and
4. To promote appropriate use of antimicrobials in human and animal health.

Facilitators required to achieve these objectives include (DoH, 2014):

1. Legislative and policy reform to strengthen health systems;
2. Education on the following topics: AMS, infection control, infectious diseases, microbiology and pharmacology;
3. Communicating with the public to create awareness and patient advocacy, and
4. Researching various fields such as point-of-care testing, clinical trials treatment duration, antimicrobial consumption and new antimicrobial use.

SA is one of the countries reporting AMR surveillance data to GLASS since 2016 through the National Institute for Communicable Diseases. In the 2016/2017 report, 27 hospitals were included in the surveillance system (WHO, 2017a). In the 2017/2018 GLASS report SA had 31 surveillance sites, 27 hospitals and four outpatient facilities (WHO, 2018b). These results show the extension of AMR surveillance and the inclusion of primary healthcare into the surveillance system.

In a systematic review (Tadesse et al., 2017), AMR was investigated in SA. The majority of the available data were from East Africa (40.9%), while the South African region only accounted for 4.2%. *E. coli* accounted for the most common bacterium isolated (60.4%). The median resistance to amoxicillin and cotrimoxazole was 72.9% and 75%, respectively. Low to moderate resistance was found to ciprofloxacin (median resistance: 16.7%). The lowest overall median resistance was found for imipenem (3%). *E. coli* was isolated from patients with UTIs in 19.5% of the cases. *Citrobacter* was a common bacterium isolated from UTI samples (36.8%). Resistance of *E. coli* and *Klebsiell*a to carbapenems and fluoroquinolones were low. This review emphasises the importance of surveillance systems in SA and the impact of AMR.

2.3 AMS

AMS is a strategy to improve antimicrobial use to ultimately improve patient health outcome and to combat AMR in any healthcare setting where antimicrobials are used (Sanchez et al., 2016; Dyar, Tebano & Pulcini, 2017). Also, AMS programmes sought to promote behavioural change to optimise antimicrobials in accordance with evidence-based guidelines (Sanchez et al., 2016; Kpokiri, Taylor & Smith, 2020). AMS programmes impact prescribers, patients, medication suppliers, policymakers and the public (Cox et al., 2017). A critical aspect of AMS is to have access to evidence-based guidelines to ensure rational antibiotic prescribing (Gasson, Blockman & Willems, 2018).

An AMS team should ideally consist of a multidisciplinary team with a pharmacist and physician as the core team members (DoH, 2014; Sutthiruk et al., 2018; Baraka et al., 2019). Establishing a successful AMS team might be challenging (Bassetti et al., 2019) as it demands accountability from each healthcare professional involved in antimicrobial prescribing (Brink, 2015; Dyar, Tebano & Pulcini, 2017). To ensure a multidisciplinary integrated approach, healthcare professional from various disciplines should form part of the AMS team. These include all healthcare professionals including physicians, pharmacists, nurses, microbiologists, virologists and management staff (Kpokiri, Taylor & Smith, 2020).

Interventions associated with AMS can be grouped into persuasive, restrictive and structural. Persuasive interventions include various kinds of educational platforms, audit and feedback, reminders and opinions. Formulary restrictions, special authorisation and AMS policies are part of restrictive interventions. Structural interventions include implementation of computerised records, rapid diagnostic tests and quality monitoring measurements (Davey et al., 2013).

2.3.1 Global AMS perspective

AMS is recognised as an international approach to combat AMR across various healthcare sectors (WHO, 2015; 2017a; 2019b). International governance and accountability are essential to ensure successful implementation of AMS programmes (Dyar, Tebano & Pulcini, 2017). Although no golden approach for a successful AMS programme has been identified, this programme is not a one-size-fits-all (Mendelson et al., 2020). International AMS activities should be compatible with local contexts (Rubin, 2019).

For AMS programmes to be successful, international and national policies and guidelines need to be aligned with global AMS action plans. Further monitoring and evaluation of AMS activities should be implemented to monitor effectiveness. Thus, standardising implementation processes and policies are critical. Also, continuous updates and reviews are important to combat AMR (Tiong, Loo & Mai, 2016; Coates & Hu, 2019).

The WHO compiled a toolkit for AMS programmes for low- and middle-income countries to optimise antimicrobial use at national and facility level (WHO, 2019). This toolkit includes guidance on AMS-related structures, interventions and education. These documents are aligned with the global action plan (WHO, 2015).

2.3.2 SA AMS perspective

AMS could improve antimicrobial use and reduce inappropriate use through protocols, structures and various interventions. Each institution should have an active AMS team to ensure appropriate prescribing and to optimise antimicrobial use. An AMS team should ideally include a pharmacist and physician as key members (DoH, 2014).

Various challenges were identified for the implementation of successful AMS programmes in low- and middle-income countries. These challenges were identified as a lack of human resources, poor prescription-based stewardship strategies and limited continuous professional development (Brinkmann & Kibuule, 2019).

In a Nigerian study (Kpokiri, Taylor & Smith, 2020), the development of an AMS programme was investigated. Broad spectrum antibiotics were the most common antibiotics prescribed accounting for 75% of prescriptions; common antibiotics prescribed included metronidazole, amoxicillin, amoxicillin-clavulanic acid, cefuroxime and ciprofloxacin. In only 15% of the cases, microbial culture and sensitivity tests were conducted. Limited support and laboratory services as well as work overload resulted in a lack of diagnostic investigations fuelling empiric prescribing. According to the participants various concerns and awareness about suboptimal prescribing were shared.

In a bottom-up approach study for AMS programmes in Nigerian hospitals (Kpokiri, Taylor & Smith, 2020), various actions were identified for implementation. These included improved diagnostic services, education and training of prescribers, increased awareness, providing and maintaining policies and

prescribing guidelines, continuous audits to inform guidelines and monitoring of practices. These actions emphasise the recommendations from various international documents (O'Neil, 2014; WHO, 2015; 2017a).

The South African ministerial advisory committee play an important role in (DoH, 2014):

1. Selecting antimicrobial inclusion in the Essential Medicines List (EML);
2. Guiding antimicrobial inclusion in the EML based on resistance patterns;
3. Providing leadership and guidance on the implementation of AMS programmes;
4. Enhancing IPC and vaccines; and
5. Advising on AMR curricula, patient advocacy and awareness campaigns.

The South African Antibiotic Stewardship Programme (SAASP) provides leadership and strengthens antibiotic stewardship in the public and private sector. Also, it assists with guidelines for various infections in both adults and children which includes the AMS principles. Further, SAASP recommends evidence-based AMS interventions, provides structure and organisation of AMS programmes with high impact interventions for various settings (Federation of Infectious Diseases Societies of Southern Africa, 2020).

A scoping review was conducted to determine AMS interventions in both the public and private sector of SA (Chetty et al., 2019). Although various AMS strategies were implemented in both the public and private sector there remained a need for effective AMS implementation in accordance with the national AMR strategy of SA to address inappropriate antimicrobial prescribing practices. Also, the study emphasised the need for grouping roles and responsibilities among healthcare professionals. Pharmacists had a critical role to play in AMS in both the public and private sector. The study showed the importance of AMS principles practices across all healthcare sectors.

2.3.3 AMS in hospitals

The WHO's (2018c) point prevalence survey have the following objectives for AMR surveillance to assist AMS in hospitals:

1. To standardise the estimate of prevalence of antibiotic use in hospitals,
2. To collect information on prescribing of antibiotics,
3. To support policymakers and practitioners to improve antibiotic use through awareness, training and identifying prescribing issues, and
4. To provide a standardised tool for hospitals to monitor and evaluate antibiotic use.

In a Cochrane review (Davey et al., 2017), the effectiveness and safety of interventions to improve antibiotic prescribing in inpatients were investigated. Enablement interventions were associated with an increase in compliance to antibiotic prescribing policies (risk difference of 15%; high certainty evidence). Also, implementing AMS interventions was associated with a decrease in length of stay of 1.95 d (high certainty evidence). Although both enablement and restrictive interventions were associated with an increase in compliance, enablement interventions were more successful. When feedback was included with interventions the effect was enhanced.

The effects of AMS in hospitals were investigated through a systematic review and meta-analysis (Schuts et al., 2016). Though the quality of these studies were low, various benefits of AMS were observed. A relative risk reduction of mortality of 35% was associated with guideline-adherent empiric therapy ($P < 0.001$). Also, de-escalation was associated with a relative risk reduction for mortality of 56% ($p < 0.0001$). Intravenous to oral switch, therapeutic drug monitoring, restrictions on antibiotics and bedside consultations were associated with beneficial clinical outcomes.

A systematic review was conducted in low- and middle-income countries to review the effectiveness of AMS interventions (Van Dijck, Vlieghe & Cox, 2018). Various types of studies which investigated structural, persuasive and enabling interventions

were included with medium- to high-risk of bias. Overall, a positive effect of AMS interventions in hospitals were observed; however, true effectiveness could not be determined due to low quality, heterogeneity and a lack of studies from various settings. Thus, more studies investigating AMS in hospitals from low- and middle-income countries were needed.

In a Thai hospital study (Sutthiruk et al., 2018), only 37.6% of the clinicians (doctors, nurses and pharmacists) reported that they experienced working with AMS programmes in healthcare facilities. The study highlighted the need for AMR awareness and AMS education.

A successful AMS programme was implemented in the Western Cape, incorporating SAASP principles and education, as well as following, monitoring, and evaluating a multidisciplinary approach. This programme's success was due to sound relationships, respect among the healthcare professionals and accountability. The study by Von Pressentin et al. (2019) emphasised the need for all healthcare professionals to practice AMS, for AMS to be supported by management to create a supportive environment, and the importance of AMS training. Further the study provides evidence that implementation of AMS programs is possible.

From the literature it is evident that hospital AMS programs have numerous beneficial effects. AMS in hospitals in high-income countries showed beneficial effects for length of stay, reduction in AMR and costs, re-admission rates as well as decrease in mortality (Nathwani et al., 2019). Various challenges need to be addressed in low- and middle-income countries to measure the success of AMS in hospitals in low- and middle-income countries.

2.3.4 AMS in primary healthcare

A guide to AMS programs in hospitals was compiled from an international perspective including low- and middle-income countries (Mendelson et al., 2020). Such a guide for primary healthcare is still lacking. Multidisciplinary AMS teams

in hospitals are successful, yet the golden thread had not been applied to primary healthcare levels (Dyar, Tebano & Pulcini, 2017; Laxminarayan et al., 2020).

The CDC (Sanchez et al., 2016) provided four core elements to ensure rational antibiotic prescribing for AMS in the outpatient settings: (1) commitment, (2) action for policy and practice, (3) tracking and reporting, and (4) education and expertise. Implementation of these four core elements require careful implementation and continuous improvement to optimise antibiotic use in the outpatient settings.

A Spanish study was conducted to measure antibiotic consumption after implementation of the four core elements in primary healthcare (March-López et al., 2020). Overall, the defined daily doses decreased from 16.01 to 13.31 from baseline to the sustainability period. Also, patients treated with antibiotics decreased from 26.99% to 22.41%. Fluoroquinolone consumption decreased with an increase in narrow-spectrum antibiotics. The study proves that a multifaceted approach is critical to address AMS in primary healthcare.

In a Namibian study (Brinkmann & Kibuule, 2019), the effectiveness of AMS programs in primary healthcare were investigated through interviewing key informants involved in AMS programs. Monitoring antimicrobial use was the role most fulfilled by interviewees (50%), followed by ensuring appropriate antimicrobial prescribing (40%), controlling infection (40%) and surveying disease (10%). According to the Strength Weakness Opportunities and Threats (SWOT) analysis, major strengths were to ensure accurate prescribing (70%) and educating healthcare professionals (60%). Continuous education for healthcare professionals, compliance to policies and systems and antimicrobial-specific policies were among the weaknesses in the SWOT analysis. Policies and systems for local resistance pattern education, AMS programs, multidisciplinary AMS committees, IPC committees and standard operating procedures for antimicrobial prescribing were lacking in most facilities. Clinics' compliance to AMS policies were poor – varying between 9.1% and 36.4%.

A study investigating pharmacists' perceptions and experiences with AMS in the community setting (Jones et al., 2018) revealed various interventions to improve AMS in primary healthcare. Pharmacists, the core members of the AMS team, were unaware of AMS activities in their community setting. However, they felt that they could contribute as pharmacists when AMS was explained. The issue of missing diagnosis on prescriptions were identified as a barrier to AMS since it prohibited the pharmacists to practice the AMS principles. This study will focus on antimicrobial prescribing in primary healthcare.

2.3.5 Prescribing practices in primary healthcare

Approximately 80% of antibiotic prescribing occurs in the primary healthcare setting (DoH, 1997) where almost 30% of antibiotics prescribed are unnecessary (CDC, 2019a). UTIs are among the most common treated primary healthcare conditions (Schmiemann et al., 2010).

A prospective cohort study was conducted in the outpatient setting in New York (Garau et al., 2014), following a pragmatic approach to determine the overprescribing of antibiotics and the associated disease to identify antibiotic stewardship interventions. A total of 1 603 prescriptions were included and in 40% of the patients who were prescribed antibiotics, prescribing was inappropriate. UTIs (21%) accounted for most of the indications for inappropriately prescribed antibiotics. Approximately 50% of ciprofloxacin prescriptions, the most common antibiotic prescribed for UTIs, were prescribed unnecessarily for asymptomatic bacteriuria. The following prescribing patterns were appropriate in treating UTIs: aligned with guideline diagnostic criteria (54.4%), correct antibiotic (54.9%), correct dosage (70.5%), correct duration (52.9%). These results emphasise the need for AMS programmes to be implemented at primary healthcare level to optimise antibiotic prescribing in primary healthcare.

In another study (Shively et al., 2018), the most common condition for antibiotic prescriptions in the primary healthcare setting was UTIs. Antibiotics were prescribed optimally in only 29% of the cases. Antibiotics were not indicated in

30% of the cases and the antibiotic choice and duration were not aligned with guideline recommendations in 28% and 13% of the cases, respectively.

Evaluating antibiotic prescribing in primary healthcare in SA is limited (Gasson, Blockman & Willems, 2018). Understanding prescribing practices of antimicrobials are important to address AMS policies and to recommend interventions to optimise antibiotic use (WHO, 2016; Gasson, Blockman & Willems, 2018). A Capetonian study (Gasson, Blockman & Willems, 2018) in primary healthcare facilities in the Metropole district was conducted to assess antibiotic prescribing and adherence to guidelines. Females accounted for the most patient prescriptions reviewed (61.8%). Most of the patients were seen by nurses (64.7%). In 16.7% of the cases the diagnosis was unknown. In 71% of the cases with a known diagnosis an antibiotic was prescribed with only 37.2% adhering to guidelines. In all the prescriptions reviewed the overall adherence rate was 32.1%. Of the prescriptions with no diagnosis an antibiotic was prescribed in 56.9% of the cases. Antibiotic prescribing was associated with non-adherence to the guidelines (OR: 0.17 95% CI 0.1–-0.24; P < 0.001). Adherence to guidelines varied among the healthcare facilities. Urology conditions were among the most common infections treated (7.5%) and identified as a condition associated with non-adherence to the guidelines. Ciprofloxacin, an antibiotic indicated for treating UTIs, was among the antibiotics prescribed for an unknown diagnosis (17%). For urology conditions incorrect duration (51.2%), incorrect drug and diagnoses unspecified (17.1%) were the most common reasons for non-adherence in prescriptions reviewed. This study showed poor adherence to guidelines in primary healthcare in Cape Town. The study recommended focused education for healthcare professionals and patients to aid in their understanding of antibiotic use. Also, it was suggested that technology be enhanced to ensure availability of prescribing guidelines. The study emphasised the need to empower pharmacists to fulfil their role as gatekeepers of antibiotics.

2.3.6 AMS programme challenges

Although AMS is a global health threat, each country requires an exclusive approach to address various challenges. Though groundbreaking work has been done, various opportunities exist to ensure more feasible and multifaceted initiatives to address AMS in countries across the globe (Tiong, Loo & Mai, 2016).

Various challenges are faced at primary healthcare level to implement AMS and multiple opportunities exist to implement successful strategies (Laxminarayan et al., 2020). These include both a lack of human and financial resources (Brinkmann & Kibuule, 2019). In low- and middle-income countries, limited resources and a lack of bacterial susceptibility force the prescriber to follow an empiric treatment approach (Mouiche et al., 2019). However, the lack of various support systems should not prohibit the initiation of an AMS programme (Mendelson et al., 2020). It is proposed that the AMS team should consist of nurses, pharmacists, physicians and staff from long care facilities (Dyar, Pagani & Pulcini, 2015; Dyar, Tebano & Pulcini, 2017). Local governance in institutions and primary healthcare was critical to address basic education on antimicrobials and managing infection (Dyar, Tebano & Pulcini, 2017). Challenges related to this study included: (1) impact of carbapenem-sparing strategies, and (2) defining and improving compliance to de-escalation standards and appropriate duration of therapy.

Another challenge for AMS in primary healthcare is the impact of available antibiotic pack sizes. In Switzerland oral antibiotics were dispensed in pack sizes compared to exact pill count. In a Swiss study (Bassetti et al., 2019) the impact of antibiotic packs on AMS was investigated focusing on five conditions. In only 36% of the cases optimal packs were available for the recommended regimens according to the included guidelines. Fosfomycin, moxifloxacin and norfloxacin, not included in the WHO's Access group, were included in the optimal matching category. No package matching recommendations existed for clindamycin, nitrofurantoin and phenoxymethylpenicillin. Optimal antibiotic packs were available for 63% of regimes which included antibiotics from the Watch antibiotics. The latter might lead to an increase in antibiotic dispensing of the Watch group fuelling AMR. The

study supported an exact pill count system instead of dispensing fixed antibiotic packs. For a country dispensing only fixed antibiotic packs it might fuel AMR and such an approach might lead to failure of the WHO's goal. Fixed-therapy durations have the potential to cause undertreatment or lead to extended duration of therapy which might fuel AMR.

Communication among prescribers and pharmacists, as well as among patients and prescribers is an important challenge especially in an overwhelmed healthcare system such as in SA (Dyar, Tebano & Pulcini, 2017; Mendelson et al., 2020). However, communication is an important aspect that needs to be improved in primary healthcare to combat AMR (Llor & Bjerrum, 2014; Brink, 2015).

Prescribers practicing in primary healthcare in the Cape Metropole share various challenges which have the potential to influence AMS in primary healthcare. According to prescribers, laboratory results rarely influenced their results due to limited laboratory services. Due to overcrowded facilities follow-up appointments were limited in primary healthcare facilities. Stock shortages were another challenge faced by prescribers. Patients were not considered partners in the treatment decisions. Though point-of-care testing was limited in the Western Cape, it was perceived by prescribers to have positive impact on AMS in primary healthcare as it may reduce inappropriate antibiotic prescribing, laboratory costs and unnecessary referrals, as well as improve the health service delivery and AMR (Van Hecke et al., 2019). For point-of-care testing to be effective it should be accurate, precise, user-friendly, affordable, easily interpretable and quick in providing results (Cals & Van Weert, 2013).

2.4 Guidelines

Various studies support the implementation of guidelines to combat AMR (Darj, Newaz & Zaman, 2020). The practice of evidence-based medicine, diagnostics and updated treatment guidelines are essential to ensure rational medicine use. Restrictive and appropriate use of antibiotics are important to ensure rational antibiotic use (Holloway & Van Dijk, 2011).

In a prospective study by Michelangeli et al. (2020) the impact of internal guidelines with selective reporting of antibiotic susceptibility tests were investigated to determine antibiotic adequacy in healthcare clinics in an inpatient setting. UTIs accounted for the most common infections (32%) with *E. coli* (27%) being the most common isolated bacteria. Although the study had some limitations, the proposed approach resulted in empiric therapy alignment with guidelines in almost 50% of the cases. The study emphasises the need for an integrated approach as well as the importance of guidelines and antibiotic susceptibility to ensure appropriate antibiotic prescribing.

A study was conducted by Elias et al. (2017) to determine if resistance patterns were considered when recommending empiric antibiotic in prescribing guidelines for five infectious diseases – community-acquired pneumonia, UTIs, acute otitis media, rhinosinusitis and pharyngitis. The guidelines were grouped into three groups based on the level of satisfaction of resistance patterns:

1. Satisfactory (empiric antibiotic recommendations were supported by country-specific resistance patterns),
2. Partial satisfactory (empiric antibiotic recommendations were supported by inconsistent resistance patterns), and
3. Unsatisfactory (empiric antibiotic recommendations did not support any resistance pattern or were not justified by country-specific resistance patterns).

Overall, 6.4% of the guideline recommendations were grouped as satisfactory, compared to 27.5% of recommendations that were grouped as partially. Fluoroquinolones (12.7%) were a frequent alternative antibiotic recommended for treating UTIs. According to the study, UTI-specific guideline recommendations were grouped as unsatisfactory in 74.6% of cases, followed by partial satisfactory (17.4%) and satisfactory (7.9%).

2.4.1 Global perspective on clinical practice guidelines

The WHO recommends implementing national policies, evidence-based guidelines, drug and therapeutic committees and public education to improve rational medicine use (Holloway & Van Dijk, 2011; WHO, 2016). One of the WHO's requests to combat AMR is the national implementation of policies to address AMR. A policy package has to include five important aspects (Gelband & Delahoy, 2014):

1. Surveillance,
2. Regulations and rational use,
3. Antimicrobial use in food-producing animals,
4. Health centre infection control and prevention, and
5. Technology and innovation.

The Global Antibiotic Resistance Partnership aims to implement antibiotic resistant policies in various countries based on six strategies (Gelband et al., 2015):

1. Reduce antibiotic needs,
2. Improve hospital AMS and IPC,
3. Change incentive approaches,
4. Reduce antibiotic use in agriculture,
5. Educate healthcare professionals, policymakers and the public, and
6. Ensure commitment.

The success of AMS interventions is multifactorial and needs investigation. Multifaceted interventions are not superior to single interventions. Interventions shown to be beneficial include reminders, educational sessions, auditing and feedback. The success of interventions is country-specific. In developing countries, a multifaceted interventions were more effective than a single intervention (Holloway & Van Dijk, 2011). Thus, guideline implementation and policies should address the needs of the specific healthcare facilities.

2.4.2 Local perspective on clinical practice guidelines

In an international analysis document, policy awareness and specifically AMR policy implementation was identified as a recommendation to combat AMR in a low-income country (Adeniji, 2018). Although healthcare workers acknowledged policies and guidelines, the availability of updated and detailed guidelines were often limited (Kpokiri, Taylor & Smith, 2020).

The absence of policies and a system-specific approach to address irrational antimicrobial use is a big challenge in low- and middle-income countries which complicates the process to optimise antimicrobial use (Brinkmann & Kibuule, 2019). Policies and guidelines need to be continuously updated to ensure rational antimicrobial use (Brinkmann & Kibuule, 2019; Kpokiri, Taylor & Smith, 2020).

In SA, the STGs and EML for primary healthcare (DoH, 2020) and hospital level (DoH, 2019b) are evidence-based guidelines used in the public sector to ensure rational medicine use. A South African study was conducted in public hospitals to ascertain AMS policies and guidelines, the pharmacists' roles as well as the process of interchanging policies when medicine shortages/stockouts were noted. Most facilities reported to have an active pharmacy and therapeutic committee (86.9%) as well as an AMS committee (70.2%). Only 42.4% of participants reported to have an interchange policy in place when antibiotic substitution was required. Also, participants agreed that pharmacists had to manage the interchange process. The study recommended the implementation of interchange policies at all levels of care to facilitate the interchange process. Such a policy ensured rational antimicrobial use through an evidence-based approach. The perceived role of the pharmacist in the therapeutic interchange process, a key healthcare member of the AMS team was vast. Some roles included sharing information on rational antimicrobial use and available treatment options, involving interchange policy development, working with the multidisciplinary team to recommend the most appropriate alternative therapy and involving research (Chigome et al., 2020).

2.4.3 Non-adherence to clinical practice guidelines

Less than 40% of patients in the public sector's therapy were aligned with the guidelines (Holloway & Van Dijk, 2011). In a Bangladeshi study (Darj, Newaz & Zaman, 2020), conducted in the community setting, pharmacists shared concerns that prescribers were not adhering to antibiotic guidelines and that spontaneous prescribing of broad-spectrum antimicrobials fuelled AMR in their country. Another concern was that empiric prescribing of antimicrobials were based on previous experience and the specific condition; however, de-escalation of therapy was not fully implemented.

Adherence to the Infectious Diseases Society of America's guidelines for treating cystitis in primary healthcare is low. Fluoroquinolones were the most common antibiotic prescribed for cystitis (51.6%), followed by nitrofurantoin (33.5%) and cotrimoxazole (12%). A duration of therapy longer than recommended was common with antibiotic prescribing, being more common in the elderly and diabetics (Grigoryan et al., 2015). It was evident that antibiotic prescribing was not aligned with the STGs and EML primary healthcare recommendations (Gasson, Blockman & Willems, 2018).

2.5 UTIs

Approximately 150 million people globally suffer from UTIs per year. In high-income countries antibiotics are used for respiratory tract infections, UTIs and skin and soft tissue infections, respectively (BSAC, 2018). A total of 10.8 million people presented over a period of three years to the emergency department (ED) in the US for treating UTIs. Most of these patients were treated in the outpatient setting with 1.8 million people admitted to hospital for further management (Sammon et al., 2014).

The exact prevalence of UTIs has not been determined due to various limitations such as surveillance and laboratory limitations (Öztürk & Murt, 2020). The most common uropathogen-causing UTIs are *E.coli* (Gupta & Trautner, 2018; Fernandez & Coyle, 2019; Medina & Castillo-Pino, 2019; Öztürk & Murt, 2020).

UTIs occurr mostly in women – approximately 50% to 80% will develop at least one UTI (Gupta & Trautner, 2018). The treatment outcome of UTIs is multifactorial depending on patient characteristics, prescribers, AMS practices, the antibiotic regimen and the dispensing process. Also, healthcare professionals' knowledge and experience play a role in the dispensing process and treatment outcomes. UTIs are among various diseases that require standardisation in terms of definitions and international classifications. It is important to optimise antibiotic use to combat AMR. UTIs are among many infectious conditions which increase the healthcare burden as AMR increases (WHO, 2017a). UTIs are common infections in primary healthcare where AMS could improve patient care and reduce AMR.

2.5.1 AMR in UTIs

Globally, a rise in resistance against antimicrobials is evident. Community-acquired UTIs, a major healthcare burden attributed to AMR, is emerging as untreatable infections (Garau et al., 2014). AMR complicates UTI treatment (Gupta & Trautner, 2018; Öztürk & Murt, 2020). Resistance in hospital-acquired UTIs is an international problem and urgent novel antibiotics are required to preserve the current antibiotics (Naber & Wagenlehner, 2019). AMR is concerning for UTIs during pregnancy as well (Matuszkiewicz-Rowińska, Małyszko & Wieliczko, 2015). Overall resistance to antibiotics prescribed for treating UTIs are rising. Also, a rise in *E. coli* resistance to third generation cephalosporins and fluoroquinolones has been noted. Resistance to ciprofloxacin, an antibiotic widely used to treat UTIs, ranged from 8% to 65% (Mehnert-Kay, 2005; Flores-Mireles et al., 2015). Also, resistance of *E. coli* to cotrimoxazole is increasing (Mehnert-Kay, 2005).

2.5.1.1 Global and local perspective on AMR in UTI

Resistance patterns for UTIs are limited in various sectors and countries (Elias et al., 2017). *E. coli* and *Klebsiella pneumoniae* (*K. pneumoniae*) were among the key GLASS bacteria to survey for AMR since they had the potential to cause common hospital and community-acquired infections globally (WHO, 2017a).

The outcomes for patients with UTIs caused by resistant *E. coli* were investigated in the UK (Butler et al., 2006). It was found that UTIs caused by resistant organisms were associated with patients being symptomatic and "feeling poorly", "experiencing pain and frequency" and "being out of action for more than five days". ABR in UTIs might lead to a second visit to the clinic for re-consultation and/or a second antibiotic being prescribed, fuelling ABR.

According to a systematic review and meta-analysis to determine implications of AMR in the community setting (Van Hecke et al., 2017), *E. coli* was the most common (> 65%) bacteria isolated from UTI specimens. Approximately 57% to 95% of clinical suspected UTIs were confirmed with laboratory tests. Antibiotic resistant *E. coli* strains were significantly associated with response failure (OR: 4.19, 95% CI 3.27–5.37; P < 0.001) and re-consultation (OR: 5.07, 95% CI 2.17–11.82). Longer duration of symptoms, symptom severity and response failure were associated with antibiotic resistant strains of *E. coli* UTIs. The study revealed the impact of AMR in the community setting.

A systematic review and meta-analysis were conducted to determine the effect of AMR on patients in the community setting (Costelloe et al., 2010). ABR was more prevalent during the first month after exposure to antibiotics with effects up to 12 months after exposure. Also, the study supported the recommendation of shorter duration of therapy, if possible, to reduce AMR and to follow guideline recommendations for first line therapy. Further, the study emphasised the importance of AMS in primary healthcare where most antibiotics are prescribed.

In a Turkish study (Erdem et al., 2018), the resistance patterns of uropathogens were determined. The study followed a retrospective folder review of 90 females who presented to the university hospital. The most common risk factors identified were urolithiasis (20%) and diabetes mellitus (15.6%). The most common uropathogens associated with UTIs were *E. coli* (66.6%) followed by *K. pneumoniae*, (16.6%), *Enterobacter* (7.7%), *Enterococcus* (3.3%), *Pseudomonas aeruginosa* (*P. aeruginosa*), *Citrobacter freundii* (*C. freundii*) and *Staphylococcus saprophyticus*

(*S. saprophyticus*) (1.2%). Resistance patterns were reported for ampicillin (86.6%), trimethoprim-sulfamethoxazole (47.7%) and ciprofloxacin (33.3%). Extended-spectrum-beta-lactamase (ESBL)-producing enzymes such as *E. coli* were resistant to cotrimoxazole (77.7%), ciprofloxacin (72.7%), fosfomycin (13.6%) and nitrofurantoin (18.2%). Organisms were mostly susceptible to fosfomycin and nitrofurantoin. The study emphasised the need to develop antibiograms to guide the prescriber in empiric antibiotic prescribing.

A prospective cross-sectional study was conducted in Dakar (Bosch, Van Vuuren & Joubert, 2011) to determine antimicrobial susceptibility in community-acquired UTIs in adults. The prevalence of UTIs were 26.7% (132/494) mostly caused by gram negative organisms (90%). Resistance in cotrimoxazole was 73% followed by 69% for nalidixic acid and 60% for fluoroquinolones. Again, the study emphasised the dire need for ABR mapping to guide prescribers in choosing the most appropriate empiric antibiotic for treating UTIs at primary healthcare level.

A systematic review and meta-analysis from Cameroon investigated AMR from a one health perspective (Mouiche et al., 2019). Interestingly 64.4% of the studies investigated UTIs. Urine samples were the most common sample collected (57.8%). *E. coli* (51.1%) and *Klebsiella* species (42.2%) were among the most common organisms isolated. Overall, the pooled prevalence for multidrug resistance *E. coli* and *Klebsiella* species were 47.1% and 51%, respectively.

In another Cameroonian study (Nzalie, Gonsu & Koulla-Shiro, 2016), the most common organisms associated with community-acquired UTIs and resistance to empiric antibiotics prescribed were investigated. A total of 92 patients were included in the study between the ages of 15 to 75 years. The prevalence of community-acquired UTIs was significant in the female population, leading to a statistically significant difference in the prevalence of UTIs in sexual distribution ($p = 0.002$). Ciprofloxacin (30.9%) and amoxicillin-clavulanic acid (23.6%) was the most prevalent prescribed empiric antibiotics. Gram negative organisms (96.4%) were isolated from the urine samples with *E. coli* and *K. pneumonia*e the

most prevalent gram-negative bacteria. According to antimicrobial susceptibilities, 40% of the isolates were resistant to ciprofloxacin and 60% were resistant to amoxicillin/clavulanic acid. The study supported the need to practice AMS at community level to optimise antibiotic use and improve patient health outcome.

In a Ugandan study the following were investigated for community-acquired UTI: the associated risk factors, the most prevalent uropathogens and antibiotic sensitivity patterns for the uropathogens (Kabugo et al., 2016). A total of 139 patients were included in the study, mostly married females with the most prevalent uropathogens being *E. Coli* (50%) and *Staphylococcus aureus* (*S. aureus*) (15.4%). *E. coli* was sensitive to ampicillin (78.6%), nitrofurantoin (64.3%) and ciprofloxacin (57.1%), while *S. aureus* was sensitive to ciprofloxacin (100%), nitrofurantoin, gentamicin and cotrimoxazole (66.7%). Females (aOR: 3.33; 95% CI 1.11–9.95), above the age of 26 years (aOR: 2.59; 95% CI 1.12–5.99) had an increased risk of UTIs. The study supported the importance of antibiotic surveillance in diagnosing UTIs and prescribing appropriate antibiotics.

Antimicrobial susceptibility of *Enterobacteriaceae* in UTIs in Africa was investigated (Tansarli, Athanasiou & Falagas, 2013). Antimicrobial susceptibility of more than 15 isolates of *Enterobacteriaceae* from adult patients with a UTI, diagnosed either clinically or microbiologically were included. Susceptibility data from Africa (381 899 isolates) accounted for the most data collected across 14 African countries. The most common uropathogens were *E. coli, Klebsiella* and *Proteus*. In the outpatient setting, susceptibility rates were 16% to 89% for amoxicillin/clavulanic acid, 100% for imipenem, 68% to 91% for ciprofloxacin and 52% to 92% for nalidixic acid. Cotrimoxazole susceptibility varied from 15% to 66%, 70% to 90% for nitrofurantoin and 98% to 100% for fosfomycin. ESBL *E. coli* susceptibility varied from 29% for ciprofloxacin and nalidixic acid, 0% for co-trimoxazole and 100% fosfomycin. Susceptibility for *Klebsiella* varied from 0% to 69% for amoxicillin/clavulanic acid, ciprofloxacin 53% to 100%, cotrimoxazole 0% to 56%, nitrofurantoin 40% to 78%, fosfomycin 100%. The study highlighted the need for susceptibility and surveillance data to ensure rational antibiotic

prescribing in the treatment of UTIs, especially when selecting empiric antibiotic therapy.

Approximately 30% resistance was seen in amoxicillin and trimethoprim/sulfamethoxazole, this resistance pattern was also seen in a South African study (Bosch, Van Vuuren & Joubert, 2011). In SA, cotrimoxazole are used to prevent opportunistic infections in immune-compromised retroviral disease positive patients and might fuel AMR. In a study conducted in Bloemfontein, SA, the organisms associated with community-acquired UTIs in adults and antimicrobial susceptibility were determined. *E. coli* accounted for 75% of uncomplicated UTIs, with no ESBL organisms and 59% of complicated UTIs. In uncomplicated UTIs, *E. coli* resistant rates were highest for cotrimoxazole (52%) and amoxicillin (57%) followed by amoxicillin-clavulanic acid and ciprofloxacin (5%). Amoxicillin-clavulanic acid was the most common antibiotic prescribed (38%) followed by ciprofloxacin (19%), amoxicillin (14%), cefuroxime (10%) and nitrofurantoin (5%). The duration of therapy varied between 5 d (46%), 7 d (7%) and 10 d (7%). According to the antibiogram, the prescribed antibiotic was appropriate in 75% of the cases. In complicated UTIs the resistance rate of *E. coli* was highest for cotrimoxazole (82%) and amoxicillin (73%) followed by ciprofloxacin (45%), cefuroxime and amoxicillin-clavulanic acid (9%). In contrast, nitrofurantoin had 100% susceptibility rates. Ciprofloxacin was the most common antibiotic prescribed (35%), followed by amoxicillin-clavulanic acid (19%), amoxicillin, cotrimoxazole and nitrofurantoin (11%). Duration of treatment for complicated UTIs varied from 1 d to 3 d (5%), 5 d (24%), 7 d (5%) to 10 d (19%). Empiric antibiotics prescribed were appropriate in 75% of uncomplicated UTI cases, compared to 46% in complicated UTI cases (Bosch, Van Vuuren & Joubert, 2011). The study emphasised the need to use antibiograms in selecting empiric antibiotic therapy, to practice evidence-based medicine and to determine guideline adherence.

In a South African study antimicrobial susceptibility patterns for *E. coli* was investigated between 2007 and 2011 in both the private and public sector (Bamford

et al., 2012). Approximately 65 000 to 84 000 of *E. coli* isolates were reported from 19 laboratories per year, mostly from the private sector. Over the five-year period, the isolates increased in both the public and private sector by 38% and 26%, respectively. In the public sector, cotrimoxazole susceptibility ranged from 31% to 33%, while susceptibility ranged from 92% to 94% for nitrofurantoin. Ciprofloxacin susceptibility in the public sector decreased from 86% to 81% compared to a reduction of 80% to 73% in the private sector. ESBL *E. coli* increased from 7% to 9% in the public sector over the five-year period. The results could not be separated for outpatient and inpatient setting. Surveillance data would assist prescribers in prescribing appropriate empiric antibiotics which would reduce treatment failure and associated healthcare costs. Also, antibiotics would be preserved, reducing ABR (Bamford et al., 2012; Tansarli, Athanasiou & Falagas, 2013). Local antimicrobial susceptible patterns would assist in guiding empiric therapy for UTIs in the emerging setting of resistance (Bosch, Van Vuuren & Joubert, 2011).

Antibiograms had the potential to guide prescribers in treating UTIs with the potential to reduce AMR and to ensure rational antibiotic prescribing (Chu & Lowder, 2018). The process to combat resistance, empiric antibiotic therapy for treating UTIs should be led by local antimicrobial susceptibility patterns (American College of Obstetricians & Gynecologists [ACOG], 2008; Bosch, Van Vuuren & Joubert, 2011; Fernandez & Coyle, 2019). However, to achieve the latter surveillance data is critical to build towards ABR mapping.

2.5.2 AMS in UTIs

2.5.2.1 Global and local perspective on AMS in UTIs

AMS could be implemented in any healthcare facility to improve optimal patient health outcome and to reduce ABR (Sanchez et al., 2016). UTIs are common bacterial infections in the outpatient setting where AMS implementation could improve rational antibiotic use (Lee & Le, 2018). The increase in antibiotic prescribing increase antibiotic use and create the opportunity for pharmacists to be involved in AMS implementation programs in the primary healthcare setting

(Flores-Mireles et al., 2015; Nzalie, Gonsu & Koulla-Shiro, 2016; Rojas, 2018). Pharmacists are ideally situated at community level to practice, lead and implement AMS principles acting as antibiotic guardians (Rojas, 2018). There is a need for the implementation of AMS in primary healthcare to focus on UTIs. Benefits expected from AMS in primary healthcare include optimal patient health outcomes, reducing adverse events and ABR (Barlam et al., 2016). Applicable AMS principles in treating UTIs are: (1) indication for antibiotics, (2) antibiotic choice, (3) dosage, (4) route, and (5) therapy duration. Additional factors to consider with antibiotic prescribing for UTIs included: (1) antibiotic spectrum, (2) efficacy, (3) ability to cause collateral damage, (4) safety and tolerability, (5) side effects, and (6) costs (Bartoletti et al., 2016).

Also, pharmacists have a vital role to fulfil during the dispensing process of antibiotics to ensure safe antibiotic use and to educate patients on safe antibiotic use. Further, they have a role to play in antibiotic use in UTIs, recommending appropriate antibiotics, doses, frequency and treatment duration. Point-of-care testing and urine cultures are not always available; therefore, these infections are often treated empirically with broad spectrum antibiotics until further results are available (Nzalie, Gonsu & Koulla-Shiro, 2016). Thus, the choice of empiric therapy is not only critical to ensure optimal patient health outcomes, but also to reduce ABR and recurrence.

A pre- and post-intervention study was conducted in the outpatient ED to determine the effect of recommendations for treating uncomplicated UTIs based on institutional-specific recommendations and a local antibiogram (Percival et al., 2015). ED physicians received educational sessions from pharmacists on the above-mentioned documents. A total of 350 patients were included in the study. Empiric therapy in the post-intervention phase was aligned with recommendations as in the pre-intervention phase (pre-intervention: 44.8%, post-intervention: 83%, difference 38.2% 95% CI 33–43, $p < 0.001$). A significant reduction in fluoroquinolones and cotrimoxazole prescribing was reported in the post-intervention phase with a significant increase in nitrofurantoin prescribing in the treatment of cystitis. Similar

prescribing patterns were reported in treating pyelonephritis (Percival et al., 2015). Education and training sessions on local antibiograms, availability of antibiograms and guidelines have the potential to improve rational prescribing of antibiotics to treat UTIs. Availability of antibiograms have the potential to positively impact prescribing patterns and improve patient health outcomes (ACOG, 2008). Pharmacists are ideally situated to lead AMS and training in their facilities; however, baseline knowledge needed to be ascertained.

A retrospective cohort study conducted by Durkin et al. (2018) in the outpatient setting evaluated guideline adherence for treating uncomplicated UTIs. The study reported non-compliance to guidelines. Fluoroquinolones, a second line agent for uncomplicated UTIs, accounted for 43% of the prescriptions. The duration of antibiotics prescribed varied across the prescriptions with a compliance to guideline recommendations of less than 50%, with the most common duration being 7 d. The study emphasised the importance of guideline adherence and the implementation of AMS at primary healthcare facilities.

A qualitative study was conducted to comprehend prescribers' knowledge and attitude on antibiotic use in treating UTIs as well as to determine barriers to prescribing (Grigoryan et al., 2019). Eighteen primary healthcare physicians were individually interviewed for 30 min by means of a semi-structured interview. The study found that physicians prescribed fluoroquinolones because of the perceived efficacy and short duration of therapy. Patient characteristics such as allergies, sex, pregnancy, past antibiotic experience, previous antibiotic susceptibility, diabetes, age, cost, and UTI frequency influenced prescribing patterns. There were mixed perceptions about the use of nitrofurantoin as some physicians appreciated the low cost, few side effects and good tolerance; however, some physicians did not support the use as it was bacteriostatic and not a quick symptom reliever. Most physicians were unfamiliar with fosfomycin as a treatment option for UTIs. Reference material or guidelines that were mentioned included Up to Date and the Infectious Diseases Society of America's guidelines. Although the physicians were aware of ABR, they did not consider it a problem in their practice.

2.5.3 UTI types

UTIs are broadly grouped into complicated and uncomplicated infections (Bonkat et al., 2018; Gupta and Trautner, 2018; Fernandez & Coyle, 2019). Uncomplicated infections occurred in healthy non-pregnant premenopausal females, without any structural abnormalities. All other UTIs are classified as complicated UTIs. Further, UTIs could be grouped into an infection of the bladder in the lower urinary tract (cystitis) or an infection of the kidneys in the upper urinary tract (pyelonephritis) (Vasudevan, 2014; Wasserman, Boyles & Mendelson, 2015; Bonkat et al., 2018; Fernandez & Coyle, 2019). Grouping UTIs as complicated, uncomplicated, cystitis or pyelonephritis is vital to guide the prescriber in selecting the most appropriate empiric antibiotic.

Recurrent UTIs could either be caused by re-infection or relapse (Fernandez & Coyle, 2019). A recurrent UTI is defined as a UTI occurring at least three times in a period of 12 months or at least twice in a period of six months (Bonkat et al., 2018; Fernandez & Coyle, 2019). A re-infection is a new infection usually two weeks after the prior UTI. A relapse occur within two weeks of the prior UTI and is often the result of AMR, unsuccessful treatment or anatomical abnormalities (Vasudevan, 2014; Lee & Le, 2018; Bonkat et al., 2018; Fernandez & Coyle, 2019). A recurrent UTI could be complicated or uncomplicated. Recurrent UTIs accoun for 10% to 15% of overall antibiotic prescriptions in the community setting (Garau et al., 2014). Table 2.1 summarises the classification of UTIs.

Table 2.1: UTI classification
(Wasserman, Boyles & Mendelson, 2015; Bonkat et al., 2018; Gupta & Trautner, 2018; Fernandez & Coyle, 2019; DoH, 2019b).

Uncomplicated UTI	Complicated UTI
Urinary tract infections defined	
UTIs in healthy premenopausal women (19-45 years)	Catheter associated UTIs UTIs during pregnancy UTIs in men UTIs in post-menopausal women (>46 years) UTIs in patients with urinary tract abnormalities UTIs in patients with concomitant immunocompromised conditions e.g. diabetes mellitus, human immunodeficiency virus Recurrent UTIs Upper UTIs

Further UTIs can either be community-acquired, hospital-acquired or catheter-associated depending on epidemiological factors (Öztürk & Murt, 2020). Asymptomatic bacteriuria is the presence of bacteria ($\geq 10^5$ CFU/ml [(colony forming unit)]/ml) in two consecutive urine samples in the absence of UTI symptoms irrespective of the presence of pyuria in women. In men, asymptomatic bacteriuria is defined as bacteriuria ($\geq 10^5$ CFU/ml) in one urine sample in the absence of symptoms (Lee & Le, 2018). The elderly, kidney transplant patients, diabetics and pregnant women are at increased risk of asymptomatic bacteriuria. In pregnant women, screening and treatment is recommended as asymptomatic bacteriuria could lead to pyelonephritis which might result in preterm birth and post-partum complications. Pregnant women with asymptomatic bacteriuria caused by G*roup B streptococci* require intrapartum antibiotic prophylaxis (Bonkat et al., 2018; Fernandez & Coyle, 2019; Nicolle et al., 2019).

2.5.4 Risk factors

Multiple risk factors exist for UTIs, these factors include (ACOG, 2008; Vasudevan, 2014; Wasserman, Boyles & Mendelson, 2015; Velez, Richmond & Dudley-Brown, 2017; Bonkat et al., 2018; Gupta & Trautner, 2018; Lee & Le, 2018; Lee, Lee & Choe, 2018; Öztürk & Murt, 2020):

1. Sex (female) and age (elderly);
2. Infections such as previous UTI or vaginal infections,
3. Co-morbid conditions (e.g., diabetes mellitus, sickle cell disease),
4. Congenital abnormalities,
5. Sexual intercourse (e.g., frequent sexual activity, spermicide use, diaphragm contraception),
6. Pregnancy (e.g., gestational age, increase in parity),
7. Immunosuppressant therapy,
8. Obesity, and
9. Patients with kidney transplants and spinal cord injuries.

Risk factors for UTIs in postmenopausal women and the elderly include previous UTIs, poor hygiene, urinary incontinence, oestrogen deficiency and urinary catheterisation (ACOG, 2008; Lee & Le, 2018; Bonkat et al., 2018). Risk factors

for UTIs associated with multi-drug resistant (MDR) uropathogens include the use of antimicrobials three to 12 months prior. Patients with diabetes mellitus, hospitalised for at least 48 h, with a history of a UTI, living in nursing home and who received haemodialysis three months prior also had an increased risk for UTIs caused by MDR organisms. Also, exposure to the following antibiotics are associated with MDR uropathogens: fluoroquinolones, cephalosporins, penicillin and cotrimoxazole (Khawcharoenporn, Vasoo & Singh, 2013; Walker et al., 2016).

UTIs caused by ESBL infections are associated with prolonged hospital stay, increased hospitalisation cost, morbidity and mortality attributable to inappropriate antibiotic prescribing. Risk factors associated with ESBL community-acquired UTIs are recurrent UTIs, urinary catheter use, neurogenic bladder and use of third generation cephalosporins/fluoroquinolones three months' prior diagnosis of UTI (Goyal et al., 2019).

Approximately 3% to 5% of women would have recurrent UTIs. Risk factors for recurrent UTIs are frequent intercourse, contraceptive methods such as spermicides and diaphragms, initial UTI at a young age, having a mother with a UTI, oestrogen deficiency and inappropriate treatment of previous UTIs (Mody & Juthani-Mehta, 2014; Bartoletti et al., 2016; Gupta & Trautner, 2018; Fernandez & Coyle, 2019). Circumcision reduced the risk of UTI in men (Gupta & Trautner, 2018).

2.5.5 Pathogens associated with UTIs

According to Flores-Mireles et al. (2015) UTIs are a public healthcare threat caused by gram negative organisms such as *Enterobacteriaceae*; i.e., *E. coli, K. pneumoniae, Proteus mirabilis* (*P. mirabilis*) and *Enterobacter*. Gram positive organisms causing UTIs included coagulase negative *staphylococci*; i.e., *S. saprophyticus, Enterococcus* species, mostly *Enterococcus faecalis.* Other organisms included *Group B Streptococcus, P. aeruginosa, S. aureus* and *Candida* (Bosch, Van Vuuren & Joubert, 2011; Wasserman, Boyles & Mendelson, 2015; Gupta & Trautner, 2018; Fernandez & Coyle, 2019).

E. coli is the most prevalent organism globally and in SA, causing community-acquired infections such as UTIs (DoH, 2018b; Zwane, Shuping & Perovic, 2021). Approximately 70% to 95% of UTIs are caused by *E. coli*. Organisms associated with uncomplicated UTIs include *E. coli, S. saprophyticus, Enterococcus, K. pneumoniae and P. mirabilis* (Mehnert-Kay, 2005; Butler et al., 2006; Vasudevan, 2014; Lee & Le, 2018; Erdem et al., 2018; Lee, Lee & Choe, 2018). The following organisms are more associated with complicated UTIs: resistant strains *of E. coli, P. aeruginosa, Acinetobacter baumannii, Enterococcus, P. mirabilis* and *Staphylococcus* (Lee & Le, 2018). According to GLASS (WHO, 2017a), *E. coli* and *K. pneumoniae* are common global growing resistant organisms in the community. Also, UTIs could be caused by *Candida* especially in immunocompromised or critically-ill patients (Fernandez & Coyle, 2019).

E. coli is a common organism causing UTIs in pregnant women. Gram negative bacterial organisms were isolated from pregnant women with *E. coli* being the most common isolate (45.7%). Gram positive isolates included coagulase negative S*taphylococcus* and *S. aureus* (Demilie et al., 2014). Recurrent infections were often caused by *Serratia* and *Pseudomonas, Staphylococcus*, resistant strains of *E.coli, Enterococcus, Enterobacter, P. mirabilis* and *K. pneumoniae* (Mehnert-Kay, 2005; Vasudevan, 2014; Lee & Le, 2018).

2.5.6 Clinical presentation

The most common symptoms in pre-menopausal women indicative of a UTI are urgency, frequency and dysuria (Wasserman, Boyles & Mendelson, 2015; Bonkat et al., 2018; Chu & Lowder, 2018; Lee & Le, 2018; Fernandez & Coyle, 2019). Suprapubic pain, vaginal and urethral tenderness and haematuria might also be present. Pyelonephritis must be considered when patients present with nausea, vomiting, upper back pain, flank pain, malaise, suprapubic pain and fever. Vaginal discharge is less likely to be associated with a UTI (Mehnert-Kay, 2005; Chu & Lowder, 2018; Lee & Le, 2018; Fernandez & Coyle, 2019). Pregnant women might present with urinary frequency, suprapubic pain and dysuria (Chu & Lowder, 2018).

It is important to consider patient characteristics when managing UTIs. Elderly patients do not present with typical UTI symptoms. In post-menopausal women, symptoms such as urgency, frequency, incontinence and difficulty emptying bladder might be likely associated with a UTI (ACOG, 2008; Chu & Lowder, 2018). Elderly patients might also present with altered mental status, gastrointestinal symptoms and eating habit changes (Fernandez & Coyle, 2019). Dysuria, urine changes and mental status changes might be associated with UTIs in women in nursing facilities (Chu & Lowder, 2018). In contrast, patients with asymptomatic bacteriuria, a risk factor for UTIs, did not present clinically with any typical signs or symptoms associated with UTIs (Bartoletti et al., 2016; Nicolle et al., 2019).

2.5.7 UTI diagnosis

Diagnosing UTIs are complex and a holistic approach inclusive of clinical presentation, laboratory investigation and patient characteristics should be followed (Chu & Lowder, 2018). UTIs should ideally be diagnosed based on (1) clinical signs and symptoms, (2) laboratory investigations, and (3) a thorough history taking. UTIs could be diagnosed using urine dipstick analysis, microscopic analysis and urine culture (Chu & Lowder, 2018; Gupta & Trautner, 2018). A clinical diagnosis is based on signs and symptoms and urine dipsticks, while laboratory investigations include urine microscopy, urine culture and sensitivities (Van Schoor, 2016). A urine culture is the gold standard for diagnosing UTIs while urine dipstick and microscopic analysis guide the prescriber as it influences the probability of a UTI. Once diagnosed, grouping UTIs into complicated or uncomplicated UTIs are essential as it guides the physician in choosing the appropriate empiric antibiotic therapy (Walker et al., 2016).

A urine dipstick is often the first test to be conducted when suspecting a UTI and available as a point-of-care test to screen for UTIs. Leukocyte esterase, nitrite and red blood cells are urine components analysed by a urine dipstick. A urine dipstick could indicate pyuria (presence of white leukocytes), bacteriuria (presence of nitrites) and haematuria (blood). Bacteriuria (nitrites) is strongly indicative of a UTI compared with pyuria and haematuria (Fernandez & Coyle, 2019).

If acute uncomplicated cystitis is suspected, urinalysis using dipsticks are appropriate to screen for a UTI (ACOG, 2008; Lee & Le, 2018; Bonkat et al., 2018). Urinalysis positive for nitrites confirm bacteriuria and is predictive of a UTI. A UTI is confirmed if the dipstick is positive for both nitrites and leukocyte esterase (Bonkat et al., 2018). Nitrites are both sensitive and specific for UTI diagnoses than leukocytes alone. However, certain organisms, *S. saprophyticus* and *Enterococci* do not have the ability to reduce nitrates; thus, in the presence of these organisms a urine dipstick might be false negative. Bacteriuria is more specific than pyuria and likely indicative of a UTI (Mehnert-Kay, 2005; Bonkat et al., 2018). A bacterial count of 10^5 CFU/ml of a midstream clean catch urine is considered significant; however, in symptomatic patients a bacterial count of 10^2 CFU/ml is considered significant (Fernandez & Coyle, 2019).

Laboratory investigations, urine microscopy culture and sensitivity, remains the gold standard for diagnosing UTIs. Also, it guides the prescriber to prescribe definitive therapy (Mehnert-Kay, 2005; Chu & Lowder, 2018). Urine microscopy culture and sensitivity is recommended in treating:

1. Complicated UTIs,
2. Recurrent UTIs,
3. Pyelonephritis,
4. UTIs during pregnancy (Bonkat et al., 2018),
5. In a setting where resistant uropathogens are suspected,
6. In women who present atypically,
7. In those who do not clinically improve after 48 h of treatment, and
8. In symptomatic patients with a negative dipstick.

Ideally a urine microscopy culture and sensitivity test should be performed for every suspected UTI (ACOG, 2008; Bonkat et al., 2018; Matuszkiewicz-Rowińska, Małyszko & Wieliczko, 2015; Wasserman, Boyles & Mendelson, 2015; Walker et al., 2016; Van Schoor, 2016; Kang et al., 2018; DoH, 2018a; 2019b; De Rossi et al., 2020). Laboratory investigations are crucial for the diagnosis of a UTI and

antimicrobial susceptibility is essential to optimise antibiotic therapy in treating UTIs (Lee, Lee & Choe, 2018).

UTIs are common infections, complicating pregnancy. It is often preceded by asymptomatic bacteriuria (Kamgang, Maise & Moodley, 2016). Urine analysis by means of dipsticks are the recommended method for UTI screening in antenatal care. Pregnant women should be screened and treated for asymptomatic bacteriuria since it increased the risk for preterm delivery (Nicolle et al., 2019). Complications of UTIs during pregnancy include septicaemia, anaemia, preterm labour and intrauterine growth restriction, premature rupture of membranes and pre-eclampsia. (Kamgang, Maise & Moodley, 2016; Lee and Le, 2018; Nicolle et al., 2019). During pregnancy, women should be screen at the first antenatal period and at 28 weeks of gestation (Fernandez & Coyle, 2019). Imaging is recommended to exclude urological disorders in patients with pyelonephritis (Bonkat et al., 2018).

Screening and treatment of asymptomatic bacteriuria is not recommended in diabetics, the elderly and patients with indwelling catheters. However, treatment is recommended in pregnant women (Wasserman, Boyles & Mendelson, 2015; Nicolle et al., 2019). In the elderly, a culture should be considered in patients with fever, dysuria, new or worsening urinary urgency, change in frequency, new incontinence, gross haematuria and suprapubic pain (Mody & Juthani-Mehta, 2014).

2.5.7.1 Differential diagnosis

UTIs should be differentiated from asymptomatic bacteriuria. Asymptomatic bacteriuria is a colonisation rather than an infection with microorganisms. It was defined as identifying bacteria in the urine ($> 10^5$CFU/ml) in the absence of symptoms in two consecutive urine samples in women and one urine sample in men (Lee & Le, 2018; Nicolle et al., 2019). Other differential diagnosis of cystitis include pyelonephritis and vulvovaginal infections such as candidiasis and genital herpes (De Rossi et al., 2020). Also, UTIs should be differentiated from sexually-transmitted infections as they might share similar symptoms (Tomas et al., 2015).

2.5.8 Managing UTIs

The goals of therapy for UTI treatment are to eradicate the infection, to prevent complications and recurrence and to reduce AMR. The choice of the regimen should be guided by the severity of signs and symptoms, infection site and if the UTI was complicated or uncomplicated. Other important factors to consider include side effects, cost and previous antimicrobial exposure. Managing UTIs include evaluating and selecting an appropriate antimicrobial regimen and follow-up evaluation (Fernandez & Coyle, 2019). Factors to consider when selecting empiric antibiotic therapy for community UTIs include: (1) individual patient characteristics, (2) ABR in the community, (3) cost, (4) treatment failure, and (5) previous antibiotic exposure (Lee & Le, 2018; Kang et al., 2018).

Empiric antibiotic treatment is recommended in the following scenarios: (1) if the urine dipstick is positive for leukocytes and nitrites, and (2) if the urine dipstick is positive for leukocytes or nitrites with symptoms or systemic signs and symptoms (Mehnert-Kay, 2005; DoH, 2018a). Appropriate empiric therapy is vital to ensure treatment success and to prevent complications; however, antibiotics must be considered carefully with the current ABR dilemma (Bahadin, Teo & Mathew, 2011; Bosch, Van Vuuren & Joubert, 2011; Nzalie, Gonsu & Koulla-Shiro, 2016; Chervet et al., 2018). De-escalation to definitive therapy should be considered once the uropathogen is confirmed (Garau et al., 2014).

The spectrum of empiric antibiotics for treating UTIs include gram negative organisms' coverage as these organisms are associated with UTIs. Also, antibiotics with minimal collateral damage and low resistance should be first line choices in treating uncomplicated UTIs. These antibiotics included nitrofurantoin, fosfomycin and cotrimoxazole (Chu & Lowder, 2018). It is recommended that local community and hospital surveillance data be used to guide empiric therapy. Also, a resistance rate of 15% to 20% to an antibiotic require a different selection of antibiotics with fosfomycin, ciprofloxacin and nitrofurantoin being the preferred antibiotics (Bosch, Van Vuuren & Joubert, 2011; Chu & Lowder, 2018). In addition to spectrum and susceptibility patterns, tolerability, adverse ecological effects, cost and availability

must be considered. If antibiotics are appropriate, patients should respond to therapy within 48 h (Hooton & Gupta, 2020). Adherence to UTI guidelines are poor, specifically antibiotic selection, dose and duration of therapy (Chu & Lowder, 2018; Gasson, Blockman & Willems, 2018). Approximately 30% of antibiotics are prescribed inappropriately for treating asymptomatic bacteriuria in old-age care facilities (BSAC, 2018).

In a study conducted to determine community pharmacists' response to pseudo-patients presenting with viral upper respiratory tract infections and uncomplicated UTIs (Zawahir, Lekamwasam & Aslani, 2019), poor history taking was observed. Overall, in patients whom antibiotics were dispensed, only 36% of patients were asked about comorbid conditions, questions about concurrent medicine use were lower (2%). Overall, in those to whom an antibiotic was dispensed, no women were asked about their pregnancy status and only 10% of patients were asked about medicinal allergies. In general, history taking about action taken for the current conditions only occurred in 12% of patients. Focusing on UTIs, 55% of the pseudo-patients were given antibiotics and only 24% of patients who presented with a UTI were recommended to visit a physician for further care. Ciprofloxacin was the most common antibiotic prescribed for UTIs in females (77%) (Zawahir, Lekamwasam & Aslani, 2019). Like many other conditions, history taking was a key factor in the diagnosis process, containing clinical pearls which might influence antibiotic prescribing and managing. Important aspects to consider was time of onset, location, duration and severity of symptoms, as well as the presence of systemic symptoms such as fever. It was important to investigate previous antibiotic exposure for either previous UTIs or other conditions, since this might influence the prescriber's antibiotic choice (Velez, Richmond & Dudley-Brown, 2017). Overall, only 60% of patients were counselled on instructions on how to take their medicines, 47% of patients were counselled on the frequency of the medicines prescribed and only 22% were counselled on when to discontinue medication prescribed. The results for the counselling points reduced with almost 50% for patients with UTIs (Zawahir, Lekamwasam & Aslani, 2019). These principles are critical regarding dispensing medicines, especially with the dispensing of

antibiotics. The study emphasised the need to determine dispensing practices of antibiotics in primary healthcare and to understand reasons for the lack in dispensing practices. Further interventions must be implemented to improve patient care and ABR.

2.5.8.1 Pharmacological therapy

Antimicrobials for treating UTIs should achieve high urinary concentrations, the spectrum should cover the potential organism uropathogen, antimicrobials should be tolerated (Fernandez & Coyle, 2019), effective, cost-effective and available (Bonkat et al., 2018; De Rossi et al., 2020). UTIs could be treated with oral therapy; however, intravenous therapy should be considered in patients presenting with severe symptoms (Fernandez & Coyle, 2019). According to the AWaRe classification the following antibiotics were regarded as first line options for treating cystitis: nitrofurantoin, amoxicillin, amoxicillin-clavulanic acid and cotrimoxazole. For treating pyelonephritis ceftriaxone and ciprofloxacin is recommended (WHO, 2020a). It is recommended that cotrimoxazole only be used for treating cystitis and/or ciprofloxacin for treating pyelonephritis if the resistance rates are below 20% and 10%, respectively (Gupta et al., 2011). Fosfomycin might be used due to its low resistance. Amikacin is preferred above gentamicin due to good *Enterobacteriaceae* spectrum. Fosfomycin is regarded as a reserve group of antibiotics (WHO, 2020a).

The CDC (2017) recommends the following antibiotics for acute uncomplicated cystitis in adult non-pregnant women: nitrofurantoin, trimethoprim/ sulfamethoxazole (if local resistance < 20%) and fosfomycin as first line agents. Fluoroquinolones are recommended as second line agents; however, it is associated with a higher incidence of collateral damage. The SAASP authors recommended ciprofloxacin 500 mg 12 hourly for 3 d for the treatment of uncomplicated cystitis. They further recommend a seven-day course of ciprofloxacin 500 mg 12 hourly as outpatient treatment for pyelonephritis, while ceftriaxone or gentamicin is recommended as inpatient treatment if needed. Also, it is recommended to consider

intravenous to oral switch once indicated (Wasserman, Boyles & Mendelson, 2015).

Nitrofurantoin and fosfomycin are currently regarded as alternative first line treatment options for treating uncomplicated UTIs, due to low resistance rates (Chu & Lowder, 2018). A five-day course of nitrofurantoin, one dose of fosfomycin and a three-day course of cotrimoxazole (if the resistance rates are <20%) are first line regimens for treating UTIs. These antibiotics are associated with a lower risk of collateral damage. Second-line therapy include fluoroquinolones which are associated with a higher risk of collateral damage (Chu & Lowder, 2018; Fernandez & Coyle, 2019). According to the results from a multinational randomised controlled trial, a five-day course of nitrofurantoin was associated with earlier clinical response ($p < 0.004$) and bacteriological response ($p < 0.04$) compared to a single dose of fosfomycin (Huttner et al., 2018). Second line antibiotics include fluoroquinolones, beta-lactams and trimethoprim-sulfamethoxazole, only if local resistance are less than 20% (ACOG, 2008; Gupta et al., 2011; Bonkat et al., 2018; DoH, 2019a).

Ciprofloxacin should be considered as alternative therapy for treating uncomplicated UTIs, not only due to associated side effects, also because of resistance (Walker et al., 2016). In 2018, the US Food and Drug Administration (FDA, 2018) warned healthcare professionals about the potential adverse events of fluoroquinolones. Reported adverse events included an increase in tendon rupture, tendonitis and aortic aneurysm leading to bleeding complications in patients with a history of hypertension, aneurysms, QT prolongation, neuropathy and aortic rupture and elderly patients (DoH, 2019a). This warning urged the DoH to circulate a notice (DoH, 2019a) regarding the use of fluoroquinolones in the public sector. It was recommended that fluoroquinolones should no longer be prescribed in the following conditions: non-severe bacterial infections where other antibiotics were more effective, non-bacterial infections, prophylaxis of traveller's disease and prophylaxis of complicated UTIs. Alternative therapy for uncomplicated cystitis includes nitrofurantoin, fosfomycin and gentamicin. Ciprofloxacin is still indicated

for complicated cystitis and pyelonephritis; however, for complicated cystitis during pregnancy nitrofurantoin is recommended. Fosfomycin, nitrofurantoin and amoxicillin/clavulanic acid are available options for treating UTIs in pregnant women.

Fluoroquinolones should be carefully considered in treating UTIs, especially in the elderly, immunocompromised, athletes and pregnant women (Chu & Lowder, 2018; Fernandez & Coyle, 2019). In a study conducted to determine fluoroquinolone prescribing practices in primary healthcare after the boxed warning of the FDA (FDA, 2018), fluoroquinolone prescribing for uncomplicated UTIs resulted in a 33% reduction of fluoroquinolone prescribing (adjusted odds ratio: 0.67 95% CI 0.41–1.10; p = 0.12). Fluoroquinolones were more likely prescribed for treating UTIs in the elderly. Compliance to the clinical practice guidelines for uncomplicated UTIs from the Infectious Diseases Society of America was low (Cowart et al., 2019).

The above warnings led to a change in the STGs recommendations for UTI treatment in 2020 (DoH, 2020). The following was recommended for the treatment of uncomplicated cystitis:

1. Gentamicin 160 mg IM single dose as preferred treatment.
2. If gentamicin was contraindicated or not available, fosfomycin 3 g orally as a single dose is recommended.
3. Nitrofurantoin 100 mg orally 6 hourly for 5 d is recommended as the last option.
4. Further fosfomycin and nitrofurantoin is preferred in pregnancy.

Ciprofloxacin is still recommended for treating complicated cystitis and complicated UTIs. The duration of antibiotic therapy depends on the type of UTI and antibiotic prescribed. Clinical efficacy was approximately 93% with a five- to seven-day course of nitrofurantoin, 90% to 100% with a three-day course of cotrimoxazole (if the resistance was less than 20%) and 91% with fosfomycin (Chu & Lowder, 2018). A short course was shown to be equally effective for treating

uncomplicated UTIs; i.e., an antibiotic course for 3 d was recommended above 5 d to 7 d (Barlam et al., 2016). Recurrent UTIs should be treated with antibiotics for a longer duration, typically 7 d. In patients with recurrent UTIs, urinalysis, culture and sensitivity should be performed before treatment was initiated. In patients with pyelonephritis, fluoroquinolones are indicated for 7 d to 14 d, alternatively third generation cephalosporins might be used. A urine culture is recommended to prescribe appropriate antibiotic therapy for treatment of pyelonephritis (ACOG, 2008; Bonkat et al., 2018; DoH, 2018a). Males require longer treatment of UTIs (Fernandez & Coyle, 2019) since these UTIs are classified as complicated. Table 2.2 summarises the various treatment recommendations for uncomplicated UTIs.

Table 2.2: Treatment recommendations for cystitis
(Gupta et al., 2011; Wasserman, Boyles & Mendelson, 2015; Bonkat et al., 2018; Lee & Le, 2018; DoH, 2018a; 2019b; Fernandez & Coyle, 2019; Gupta & Trautner, 2018; De Rossi, 2020)

Antimicrobial	Dose	Route	Frequency	Duration	Notes
Uncomplicated Cystitis					
Amoxicillin-clavulanic acid	500mg	PO	8 hourly	5-7 days	
Cephalexin	500mg	PO	12 hourly	5-7 days	
Ciprofloxacin	250mg-500mg	PO	12 hourly	3 days	Not recommended during pregnancy
Cotrimoxazole	960mg	PO	12 hourly	2 days 7 days (men)	Not safe in the first and last trimester
Fosfomycin	3g	PO	Once	Single dose	Do not use after 37 weeks of gestation
Gentamicin	5mg/kg	IV	Once	Single dose	
Levofloxacin	250mg	PO	Daily	3 days	Not recommended during pregnancy
Nitrofurantoin	50-100mg		6 hourly	5 days	
Nitrofurantoin monohydrate	100mg	PO	12 hourly	5 days	
Complicated Cystitis					
Amoxicillin-clavulanic acid	500mg	PO	8 hourly	7-10 days	
	1 000mg	PO	12 hourly	7 days	
Cefuroxime	250mg	PO	12 hourly	7 days	
Ciprofloxacin	250-500mg	PO	12 hourly	7-10 days	
Fosfomycin	3g	PO	Once	Single dose	
Nitrofurantoin	100mg	PO	6 hourly	5-7 days	

Table 2.3 summarises the treatment regimens for pyelonephritis.

Table 2.3: Treatment recommendations for pyelonephritis
(Gupta et al., 2011; Lee & Le, 2018; DoH, 2018a; 2019b Fernandez & Coyle, 2019).

Antimicrobial	Dose	Route	Frequency	Duration
Amikacin	15mg/kg	IV	Daily	
Amoxicillin clavulanic acid	1g	PO	12 hourly	7 days
Cefepime	1-2g	IV	Daily	
Cefotaxime	2g	IV	8 hourly	
Cefpodoxime	200mg	PO	12 hourly	10-14 days
Ceftazidime	1-2g	IV	8 hourly	
Ceftriaxone	1-2g	IV	Daily	
Ciprofloxacin	400mg	IV	12 hourly	
	500mg	PO	12 hourly	7-14 days
Cotrimoxazole	960mg	PO	12 hourly	14 days
Doripenem	500mg	IV	8 hourly	
Ertapenem	1g	IV	Daily	
Gentamicin	3-5mg/kg	IV	Daily	
Imipenem-cilastatin	0.5g	IV	8 hourly	
Levofloxacin	250mg	PO	Daily	10 days
	500mg	IV	Daily	7 days
	750mg	PO	Daily	5 days
Meropenem	1g	IV	8 hourly	
Piperacillin-tazobactam	2.5-4.5g	IV	6-8 hourly	

Treating UTIs during pregnancy require careful consideration for both the mother and foetus. Antibiotics regarded as safe for treating UTI during pregnancy include amoxicillin, amoxicillin-clavulanic acid, cephalosporins, nitrofurantoin and fosfomycin (Matuszkiewicz-Rowińska, Małyszko & Wieliczko, 2015; De Rossi et al., 2020). In pregnant women, standard short course therapy are preferred over single dose therapy to reduce incidences of low birthweight (Bonkat et al., 2018). According to the ACOG (2008) guidelines, pyelonephritis should be treated for 14 d.

Patients with asymptomatic bacteriuria do not usually require treatment, unless pregnant. Other patients who require treatment of asymptomatic bacteriuria include women who require a urological procedure. Treating asymptomatic bacteriuria with antibiotics when not indicated increases healthcare-related costs and the risk of infection, as well as fuel AMR (ACOG, 2008; Garau et al., 2014; Matuszkiewicz-

Rowińska, Małyszko & Wieliczko, 2015; Bartoletti et al., 2016; Bonkat et al., 2018; De Rossi et al., 2020). Treatment of asymptomatic bacteriuria is not recommended in the following patients: diabetic patients, the elderly, non-pregnant healthy women, patients with spinal cord injuries, and postmenopausal women (Bonkat et al., 2018; Nicolle et al., 2019; De Rossi et al., 2020). Table 2.4 summarises the treatment of asymptomatic bacteriuria.

Table 2.4: Treatment recommendations for asymptomatic bacteriuria (Lee & Le, 2018; De Rossi et al., 2020)

Antimicrobial	Dose	Frequency	Duration
Amoxicillin	500mg	8 hourly	7 days
	875mg	12 hourly	7 days
Cephalexin	500mg	6 hourly	7 days
Fosfomycin	3g	Once	Single dose
Nitrofurantoin	100mg	6 hourly	5 days

Recurrent UTIs can be managed by any of the three options: (1) continuous, (2) postcoital, and (3) self-initiated antimicrobial prophylaxis to reduce the frequency of recurrent UTIs (Fernandez & Coyle, 2019; De Rossi et al., 2020). The most common antibiotics used for prophylaxis are once daily doses of nitrofurantoin, cotrimoxazole and ciprofloxacin with a treatment duration of six to 12 months. Postcoital prophylaxis with a single dose of antibiotics might be considered in women with recurrent UTIs mostly associated after sexual intercourse (ACOG, 2008; De Rossi et al., 2020; Hooton & Gupta, 2020). Continuous long-term prophylaxis (six to 12 months) antibiotic therapy reduced UTI recurrence in non-pregnant women (Albert et al., 2004). Although long-term antibiotic therapy with cotrimoxazole and nitrofurantoin reduced the risk of recurrent UTIs in post-menopausal women it was associated with AMR (Mody & Juthani-Mehta, 2014; Ahmed et al., 2017). The efficacy of nitrofurantoin was comparable with norfloxacin, cotrimoxazole, and cefaclor in reducing UTI recurrence. However, nitrofurantoin had lower collateral damage effects (Price et al., 2016; Muller et al., 2017). Table 2.5 summarises the treatment recommendations for recurrent UTIs.

Table 2.5: Treatment recommendations for managing recurrent UTIs (Fernandez & Coyle, 2019; DoH, 2019b; De Rossi et al., 2020).

Antimicrobial	Dose	Frequency
Cephalexin	125-500mg	Daily
Cotrimoxazole	240-480mg	Once daily
Fosfomycin	3g	Every 10 days
Nitrofurantoin	50-100mg	Daily

Phenazopyridine hydrochloride was often used for symptomatic relief of UTIs (Fernandez & Coyle, 2019; De Rossi et al., 2020). Also, vaginal oestrogen replacement therapy in post-menopausal women might prevent recurrent UTIs (Mody & Juthani-Mehta, 2014; Bonkat et al., 2018; Fernandez & Coyle, 2019; De Rossi et al., 2020; Anger et al., 2019).

2.5.8.2 Other pharmacological therapies

Paracetamol and ibuprofen might be prescribed to alleviate symptoms associated with UTIs (Lee & Le, 2018).

2.5.8.3 Non-pharmacological therapy

Non-pharmacological measures to prevent UTIs include drinking cranberry juice (Anger et al., 2019). According to a Cochrane review (Jepson, Mihaljevic & Craig, 2009), more evidence is required to determine the effectiveness of cranberry juice preventing UTIs. However, ACOG (2008) recommended cranberry juice for symptomatic relief of UTIs, this was supported by a meta-analysis which reported cranberry juice was more effective than placebo. Patients with recurrent UTIs should be advised to void the bladder after intercourse; however, this has not been proven to be an effective way to prevent UTIs. Other recommendations include voiding the bladder as needed and changing to an alternative contraceptive method if the diaphragm is used (ACOG, 2008; DoH, 2018a; De Rossi et al., 2020).

Increased fluid intake is a behaviour modification recommended for the prevention of UTIs (DoH, 2019b; De Rossi et al., 2020). Fluid hydration dilute bacteria and increase urine voiding (Fernandez & Coyle, 2019). According to the results from a randomised controlled trial (Hooton et al., 2018), premenopausal females who were

randomised to drink 1.5 L of water in addition to their daily fluid intake had less cystitis episodes ($p < 0.001$) compared to placebo. Also, antibiotic use and time between cystitis episodes were reduced ($p < 0.001$) in the intervention group compared to placebo. Postcoital voiding, non-occlusive underwear, avoidance of vaginal douching and wiping from the front to the back were other behavioural modifications that prevented recurrence (De Rossi et al., 2020). Also, *Lactobacillus* probiotics might prevent UTIs (Fernandez & Coyle, 2019).

2.5.8.4 UTI complications

UTIs affect patients' quality of life and increase the healthcare burden (Öztürk & Murt, 2020). UTIs might lead to significant complications such as recurrence, pyelonephritis with sepsis, bacteraemia, renal damage, pre-term birth and *Clostridioides difficile* infections (Chu & Lowder, 2018). The complications of inappropriately treated UTIs might include recurrence, pyelonephritis, sepsis and renal damage (Öztürk & Murt, 2020). Urosepsis is a life-threatening condition caused by an over reacting immune system due to an infection of the urinary tract (Bonkat et al., 2018). Complications of UTIs were patient dependent. Asymptomatic bacteriuria in pregnant women could lead to pyelonephritis which might complicate the pregnancy further leading to premature delivery (Chu & Lowder, 2018; Gupta & Trautner, 2018), low birth weight infants and pre-eclampsia (Matuszkiewicz-Rowińska, Małyszko & Wieliczko, 2015). According to the STGs primary healthcare level in SA, the following patients with acute pyelonephritis should be referred for further care: patients with vomiting, sepsis or diabetes mellitus, pregnant women, men and post-menopausal women. Also, those who are unresponsive to treatment, women with more than three UTIs and men with more than one UTI annually should also be referred (DoH, 2018a).

2.5.8.5 Follow-up and monitoring

A follow-up urine culture one to two weeks after treatment is important in pregnant women due to the increased risk of recurrence (Bonkat et al., 2018; DoH, 2019b; De Rossi et al., 2020). Follow-up and monitoring is important in acute pyelonephritis and in UTIs in males (Fernandez & Coyle, 2019).

3 STUDY METHODOLOGY

This chapter explains the study design, study site and population, data collection process, statistical analysis and ethics. A summary concludes the chapter.

3.1 Study design

This was an observational, multicentre retrospective folder review, designed to describe the management of UTIs in the primary healthcare setting in the Cape Metropole of the Western Cape. The study followed a pragmatic data collection approach to contribute to the study findings and conclusions. Since the management of UTIs are not clearly understood it was believed that an observational study would aid in understanding the management of UTIs following a pragmatic approach. Being an observational study, this study serves as the baseline for further research in the field by describing the current managing and focusing on the treating of UTIs in the Western Cape primary care setting (Mariani & Pêgo-Fernandes, 2014; Centre for Evidence-Based Medicine, 2014).

The data was collected by the researcher only. Data was collected from six primary healthcare facilities across three substructures in the Cape Metropole identified through a random selection process. A pilot study was conducted to evaluate and refine the data collection tool. The following changes were made to the data collection tool: The list of the concurrent medicines prescribed were expanded and screening and laboratory investigations were separated.

The retrospective folder review addressed Objective 2 of the study. It was conducted for the purpose of describing how UTIs were diagnosed and treated at primary healthcare level. Further prescribing practices were explored to determine if prescribing practices for treating UTIs were aligned with recommendations from STGs and EML for primary healthcare level. Quantitative data from patient folders was collected using a standardised data collection tool. Dispensing data was also reviewed using the Jack Andy and Carol (JAC) system.

3.2 Study description

This was an observational study conducted in the primary healthcare setting of the Western Cape public sector.

3.3 Study setting

The study was conducted in the public sector of the Western Cape, Cape Metropole at primary healthcare level. Primary healthcare facilities in the public sector are government-funded facilities that provide primary healthcare to the surrounding community. This includes clinics, community healthcare centres and community day centres. Only community healthcare centres and community day centres were included in the study as data collection sites. A total of six primary healthcare facilities, two from three of the four substructures in the Cape Metropole, were included.

3.4 Study population and sampling

The primary healthcare facilities recruited were facilities where a prescriber (doctor or nurse), nurse and pharmacist were employed. Only facilities using the JAC dispensing system were included as this system allowed access to dispensing data. The JAC system is a computerised system used in the Western Cape for stock ordering and dispensing medicines. It is an integrated system; thus, all facilities with access to JAC are linked to ensure continuity of care. Dispensing information was easily accessible and provided information on medicines dispensed, quantity as well as instructions for use. The TRACE function in JAC could be used to filter information for specific medicines over a specified period (e.g., fosfomycin dispensed over six-month period) to deliver a transactional report. Since there was no data available on the prevalence of UTIs in the Western Cape, a prevalence was set at 50% to calculate the sample size. Based on this prevalence, 400 prescriptions would be sufficient as a sample size for data collection (see formula below). The formula to calculate sample size was (Naing, Winn & Rusli, 2006):

$$n = \frac{p(1-p)z^2}{d^2}$$

n = sample size

p = prevalence

d = desired precision

z = 1.96 (95% level of confidence)

$$n = \frac{0.5(1-0.5)1.96^2}{0.05^2}$$

n = 385

n = 400

n = 100 folders per facility

However, all community healthcare and community day centres were included in the DoH application process. Based on approval of facilities these facilities were included in the randomisation process (using Excel) to identify eight primary healthcare facilities, two per substructure, as data collection sites opposed to one facility per substructure. This decision was based on multiple approvals from substructures. Six facilities, two per substructure, were included in the study. Thus, it was decided by the researcher to collect a minimum of 100 folders per substructure and a minimum total of 400. One substructure had to be excluded due to limited approval from facilities in the specific substructure and different processed followed than the other facilities included here. The study followed a retrospective folder review on patients diagnosed with UTIs. Folders were identified through selective sampling following a pragmatic approach.

3.5 Data collection tools

A data collection tool was designed by a team consisting of pharmacists and a doctor. A pilot study was conducted to evaluate and refine the data collection tool using 10 patient folders, collected over a period of one week, from a facility not included here.

3.5.1 Data collection tool

Data was collected through a retrospective folder review by means of a MUE. The retrospective folder review was performed using a standardised data collection tool (Appendix A). The following information was collected:

- demographics,
- diagnosis,
- results from any diagnostic test performed (urine dipsticks or urine culture microscopy and sensitivity),
- antibiotics prescribed and dosage, as well as
- frequency and duration of antibiotics.

Dispensing data was also reviewed through JAC (Appendix B). For diagnostic data not collected in the patient folder a follow-up was done through collecting data for urine microscopy culture and sensitivity through The National Health Laboratory Service (NHLS).

3.6 Data collection

Data was collected by the researcher only during the period October 2020 to February 2021. Prescribers and pharmacists were informed about the study and the study process after ethical approval was granted. Pharmacists identified medical folders of patients diagnosed with a UTI through microbiological or clinical diagnosis. The identified folders were kept aside, or patient stickers were kept and used to retrieve folders for data collection depending on the type of facilities. Folders were collected daily, excluding the day when the researcher collected data. All available consecutive folders were kept for the researcher to review on a specific day of the week which was convenient for both the facility and researcher. The process was repeated until 100 folders per substructure and 400 folders in total were reviewed. Prescriptions included were reviewed using a standardised data collection tool. To account for missing data and report on true antibiotic dispensing, the TRACE function in JAC was used to collect actual dispensing data for nitrofurantoin and fosfomycin over the period of data collection.

Figure 3.1 shows how the folders were identified in the pharmacy:

1. Pharmacists identified folders of adult patients (>18 years) diagnosed with a UTI.
2. Folders or folder numbers were kept in the pharmacy.

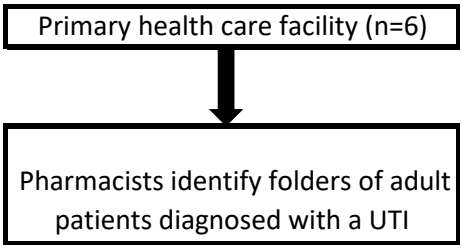

Figure 3.1: Identification of folders

Data collection process by the researcher:

1. Paediatric patients were excluded (< 18 years).
2. A data collection tool was used to collect data from the identified folders.
3. Dispensing data from JAC was reviewed using a data collection tool.
4. Also, the NHLS system was consulted for missing diagnostic data.
5. This process was repeated until 100 folders per substructure and 400 folders in total were reviewed.
6. For the period of data collection, the TRACE function in JAC was used to collect data for nitrofurantoin and fosfomycin to review actual dispensing data.

Inclusion criteria:

- Adults (>18 years)
- With a clinical or microbiological diagnosis of a UTI.

3.7 Data analysis

Data was anonymised before it was analysed. Data was analysed in Microsoft Excel® (2016) using drop-down lists to ease the data capturing process, to ensure consistent data capturing and efficient data analysis. This method was used to

reduce the time for data cleaning. Data was analysed using basic descriptive statistics.

3.8 Data validity and reliability

Primary healthcare facilities were included based on a random selection process. Quantitative data was collected using standardized data collection sheet following a pragmatic approach. Following a pragmatic approach allowed to describe the management of UTIs at primary healthcare level realistically. Data collected was assumed to be valid and dependable since data was collected from patient folders using a standardised data collection tool by the researcher only.

3.9 Ethical considerations

3.9.1 Permission and informed consent

The study was conducted in full conformity with the current revision of the Declaration of Helsinki (World Medical Association, 2013) and/or the International Conference for Harmonization Good Clinical Practice regulations and guidelines, whichever afforded the greater protection to the subject. According to the National Health Act 61 of 2003 (Republic of South Africa, 2004), informed consent from the prescriber is required for research purposes once the prescriber was informed about the positive and negative consequences of the research. However, informed consent is not necessary if a healthcare provider used patient information from health records for research purposes; however, approval was necessary from research ethics committees. The study commenced once approval was granted from the Biomedical Research Ethics Committee (BM20/5/17) (Appendix B) form the University of the Western Cape (UWC) as well as the Health Research Committee from the Western Cape DoH (WC_202006_038) (Appendix C).

3.9.2 Informed consent form

No informed consent was required during the retrospective folder review. Access to patient folders was granted by the Health Research Ethics Committee.

3.9.3 Confidentiality

Patient confidentiality was maintained throughout the data collection and analysis phase. Patients were identified through their date of birth and facilities during data collection, but data was anonymised before data analysis. Data collection forms were kept in a locked location at the School of Pharmacy, UWC. Also, electronically-stored data was password protected.

3.9.4 Anticipated risks and precautions

Since this was an observational study that aimed to describe the management of UTIs at primary healthcare level, no interventions were made if inappropriate prescribing/antibiotic use was observed. However, future patients would benefit from the study's outcomes. The study would contribute to improving the quality of care provided for future patients with UTIs treated at primary healthcare level.

3.9.5 Funding

Funding for administrative functions was provided by the School of Pharmacy, UWC and the National Research Foundation grant (**Grant No: CEC 180513328650**). The largest expected cost of this project was the printing of the data collection tool.

3.10 Summary

This chapter described the study's methodology. The following chapter will present the results.

4 RESULTS

4.1 Introduction

This chapter presents the study's results in the form of two manuscripts and a note that includes additional results. Manuscript one was submitted for publication to the *South African Medical Journal*, a peer-reviewed journal publishing research that impacts clinical care in Africa. Authorship details and author guidelines from the journal is included as appendices (Appendices D and E). A second manuscript was prepared for publication in the *Journal of Pharmacy Practice*. Authorship details and author guidelines from the journal is included as appendices (Appendices F and G). The chapter concludes with a summary.

4.2 Published manuscript one (*South African Medical Journal*)

The manuscript presented in this section was prepared and submitted to the *South African Medical Journal* on 14 November 2021 (reference number: SAMJ16258). The manuscript was accepted for publication on 17 December 2021. Refer to appendix H for acceptance email. References were included in the results section as part of the original accepted manuscript.

Pharmaceutical perspective of treating urinary tract infections in public sector primary healthcare facilities in Cape Town, South Africa

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Abstract

Background

Antibiotic resistance is a global healthcare burden complicating the management of infections. Urinary tract infections (UTIs) are commonly treated in primary care. Appropriately managing UTIs in primary care can combat antibiotic resistance. The

treatment practices of UTIs in primary care in the Western Cape are not well described.

Objective

To describe treating UTIs in adults in primary care in the Cape Metropole public sector of the Western Cape province.

Method

A retrospective multicentre medical records review of patients diagnosed with UTIs was conducted during 1 October 2020 to 28 February 2021. Six public sector primary healthcare facilities were included in the study through random selection from three of the four substructures in the Cape Metropole. Medical records of adult patients diagnosed with UTIs, through clinical diagnosis or microbiological testing, were identified through a selective sampling process. Data was collected from medical records using a standardised data collection tool.

Results

A total of 401 UTI episodes occurred in 383 patients during the study period. The majority of UTI episodes (84.3%) occurred in females; complicated UTIs (74.1%) were more common than uncomplicated UTIs and nitrofurantoin (57.1%) was frequently prescribed, followed by ciprofloxacin (39.7%). Complying to urine microscopy recommendations was low, and antibiotics were appropriately selected in the majority of uncomplicated (75%) and complicated UTI episodes (70%).

Conclusion

Interventions are required by management to improve compliance to treatment recommendations as per the standard treatment guidelines especially when selecting the appropriate antibiotic, duration of therapy and urine microscopy.

Keywords: nitrofurantoin, ciprofloxacin, urinary tract infection, antibiotic resistance, primary care.

Background

Antibiotic resistance is one of the greatest global healthcare threats the world is facing.[1] Failure to respond with action may lead to a post-antibiotic era where ordinary infections will be untreatable.[2] Irrational prescribing is one of the factors fuelling antibiotic resistance.[3,4] Approximately 80% of antibiotic prescribing occurs in the primary healthcare setting[5] where almost 30% of prescribed antibiotics are unnecessary.[6] Antibiotic stewardship programmes have been identified as a key strategy to optimise antibiotic use in an attempt to reduce antibiotic resistance at both hospital and community level.[7] Low- and middle-income countries face various challenges to successfully implement antibiotic stewardship programmes.[8] Implementing stewardship programmes in primary care in South Africa is still developing.[9,10] The Antimicrobial Resistance National Strategy Framework 2014-2024 was developed to support antibiotic stewardship in South Africa.[11]

In the Western Cape primary care setting, prescribing is guided by the Standard Treatment Guidelines (STGs) and Essential Medicines List: Primary Healthcare level.[12] In a study conducted by Gasson et al.[13], adhering to STGs guidelines for infections in primary care was investigated. Urology infections accounted for 7.5% of infections and complying with primary care guidelines for treating urological infections were the lowest. In terms of treating urological infections, the duration of antibiotic therapy and antibiotic selection was inappropriate in half of the cases (51.2%) and 17.1% of the cases, respectively. Adhering to guideline recommendations for ciprofloxacin prescribing was poor.[13] Urinary tract infections (UTIs) are among the most commonly treated primary healthcare conditions requiring antibiotic therapy[14,15] which may increase the healthcare burden as antibiotic resistance increases.[16] UTIs affect a patient's quality of life and the sequelae of UTI complications may include urosepsis, recurrence, pyelonephritis, sepsis, renal damage, bacteraemia, preterm birth and even *Clostridioides difficile* infections.[17,18] If asymptomatic bacteriuria in pregnancy remains untreated it may lead to pyelonephritis, preterm birth and low birthweight.[19,20] The goals for UTI treatment therapy are to eradicate the infection, prevent complications and recurrence as well as limiting antibiotic resistance.[21]

Practicing antibiotic stewardship in primary care can optimise patient health outcomes and reduce antibiotic resistance. Appropriate empiric therapy is vital to ensure treatment success and to prevent complications; however, antibiotics should be considered carefully with the current antibiotic resistance dilemma.[22,23] Local antimicrobial susceptible patterns will assist in guiding empiric therapy for UTIs in the emerging setting of resistance.[22] A few surveillance studies have been conducted in South Africa [22,24-26] and it is evident that surveillance data is area-specific and continuous monitoring is needed to recommend appropriate empiric therapy. Surveillance data in the Western Cape could guide prescribing the appropriate antibiotic therapy for treating UTIs. Classifying UTI in terms of complicated and uncomplicated infections require standardisation[27] to promote rational antibiotic use and to optimise patient health outcome.

Various communications[28,29] on the potential risks of fluoroquinolones led to the National Department of Health amending the STGs for UTIs in 2019 recommending that ciprofloxacin not be used for uncomplicated UTIs.[30] To our knowledge treating UTIs and prescribing practices in the primary care setting of the Western Cape public sector has not been described. This study's aim is to describe how UTIs are treated in primary healthcare and to determine compliance to current local guidelines.

Method

Study design and setting

A retrospective multicentre medical records review of patients with UTIs was conducted in the primary healthcare setting of the Western Cape public sector for the period 1 October 2020 to 28 February 2021.

Study population and sampling

Adult outpatients (≥ 18 years of age) diagnosed with UTIs, either clinically or with microbiological confirmation, at community day centres (CDC) or community healthcare centres (CHC) in the Cape Metropole were included here. These facilities were identified through a random selection process using Microsoft Office Excel® (2016) to identify two facilities per substructure from the following three

substructures in the Cape Metropole: Northern/Tygerberg, Klipfontein/Mitchell's plain and Eastern/Khayelitsha. One substructure had to be excluded due to different operating procedures. For anonymity, the data presented in the manuscript would not be presented according to the substructure specific names.

A prevalence was set at 50% to calculate the sample size.[31] Medical records were identified through a selective sampling process following a pragmatic approach. Pharmacists daily identified folders of adult patients who presented with UTIs. Data was collected by the researcher on a continuous basis until a minimum of 100 records per substructure or until a total of 400 records were reviewed. Patients that were referred to a higher level of care were excluded from the study.

Collecting and analysing data

A data collection tool was designed by the research pharmacists and a physician to collect the following data from patient medical records: demographics, diagnosis, results from diagnostic investigations, antibiotic regimen prescribed, concurrent conditions, concurrent medicines prescribed and dispensing data. The 2018 Primary Healthcare Level STG[12] and Circular H53/2019 [30] were used to inform on the criteria for the data collection tool. To test the data collection tool and study process a pilot study was conducted using 10 patient folders from a facility not included here. The pilot study followed the same procedures. Data was analysed using descriptive statistics and Microsoft Excel® (2016).

Current guidelines in place at the time of the study were used to assess appropriate management of UTIs; i.e., the 2018 Primary Healthcare Level STGs (PHC EML 2018)[12] and Circular H53/2019[30] which provided updated antibiotic treatment recommendations after notification of ciprofloxacin safety warnings. At primary healthcare level, it is expected that management for UTIs should predominantly conform to STGs.

Classifying UTIs is not clear in the literature and for this study's purpose, UTIs were categorised into complicated and uncomplicated UTIs based on national and international guidelines.[12,21,32,33] Table 1 provides a summary of the classification, recommended investigations and treating complicated and uncomplicated UTIs.

UTIs in healthy, pre-menopausal, non-pregnant females (19 to 45 years of age) were categorised as uncomplicated UTIs and all other UTIs were categorised as complicated UTIs.[21]

Table 1: Classification, recommended investigations and treatment for complicated and uncomplicated UTIs [12,21,30,32-34]

Uncomplicated UTI	**Complicated UTI**
Urinary tract infections defined	
UTI in healthy premenopausal women (19-45 years)	Catheter associated UTIs
	UTI during pregnancy
	UTI in men
	UTIs in post-menopausal women (>46 years)
	UTIs in patients with urinary tract abnormalities
	UTIs in patients with concomitant immunocompromised conditions e.g., diabetes mellitus, human immunodeficiency virus
	Recurrent UTI
	Upper UTI
Recommended investigations	
Urine dipstick	Urine dipstick
	Urine microscopy and sensitivity
Treatment Recommendations	
Standard Treatment Guidelines – Primary Healthcare Level (2018)	
Cystitis	
ciprofloxacin 500mg po 12 hourly for 3 days	ciprofloxacin 500mg po 12 hourly for 7 days
	Pregnant/adolescent: nitrofurantoin 100mg po 6 hourly for 7 days
Pyelonephritis	

	ciprofloxacin 500mg po 12 hourly for 7-10 days
	Pregnant: ceftriaxone 1g IV single dose
Updated treatment guidelines: Circular H53/2019	
Cystitis	
nitrofurantoin 100mg po 6 hourly for 5 days OR	ciprofloxacin 500mg po 12 hourly for 7 days
fosfomycin 3g po single dose OR	
gentamicin 5mg/kg IM single dose	
Pyelonephritis	
	ciprofloxacin 500mg po 12 hourly for 7 – 10 days
Referral	
Pyelonephritis with vomiting, sepsis, fever and in patients with diabetes, pregnancy, women beyond reproductive age, men; women with more than three UTIs in one year, men with more than one UTI, cystitis in pregnancy with no response to therapy or detected resistant organisms	

Ethical considerations

Approval was granted from the University of the Western Cape's Biomedical Research Ethics Committee (BM20/5/17) and the Western Cape Government Health (WC_202006_038). This was a retrospective medical record review, data was anonymised before analysis; thus, no informed consent was required from patients.

Results

A total of 401 UTI episodes from 383 patients were reviewed from six primary care facilities across three substructures in the Cape Metropole. Facilities comprised of CDCs (83%) and CHCs (17%). The majority of UTI episodes occurred in females (338/401; 84.3%). Seventy-five pregnant women (75/321; 23.4%) presented with 84 UTI episodes during the study period. In terms of age, UTIs occurred more

frequently in younger pre-menopausal women (19 to 39 years age category) compared to men (50 to 69 years age category). Table 2 includes more details.

Fifty-two patients (52/383; 13.6%), 44 females and eight males, were exposed to an antibiotic during the preceding 90 days. Penicillin (41.1%), nitrofurantoin (20.5%) and ciprofloxacin (19.2%) were amongst the most common antibiotics patients were exposed to previously.

Table 2: Demographics

	Total, *N* (%)	**Female, *n* (%)**	**Male, *n* (%)**
Age			
Minimum	19	19	19
Maximum	89	89	84
Mean (SD)	45 (18.13)	44 (18.02)	54 (16.01)
Median	43	38	59
Categories (years)			
19-29	96 (25.1)	91 (28.3)	5 (8.1)
30-39	82 (21.4)	74 (23.1)	8(12.9)
40-49	46 (12.0)	39 (12.1)	7 (11.3)
50-59	54 (14.1)	39 (12.1)	15 (24.2)
60-69	62 (16.2)	44 (13.7)	18 (29.0)
70-79	32 (8.4)	24 (7.5)	8 (12.9)
80-89	11 (2.9)	10 (3.1)	1 (1.6)
Patients	383 (100)	321 (83.8)	62 (16.2)
UTI episodes	401 (100)	338 (84.3)	63 (15.7)

Documenting allergies were reported in patient folders (88.3%). Hypertension (37.6%) and diabetes mellitus (16.7%) were common comorbid conditions. Analgesia was the most frequent medicines prescribed concurrently (Table 3). The study included eight wheelchair-bound patients (2.1%), one patient with tetraplegia due to a spinal injury (0.3%) and five patients had a catheter (1.3%). A urine

alkaliser was prescribed in 53 UTI episodes and concurrently with ciprofloxacin in 22 episodes.

Table 3: Documented allergies and comorbid conditions and concurrent medicines prescribed

	Total, *n* (%)
Allergies	
Documented	338 (88.3)
No allergies	309 (80.7)
Antibiotics	14 (3.7)
Other*	19 (5.0)
Not documented	45 (11.7)
Comorbid conditions	
Cancer	9 (2.3)
Diabetes mellitus	64 (16.7)
Human immunodeficiency virus	20 (5.2)
Hypertension	114 (37.6)
Pregnancy	75 (19.6)
Osteoarthritis	49 (12.8)
Spinal injury	2 (0.5)
Benign prostate hypertrophy	6 (1.6)
Urinary incontinence	3 (0.8)
Other	232 (60.6)
Concurrent medicine	
Analgesia†	324 (22.4)
Antimicrobials	33 (2.3)
Contraceptives in WOCBA‡	31 (2.1)
Supplements§	66 (4.60
Urine alkaliser	53 (3.7)
Anti-diabetic	110 (7.6)
Anti-hypertensive	306 (21.2)
Other	521 (36.1)

Total	1 444 (100)

*non-steroidal anti-inflammatory medicines, iodine, opioids

†Paracetamol, ibuprofen, tramadol

‡Women of childbearing age

§iron, folic acid, calcium, vitamin D

The majority of UTI episodes were complicated (74.1%) occurring mostly in females (84.3%). Antibiotics were prescribed in almost all UTI episodes (98.8%); i.e., in all male and 98.5% of female UTI episodes. Antibiotics were prescribed in all uncomplicated UTI episodes and 98.3% of complicated UTI episodes. A total of 729 nitrofurantoin issues were recorded on the electronic dispensing system, while 229 nitrofurantoin prescriptions from patient records were reviewed for the study period. Similarly, four fosfomycin issues were recorded while no prescriptions were reviewed for the study period. Nitrofurantoin was prescribed in the majority of UTI episodes (57.1%) followed by ciprofloxacin (39.7%). Nitrofurantoin was more frequently prescribed in uncomplicated (75.0%), complicated (50.8%) UTI episodes and in UTI episodes in women (63.9%). Ciprofloxacin was mostly prescribed in UTI episodes in men (79.4%) and in complicated UTI episodes (45.1%). A urine dipstick was performed in the majority of UTI episodes (88.0%); while urine microscopy was conducted in only 6.7% of complicated UTI episodes. In terms of complying with STG recommendations, nitrofurantoin was appropriately selected in 75.0% of uncomplicated UTI episodes. However, for complicated UTIs, ciprofloxacin (44.4%) showed greater compliance in terms of antibiotic choice compared to nitrofurantoin (25.6%). Total daily dose of appropriately selected antibiotic was prescribed for about 99% of prescriptions of nitrofurantoin and ciprofloxacin; while duration of appropriate antibiotic and total daily dose were lower. In complicated UTIs duration of appropriate antibiotic and total daily dose was lowest for ciprofloxacin (68.9%). Overall compliance in prescribing was greater in uncomplicated UTIs (61.5%) compared to complicated UTI episodes (52.9%). Overall compliance in uncomplicated UTIs were greater with nitrofurantoin; compliance was greater with ciprofloxacin for complicated

UTIs. Failure to comply to STG recommendations were mostly due to inappropriate antibiotic selection for complicated UTIs and duration of therapy (Tables 4 and 5).

Four females were diagnosed with asymptomatic bacteriuria. Two pregnant women were treated with antibiotics, amoxicillin-clavulanic acid and nitrofurantoin; an elderly diabetic patient was treated with ciprofloxacin, and antibiotics were unknown in one patient. Eighteen recurrent UTI episodes occurred in 17 patients during the five-month study period. Fifteen women and one man experienced two UTI episodes, also one woman experienced three UTI episodes during the study period. A urine microscopy was only conducted in three recurrent UTI episodes. Nitrofurantoin was mostly prescribed in the first (70.6%) and second (58.8%) UTI episodes.

Twenty-five urine samples were sent for urine microscopy and culture sensitivity analysis with *Escherichia coli* (*E. coli*) being the most common organism identified (32.0%). It was unknown if a urine microscopy was conducted in 93.3% of complicated UTI episodes.

Table 4: Prescribing patterns, investigations and compliance to STGs and policy recommendations for UTIs

	Total, *N* (%)	**Uncomplicated, *n* (%)**	**Complicated, *n* (%)**
Patient gender	**383**	**104 (27.2)**	**279 (72.8)**
Female	321 (83.8)	104 (32.4)	217 (67.6)
Male	62 (16.2)	-	62 (100.0)
Episodes*	**401**	**104 (25.9)**	**297 (74.1)**
Female	338 (84.3)	104 (100.0)	234 (78.8)
Male	63 (15.7)	-	63 (21.2)
Investigations*			
Urine dipstick	353 (88.0)	95 (91.3)	258 (86.9)
Unknown	48 (12.0)	9 (8.7)	39 (13.1)
Urine microscopy	25 (6.2)	5 (4.8)	20 (6.7)
Unknown	376 (93.8)	99 (95.2)	277 (93.3)

Urine microscopy results			
Escherichia coli	8 (32.0)	1 (20.0)	7 (35.0)
Candida	1 (4.0)	-	1 (5.0)
Klebsiella pneumoniae	1 (4.0)	1 (20.0)	-
Proteus mirabilis	1 (4.0)	-	1 (5.0)
No growth	4 (16.0)	2 (40.0)	2 (10.0)
Mixed growth	4 (16.0)	1 (20.0)	3 (15.0)
Unknown	6 (24.0)	-	6 (30.0)
Antibiotic prescribed*			
Amoxicillin†	2 (0.5)	-	2 (0.7)
Amoxicillin-clavulanic acid†	6 (1.5)	1 (1.0)	5 (1.7)
Ciprofloxacin	159 (39.7)	25 (24.0)	134 (45.1)
Nitrofurantoin	229 (57.1)	78 (75.0)	151 (50.8)
Total	396 (98.8)	104 (100.0)	292 (98.3)
Unknown†	5 (1.2)	-	5 (1.7)
Compliance to STG*			
Antibiotic choice			
Nitrofurantoin	154 (38.4)	78 (75.0)	76 (25.6)
Ciprofloxacin	132 (32.9)	-	132 (44.4)
Total	286 (71.3)	78 (75.0)	208 (70.0)
Total daily dose of appropriate antibiotic			
Nitrofurantoin	153 (38.2)	77 (98.7)	76 (100.0)
Ciprofloxacin	132 (32.9)	-	132 (100.0)
Duration of appropriate antibiotic and total daily dose			
Nitrofurantoin	130 (32.4)	64 (83.1)	66 (86.8)
Ciprofloxacin	91 (22.7)	-	91 (68.9)
Overall‡			
Nitrofurantoin	130 (32.4)	64 (61.5)	66 (22.2)
Ciprofloxacin	91 (22.7)	-	91 (30.6)

Total	221 (55.1)	64 (61.5)	66 (52.9)

*As per UTI episodes: Total = 401 UTI episodes; uncomplicated = 104 UTI episodes, complicated = 279 UTI episodes

†Amoxicillin, amoxicillin-clavulanic acid and unknown were considered non-compliant in terms of STG recommendations, therefore, only nitrofurantoin and ciprofloxacin were assessed for compliance with STGs

‡Overall compliance: includes the correct antibiotic, total daily dose, duration

Discussion

This study aimed to describe treating UTIs at primary healthcare level and to determine compliance to STG recommendations. This pragmatic study provides novel information and a broad overview on the treatment of UTIs at primary healthcare level in the Western Cape Metropole public sector. Further areas for improvement to optimise compliance to local guidelines and rational antibiotic use were identified.

According to the Pharmacy Information System, electronic data indicated that 729 prescriptions of nitrofurantoin and four prescriptions of fosfomycin were dispensed over the study period for all six facilities. This study had a good representative sample including approximately a third (229/729; 31.4%) of nitrofurantoin prescriptions.

In previous South African studies[22,24-26] *E. coli* accounted for the most common causative organism (54.2% to 79.6%). Although our urine cultures could only be analysed for 11 urine samples, *E. coli* was the most common organism detected (32%).

According to Wattengel et al.[35] prescribing antibiotics for UTIs was suboptimal. A retrospective analysis showed 68% of patients treated for UTIs were treated inappropriately. Incorrect duration (50.9%) was the most common error followed by inappropriate choice of antibiotics (35.1%) and incorrect dosing (12.4%).[35] In a South African study conducted by Gasson et al.[13] the duration of therapy was

mostly inappropriate in 51.2% of urological infections with inappropriate antibiotic selection in 17.1% of these infections. Our study showed greater compliance in terms of overall antibiotic selection; however, antibiotic selection for treating complicated UTIs was mostly inappropriate which was concerning considering UTI complications and antibiotic resistance. Similar to the Gasson et al. study[13], ciprofloxacin compliance to guideline recommendations were poor. The total daily dose of appropriately selected antibiotics showed great compliance (98.7%-100.0%), however; duration of appropriate antibiotics selected and total daily dose were less complaint to guideline recommendations. Overall, compliance with STG recommendations were poor.

In a study conducted by Bosch et al.[22] in Bloemfontein in 2008, showed that the most common antibiotic prescribed for uncomplicated UTIs were amoxicillin-clavulanic acid (36%) compared to ciprofloxacin for complicated UTIs. In a Gauteng study[26] conducted in 2011, ciprofloxacin was the most common antibiotic prescribed (50.3%). From the REWIND study[36] conducted in Brazil, Belgium, Italy and Russia, during the period between 2016 and 2017, fosfomycin (21.6% to 39.7%) was the most common antibiotic prescribed followed by ciprofloxacin (9.6% to 24.6%). Here, nitrofurantoin and ciprofloxacin were frequently prescribed. These studies show that antibiotic treatment selection varied; thus, it was important to survey data to inform local STGs which recommended appropriate management of UTIs and to limit emerging resistance.

UTIs in male patients were categorised as "complicated" and the recommended therapy was fluoroquinolones.[12,32] Here, 20.6% of male UTI episodes were treated with nitrofurantoin. There was conflicting evidence for the use of nitrofurantoin in men.[37,38]

According to a Cochrane review[39], there was insufficient evidence to recommend urinary alkalisers for symptomatic relief of uncomplicated UTIs. The STGs recommended against the use of alkalising agents.[12] Citro-Soda®, a urinary alkaliser was prescribed in 13.2% of UTI episodes. In 41.5% of these episodes ciprofloxacin was concurrently used – interfering with the effectiveness of ciprofloxacin.[40]

According to various guidelines asymptomatic bacteriuria should not be treated in the elderly and diabetic patients[20,32]; however, one elderly patient was prescribed antibiotic therapy for treating asymptomatic bacteriuria. Here, asymptomatic bacteriuria was appropriately treated with antibiotics during pregnancy. Therapy was unknown in one patient.

Antimicrobial resistance surveillance is a critical pillar in the fight against antibiotic resistance. Urine microscopy and sensitivity analysis could strengthen surveillance and guide empiric therapy. According to the STGs[12] recommendations, a urine microscopy was recommended in complicated and recurrent UTIs, UTIs in men and pregnant women and upper UTIs. A urine microscopy was conducted in 20 complicated UTI episodes (6.7%), 7.9% of UTIs episodes in men and 7.1% UTI episodes during pregnancy. Urine microscopy frequency was relatively low considering STG recommendations; thus, reasons for this should be considered as well as access to urine microscopy services.

Recurrent UTIs were defined as a UTI occurring at least three times in a period of 12 months or at least twice in a period of six months. Recurrent UTIs could be caused by a re-infection or relapse.[21,32] It was not possible to determine true recurrence during our study or differentiate between re-infection or relapse. However, during the study period 16 patients experienced two UTI episodes and one female experienced three episodes. Nitrofurantoin was the most frequently prescribed antibiotic during the first and second UTI episodes. In the case of the female who presented with three UTI episodes, nitrofurantoin was prescribed for treating all three episodes. As described, urine microscopy frequency was low in recurrent UTI episodes.

This study identified recommendations for the multidisciplinary team for practice and future research to promote rational antibiotic prescribing and use. Interviews with pharmacists and prescribers would assist in understanding the knowledge on antibiotic use and prescribing to identify targeted interventions.

Recommendations

Differentiating between complicated and uncomplicated UTIs was critical as it influenced diagnostic investigations and antibiotic therapy. This differentiation must be clearly described in the evidence-based guidelines of the National Department of Health (e.g., STGs) to optimise antibiotic therapy. Also, recommendations for managing asymptomatic bacteriuria should be explicitly described.

Considering the antibiotic resistance crisis, it was important to monitor resistance of uropathogens to nitrofurantoin and ciprofloxacin. Future research is needed to investigate and address the low compliance with urine microscopy to consider feasible and appropriate recommendations.

Prescribing patterns should be monitored on a continuous basis through collaboration between the Department of Health stakeholders and the Medicine Use Evaluation Committee as it highlights areas for improvement. Subsequent to this study, the UTI recommendations were amended again (Primary Healthcare Level, 2020).[41] Through this process guidelines adoption can be monitored and improved. Pharmacists form an integral part in the antibiotic stewardship programmes in primary healthcare.[42] The pharmacist's role in antibiotic stewardship includes, but is not limited to educating and training other healthcare professionals as well as the public, reviewing antibiotic prescriptions on a daily basis and determining compliance to STGs and evidence-based medicine recommendations.[13,42] This study has shown that a collaborative, pharmacist-led investigation exposed inappropriate use of antibiotics and highlighted areas for improvement in managing UTIs; reflecting the important role pharmacists can fulfil at primary healthcare level in addressing antimicrobial stewardship.

Study strengths and limitations

This was a multicentre study with a reasonable sample size (power 80%) and limited missing data. Facilities were identified through a random selection process and objectives measures were used for assessment. Our study was conducted at six primary healthcare facilities, in the urban setting only, across three of the four

substructures in the public sector of the Cape Metropole in the Western Cape and could not be generalised to rural and private settings. Differentiating between cystitis and pyelonephritis was not possible due to the inconsistent documented diagnoses in patient medical folders. Documented diagnosis varied; therefore, the researchers categorised and analysed UTIs according to complicated and uncomplicated UTIs based on national and international guidelines and societies.[12,21,32,33] However, this classification did not compromise our assessment of compliance with UTI STGs recommendations.

Conclusion

Interventions are required to improve compliance of prescribing antibiotics as per guideline recommendations, specifically selecting the appropriate antibiotic, duration of therapy and urine microscopy.

Acknowledgements

The authors acknowledge all healthcare staff involved in assisting with access to patient medical folders.

Competing interests

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

Authors' contribution

NK, YJ and RC developed the study. NK collected and analysed the data, as well as wrote the manuscript's initial draft. YJ and RC reviewed and edited the manuscript.

Funding

No funding was received.

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4.3 Prepared manuscript for publication (*Journal of Pharmacy Practice*)

The manuscript presented in this section was prepared and submitted to the *Journal of Pharmacy Practice* on 26 November 2021 (reference number: JPP-21-0688). The manuscript is currently under review (see appendix I for latest correspondence). References were included in the results section as part of the original submitted manuscript.

Describing antibiotic labelling for the treatment of urinary tract infections in public sector primary health care facilities in the Cape Metropole

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Describing antibiotic labelling for the treatment of urinary tract infections in public sector primary health care facilities in the Cape Metropole

ABSTRACT

BACKGROUND

Miscommunication in health care may fuel antibiotic resistance. Instructions on labelling of antibiotics should be explicit. Pharmacists can optimize medicine labelling to improve medicine use.

OBJECTIVE

This study aims to describe the labelling of dispensed antibiotics for urinary tract infection (UTI) treatment and to determine if label instructions were compliant with the instructions for the antibiotic prescribed.

METHOD

A retrospective multicenter medical records review of adult patients diagnosed with UTIs was conducted. A random selection process was followed and six primary health care facilities in the Cape Metropole were included. Instructions on labels of dispensed antibiotics were reviewed on the computerized dispensing system and compared to prescribed instructions for compliance.

RESULTS

A total of 401 UTI episodes were identified during the study period; antibiotics were prescribed in 98.8% of episodes. The antibiotic name, dosage and frequency were documented on all labels. Duration of therapy was mostly omitted (50.4%). The antibiotic dispensed, dosage and frequency were compliant with the prescriptions (98.7% to 99.7%), except for duration (43.7%). Incorrect quantity of antibiotic was dispensed in 8.7% of antibiotic prescriptions.

CONCLUSION

Interventions are required to include duration of therapy on dispensing labels of antibiotics. Inappropriate duration of therapy might affect patient health outcomes and antibiotic resistance.

Keywords: antibiotic name, medicine label, pharmacist

BACKGROUND

Patient safety is defined as “a framework of organized activities that creates cultures, pro-cesses, procedures, behaviors, technologies and environments in health care that consistently and sustainably lower risks, reduce the occurrence of avoidable harm, make errors less likely and reduce its impact when it does occur” [1]. Patient safety is the core of quality health care with the aim to prevent harm.

Medication adherence and health literacy are factors which can impact patient safety. Medication adherence is complex and multifactorial. Miscommunication between health care workers and patients may lead to errors, adverse events and therapeutic failure [2]. Table 1 shows how errors in miscommunication can broadly be categorized into patient- and medication-related factors [2]. Incorrect dosing instructions may lead to taking medicine at the wrong time, through the wrong route or for the wrong duration [3].

Low health literacy is an important patient factor associated with misunderstanding of medicine use [4] and medicine errors. Health literacy is defined as “the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions” [5].

Medication errors can be reduced by providing appropriate and clear instructions on prescriptions and medicine labelling [6]. Patient-centered labels have the potential to enhance a patient’s understanding of their prescribed medicine and medication use [7]. A patient-centered label aims to transcribe the instructions for medicine use from a patient perspective with the aim to provide instructions for use in a clear and understandable manner to provide comprehensive and safe

information. This approach recommends the use of a standardized time known as the universal medicine schedule for medicine administration instructions (e.g., “morning” and “night” instead of “twice daily”). Further, it is recommended to use numeric information instead of words [6–8].

Table 1: Patient- and medication related factors leading to miscommunication [2,4,9–19].

Related factor	Factor	Recommendation
Patient-related	Low literacy level	Align instructions with patient educational level and culture. Concordant prescription instructions. Language specific instructions. Speak slowly. Avoid medical jargon.
	Language barrier	Ask open-ended questions. Use teach back method. Make use of a translator. Assistance from community care workers.

	Age	Explicit language and instructions of warning labels. Pictograms with explicit text.
Medication-related	Number of medicines prescribed	Medication reconciliation.
	Format and organization of instructions	Standard guidelines with instructions.
	Complexity of dosing instructions	Provide simple instructions, avoid ambiguous instructions with multiple instructions.
	Precision of dosing instructions	Patient-centered care labels, labels with explicit time periods and specific times ("morning," "night"). Avoid "times per day" rather specify hourly intervals.
	Use of icons and pictograms	Useful for patients with low literacy.

		May improve understanding and improve adherence

The prescriber and pharmacist are two essential health care workers who have the potential to positively influence patient safety and correct medicine use by reducing errors in miscommunication through verbal and non-verbal communication. At the end of a patient visit, the pharmacist is an invaluable connection between the patient and prescriber [2]. A study was conducted in Pennsylvania to determine medication-taking practices in elderly patients using high risk medicines. From this study 46% patients reported that they were given instructions by pharmacists, 35% reported that they received instructions from prescribers and approximately 32% of patients received no medicine information from either the pharmacist or prescriber for the prescribed medicine [20]. This is a major concern for patient safety and a multidisciplinary approach is needed [21] to promote adherence and improve patient safety. Further, it was reported that patients who receive better instructions on how to use their medicines as well as information on their treatment are more adherent [22–23].

Medicine information may be provided through written instructions or verbal communication. Written information may be in the form of medicine dispensing labels, special instructions for medicine use, special warnings or precautions, patient information leaflets and manufacturer labels (e.g. product labels) [2]. During the dispensing process, the pharmacist dispenses the medicines and provides counselling and education on medicine use. Instructions on how to use the medicine should be accurate and understandable to the patient. Also, pharmacists need to

transcribe medical jargon to the patient in understandable terms through counselling and instructions provided on medicine labels [24]. The medicine name, strength, frequency, duration, route of administration and any special instructions for medicine use are considered minimum information to be included during the counselling session. It is recommended that dispensing labels include dosing instructions to ensure the correct use of the prescribed medicine and auxiliary labels containing warning information [2]. The International Pharmaceutical Federation (FIP) [25] recommends that a label should complement verbal instructions. According to Good Pharmacy Practice [26] and Medicine and Related Substances Act 101 of 1965, South Africa [27], medication labels should be clear, legible, indelible and should preferably be printed. Further written instructions from the pharmacist should be understandable, readable and comprehensive [28].

In the primary health care setting, urinary tract infections (UTIs) are common and frequently require antibiotic therapy [29,30]. Unnecessary antibiotic prescribing, inappropriate doses and duration may fuel antibiotic resistance. Thus, to combat antibiotic resistance, patients should receive the right antibiotic for the right indication, at the right dose and time for the right duration [31–33]. Antimicrobial stewardship (AMS) is a multi-disciplinary approach which aims to ensure rational antimicrobial use through optimizing antimicrobial regimens. It is a strategy aimed at improving antimicrobial use to improve patient health outcomes and to combat antimicrobial resistance across various health care settings [34]. Benefits expected from AMS practices include optimal patient health outcomes, reduction in adverse events and antibiotic resistance [35]. Through the practice of AMS in primary health care, pharmacists can optimize antibiotic use. To ensure that patients

understand instructions, directions for medicine use on labels should include the dose, frequency and duration and any other special instructions ("on an empty stomach," "after food") [25]. Pharmacists are ideally situated to act as a core member of the AMS team in primary health care [36]. Provision of information on safe antibiotic use has been identified as a role of the pharmacist to optimize antibiotic use and to reduce antibiotic resistance. This information can be shared through counselling and written instructions on medicine labels of dispensed antibiotics [37].

This study was part of a bigger study conducted to describe prescribing patterns for UTI in the primary health care setting of the Western Cape and to determine compliance with primary health care standard treatment guideline recommendations [38]. This study aimed to describe the instructions included on dispensing labels of prescribed antibiotics for the treatment of UTIs in the primary health care setting of the Western Cape in South Africa and to ascertain compliance with the prescription.

STUDY METHOD

Study Design and Setting

During 1 October 2020 to 28 February 2021 medical folders of adult patients (≥ 18 years of age) diagnosed with a UTI were identified retrospectively from six primary health care facilities in the public sector of the Western Cape. Community day centers or community health care centers were identified through a random selection process using Microsoft Excel® (2016). Two facilities per substructure, from three substructures in the Cape Metropole were identified; i.e.,

Northern/Tygerberg, Klipfontein/Mitchell's Plain and East-ern/Khayelitsha. Due to different operating procedures one substructure was excluded.

Data Collection

Data was collected using a standardized data collection sheet. Dispensing data from prescriptions were extracted from the pharmacy's computerized dispensing system. Data collected included antibiotic dispensed, dose, duration, quantity, frequency and special instructions for use. Further, the dispensing information was analyzed to determine if the antibiotic, dose, duration and quantity was compliant with the written prescription. Microsoft Excel® (2016) was used to analyze the data. Missing information was excluded from data analysis. The prescribed antibiotic route was excluded as it was recommended to include the route if a route other than oral was recommended [25].

Ethical Considerations

The University of the Western Cape's Biomedical Research Ethics Committee (BM20/5/17) and the Western Cape Government Health (WC_202006_038) approved this study. This was a retrospective medical record review, data was anonymised before analysis; thus, no informed consent was required from patients.

RESULTS

A total of 401 UTI episodes were identified during the study period. Antibiotics were pre-scribed in 396 UTI episodes (98.8%); nitrofurantoin was prescribed in the majority of UTI episodes (57.1%), followed by ciprofloxacin (39.7%), amoxicillin-clavulanic acid (1.5%) and amoxicillin (0.5%). A total of 391 medicine labels of the dispensed antibiotics were analyzed as no dispensing information was available

for four UTI episodes and one patient folder could not be traced. The name, dosage, frequency and duration of antibiotics were documented in almost all written prescriptions (99.7% to 100%). The name, dosage and frequency of the prescribed antibiotic was documented on all medicine labels. However, the duration of antibiotic therapy was documented in less than half (49.6%) of the labels. The name of the antibiotic, dosage and frequency on the labels were according to the information on the written prescriptions in 99.7%, 99.0%, 98.7% cases, respectively; with a lower compliance in terms of duration of therapy (43.7%) and quantity dispensed (91.3%). Table 2 provides more information.

Table 2: Criteria documented on prescription, label and accordance.

Criteria	**Documented on written prescription (n=396)**	**Documented on label (n=391)**	**Label according to written prescription (n=391)**
	N (%)	n (%)	n (%)
Antibiotic name	396 (100.0)	391 (100.0)	390 (99.7)
Dosage	395 (99.7)	391 (100.0)	387 (99.0)
Frequency	395 (99.7)	391 (100.0)	386 (98.7)
Duration	396 (100.0)	194 (49.6)	171 (43.7)
Quantity*	395 (99.7)	391 (100.0)	357 (91.3)

Table 3 shows the frequency for administration of antibiotics was documented on labels mostly as “times per day” (98.2%). In some labels the frequency was documented as both hourly and “times per day” (17.6%).

Table 3: Instructions for frequency of administration of antibiotic as per label.

Criteria	n (%)
Times per day	384 (98.2)
Per hourly interval	73 (18.7)
Times per day + per hourly interval	69 (17.6)
Administration frequency document on label	391 (100.0)

Three types of special instructions for antibiotic use were included on 28 labels (7.2%). Of these labels, “complete the course” (77.4%), “take with/after food” (19.4%) and “antibiotic” (3.2%) were included as special instructions for antibiotic use.

DISCUSSION

This study described the instructions included on dispensed antibiotics for the treatment of UTIs and ascertained compliance with the written prescription. The results indicated the importance of complete instructions on medicine labels, especially antibiotics to optimize patient safety and potentially reduce antibiotic resistance.

The quality and safety of medicine use could be significantly influenced by the design and content included on medicine dispensing labels. The dispensing label

should contain sufficient information to enable patients to make safe and informed decisions of the prescribed medicine [39]. As per FIP [25] the purpose of a prescribed medicine label was to describe and identify the medicine, prevent medicine errors, ensure optimal therapeutic outcome, achieve appropriate handling and storage of medicines and for traceability for problems with manufacturing, prescribing or dispensing. Individual dosage instructions and indication (as per the prescriber), batch identification, any special instructions for use ("Do not chew," "Take with a meal"), special storage instructions (Store between 2˚C to 8˚C) and any special warnings or precautions ("Do not drink alcohol") [25].

Here, the name, dosage and frequency were documented on the label and compliant with the prescription. The duration of antibiotic therapy was omitted on half of the medicine labels (50.4%) with poor compliance with the prescription (43.7%). Quantity dispensed was compliant with the majority of prescriptions (91.3%). Wrong antibiotic, dose, frequency and duration were identified as measures to improve antibiotic prescribing as part of AMS practices. Duration of antibiotic therapy was a core element of AMS [40]. In Machanayake et al.'s study [28] dispensing labels from the community pharmacy and hospital pharmacy in Sri Lanka were analyzed for completeness, readability and patient knowledge regarding the dispensed medicine. Duration of therapy was omitted in the majority of prescriptions; duration of therapy was mostly documented on labels from the community pharmacy compared to the hospital setting (0.65% vs 0.25%). In Mekonen's study [41], the quality of medicine dispensing and patient knowledge on dispensed medicines were assessed by analyzing label information. The following instructions for medicine use was mostly omitted: dose, frequency and

duration of therapy [41]. Anti-infectives accounted for 40% of the dispensed medicine. Our study showed greater compliance in terms of duration of therapy documented on dispensing labels.

Misunderstanding of medicine instructions on dispensing labels might lead to medicine errors and was a patient safety concern. Patients who did not know the medicines they were taking might use the wrong strength of medicine, the wrong medicine or use duplicate medicine therapy [28]. A study was conducted in the US to determine the effect of explicit language use in medicine labels for dispensed medicines (glyburide, atenolol, metformin). Correct label interpretation varied between 53% to 89%. Label interpretation was greatest when instructions included time periods (morning, evening, every day) (89%) and specific times (8 a.m.) (77%) compared to hourly (six hourly) (53%) or number of times per day (twice daily) (61%). Instructions indicating frequency as times per days were less likely to be understood compared to specific times or time periods [14]. To optimize medicine use, pharmacists should specify time periods for medicine use instead of times per day and specific times instead of hourly intervals [2]. Here, the majority of the labels reviewed were documented as times per day (98.2%) or hourly intervals (18.7%). In some labels, frequency was documented as both times per day and hourly intervals (17.6%). The study's results indicated the need for frequency of prescribed medicine to be documented as to be taken at specific times per day.

From the community pharmacy setting in the Machanayake et al. study [28], special instructions were documented in 54.0% of labels; instructions for taking the medicine with relationships to meals (if applicable) were documented in 99.6% of

labels. Here, additional information was included in 28 labels (7.2%). “Complete the course” was the most frequent special instruction for use included (77.4%).

Various practices might optimize antibiotic use at primary health care level. Pharmacists play an important role in optimizing patient safety at primary health care through daily practice [36] and might address patient- and medication-related factors to prevent or reduce miscommunication. One way for pharmacists to optimize antibiotic use is to provide appropriate and clear instructions for antibiotic use through counselling and medicine labels [2,9]. First, the pharmacist would need to ascertain if it is the appropriate antibiotic, dose and duration prescribed for the patient’s diagnosis. Second, the pharma-cist should ensure that the label was aligned with the prescription and instructions for use was clear and explicit to complement verbal communication and counselling [25]. Clear instructions for medicine use should include the appropriate dose (how many tab-lets/capsules), frequency (documented as specific time periods – morning or specific times – 8 a.m.) and duration (in days) of the prescribed medicine [14,25]. Third, appropriate additional labels might be included to act as reminders [16,17]. This practice would empower patients to be better educated, improve patient care and promote patient safety. Additional activities performed by pharmacists to ensure rational medicine use includes medication history-taking and medication reconciliation [42]. Other recommendations as mentioned in Table 1 should also be explored by pharmacists to optimize patient health outcome.

The study was not without limitations. Here, compliance to written prescriptions were determined and not appropriateness of the prescription or label. Patient interpretation of label information and verbal instructions for medicine use were

not assessed. This was a retrospective study; therefore, it was not possible to report on the use of auxiliary labels on medicine boxes (e.g., “antibiotics,” “complete the course”). Auxiliary labels might complement medicine labels and verbal instructions by acting as warning information [2]. The results from this study could not be generalized to other medicine classes (e.g., chronic medicines). The study was only conducted in six public primary health care facilities from three substructures of the Cape Metropole and cannot be generalized to all primary health care facilities.

CONCLUSION

Instructions for antibiotic use were mostly included and aligned with the written prescription; however, interventions are required to include duration of therapy on dispensing labels of antibiotics. Inappropriate duration of therapy might affect patient health outcomes and antibiotic resistance.

COMPETING INTERESTS

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

AUTHORS’ CONTRIBUTION

Conceptualization, N.K., R.C., Y.J; methodology, N.K., R.C., Y.J; formal analysis, N.K.; data curation, N.K.; writing—original draft preparation, N.K.; writing—review and editing, R.C., Y.J. supervision, R.C., J.Y. All authors have read and agreed to the published version of the manuscript.

FUNDING

No funding was received.

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4.4 Additional results

Appendix J contains the study's additional results which were not included in the published manuscripts.

4.5 Summary

This chapter presented this study's results and important findings by means of two published manuscripts. The following chapter presents a discussion of the study's additional findings which were not included in this chapter.

5 DISCUSSION

5.1 Introduction

This chapter provides a brief discussion of the findings that were presented in Chapter 4 and not discussed in the published and submitted manuscript. The results will be discussed in the following sub-sections: defining UTIs, risk factors, diagnosis, and treating UTIs at primary healthcare level and the pharmacist's role. The chapter concludes with a summary.

5.2 Defining UTIs

Grouping UTIs was not clearly defined and discrepancies existed in the literature. UTI is an umbrella term for infections occurring in the urinary tract. UTIs are grouped as complicated and uncomplicated, symptomatic or asymptomatic, cystitis and pyelonephritis (Gupta et al., 2011; Smelov, Naber & Bjerklund Johansen, 2016; Tan & Chlebicki, 2016; Fernandez & Coyle, 2019; DoH, 2019b; 2020; Bonkat et al., 2020). Clear definitions and groups of UTIs might assist in treating UTIs appropriately optimising therapy and patient health outcomes. Also, it might assist in research and teaching opportunities (Johansen et al., 2011). Appropriate therapy could optimise antibiotic use and patient health outcomes.

Here the documented diagnoses in folders were inconsistent; therefore, grouped by the researcher into complicated and uncomplicated UTIs for analysis and compliance to STGs recommendations. Complicated UTIs (74.1%) were more prevalent than uncomplicated UTIs (25.9%) occurring in all males and most females (67.6%). From the literature and results it is evident that the diagnosis of UTIs need to be standardised to optimise patient health outcomes and to promote rational antibiotic use in treating UTIs.

5.3 UTI risk factors

A new classification system of UTIs was proposed based on risk factors and severity. Thorough assessment and history taking should form part of the patient assessment including clinical criteria, risk factors, the causative agent, the situation and therapeutic options. Clinical criteria included clinical presentation, specificity

of symptoms, severity of symptoms and pattern of infection. Risk factors might include patient characteristics, comorbid conditions and nephrology, urological, catheters, as well as asymptomatic bacteriuria. Antimicrobial susceptibility, pathogen type, virulence and bacterial count of the pathogen ought to be considered. The setting where the UTI was acquired was a crucial factor that required consideration. Treatment options were dependent on the pathogen susceptibility and resistance. Host risk factors were grouped according to the ORENUC system (Johansen et al., 2011):

O: N**O** known risk factor,

R: Risk for **R**ecurrent UTI, but without risk of more severe outcome,

E: Extra-urogenital risk factors,

N: Relevant **N**ephropathic diseases,

U: Urological resolvable (transient) risk factors,

C: Permanent external urinary **C**atheter and non-resolved urological risk factors.

Various risk factors have been identified for UTIs. These risk factors include sex (female), age (elderly), co-morbid conditions (diabetes mellitus), congenital abnormalities, modifiable factors (sexual intercourse, spermicide use, diaphragm contraception, pregnancy), immunosuppressant therapy, obesity and patients with kidney transplants and spinal cord injuries (ACOG, 2008; Vasudevan, 2014; Wasserman, Boyles & Mendelson, 2015; Velez, Richmond & Dudley-Brown, 2017; Bonkat et al., 2018; Gupta & Trautner, 2018; Lee & Le, 2018; Lee et al., 2018; Nicolle et al., 2019; Öztürk & Murt, 2020). Here, UTIs occurred in females (84.3%) who presented with complicated UTIs (69.2%). According to the literature diabetes is another risk factor for UTIs (Johansen et al., 2011; Lee & Le, 2018; Bonkat et al., 2020). Approximately 17% (16.7%) of patients who presented with UTIs in our study were diabetic. Seventy-five pregnant women (19.6%) presented with UTIs. Risk factors were important to appropriately diagnose and eventually treat UTIs. Modifiable risk factors were not investigated here (e.g., spermicide use) but during counselling it was an opportunity for the prescriber and pharmacist to identify these factors and recommend a change in behaviour (e.g., avoid spermicide use) or non-pharmacological therapy (e.g., voiding after intercourse).

A urine dipstick is a point-of-care test used to screen for UTIs. Based on the results of a urine dipstick, empiric treatment of UTIs was recommended in the following scenarios: detecting leucocytes or nitrites with UTI symptoms, detecting leucocytes and nitrites, and detecting leucocytes on two urine specimens (DoH, 2020). In complicated UTIs, recurrent episodes and UTI during pregnancy a urine culture was recommended (DoH, 2019b; 2020).

From the urine analyses conducted here it appeared that most UTI episodes were diagnosed clinically. Diagnosing and treating UTIs were challenging; however, thorough history taking could assist in identifying risk factors which complemented presenting signs and symptoms, screening and diagnostic investigations to group UTIs and identifying appropriate empiric therapy. Thus, a systematic integrated approach is required to diagnose and treat UTIs appropriately.

5.4 Diagnosing UTIs

A urine microscopy guides the physician in initiating definitive therapy. Unfortunately, in our study culture results were not available in most urine sent for microscopy (56%). A differential diagnosis to consider and exclude with UTIs were sexually transmitted infections (STIs). However, this differentiation was challenging and might lead to unnecessary treatment of either of these conditions. Overdiagnosis UTIs and underdiagnosing STIs have been reported (Tomas et al., 2015). This overdiagnosis could lead to unnecessary antibiotic treatment.

5.5 Pathogens associated with UTIs

In a study conducted in Gauteng over the period January 2015 to December 2019, urine cultures of women attending antenatal clinic were analysed. *E. coli* was the most common organism identified (56%) followed by *E. faecalis*, and *P mirabilis* increased slowly over the period from 4% to 7%. Other pathogens identified were *K. pneumoniae* and *S. agalactiae*. Susceptibility to first line agents, gentamicin and nitrofurantoin, remained high (Zwane, Shuping & Perovic, 2021). Here, *E. coli* was identified in 32% of UTI episodes with 100% sensitivity to nitrofurantoin and gentamicin, recommendations for uncomplicated UTIs and only 40% sensitivity to

ciprofloxacin, recommended therapy for treatment of complicated UTIs. However, this was not a true reflection as most of the results were not available (56%).

5.6 Treating UTIs

Treating UTIs is challenging in the AMR dilemma and implementing AMS have the potential to optimise therapy. Unnecessary and inappropriate antibiotic use in treating UTIs fuel AMR and needs to be addressed. Asymptomatic bacteriuria has been identified as a target for AMS in both the inpatient and outpatient setting to optimise patient health outcome and preserve antibiotics (Wiley, Jacob & Burd, 2020).

Treating asymptomatic bacteriuria is not recommended in the following cases (regardless of multidrug resistant organisms being detected): elderly women with cognitive dysfunction, non-pregnant healthy women, postmenopausal women, diabetic patients, patients with indwelling catheters, spinal cord injury and transplant patients, elective non-urological surgery, paediatric patients and before urological device implantation (Nicolle et al., 2019; Wiley, Jacob & Burd, 2020). It is recommended to treat asymptomatic bacteriuria during pregnancy according to culture results and safety (De Rossi et al., 2020). In a study conducted in the ED (Petty et al., 2020), 74.4% with asymptomatic bacteriuria were treated with antibiotic therapy. Patients started on antibiotics were likely to stay on antibiotics for 3 d. Further antibiotics were associated with prolonged hospital stay and *Clostridioides difficile*. Here, asymptomatic bacteriuria was treated in an elderly diabetic patient. Age, diabetes mellitus and pregnancy were identified as risk factors for asymptomatic bacteriuria in the UTI episodes of this study. The definition of asymptomatic bacteriuria and treatment is not clearly defined in the STGs and might lead to inappropriate treatment and unnecessary antibiotic therapy fuelling AMR.

Another target identified for AMS in UTIs was recurrent UTIs (Abou Heidar et al., 2019). Recurrence is defined as more than three episodes in 12 months or more than two episodes in six months in females and more than one episode in males (DoH, 2018a). Recurrence could further be grouped into reinfection and relapse

(Fernandez & Coyle, 2019). True recurrence could not be determined due to unknown previous UTI episodes. Here, 4.4% of patients experienced more than one UTI episode. In a recurrent episode a culture was recommended to identify appropriate therapy to eradicate the infection and prevent treatment failure (DoH, 2020). In the second UTI episode, a culture was conducted in only 17.6% of episodes and none in the third episode. The results of a urine culture provided an opportunity for the prescriber to optimise antibiotic therapy and to promote rational medicine use by changing empiric therapy to definitive therapy. Pharmacists could conduct history taking, enquire about previous antibiotic use and history of UTI episodes during counselling. Inappropriate management of UTIs might lead to complications and compromise patient health outcomes. Complications of UTIs were patient dependent. Asymptomatic bacteriuria in pregnant women could lead to complications (Gupta & Trautner, 2018; Matuszkiewicz-Rowińska, Małyszko & Wieliczko, 2015; Chu & Lowder, 2018). Inappropriate therapy might lead to relapse. Another aspect of continuity of care was to follow-up and react on cultures. In one of the culture results, *P. mirabilis* was detected and treated with empiric nitrofurantoin therapy. *P. mirabilis* is resistant to nitrofurantoin (Gajdács & Urbán, 2019) and in this case the culture results would have required a change in antibiotic therapy to successfully eradicate the infection.

Fosfomycin is recommended (DoH, 2019a) for treating uncomplicated cystitis. It was dispensed four times during the study period; however, not identified during data collection. This might be due to cost implications and nitrofurantoin being frequently used. With the change in guidelines, gentamicin was now preferred for treating uncomplicated cystitis, followed by fosfomycin with nitrofurantoin as a last resort (DoH, 2020). Fosfomycin was non-inferior to ciprofloxacin in treating febrile UTI as oral stepdown therapy after completing three days of intravenous antibiotics (Doesschate et al., 2021). Compared to ciprofloxacin, fosfomycin was more associated with diarrhoea, however discontinuation of fosfomycin was not influenced by this side effect. A specific dosage regimen of fosfomycin for the treatment of febrile UTIs still needs to be determined (Rosso-Fernández et al.,

2015). The use of fosfomycin for complicated UTIs may reduce hospitalisations, and be more acceptable to patients (Doesschate et al., 2021).

5.7 Pharmacists' role

Pharmacists could optimise patient health outcomes during the dispensing process through counselling and non-pharmacological recommendations (De Rossi et al., 2020). Pharmacists are ideally placed to identify UTI risk factors of patients, to address these modifiable risk factors through educating the patient on safe antibiotic use during the dispensing process. Through the practice of AMS, pharmacists could promote rational and safe antibiotic use in UTI treatment, especially in recurrent UTI episodes and asymptomatic bacteriuria.

5.8 Summary

A discussion of the additional findings of the study, not included in the published manuscripts was presented here. The overall conclusion, limitations as well as recommendations for future research are presented in the following chapter.

6 CONCLUSIONS, LIMITATIONS AND RECOMMENDATION

This chapter provides the study's conclusion. The study's limitations are described and recommendations for future research are mentioned.

6.1 Conclusion

In the primary healthcare setting of the Western Cape, more adult female patients presented with complicated UTIs than uncomplicated UTIs. Nitrofurantoin was a common antibiotic prescribed for treating UTIs followed by ciprofloxacin. Compliance to STG was greater for complicated UTIs compared to uncomplicated UTIs and nitrofurantoin compared to ciprofloxacin. The antibiotic name, dose and frequency were included in medicine labels and in accordance with most prescriptions, except for duration of therapy. Interventions are required to increase compliance to STG recommendations for UTI treatment. Instructions for dispensed antibiotics should be clear and thorough to improve patient health outcomes.

6.2 Limitations

The study had the following limitations:

- UTI classifications were not standardised; therefore, the researcher grouped UTIs based on national and international guidelines and society definitions. This however did not compromise the assessment of compliance with UTI STG recommendations.
- The study was conducted at six primary healthcare facilities across three of the four substructures in the public sector of the Cape Metropole in the Western Cape and could not be generalised to all primary healthcare facilities in the Western Cape.
- The study did not include the private sector, and antimicrobial prescribing in the private sector still needed to be explored.
- The study focused on antibiotic prescribing for UTIs and could not be generalised to antibiotic prescribing in other infectious diseases.
- AMS focused on prescribing of antibiotics, antivirals and antifungals; however, this study focused only on antibiotic prescribing.

- The occurrence of cystitis and pyelonephritis could not be determined due to inconsistent diagnosis documentation.
- Patient interpretation of label information and verbal instructions for medicine use were not assessed. Additional labels on dispensed antibiotics could not be assessed.

6.3 Recommendations

6.3.1 Recommendations for practice

- Evidence-based guidelines should clearly differentiate between distinct types of UTIs and their explicit management.
- Sexually transmitted diseases should be included as a differential diagnosis in the UTI section in the STGs.
- Pharmacists need to form part of antibiotic stewardship programmes in primary healthcare.
- Investigate pharmacists' knowledge on antibiotic use in primary healthcare through a survey.
- Perform interviews with prescribers to describe their knowledge on antibiotic prescribing for UTIs.

6.3.2 Recommendations for future research

- Monitor resistance patterns of uropathogens to update guidelines and to identify the most appropriate empiric therapy.
- Investigate and address the low compliance with urine microscopy as per STGs recommendations.
- Monitor prescribing patterns to ensure rational medicine use.
- Investigate patients' knowledge on antibiotic use for UTIs after dispensing of antibiotic therapy to assess the knowledge shared during the consultations and dispensing process.
- Investigate barriers and facilitators for the implementation of AMS at primary healthcare through interviews/surveys with pharmacists and prescribers.
- Repeat the study in rural areas of the Western Cape to investigate rural antibiotic prescribing practices and compliance to EML.

- Investigate patients' knowledge of prescribed antibiotic use in primary care to determine how prescription labels can be improved.
- Explore asymptomatic bacteriuria at primary healthcare and hospital level to implement targeted interventions.

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APPENDICES

Appendix A: Data collection tool

Facility name		CHC	CDC
Data Collector's Name		Date	

Complete below by filling in the demographic details and making a cross (X) in the appropriate block

	Folder	1	2	3	4	5	6	7	8	9	10
	Patient folder number										
	Sex										
	Date of Birth										
	Prescription date										
	Medicine allergies noted (Y/N)										
	Medicine Allergies										
1.	Diagnosis										
	Asymptomatic bacteriuria	1	1	1	1	1	1	1	1	1	1
	Cystitis	1	1	1	1	1	1	1	1	1	1
	Pyelonephritis	1	1	1	1	1	1	1	1	1	1
	Urinary tract infection	1	1	1	1	1	1	1	1	1	1
	Uncomplicated urinary tract infection	1	1	1	1	1	1	1	1	1	1
	Complicated urinary tract infection	1	1	1	1	1	1	1	1	1	1
	Recurrent urinary tract infection	1	1	1	1	1	1	1	1	1	1
	Unknown	1	1	1	1	1	1	1	1	1	1
	Other (specify)										
2.	Previous antibiotic use										
	Antibiotic use in the past 90 d	1	1	1	1	1	1	1	1	1	1
	Name of antibiotic(s) used										
3.	Screening										
	Urine analysis (Dipstick) (mark if done)	1	1	1	1	1	1	1	1	1	1
	Blood										
	Leukocytes										
	Nitrates										
	Protein										
	Other relevant information:										

4.	Laboratory investigations										
	Urine microscopy, culture and sensitivity (mark if done)	1	1	1	1	1	1	1	1	1	1
	Organism detected: Candida	1	1	1	1	1	1	1	1	1	1
	Enterobacter	1	1	1	1	1	1	1	1	1	1
	Enterococcus species	1	1	1	1	1	1	1	1	1	1
	Escherichia coli	1	1	1	1	1	1	1	1	1	1
	Klebsiella pneumoniae	1	1	1	1	1	1	1	1	1	1
	Proteus mirabilis	1	1	1	1	1	1	1	1	1	1
	Pseudomonas aeruginosa	1	1	1	1	1	1	1	1	1	1
	Staphylococcus saprophyticus	1	1	1	1	1	1	1	1	1	1
	Other										
	Recommended antibiotic: (S,R,I)										
	Amoxicillin										
	Amoxicillin-clavulanic acid										
	Ciprofloxacin										
	Co-trimoxazole										
	Fosfomycin										
	Gentamicin										
	Nitrofurantoin										
	Other										
	MIC										
	Other Laboratory investigations										
	CrCl										
	eGFR										
5.	Inflammatory/infection signs and symptoms										
	Blood pressure										
	Heart rate										
	Respiratory rate										

	Temperature										
6.	Inflammatory/infection markers										
	C-reactive protein										
	White blood cell count										
7.	Antibiotics prescribed										
	Amoxicillin	1	1	1	1	1	1	1	1	1	1
	Amoxicillin-clavulanic acid	1	1	1	1	1	1	1	1	1	1
	Ciprofloxacin	1	1	1	1	1	1	1	1	1	1
	Co-trimoxazole	1	1	1	1	1	1	1	1	1	1
	Fosfomycin	1	1	1	1	1	1	1	1	1	1
	Gentamicin	1	1	1	1	1	1	1	1	1	1
	Nitrofurantoin	1	1	1	1	1	1	1	1	1	1
	Other										
8.	Antibiotics prescribed – Total daily dose										
	400mg	1	1	1	1	1	1	1	1	1	1
	500mg	1	1	1	1	1	1	1	1	1	1
	1g	1	1	1	1	1	1	1	1	1	1
	2g	1	1	1	1	1	1	1	1	1	1
	3g	1	1	1	1	1	1	1	1	1	1
	80/400mg	1	1	1	1	1	1	1	1	1	1
	320/1600mg	1	1	1	1	1	1	1	1	1	1
	Other:										
9.	Antibiotics prescribed – Total duration (days)										
	1	1	1	1	1	1	1	1	1	1	1
	3	1	1	1	1	1	1	1	1	1	1
	5	1	1	1	1	1	1	1	1	1	1
	7	1	1	1	1	1	1	1	1	1	1
	10	1	1	1	1	1	1	1	1	1	1
	Other:										

10.	Other conditions / Co-morbid conditions										
	Chronic Kidney Disease/Kidney impairment	1	1	1	1	1	1	1	1	1	1
	Diabetes mellitus	1	1	1	1	1	1	1	1	1	1
	Pregnant (if applicable and pregnant: mark)	1	1	1	1	1	1	1	1	1	1
	Trimester (weeks)										
	Retroviral disease positive	1	1	1	1	1	1	1	1	1	1
	Tuberculosis	1	1	1	1	1	1	1	1	1	1
	Urinary tract abnormalities	1	1	1	1	1	1	1	1	1	1
	Other: (specify)										
11.	Concurrent medicines prescribed										
	Pain medication Ibuprofen	1	1	1	1	1	1	1	1	1	1
	Paracetamol	1	1	1	1	1	1	1	1	1	1
	Other (specify)										
	Supplements: Iron supplements	1	1	1	1	1	1	1	1	1	1
	Folic acid	1	1	1	1	1	1	1	1	1	1
	Other (specify)										
	Immunosuppressive therapy (corticosteroids, methotrexate, tacrolimus)										
	Contraceptive Combined oral contraceptive	1	1	1	1	1	1	1	1	1	1
	Implant	1	1	1	1	1	1	1	1	1	1
	Intra-uterine device	1	1	1	1	1	1	1	1	1	1
	Progesterone only tablet	1	1	1	1	1	1	1	1	1	1
	Progesterone injection	1	1	1	1	1	1	1	1	1	1
	Unknown	1	1	1	1	1	1	1	1	1	1

	Other ACE-Inhibitor	1	1	1	1	1	1	1	1	1	1
	Antibiotics	1	1	1	1	1	1	1	1	1	1
	ARB	1	1	1	1	1	1	1	1	1	1
	ARVs	1	1	1	1	1	1	1	1	1	1
	Anti-emetics	1	1	1	1	1	1	1	1	1	1
	Anti-spasmodic	1	1	1	1	1	1	1	1	1	1
	B-blocker	1	1	1	1	1	1	1	1	1	1
	Citro-soda	1	1	1	1	1	1	1	1	1	1
	Diuretics	1	1	1	1	1	1	1	1	1	1
	Hypoglycemia agents	1	1	1	1	1	1	1	1	1	1
	Insulin	1	1	1	1	1	1	1	1	1	1
	Metformin	1	1	1	1	1	1	1	1	1	1
	Proton Pump Inhibitor/H blocker	1	1	1	1	1	1	1	1	1	1
	TB medicines	1	1	1	1	1	1	1	1	1	1
	Other (specify):										

Facility name		CHC	CDC
Data Collector's Name		Date	

Complete below by filling in the folder number and making a cross (X) in the appropriate block

	Folder	1		2		3		4		5		6		7		8		9		10	
	Patient folder number																				
1.	Instructions (according to JAC)																				
	Medication name																				
	Dosage																				
	Frequency																				
	Duration																				
	Route																				
2.	Instructions (does it correlated with prescription)	YES	NO	YES	NO	YES	NO	YES	NO	YES	NO	YES	NO	YES	NO	YES	NO	YES	NO	YES	NO
	Medication name																				
	Dosage																				
	Frequency																				
	Duration																				
	Route																				
	Quantity																				
3.	Additional Label information																				
	Complete the course																				

	Antibiotic																				
	Before food																				
	After food/with food																				

Appendix B: BMREC_UWC Approval Letter

UNIVERSITY of the WESTERN CAPE

60 YEARS of hope, action & knowledge

01 July 2020

Ms NL Hoffman
School of Pharmacy
Faculty of Natural Sciences

Ethics Reference Number: BM20/5/17

Project Title: Current Practices of Urinary Tract Infection Management: An Observational Study at Primary Health Care Level

Approval Period: 01 July 2020 – 01 July 2023

I hereby certify that the Biomedical Science Research Ethics Committee of the University of the Western Cape approved the scientific methodology and ethics of the above mentioned research project.

Any amendments, extension or other modifications to the protocol must be submitted to the Ethics Committee for approval.

Please remember to submit a progress report annually by 30 November for the duration of the project.

Permission to conduct the study must be submitted to BMREC for record-keeping.

The Committee must be informed of any serious adverse event and/or termination of the study.

Ms Patricia Josias
Research Ethics Committee Officer
University of the Western Cape

Director: Research Development
University of the Western Cape
Private Bag X 17
Bellville 7535
Republic of South Africa
Tel: +27 21 959 4111
Email: research-ethics@uwc.ac.za

NHREC Registration Number: BMREC-130416-050

FROM HOPE TO ACTION THROUGH KNOWLEDGE.

Appendix C: National Department of Health Approval letter

Western Cape Government
Health

STRATEGY & HEALTH SUPPORT
Health.Research@westerncape.gov.za
tel: +27 21 483 0866; fax: +27 21 483 6058
5th Floor, Norton Rose House,, 8 Riebeek Street, Cape Town, 8001
www.capegateway.gov.za

REFERENCE: WC_202006_038
ENQUIRIES: Dr Sabela Petros

University of the Western Cape
Robert Sobukwe Road
Bellville
7535

For attention: Ms Nicole Leanne Hoffman, Prof Renier Coetzee, Mrs Yasmina Johnson

Re: Current Practices of Urinary Tract Infection Management: An Observational Study at Primary Health Care Level

Thank you for submitting your proposal to undertake the above-mentioned study. We are pleased to inform you that the department has granted you approval for your research.

Please contact the following people to assist you with any further enquiries in accessing the following sites:

[redacted]

Kindly ensure that the following are adhered to:

1. Arrangements can be made with managers, providing that normal activities at requested facilities are not interrupted.
2. Researchers, in accessing provincial health facilities, are expressing consent to provide the department with an electronic copy of the final feedback (**annexure 9**) within six months of completion of research. This can be submitted to the provincial Research Co-ordinator (Health.Research@westerncape.gov.za).
3. In the event where the research project goes beyond the estimated completion date which was submitted, researchers are expected to complete and submit a progress report (**Annexure 8**) to the provincial Research Co-ordinator (Health.Research@westerncape.gov.za).
4. The reference number above should be quoted in all future correspondence.

Yours sincerely

DR M MOODLEY
DIRECTOR: HEALTH IMPACT ASSESSMENT
DATE: 1 October 2020
CC

Appendix D: Authorship documents (*South African Medical Journal*)

UNIVERSITY OF THE WESTERN CAPE
PRIVATE BAG X 17
BELVILLE 7535
SOUTH AFRICA

PH: +27 (0) 21 959 3382

3 November 2021

Private Bag X1
Pinelands 7430
Cape Town
South Africa

Dear SAMJ Editors

RE: Pharmaceutical perspective of treating urinary tract infections in public sector primary healthcare facilities in Cape Town, South Africa

We wish to submit the above titled research paper/journal article for publication in *South African Medical Journal*. The paper was co-authored by Yasmina Johnson and Renier Coetzee.

This study describes the treatment of urinary tract infections (UTIs) in adults in primary care in the Cape Metropole public sector of the Western Cape province. A total of 401 UTI episodes occurred in 383 patients during the study period, 1 October 2020 to 28 February 2021. Compliance to urine microscopy recommendations was low, and antibiotics were appropriately selected in the majority of uncomplicated (75%) and complicated UTI episodes (70%). In conclusion, interventions are required to improve compliance to guidelines in terms of appropriate antibiotic selection, duration of antibiotic therapy and diagnostic investigations.

Further, we believe that this paper will be of interest to the readership of your journal because antibiotic resistance is a global healthcare threat fuelled by various factors including irrational prescribing. The majority of urinary tract infections, a common infection frequently treated in the primary care setting, require antibiotics. In the Western Cape, the treatment practices of UTIs are not well described. We believe this article provides valuable information regarding the treatment of UTIs in the primary care setting.

This manuscript has not been published or presented elsewhere in part or in entirety and is not under consideration by another journal. The study design was approved by the appropriate ethics review board. However, since this was a retrospective medical record review informed consent was waived/not required. We have read and understood your journal's policies, and we believe that neither the manuscript nor the study violates any of these. There are no conflicts of interest to declare.

Thank you for considering our article for publication in your journal. We look forward to hearing from you.

Sincerely,

Mrs Nicole Keuler
School of Pharmacy, University of the Western Cape, Cape Town, South Africa
University of the Western Cape, Private Bag x17, Bellville, 7535
076 054 2959
nnkeuler@uwc.ac.za

Appendix E: Author guidelines (*South African Medical Journal*)

Please note that the journal does not provide a pdf with instructions. These instructions were copied from their website for ease of reference.

Available from: http://www.samj.org.za/index.php/samj/about/submissions#authorGuidelines

Manuscript preparation

Preparing an article for anonymous review

To ensure a fair and unbiased review process, all submissions are to include an anonymised version of the manuscript. The exceptions to this are Correspondence, Book reviews and Obituary submissions.

Submitting a manuscript that needs additional blinding can slow down your review process, so please be sure to follow these simple guidelines as much as possible:

- An anonymous version should not contain any author, affiliation or particular institutional details that will enable identification.
- Please remove title page, acknowledgements, contact details, funding grants to a named person, and any running headers of author names.
- Mask self-citations by referring to your own work in third person.

General article format/layout

Accepted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction, which will delay publication.

General:

- Manuscripts must be written in UK English.
- The manuscript must be in Microsoft Word format. Text must be single-spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes).
- Please make your article concise, even if it is below the word limit.
- Qualifications, ***full*** affiliation (department, school/faculty, institution, city, country) and contact details of ALL authors must be provided in the manuscript and in the online submission process.
- Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.
- Include sections on Acknowledgements, Conflict of Interest, Author Contributions and Funding sources. If none is applicable, please state 'none'.
- Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dL).
- Litres is denoted with an uppercase L e.g. 'mL' for millilitres).
- Units should be preceded by a space (except for % and ºC), e.g. '40 kg' and '20 cm' but '50%' and '19ºC'.
- Please be sure to insert proper symbols e.g. μ not u for micro, a not a for alpha, b not B for beta, etc.
- Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160.
- Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'
- Round brackets (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.
- If you wish material to be in a box, simply indicate this in the text. You may use the table format –this is the *only* exception. Please DO NOT use fill, format lines and so on.

SAMJ is a generalist medical journal, therefore for articles covering genetics, it is the responsibility of authors to apply the following:

- Please ensure that all genes are in italics, and proteins/enzymes/hormones are not.
- Ensure that all genes are presented in the correct case e.g. TP53 not Tp53.

**NB: Copyeditors cannot be expected to pick up and correct errors wrt the above, although they will raise queries where concerned.

- Define all genes, proteins and related shorthand terms at first mention, e.g. '188del11' can be glossed as 'an 11 bp deletion at nucleotide 188.'
- Use the latest approved gene or protein symbol as appropriate:

- Human Gene Mapping Workshop (HGMW): genetic notations and symbols
- HUGO Gene Nomenclature Committee: approved gene symbols and nomenclature
- OMIM: Online Mendelian Inheritance in Man (MIM) nomenclature and instructions
- Bennet et al. Standardized human pedigree nomenclature: Update and assessment of the recommendations of the National Society of Genetic Counselors. J Genet Counsel 2008;17:424-433: standard human pedigree nomenclature.

Research

Guideline word limit: 4 000 words

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

Select figures and tables for your paper carefully and sparingly. Use only those figures that provided added value to the paper, over and above what is written in the text.
Do not replicate data in tables and in text .

Structured abstract

- This should be 250-400 words, with the following recommended headings:
  - **Background:** why the study is being done and how it relates to other published work.
  - **Objectives:** what the study intends to find out
  - **Methods:** must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.
  - **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.
  - **Conclusion:** must be supported by the data, include recommendations for further study/actions.
- Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors.
- Do not include any references in the abstracts.

Here is an example of a good abstract.

Main article

All articles are to include the following main sections: Introduction/Background, Methods, Results, Discussion, Conclusions.

The following are additional heading or section options that may appear within these:

- Objectives (within Introduction/Background): a clear statement of the main aim of the study and the major hypothesis tested or research question posed
- Design (within Methods): including factors such as prospective, randomisation, blinding, placebo control, case control, crossover, criterion standards for diagnostic tests, etc.
- Setting (within Methods): level of care, e.g. primary, secondary, number of participating centres.
- Participants (instead of patients or subjects; within Methods): numbers entering and completing the study, sex, age and any other biological, behavioural, social or cultural factors (e.g. smoking status, socioeconomic group, educational attainment, co-existing disease indicators, etc)that may have an impact on the study results. Clearly define how participants were enrolled, and describe selection and exclusion criteria.
- Interventions (within Methods): what, how, when and for how long. Typically for randomised controlled trials, crossover trials, and before and after studies.
- Main outcome measures (within Methods): those as planned in the protocol, and those ultimately measured. Explain differences, if any.

Results

- Start with description of the population and sample. Include key characteristics of comparison groups.
- Main results with (for quantitative studies) 95% confidence intervals and, where appropriate, the exact level of statistical significance and the number need to treat/harm. Whenever possible, state absolute rather than relative risks.
- Do not replicate data in tables and in text.
- If presenting mean and standard deviations, specify this clearly. Our house style is to present this as follows:
- E.g.: The mean (SD) birth weight was 2 500 (1 210) g. Do not use the ± symbol for mean (SD).
- Leave interpretation to the Discussion section. The Results section should just report the findings as per the Methods section.

Discussion

Please ensure that the discussion is concise and follows this overall structure – sub-headings are not needed:

- Statement of principal findings
- Strengths and weaknesses of the study
- Contribution to the body of knowledge
- Strengths and weaknesses in relation to other studies
- The meaning of the study – e.g. what this study means to clinicians and policymakers
- Unanswered questions and recommendations for future research

Conclusions

This may be the only section readers look at, therefore write it carefully. Include primary conclusions and their implications, suggesting areas for further research if appropriate. Do not go beyond the data in the article.

Appendix F: Authorship documents (*Journal of Pharmacy Practice*)

UNIVERSITY OF THE WESTERN CAPE
PRIVATE BAG X 17
BELVILLE 7535
SOUTH AFRICA
PH: +27 (0) 21 959 3382

26 November 2021

The Editors
Journal of Pharmacy Practice
SAGE Journals

Dear Editors

RE: Describing antibiotic labelling for the treatment of urinary tract infections in public sector primary health care facilities in the Cape Metropole

We wish to submit the above titled research paper/journal article for publication in the *Jounal of Pharmacy Practice.* The paper was co-authored by Yasmina Johnson and Renier Coetzee.

This study describes the labelling of dispensed antibiotics for urinary tract infections (UTIs) treatment and to determine if label instructions were compliant with the instructions for the antibiotic prescribed. A total of 401 UTI episodes occurred during the study period, 1 October 2020 to 28 February 2021 and antibiotics were prescribed in 98.8% of UTI episodes. The name of the antibiotic, dosage and frequency on the labels were according to the information on the written prescriptions in 99.7%, 99.0%, 98.7% cases, respectively; with a lower compliance in terms of duration of therapy (43.7%) and quantity dispensed (91.3%). In conclusion, interventions are required to include duration of therapy on

dispensing labels of antibiotics. Inappropriate duration of therapy might affect patient health outcomes and antibiotic resistance.

Further, we believe that this paper will be of interest to the readership of your journal because labelling of prescribed medicine is globally important, especially labelling of antibiotics since antibiotic resistance is a global healthcare threat. This study aimed to describe the instructions included on dispensing labels of prescribed antibiotics for the treatment of UTIs in the primary health care setting of the Western Cape in South Africa and to ascertain compliance with the prescription.
We believe this article provides valuable information regarding the labelling of prescribed antibiotics for UTI treatment in primary care setting.

This manuscript has not been published or presented elsewhere in part or in entirety and is not under consideration by another journal. The study design was approved by the appropriate ethics review board. However, since this was a retrospective medical record review informed consent was waived/not required. We have read and understood your journal's policies, and we believe that neither the manuscript nor the study violates any of these. There are no conflicts of interest to declare.

Thank you for considering our article for publication in your journal. We look forward to hearing from you.

Sincerely,

Mrs Nicole Keuler
School of Pharmacy, University of the Western Cape, Cape Town, South Africa
University of the Western Cape, Private Bag x17, Bellville, 7535
076 054 2959
nnkeuler@uwc.ac.za

INSTRUCTIONS FOR AUTHORS SUBMITTING MANUSCRIPTS TO
JOURNAL OF PHARMACY PRACTICE

To expedite manuscript review, SAGE Publications requires that a copy of the following checklist be completed and enclosed with each manuscript submitted to the *Journal of Pharmacy Practice* for publication. This information, as well as related forms required for submission, may be downloaded from the *Journal of Pharmacy Practice* Web site, http://jpp.sagepub.com (go to the "Manuscript Submission" section).

Manuscripts should be submitted at http://mc.manuscriptcentral.com/jpp, where authors will be required to set up an online account in the SAGETRACK system powered by ScholarOne.

- ☐ Provide a letter of transmittal. In this letter, please specify the corresponding author with home address including postal code (ZIP), telephone, beeper, and/or facsimile numbers and an e-mail address.
- ☐ The entire manuscript must be typed double-spaced in a font size of 12 points on 8.5 × 11-inch white paper with margins of at least 1 inch all around.
- ☐ The order of appearance of material in all manuscripts should be as follows: author identification and acknowledgments page, title page, abstract page, text, references, appendixes, tables, figures. Each of these elements should begin on a separate page.
- ☐ The author identification and acknowledgments page should carry: (1) article title; (2) first name, middle initial, and last name of each author, with highest academic degrees; (3) position title and/or academic title of each author; (4) names of departments and institutions with complete addresses to which each author is affiliated; (5) e-mail addresses of each author; and (6) any acknowledgments, financial disclosure information, and author notes.
- ☐ The title page should contain an informative descriptive title and no other information.
- ☐ The abstract page should include an abstract not to exceed 200 words and should include up to 5 keywords.
- ☐ The main manuscript file should contain no clues as to author identity. Footnotes containing information pertaining to author identity or institutional affiliation should be on the author identification page. The text should have appropriate headings and subheadings. Normally up to 2 headings are used as follows: Headings should appear in all uppercase letters (eg, STUDY METHOD); Subheadings should appear with capitalization followed by lowercase letters (eg, Questionnaire Design).
- ☐ Generic names (with salt, if applicable) should be used for all drugs. No drug or chemical names should be abbreviated. Trade names are used only to identify that a specific brand was used.
- ☐ Units and Abbreviations: traditional units must be used. Système International (SI) units or other equivalents must appear in parentheses. *Gram, gram, Gm, gm* must be abbreviated as "g"; *cc, ml* must be abbreviated as "mL". The words *percent* or *percentage* must be spelled when a component of editorial copy. The percent/percentage symbol (%) must be used when indicating potency/strength concentration. Temperatures must be expressed as Celsius/ Centigrade; the Fahrenheit equivalent may appear immediately after in parentheses ( ).
- ☐ A list of symbols used and their meanings must be included if a large number of symbols appears in the text.
- ☐ References must begin on a separate page. They must be numbered consecutively in the order in which they appear in the text by superscript Arabic numerals. References should be typed in the style adopted by the National Library of Medicine and used in *Index Medicus*, with the exception that only the first 3 authors (last name and up to 2 initials) are listed. References should not include any unpublished observations or personal communications.
- ☐ Type each table double-spaced on a separate page. They must be numbered consecutively in the order of their first citation in the text. A brief title for each table must be provided. A table legend must be provided for each table.
- ☐ Figures should be submitted as graphics files using the original program in which they were created (JPG, TIFF, or EPS; Microsoft Application Files are acceptable for line art). If using scanned images, please be sure the resolution is at least 1200 dpi for line art and 300 dpi for color or gray scale. Drawings must be uniformly sized if possible, and planned for 50% reduction. They must be numbered consecutively in the order of their first citation in the text. A figure legend must be provided for each figure.
- ☐ Permission to reproduce previously copyrighted material: The corresponding author is responsible for obtaining written releases from other publishers for SAGE Publications to publish material copyrighted by someone else. If needed, download the *Permission to Reprint Form* from the JPP Web site. Complete, date and sign, and submit this form with the manuscript.
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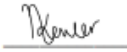
Proofreading and Reprints: Authors will receive page proofs for their accepted article, which they must correct and return as soon as possible. Authors will also receive a reprint order form.

Charges for color figures: $800.00 for the first figure and $200.00 for each additional figure. (Color reproduction in the online PDF is free of charge.)

Signature of corresponding author completing this form: 

Print name of corresponding author completing this form: Nicole Keuler

For further information or clarification please contact Henry Cohen, MS, PharmD, FCCM, BCPP, CGP, Editor in Chief, *Journal of Pharmacy Practice*, 718-604-5373 (tel); 718-604-5486 (fax); 917-205-6740 (beeper); HCohenLIU@aol.com.

Appendix G: Authorship guidelines (*Journal of Pharmacy Practice*)

Please note that the journal does not provide a pdf with instructions. These instructions were copied from their website for ease of reference. Available from: https://journals.sagepub.com/author-instructions/JPP

https://us.sagepub.com/en-us/nam/manuscript-submission-guidelines?_gl=1%2Auh0vwv%2A_ga%2AMTA0NDkxMDQxMC4xNjE0MTc5NjM5%2A_ga_60R758KFDG%2AMTYzOTkzMTQ5MC40Ni4xLjE2Mzk5MzI0MTcuMA..#PreparingYourManuscript

SAGE Publishing disseminates high-quality research and engaged scholarship globally, and we are committed to diversity and inclusion in publishing. We encourage submissions from a diverse range of authors from across all countries and backgrounds.

Only manuscripts of sufficient quality that meet the aims and scope of *JPP* will be reviewed.

There are no fees payable to submit or publish in this journal.

As part of the submission process you will be required to warrant that you are submitting your original work, that you have the rights in the work, and that you have obtained and can supply all necessary permissions for the reproduction of any copyright works not owned by you, that you are submitting the work for first publication in the Journal and that it is not being considered for publication elsewhere and has not already been published elsewhere. Please see our guidelines on prior publication and note that *JPP* may accept submissions of papers that have been posted on pre-print servers; please alert the Editorial Office when submitting (contact details are at the end of these guidelines) and include the DOI for the preprint in the designated field in the manuscript submission system. Authors should not post an updated version of their paper on the preprint server while it is being peer reviewed for possible publication in the journal. If the article is accepted for publication, the author may re-use their work according to the journal's author archiving policy. If your paper is accepted, you must include a link on your preprint to the final version of your paper.

If you have any questions about publishing with SAGE, please visit the SAGE Journal Solutions Portal.

1. What do we publish?

1.1 Aims & Scope

Journal of Pharmacy Practice is a peer-reviewed journal that offers practicing pharmacists in-depth useful reviews and research trials and surveys of new drugs and novel therapeutic approaches, pharmacotherapy reviews and controversies, pharmacokinetics, drug interactions, drug administration, adverse drug events, medication safety, pharmacy education, and other pharmacy practice topics.

1.2 Article types

- **Pharmacy Practice Review Articles**
  a. Abstract (250 word limit)
  b. Keywords (5 keywords limit)
  c. References (100 limit)
  d. Word Count (5,000)

- **Drug or Therapeutic Review Articles**
  a. Abstract (250 word limit)
  b. Keywords (5 keywords limit)
  c. References (150 limit)
  d. Word Count (5,000)

- **Continuing Education Articles**
  a. Abstract (250 word limit)
  b. Keywords (5 keywords limit)
  c. Goals and objectives (7 limit)
  d. References (150 limit)
  e. Word Count (5,000)

- **Research Reports**
  a. Structured Abstract (250 word limit) (to include Background, Objective, Methods, Results, Conclusion)
  b. Keywords (5 keywords limit)
  c. References (100 limit)
  d. Word Count (5,000)

- **Pharmacy Experiential Education**
  a. Abstract (250 word limit)
  b. Keywords (5 keywords limit)
  c. References (100 limit)
  d. Word Count (4,000)

- **Adverse Drug Event Case Reports**
  a. Abstract (250 word limit)
  b. Keywords (5 keywords limit)
  c. References (50 limit)
  d. Word Count (2,500)

- **Case Reports or Case Studies**
  a. Abstract (250 word limit)
  b. Keywords (5 keywords limit)
  c. References (50 limit)
  d. Word Count (2,500)

- **Biomedical Communications or Informatics Reviews**
  a. No Abstract
  b. Keywords (5 keywords limit)
  c. References (10 limit)
  d. Word Count (1,500)

- **Editorial or Commentary**
  a. Abstract (150 word limit)
  b. Keywords (5 keywords limit)
  c. References (20 limit)
  d. Word Count (1,500)

- **Letters to the Editor**
  a. No Abstract
  b. Keywords (5 keywords limit)
  c. References (10 limit)
  d. Word Count (750)

1.3 Writing your paper

The SAGE Author Gateway has some general advice on how to get published, plus links to further resources.

File Downloads:

- Author Submission Checklist
- Permission to Reprint Form

1.3.1 Make your article discoverable

For information and guidance on how to make your article more discoverable, visit our Gateway page on How to Help Readers Find Your Article Online

2. Editorial policies

2.1 Peer review policy

SAGE does not permit the use of author-suggested (recommended) reviewers at any stage of the submission process, be that through the web-based submission system or other communication. Reviewers should be experts in their fields and should be able to provide an objective assessment of the manuscript. Our policy is that reviewers should not be assigned to a paper if:

- The reviewer is based at the same institution as any of the co-authors
- The reviewer is based at the funding body of the paper
- The author has recommended the reviewer
- The reviewer has provided a personal (e.g. Gmail/Yahoo/Hotmail) email account and an institutional email account cannot be found after performing a basic Google search (name, department and institution).

2.2 Authorship

Papers should only be submitted for consideration once consent is given by all contributing authors. Those submitting papers should carefully check that all those whose work contributed to the paper are acknowledged as contributing authors.

The list of authors should include all those who can legitimately claim authorship. This is all those who:

1. Made a substantial contribution to the concept or design of the work; or acquisition, analysis or interpretation of data,
2. Drafted the article or revised it critically for important intellectual content,
3. Approved the version to be published,
4. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

Authors should meet the conditions of all of the points above. When a large, multicentre group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship.

4. Preparing your manuscript for submission

4.1 Formatting

The preferred format for your manuscript is Word. LaTeX files are also accepted. Word and (La)Tex templates are available on the Manuscript Submission Guidelines page of our Author Gateway.

4.2 Artwork, figures and other graphics

For guidance on the preparation of illustrations, pictures and graphs in electronic format, please visit SAGE's Manuscript Submission Guidelines

Charges for color figures: $800.00 for the first figure and $200.00 for each additional figure. Color reproduction in the online PDF is free of charge.

4.3 Supplemental material

This journal is able to host additional materials online (e.g. datasets, podcasts, videos, images etc.) alongside the full-text of the article. For more information please refer to our guidelines on submitting supplemental files

4.4 Reference style

References must begin on a separate page. They must be numbered consecutively in the order in which they appear in the text by superscript Arabic numerals. References should be typed in the style adopted by the National Library of Medicine and used in Index Medicus with the exception that only the first 3 authors (last name and up to 2 initials) are listed. For example, a standard journal article with more than 3 authors should be listed as shown below. References should not include any unpublished observations or personal communications.

1. Schoni MH, Casaulta-Aebischer C, Martinet LV, et al. Nutrition and lung function in cystic fibrosis patients: review. Clin Nutr. 2000;19:79-85.

Preparing your manuscript

Where a journal uses double-anonymize peer review, authors are required to submit a fully anonymised manuscript with a separate title page. See https://sagepub.com/Manuscript-preparation-for-double-anonymize-journal

Formatting your article

When formatting your references, please ensure you check the reference style followed by your chosen journal. Here are quick links to the SAGE Harvard reference style, the SAGE Vancouver reference style and the APA reference style.

Other styles available for certain journals are: ACS Style Guide , AMA Manual of Style, ASA Style Guide , Chicago Manual of Style and CSE Manual for Authors, Editors, and Societies .

Please refer to your journal's manuscript submission guidelines to confirm which reference style it conforms to and for other specific requirements.

Equations should to be submitted using Office Math ML and Math type.

Microsoft Word guidelines

There is no need to follow a specific template when submitting your manuscript in Word. However, please ensure your heading levels are clear, and the sections clearly defined.

(La)TeX guidelines

We welcome submissions of LaTeX files. Please download the SAGE LaTex Template, which contains comprehensive guidelines.The SAGE LaTex template files are also available in Overleaf, should you wish to write in an online environment.

If you have used any .bib or .bst files when creating your article, please include these with your submission so that we can generate the reference list and citations in the journal-specific style. If you have any queries, please consult our LaTex Frequently Asked Questions.

Artwork guidelines

Illustrations, pictures and graphs, should be supplied in the highest quality and in an electronic format that helps us to publish your article in the best way possible. Please follow the guidelines below to enable us to prepare your artwork for the printed issue as well as the online version.

- **Format:** TIFF, JPEG: Common format for pictures (containing no text or graphs).
  EPS: Preferred format for graphs and line art (retains quality when enlarging/zooming in).
- **Placement:** Figures/charts and tables created in MS Word should be included in the main text rather than at the end of the document. Figures and other files created outside Word (i.e. Excel, PowerPoint, JPG, TIFF and EPS) should be submitted separately. Please add a placeholder note in the running text (i.e. "[insert Figure 1.]")

- **Resolution:** Rasterized based files (i.e. with .tiff or .jpeg extension) require a resolution of at least **300 dpi** (dots per inch). Line art should be supplied with a minimum resolution of **800 dpi**.
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- Simplicity is the key to conveying information visually. Terms and abbreviations should match overall journal usage and style.

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Appendix H: Acceptance email from *South African Medical Journal*

Your Submission External Inbox ×

SAMJ <em@editorialmanager.com> Dec 17, 2021, 12:43 PM (2 days ago)
to me

CC: "Yasmina Johnson" yasmina.johnson@westerncape.gov.za, "Renier Coetzee" recoetzee@uwc.ac.za

Ref.: SAMJ16258
Pharmaceutical perspective of treating urinary tract infections in public sector primary healthcare facilities in Cape Town, South Africa
South African Medical Journal

Dear Mrs Keuler,

We are pleased to tell you that your work has now been accepted for publication in South African Medical Journal.

Please find payment form attached herewith. As soon as proof of payment and the completed form have been received, we will send your article into production. (Please note that we are unable to process American Express card payments). Please send proof of payment to claudian@samedical.org

Thank you for submitting your work to the journal.

Best wishes

Bridget Farham, PhD
Editor
South African Medical Journal

Appendix I: Correspondence from *Journal of Pharmacy Practice*

Journal of Pharmacy Practice JPP-21-0688 External Inbox ×

Journal of Pharmacy Practice <onbehalfof@manuscriptcentral.com> Fri, Nov 26, 11:00 PM
to me, Yasmina.Johnson, recoetzee

26-Nov-2021

Dear Mrs. Keuler:

Your manuscript entitled "Describing antibiotic labelling for the treatment of urinary tract infections in public sector primary health care facilities in the Cape Metropole" has been successfully submitted online and is presently being given full consideration for publication in Journal of Pharmacy Practice.

Your manuscript ID is JPP-21-0688.

You have listed the following individuals as authors of this manuscript:
Keuler, Nicole; Johnson, Yasmina; Coetzee, Renier

Please mention the above manuscript ID in all future correspondence or when calling the office for questions. If there are any changes in your street address or e-mail address, please log in to ScholarOne Manuscripts at https://mc.manuscriptcentral.com/jpp and edit your user information as appropriate.

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Thank you for submitting your manuscript to Journal of Pharmacy Practice.

Sincerely,
Snigdha Biswas
Journal of Pharmacy Practice
jpp@sagepub.com

Appendix J: Results

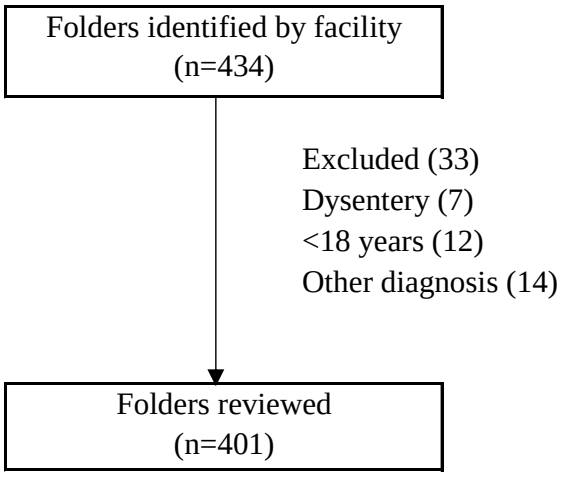

Figure 1: Folders included and excluded in the folder review

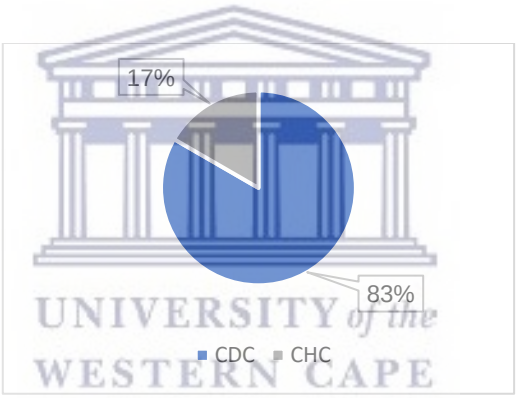

Figure 2: Type of facilities included

Table 1: Prescriptions reviewed per facility and substructure

Facility	Folders reviewed	
	n	**%**
Substructure (A)	**116**	**28.9**
Facility 1	97	24.2
Facility 2	19	4.7
Substructure (B)	**138**	**34.4**
Facility 3	78	19.5
Facility 4	60	15.0
Substructure (C)	**147**	**36.7**
Facility 5	121	30.2
Facility 6	26	6.5
Total	**401**	**100.0**

Table 2: Antibiotics prescribed per facility

	Total (n)		Facility 1		Facility 2		Facility 3		Facility 4		Facility 5		Facility 6	
Antibiotic prescribed	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**
Nitrofurantoin	229	57.1	34	14.8	14	6.1	52	22.7	2	0.9	114	49.8	13	5.7
Ciprofloxacin	159	39.7	61	38.4	4	2.5	25	15.7	54	34.0	3	1.9	12	7.5
Amoxicillin-clavulanic acid	6	1.5	0	0.0	0	0.0	0	0.0	4	66.7	1	16.7	1	16.7
Amoxicillin	2	0.5	1	50.0	0	0.0	0	0.0	0	0.0	1	50.0	0	0.0
No antibiotic prescribed	5	1.2	1	20.0	1	20.0	1	20.0	0	0.0	2	40.0	0	0.0
Total	401	100.0	97	24.2	19	4.7	78	19.5	60	15.0	121	30.2	26	6.5

Table 3: Comparing prescriptions reviewed with actual dispensing information

Facility	**Nitrofurantoin**		**Fosfomycin**	
	Folders reviewed	**Pharmacy issues**	**Folders reviewed**	**Pharmacy issues**
Substructure (A)	48	124	0	0
Facility 1	34	94	0	0
Facility 2	14	30	0	0
Substructure (B)	54	136	0	0
Facility 3	52	130	0	0
Facility 4	2	6	0	0
Substructure (C)	127	469	0	4
Facility 5	114	449	0	4
Facility 6	13	20	0	0
Total	229	729	0	4

Table 4: Urine analysis per UTI episode

	Total		1st episode		2nd episode		3rd episode	
Urine analysis	*N*	%	*n*	*%*	*n*	%	*n*	%
Urine dipstick	353	88.0	336	87.7	16	94.1	1	100.0
Urine culture	25	6.2	22	5.7	3	17.6	-	-

Table 5: Dipstick analysis from UTI episodes

Detected	*n*	%
Nitrites	83	20.7
Leucocytes	236	58.9
Blood	139	34.7
Protein	146	36.4
Nitrites and leucocytes	40	10.0

Table 6: Available urine microscopy results

Organism detected	Antibiotic prescribed	Amoxicillin	Amoxicillin-clavulanic acid	Cefuroxime (PO)	Cefuroxime (IV)	Ceftriaxone	Cefotaxime	Ciprofloxacin	Cotrimoxazole	Gentamicin	Nitrofurantoin	Piperacillin-tazobactam	Tigecycline
E. coli	Nitrofurantoin	R	S	I	S	S	S	R	S	S	S		
E. coli	Nitrofurantoin	R	S	S	S	S	S	I	S	S	S		
E. coli	Nitrofurantoin										S		
E. coli	Ciprofloxacin	R	S	S	S	S	S		R	S	S		
E. coli	Nitrofurantoin	R	I	S	S	S	S	R		S	S	R	
E. coli	Ciprofloxacin	R	S	S	S	S	S		R	S			
E. coli	Amoxicillin-clavulanic acid			S	S	S	S	S		S			
E. coli	Ciprofloxacin	S		I	S	S	S	S	S	S	S		
Candida	Ciprofloxacin												
K. pneumoniae	Ciprofloxacin	R	S	S	S		S		S	S	I		
P. Mirabilis	Nitrofurantoin	S		S	S	S	S			S	R		R

I – intermediate, R – resistant, S- sensitive

Table 7: *E. coli* sensitivity

Antibiotic	Sensitive (%)	Intermediate (%)	Resistance (%)
Amoxicillin	16.7	-	83.3
Amoxicillin-clavulanic acid	80	20	-
Cefuroxime (PO)	71.4	28.6	-
Cefuroxime (IV)	100	-	-
Ceftriaxone	100	-	-
Cefotaxime	100	-	-
Ciprofloxacin	40	20	40
Cotrimoxazole	60	-	40
Gentamicin	100	-	-
Nitrofurantoin	100	-	-
Piperacillin-tazobactam	-	-	100
Tigecycline	-	-	-

% calculated = number of sensitivity/intermediate/resistant results /total number of available sensitivity results for *E.coli*

Table 8: Antibiotic prescribed per UTI episode in patients with more than one episode

Antibiotic	1st episode (n)	2nd episode (n)	3rd episode (n)
Nitrofurantoin	12	10	1
Ciprofloxacin	3	4	-
Amoxicillin	1	-	-
Amoxicillin-clavulanic acid	1	1	-
Unknown	-	2	-

Table 9: Antibiotics prescribed during pregnancy

Antibiotic prescribed	*n*	%
Nitrofurantoin	76	90.5
Amoxicillin	1	1.2
Amoxicillin-clavulanic acid	4	4.8
Ciprofloxacin	1	1.2
No antibiotic	2	2.4
Total	84	100.0

Table 10: Contraception in non-pregnant women of child-bearing age

Contraception	*n*	%
Combined oral contraception	2	1.6
Intra-uterine device	1	0.8
Progestrone injection	27	20.9
Progesterone tablet	1	0.8
Unknown	96	74.4
Total	129	100.0

One patient was sterilised, one had a hysterectomy, during a second UTI episode an implant was documented as contraception.

Appendix K: Certificate of mini-thesis editing

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Proof of Edit

UWC/2021/02

2021/10/26

To whom it may concern,

Declaration

With this I certify that I, Louise Jean Keuler, was paid as freelance editor to proofread Nicole Keuler, Yasmina Johnson and Renier Coetzee's academic article (*Pharmaceutical perspective of treating urinary tract infections in public sector primary healthcare facilities in Cape Town, South Africa*) for submission to the *South African Family Practice Journal* (AOSIS Publishing). It should be noted that as Ms Keuler, Ms Johnson and Mr Coetzee's proofreader, I did not contribute to the content or research of the article. The work is entirely their own and my contribution to it was merely for the sake of clarity and readability.

Services rendered

Editing

- Ensured that the AOSIS Publishing's *South African Family Practice Journal* template's submission guidelines where followed.
- Followed British English spelling, grammar and language conventions.
- Implemented Plain English for ease of reading and word recognition.
- Prepared the document for distribution or publication through the following:
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  - polishing language by editing for grammar, usage, spelling and punctuation;
  - checking for consistency of mechanics and for internal consistency of facts and references; and
  - editing tables, figures and lists.

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RECEIVED BY	LJ KEULER
TOTAL AMOUNT	R540.00

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Louise Keuler at louise.jean.greyling@gmail.com or on 072 263 6805

LKeuler

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UWC/2021/03

2021/11/18

To whom it may concern,

Declaration

With this I certify that I, Louise Jean Keuler, was paid as freelance editor to proofread Nicole Keuler, Yasmina Johnson and Renier Coetzee's academic article (*Describing antibiotic labelling for the treatment of urinary tract infections in public sector primary health care facilities in the Cape Metropole*) for submission to the *Pharmacy* (MDPI). It should be noted that as Ms Keuler, Ms Johnson and Mr Coetzee's proofreader, I did not contribute to the content or research of the article. The work is entirely their own and my contribution to it was merely for the sake of clarity and readability.

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RECEIVED BY	LJ KEULER
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Proof of Edit

UWC/2021/05

2021/12/15

To whom it may concern,

Declaration

With this I certify that I, Louise Jean Keuler, was paid as freelance editor to edit Nicole Leanne Keuler's mini-thesis (*Current Practice of Urinary Tract Infection Management: An Observational Study at Primary Healthcare Level*) for submission to the School of Pharmacy at the University of the Western Cape. It should be noted that as Ms Keuler's editor, I did not contribute to the content or research of the mini-thesis. The work is entirely her own and my contribution to it was merely for the sake of clarity and readability.

Services rendered

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  - polishing language by editing for grammar, usage, spelling and punctuation;
  - checking for consistency of mechanics and for internal consistency of facts; and
  - editing tables, figures and lists.

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